THE ONTARIO CROHN’S AND COLITIS COHORT:
INCIDENCE AND OUTCOMES OF CHILDHOOD-ONSET
INFLAMMATORY BOWEL DISEASE IN ONTARIO, CANADA

by

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A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy in Clinical Epidemiology and Health Care Research
Graduate Department of Health Policy, Management & Evaluation
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Abstract

Inflammatory bowel disease (IBD), characterized by chronic gastrointestinal inflammation, represents a significant childhood chronic disease. In this thesis, a case ascertainment definition of paediatric-onset IBD was validated using administrative data and developed the Ontario Crohn’s and Colitis Cohort (OCCC). The epidemiology of paediatric IBD in Ontario was described, demonstrating that Ontario has one of the highest worldwide incidence rates. Statistically significant increases in incidence were noted in 0-4 year olds (5.0%/year, p=0.03) and 5-9 year olds (7.6%/year, p<0.0001), but not in other age groups. Lower income children were more likely to be hospitalized at least once (hazard ratio (HR) 1.17, 95% confidence intervals (CI) 1.05-1.30) or visit the ED (HR 1.21, 95% CI 1.09-1.35) and had more IBD-related physician visits (odds ratio (OR) 3.73, 95% CI 1.05-13.27). Lower income children with Crohn's disease (CD) (not ulcerative colitis [UC]) were more likely to undergo intra-abdominal surgery within 3 years of diagnosis (OR 1.22, 95% CI 1.01-1.49), especially if diagnosed after 2000 (OR 1.79, 95% CI 1.27-2.53). Finally, changes in health services utilization and surgical rates were described, as were changes in specialist care provision and immunomodulator use in children with IBD between 1994-2007. The changes to care included increased outpatient care provided by paediatric gastroenterologists, and increased immunomodulator use. Children diagnosed with CD, but not UC, in recent years had lower surgical rates. In CD patients, intra-abdominal surgical rates within three years of diagnosis decreased from 18.8% in children diagnosed in 1994-1997 to 13.6% in those diagnosed in 2001-2004 (P = 0.035). When stratified by age at diagnosis, this decrease was significant in children diagnosed ≥10 years old (OR 0.67, 95% CI 0.48-0.93). The OCCC will continue to be used to investigate the epidemiology and burden of paediatric IBD and to improve the care received by children with IBD in Ontario.
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This thesis is dedicated to all children with inflammatory bowel disease. My hope is that this research (and all future research arising from it) will improve their lives.
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List of Abbreviations

6-MP: 6-mercaptopurine
AHRQ: Agency for Healthcare Research and Quality
AUROC: area under the receiver operating characteristic curve
CA: census agglomeration
CD: Crohn's disease
CI: confidence intervals
CIHR: Canadian Institutes of Health Research
CMA: census metropolitan area
CSD: census subdivision
CT: census tract
DA: dissemination area
EA: enumeration area
ED: emergency department
FSA: forward sortation area
FY: fiscal year
GI: gastroenterologist
HMO: health maintenance organization
HR: hazard ratio
IBD: inflammatory bowel disease
IBD-U: inflammatory bowel disease type undefined
ICD: International Statistical Classification of Diseases and Related Health Problems
ICES: Institute for Clinical Evaluative Sciences
LR+: positive likelihood ratio
LR-: negative likelihood ratio
MTX: methotrexate
NPV: negative predictive value
OCCC: Ontario Crohn's and Colitis Cohort
OHIP: Ontario Health Insurance Plan
OR: odds ratio
PPV: positive predictive value
SD: standard deviation
SES: socioeconomic status
SickKids: The Hospital for Sick Children
TNF: tumour necrosis factor
UC: ulcerative colitis
Chapter 1

Introduction

The purposes of this chapter are to:
1. Present the thesis hypotheses and study questions.
2. Provide the reader with an introduction to inflammatory bowel disease (IBD) and its importance as a chronic disease in children.
3. Review trends in the epidemiology of paediatric-onset IBD
4. Discuss the use of health administrative data for surveillance and research on IBD
5. Review rates of health services utilization and surgical outcomes in paediatric IBD

1.1 Hypotheses and Study Questions

1.1.1 General Goal & Hypothesis
The overarching goal of this thesis is to create a surveillance program for paediatric-onset IBD using Ontario's health administrative databases. The hypothesis is that despite its limitations, health administrative data is an effective tool to track children with chronic diseases and therefore can be used to describe the epidemiology, health services utilization and outcomes of children with IBD. The long-term goal is to use the Ontario Crohn’s and Colitis Cohort (OCCC) to improve the quality of care received by children with IBD in Ontario and beyond.

1.1.2 Specific Hypotheses
The specific hypotheses of this thesis were:
1) Health administrative data can be used to identify and track children with IBD following rigorous validation of the methods used for identification;
2) The incidence and prevalence of paediatric IBD has increased in Ontario over the past decade;
3) Sociodemographic factors such as socioeconomic status, sex and age at diagnosis affect the rate of health services utilization and surgical outcomes. More specifically:
a) Children of lower income neighbourhoods are more likely to use the health system frequently and to have worse outcomes (in the form of hospitalization and surgical rates),
b) Children with onset of IBD at an earlier age are more likely to use the health system frequently and have worse outcomes;
4) Recently changes in medical treatments available to children with IBD have altered their health services utilization rates and surgical rates in Ontario. More specifically, the publication of the first randomized controlled clinical trial demonstrating the efficacy of 6-mercaptopurine (6-MP), an oral immunomodulator (1), has resulted in decreased surgical and hospitalization rates in recent years.

1.1.3 Study Questions
The study questions that follow from these hypotheses are as follows:
1) What is the best algorithm to identify children with IBD within Ontario's health administrative databases?
2) Are incidence and prevalence of Crohn’s disease (CD) and ulcerative colitis (UC) in children increasing over time in Ontario?
3) Among children of lower income neighbourhoods, are rates of health services use (physician visits, emergency department visits, hospitalizations) and surgical outcomes (with intestinal resection or peri-anal surgeries) different from those of higher income households?
4) How does sex and age at diagnosis affect these rates of health services use and surgical outcomes?
5) Among children diagnosed with IBD after 2000, when the first paediatric trial showing efficacy of an immunomodulator in CD (1) and the beginning of the biologic therapy era, are rates of health services use and surgical outcomes different from those diagnosed before 2000?

1.2 Background

IBD is a chronic gastrointestinal disease and with 20-25% of cases presenting in childhood, it is one of the most common paediatric chronic diseases. IBD is categorized into CD, UC or IBD type unclassified (IBD-U) (2). CD is characterized by recurrent or chronic transmural
inflammation of the gastrointestinal tract, most commonly the terminal ileum and colon. UC is defined by mucosal inflammation of the colon alone, while the classification of IBD-U is reserved for cases which do not clearly fall into the CD or UC definitions. All forms of IBD are incurable and chronic and therefore therapy is aimed at reducing areas of inflamed bowel resulting in induction and maintenance of disease remission. In Canada, approximately 0.5% of the population is afflicted with IBD and Canada has the highest incidence of CD reported globally (3). Epidemiologic studies restricted to childhood-onset IBD are more likely to reveal informative geographic and temporal trends in incidence, because of the relative lack of co-morbidities, and the likelihood that children are truly closer to disease-onset at the time of diagnosis. For example, CD developing in children (but not adults) occurs more often in males than females, a recent observation in several epidemiologic studies, but as yet not fully explored (4, 5).

The etiology of IBD is multifactorial. More than 30 genetic polymorphisms have been identified that predispose people to develop IBD, although most genes identified do not increase the odds of developing IBD more than twice the baseline population (6). Additionally, the mutations predisposing to the development of adult-onset IBD are similar to those causing childhood-onset IBD (7), implying that environmental factors play a strong role in determining whether a child develops IBD. With its high incidence of IBD, Canada is an ideal setting to examine the environmental and sociodemographic factors which may both predispose children to developing IBD and having worse outcomes. Health administrative databases, which in Canada exist for all legal residents within a province, are an excellent tool to examine trends in epidemiology and health services use as well as the impact of environmental factors on the development and outcomes of childhood-onset IBD. They are truly population-based, are relatively cost-effective to access compared with clinical population-based data and are excellent resources for longitudinal studies because patient encounters are linkable across visits.

The burden and health services utilization of paediatric IBD have not been well explored. A recent study from the United States used health administrative data to describe the higher cost of treating children with IBD when compared with adults (8). Those investigators were unable to follow patients longitudinally for more than three years, however, and the long-term burden of
disease is still unknown. Additionally, although clinical risk factors to higher morbidity (such as genotype or structuring/penetrating disease phenotype) are well understood, sociodemographic risk factors associated with poor disease course in either paediatric or adult IBD have not been well described. A cohort study from France described worse outcomes and lower surgical rates in adult IBD patients of lower socioeconomic status (SES) (9). Female children have also been found to have more severe disease than males (10). The interaction between access to care, socioeconomic status, region of residence, gender and age of diagnosis has not been described in the literature. This thesis represents a first step toward teasing out the role of these social and biologic factors on morbidity and surgical rates.

In addition, increasing research in the field of paediatric IBD has led to significant treatment changes. Immunosuppression (in the form of 6-MP, azathioprine or methotrexate) has been shown very effective at maintaining disease remission in paediatric CD (1, 11). Additionally, new biologically-derived antibodies to tumour necrosis factor (TNF) alpha were shown effective first in adult IBD (12) and then in paediatrics (13). Although proven efficacious in clinical trials, proving these new therapies effective in the real-world scenario of medical practice has been more elusive. A study from France found no association between the increased use of azathioprine in adults with CD and rates of surgical resection (14). It is therefore unclear as to whether new therapies have altered the course of disease in either adults or children. This study will describe changes to the care of children with IBD in Ontario, including specialist visit rates and prescriptions for immunomodulators, and examine whether these changes are associated with altered health services utilization or surgical rates.

This thesis validated an algorithm to identify children with IBD using Ontario's health administrative data. In so doing, the OCCC was developed as a cohort to track all Ontario residents with onset of IBD before the age of 18 years. We examined the epidemiology of childhood-onset IBD in Ontario using population-based health administrative databases, and described trends in incidence and prevalence across the province. As well, we identified and evaluated the impact of risk factors such as gender and SES on morbidity. Finally, we assessed changes in treatment over time to determine whether recent advances in medical therapy have improved outcomes. The cohort assembled for this study will provide ongoing evaluation of the
epidemiology of childhood-onset IBD and findings will help generate hypotheses regarding the etiology of IBD, evaluate the relationship between health care utilization to outcomes and may inform health policy to address the unique needs of this population.

1.3 Epidemiology of Paediatric Inflammatory Bowel Disease

The Canadian IBD Epidemiology Database used Canadian health administrative data to describe that Canada has the highest rate of CD in the world. The study found that the incidence of CD in five Canadian provinces in individuals under 20 years of age ranges from 5.4-12.0 per 100,000. Incidence of UC in this group ranges from 3.2-5.7 per 100,000 (3). These are some of the highest rates of paediatric CD and UC in the world. In Wisconsin, the only American state to report estimates of paediatric IBD, a clinical database from a tertiary care referral centre described incidence of CD at 4.6 per 100,000 and incidence of UC at 2.4 per 100,000 (15). These estimates represent the only information on childhood-onset IBD using population-based data in North America. The Canadian data are based on only five provinces, excluding Canada’s largest province, Ontario. No information is available on trends in incidence of CD or UC in North America, and the trends in paediatric IBD epidemiology are controversial (16). Recent population-based studies from Northern Europe have described an increasing incidence of CD in children (17-20). Other studies, however, have demonstrated stable rates of CD (21, 22) or increasing rates of UC (23, 24). Conflicting reports may be due to geographic variation, heterogeneity in case ascertainment, heterogeneity of age cut-offs for paediatrics or insufficient power to demonstrate changes in trends. The incidence trend in Canadian children has not yet been studied.

1.4 Identification of IBD Cases in Administrative Data

Ontario has a single-payer, government administered health care system and therefore all residents of the province with an Ontario health card are contained and tracked within the health administrative databases. These databases are maintained by the Institute for Clinical Evaluative Sciences (ICES) through a comprehensive data sharing agreement with the Ontario Ministry of
Health and Long Term Care. ICES is an independent, not-for-profit organization that conducts health services research for the province of Ontario. Most episodes of healthcare use within these databases have an associated diagnostic code formatted to the International Classification of Diseases (ICD), Ninth or Tenth Revisions (ICD-9 or ICD-10). As a result, Ontario's health administrative data represent an excellent opportunity to longitudinally track patients with chronic diseases and validated cohorts to follow patients with diabetes (25), hypertension (26), asthma (27) and chronic obstructive pulmonary disease (28) have been established at ICES following validation of algorithms used to identify patients with these diseases. Since the accuracy of health administrative data varies, particularly when used for chronic disease surveillance, validation of these data for the purpose of disease ascertainment has been identified as a priority in the fields of epidemiologic and health services research (29).

Generally, more than one visit to health providers is required to accurately diagnose a chronic disease, and therefore algorithms to identify patients from within administrative data require more than one healthcare contact to reflect a true diagnosis. In Canada, the Canadian IBD Epidemiology Database identified patients with IBD using an algorithm of five health care contacts or one hospitalization, over an 11 year period (30). This algorithm was validated with the charts of adult patients and questionnaires as confirmation of accuracy of diagnosis. The prolonged time period required for disease ascertainment and differing health services utilization pattern between children and adults make this algorithm less than ideal for the identification of patients with childhood-onset disease. Additionally, algorithms validated in older patients may be inaccurate to identify younger patients (31). Finally, the prevalence of IBD in the validation cohort for the algorithm used in the Canadian IBD Epidemiology Database was approximately 0.9, potentially falsely elevating the quoted positive and negative predictive values which vary based on disease prevalence in a population. High predictive values are extremely important to minimize misclassification error in epidemiologic studies (32). One previous study has utilized a variation on the Canadian IBD Epidemiologic Database algorithm to identify children with IBD within American health administrative data, however this variation was never validated as accurate (33). It was therefore essential to develop and validate an algorithm specially aimed at identifying children with IBD, which then allowed us to examine their health services utilization patterns and determinants of outcomes.
1.5 Surgery and Health Services Utilization in IBD

Surgical treatment in IBD represents a failure of medical management. Krebs and Nixon (34) found the probability of surgery in paediatric-onset CD was 44% after 5 years, 65% after 10 years and 94% after 14 years (cumulative probability 62%). Polito et al. (35) reported a 71% surgical rate if CD patients were diagnosed under 20 years old, compared to the 55.3% surgical rate for those diagnosed as adults. In UC, Stordal et al. (36) reported a 21% colectomy rate after five years of follow-up in paediatric patients from a population-based database as compared with 7% of adults. Both medical and surgical treatments of IBD carry significant rates of complication. As a result of all of these factors, a high hospitalization rate (37-40) and economic burden (41-45) has been reported to be associated with IBD. In fact, paediatric IBD has been associated with a higher burden of medical care than adult-onset IBD (8). At present, there is increasing interest in defining the burden of disease in patients with IBD on resource utilization. Between 1994 and 2001 the rate of hospitalization for Canadians aged 20-29 years with CD ranged between 47.9-61.0 hospitalizations per 100,000 population. The hospitalization rate for UC patients of the same age ranged between 16.6-18.8 per 100,000 (44). Other studies revealed that 57-63% of total cost of treatment of CD was associated with hospitalization (42, 43, 46, 47). Only one study (with small numbers of paediatric patients) has examined hospitalization rates in patients with childhood-onset IBD, showing a median of 9 in-patient days per year per CD patient (48). No previous studies have defined the impact of socioeconomic status on health care utilization.

Low SES has been established as a significant risk factor for poor health outcomes in children (49). In the United States, various measures of SES, insurance status and geography all impact on health services utilization and access to specialist care in paediatric chronic diseases (50-52). In Canada, all legal residents have universal access to government-paid physician visits, hospitalizations, emergency room visits and non-elective surgical procedures. Despite this, barriers to adequate health care may exist and the country's most poor children have worse health outcomes described in neonatal complex chronic diseases (53), asthma (54), type 1 diabetes (55), seizure disorders (55) and middle ear disease (56). Higher hospitalization rates for ambulatory care-sensitive conditions such as asthma, seizures, pneumonia and dehydration (57) suggests that
some of these differences in health outcomes may be mediated by medical care. Little is known about the impact of SES on the course or outcomes of IBD. IBD is a disease primarily treated in the ambulatory setting and therefore may be more affected by similar social determinants, such as access to outpatient specialist care. A recent study in French adults with IBD found that increased social deprivation was associated with higher hospitalization and lower surgical rates, despite having no impact on clinical disease severity (9). This study examined whether health services utilization (in the form of hospitalization, physician visit and emergency department visit rates) in children with IBD was affected by area-level family income. Additionally, we assessed whether surgical rates (in the form of intestinal resections and peri-anal surgical repair) were different in children living in the lowest income neighbourhoods. In so doing, we aimed to identify a group of children at greater risk for undesirable outcomes of their disease, and generate hypotheses for both disease etiology and health services research.

1.6 Changes in Evidence-based Treatment for Paediatric IBD

Systemic corticosteroids have been the mainstay of treatment in IBD, and have been shown to be highly effective for induction of remission (58, 59). However, they are not effective for maintenance of remission (60, 61). In the first years of the 21st century, two major changes took place in the treatment of IBD in children. The first was the recognition that azathioprine and its metabolite 6-MP were highly effective at maintaining remission in children with CD, perhaps more so than in adults (1). Despite its recognized efficacy, azathioprine was shown to have no significant impact on the risk of surgical resection in adults with CD (14). The second major change in treatment options came with the publication of the first randomized trials demonstrating the efficacy of infliximab, an anti-TNF recombinant biologic antibody, for induction and maintenance of remission of CD in adults with steroid-refractory and steroid-dependent disease (12), a finding that was later replicated in children with CD (13). The goal of the third part of this thesis was to examine temporal trends in health services utilization and surgical rates to determine whether recent treatment advances have improved the prognosis of paediatric IBD.
In summary, this thesis aims to build a cohort of patients with childhood-onset IBD using health administrative data and engage in ongoing surveillance in order to describe trends in epidemiology and care over time. To do so, validation of a patient identification algorithm was first undertaken, and the overall burden of disease (in terms of incidence, prevalence and health service utilization) was described in the three manuscripts which follow.
Chapter 2

Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data

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2.1 Abstract

BACKGROUND & AIMS: Health administrative databases can be used to track chronic diseases. We aimed to validate a case ascertainment definition of paediatric-onset IBD using administrative data and describe its epidemiology in Ontario, Canada.

METHODS: We used a population-based clinical database of IBD patients <15y to define cases and linked patient information to health administrative data to compare the accuracy of various patterns of healthcare use. We validated the most accurate algorithm with chart data of children <18y from twelve medical practices. We used administrative data from 1991-2008 to describe incidence and prevalence of IBD in Ontario children. We tested changes in incidence using Poisson regression.

RESULTS: Accurate identification of children with IBD required 4 physician contacts or 2 hospitalizations (with ICD codes for IBD) within 3 years if they underwent colonoscopy and 7 contacts or 3 hospitalizations within 3 years in those without colonoscopy (<12 year old children: sensitivity 90.5%, specificity >99.9%, <15y old children: sensitivity 89.6%, specificity >99.9%, <18y old children: sensitivity 91.1%, specificity 99.5%). Age- and sex-standardized prevalence per 100,000 population of paediatric IBD has increased from 42.1 (in 1994) to 56.3 (in 2005). Incidence per 100,000 has increased from 9.5 (in 1994) to 11.4 (in 2005). Statistically significant increases in incidence were noted in 0-4 year olds (5.0%/year, p=0.03) and 5-9 year olds (7.6%/year, p<0.0001), but not in 10-14 or 15-17 year olds.

CONCLUSIONS: Ontario has one of the highest rates of childhood-onset IBD in the world, and there is an accelerated increase in incidence in younger children.

2.2 Introduction

Inflammatory bowel disease (IBD) is an important childhood chronic disease, with 20-30% of patients presenting under 20 years old (62). International data on trends in incidence and prevalence of childhood-onset IBD are conflicting. Some jurisdictions report increased rates of paediatric Crohn's disease (CD) (but not ulcerative colitis [UC]) (23, 63, 64), while others report increased rates of UC but not CD (21), or stable incidences (22, 65). The incidence of CD in
Canadian provinces studied to date is amongst the highest reported worldwide (13.4 per 100,000 in all age groups) (3), although there is little known about paediatric IBD. There are no data on IBD in Ontario, Canada’s most populous province with 38% (12.2 million people) of the national population (66).

Canada's single-payer health system, in which all legal residents have universal access to all healthcare services, represents a unique opportunity to capture all cases of IBD within a large jurisdiction. Ontario's health administrative databases are a large repository of all healthcare encounters for every legal resident and these data have been used to develop surveillance programs for multiple chronic diseases including diabetes (67) and asthma (68). These population-based cohorts have been used to assess epidemiology, health services use and outcomes (27, 69, 70). Critical to the accuracy of such data, however, is the rigorous validation of the best combination of health administrative data codes (known as a diagnostic algorithm) which most accurately define true disease.

Health administrative data have been used to describe epidemiologic trends among primarily adult populations of IBD patients in one Canadian study (3) as well as among privately insured American patients (33, 71). All three studies used algorithms for assessment of disease predominantly validated in adults (30, 33, 71). Administrative data algorithms have been reported to have differing accuracies across age groups (31), and differing health care patterns in children necessitate validation of a paediatric-specific algorithm (72).

Our goal was to develop and validate a diagnostic algorithm using health administrative data to identify individuals with childhood-onset IBD and then to use the algorithm to estimate the incidence and prevalence of paediatric IBD in Ontario.
2.3 Methods

2.3.1 Administrative Data Sources
We used the health administrative databases available at the Institute for Clinical Evaluative
Sciences (ICES; Toronto, Ontario, Canada). This study was approved by the research ethics
boards of the Hospital for Sick Children (SickKids), Sunnybrook Health Sciences Centre and all
institutions involved in the validation study. The databases used in this study included: hospital
discharge abstract data mandatorily collected from all hospitals and reported to the Canadian
Institute for Health Information, billing claims for all physician services provided from the
Ontario Health Insurance Plan, and the Registered Persons Database (demographic data
including region of residence). Hospital data prior to 2002 and all physician claims have
diagnoses associated using codes from the International Classification of Disease (ICD)-9 (73).
Hospitalizations after 2002 used ICD-10 codes (49).

2.3.2 Algorithm Development Sample
We used the IBD clinical database from SickKids to identify patients with childhood-onset IBD
in Toronto. The database, created in 1980 to prospectively track all cases of IBD seen at
SickKids, contained an estimated 90% of patients aged 0-15 years old diagnosed with IBD and
residing in the census metropolitan area of Toronto in fiscal years (FY) 1991-1995 (74). The
paediatric gastroenterologists in Toronto practiced at SickKids. A survey of 69 Toronto-based
adult gastroenterologists (with a 58% response rate) found that 88% of adult gastroenterologists
did not independently manage the care of any patient <15 years old. Of those that did treat
children, no gastroenterologist treated more than two children <15 years old between 1991-1995
(74). Assuming respondents were representative of the adult gastroenterologist community, the
SickKids IBD database is population-based for Toronto children <15 years diagnosed with IBD
from 1991-1995. SickKids patient information was linked to the ICES administrative data by
health card number. Patients were excluded if they did not reside within Toronto for the entire
period of 1991-2000. The remaining population of that age residing within Toronto from 1991-
1995 was assumed not to have IBD and used as the negative reference standard.
2.3.3 Algorithm Development

We determined the diagnostic accuracy (sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]) of various combinations of physician office and procedure billings and hospital records using the diagnosis codes for CD (ICD-9: 555.x, ICD-10: K50.x) or UC (ICD-9: 556.x, ICD-10: K51.x). Ninety-five percent confidence intervals (CI) were calculated according to the efficient-score method corrected for continuity (75). We determined whether sigmoidoscopy or colonoscopy prior to diagnosis improved the accuracy of the algorithm. The final algorithm was selected and agreed upon by a committee of five experts in the fields of paediatric and adult gastroenterology, health services research, epidemiology and biostatistics (E.I.B., A.G., A.M.G., L.R., T.T.). The committee decided on the algorithm with the highest possible PPV (to minimize false positive rate) while maximizing sensitivity over the shortest possible duration to achieve accurate diagnosis.

2.3.4 Algorithm Validation

To validate the algorithm for patients <18 years old from other regions of Ontario and those treated in a variety of practice settings, 31 practices across the province (3 academic paediatric gastroenterology, 3 community-based paediatric gastroenterology, 18 community-based adult gastroenterology, 3 adult surgery, 4 consultant paediatrics) were contacted to determine whether their providers diagnosed patients aged <18 years with IBD (to ensure accuracy of the algorithm for older age groups) from 2001-2005 (to ensure accuracy of the algorithm for patients diagnosed in a later time period). Sites approached included three tertiary care paediatric hospitals and other sites were randomly selected using a provincial directory of practices. The final choices of sites to contact were based on geographic and practice diversity to ensure representation from northern, central, southern and eastern Ontario with 3-4 practices from each region randomly selected from the directory. In participating centres, all available charts of patients diagnosed with IBD from 2001-2005 were reviewed to ensure accurate diagnosis based on published criteria (76), using clinical, histological and radiological information. For every IBD chart, two charts of patients without IBD were randomly selected and reviewed to act as the negative reference standard. Preference in chart review was given to non-IBD patients who underwent colonoscopy because they were more likely to be misclassified as having IBD in the administrative data.
Chart extractions were conducted by two IBD specialists (E.I.B. and D.R.M.) and two experienced IBD research assistants. The research assistants were trained by the principal investigator (E.I.B.). Ten charts from each practice were blindly reviewed by both to ensure consistency of diagnosis. In the cases of both assistants, there was 100% agreement with the investigator on the diagnoses. Clinical information was linked to health administrative data by health card number. Using chart information as the reference standard, we determined the parameters of diagnostic accuracy of the previously developed algorithm (sensitivity, specificity, positive likelihood ratio [LR+], negative likelihood ratio [LR-]).

We determined whether patients had CD or UC using the latest clinical, histological and radiological information obtained from each chart. A diagnosis of CD, UC, or inflammatory bowel disease type undefined (IBD-U) was assigned by the data extractor based on published guidelines (33). Patients with IBD-U were excluded. Chart-based diagnoses were compared with ICD codes and an algorithm developed by assessing the combination of most recent ICD codes best able to distinguish CD from UC. The number of health services records achieving the highest possible area under the receiver operating characteristic curve (AUROC) while minimizing unclassified patients was chosen and the point of best cut-off was determined (77). Patients who could not be classified as CD or UC by our algorithm were labelled 'unclassifiable'.

2.3.5 Estimates of incidence and prevalence
The Ontario Crohn's and Colitis Cohort (OCCC) was created by using the validated algorithm to identify all children (6 months to 18 years) living in Ontario with IBD from 1994-2005, using data from 1991-2008. The date of incidence was assigned as the date of the first health services contact with a diagnosis of IBD within the cluster of health care utilization qualifying the patient as having IBD. A three-year look-back period (with no diagnoses of IBD at the time of physician contact or hospitalization) was used to ensure that cases were truly incident. This was based on the expert opinion of clinicians on the committee due to the unlikelihood that a child with IBD would be lost to follow-up for more than three years. Patients with previous diagnoses of IBD but which were not part of the diagnostic cluster of the algorithm were considered prevalent, but not incident cases.
The sex- and age-adjusted annual prevalence and incidence rates per 100,000 population were determined for 1994-2005, with corresponding 95% CI based on Gamma distribution (78). We used the Canadian censuses from 1991, 1996, 2001 and 2006 to calculate annual intercensal population estimates of children <18 years (55). Using multivariable Poisson regression, we modelled the relationship between year of diagnosis (as the main predictor variable) to changes in prevalence and incidence of over time, controlling for age group and sex. Due to a significant interaction between age group and year of incidence, we stratified the regression by age group. All statistical analysis was conducted using SAS® version 9.1.3 (SAS Institute Inc., Cary, U.S.A.).

2.4 Results

2.4.1 Algorithm Development – Study Population
Within the SickKids IBD database, 183 Toronto children were identified as having IBD diagnosed between 1991-1995 and acted as the positive reference standard. Between 1991-1995, 936,514 children under 15 years old resided in Toronto and acted as the negative reference standard.

2.4.2 Algorithm Development – Diagnostic Properties
The most accurate algorithm consisted of two steps, based on whether sigmoidoscopy or colonoscopy was performed (see Table 2.1). Those that did not undergo endoscopy required more stringent criteria for accurate ascertainment. If a patient underwent endoscopy, 4 physician contacts or 2 hospitalizations with a CD or UC diagnosis within 3 years were required for accurate diagnosis. If a patient never underwent endoscopy, 7 physician contacts or 3 hospitalizations were required. This two step algorithm accurately predicted a true IBD diagnosis (sensitivity 89.6% [95% CI 84.0-93.5%), specificity >99.9% [95% CI 99.9-100%), PPV 59.2% [95% CI 53.1-65.0%), NPV >99.9% [95% CI 99.9-100%]). For patients <12 years old, the algorithm accurately predicted IBD with higher PPV (PPV 76.0% [95% CI 68.9-82.0%]). As some jurisdictions may not have endoscopic procedure data, we also determined the
best single step algorithm, ignoring whether a patient underwent diagnostic endoscopy (see Table 2.2). A single healthcare encounter for IBD (either physician contact, procedure, or hospital admission) was a poor predictor of the positive diagnosis of IBD (PPV 7.9% [95% CI 6.8-9.0%]).

2.4.3 Algorithm Validation by Chart Review

Of the 31 sites contacted, seven practitioners failed to respond, three refused to participate and nine practices had not diagnosed a child <18 years with IBD during the relevant time period. Twelve medical practices participated in the validation study (3 academic paediatric gastroenterology, 3 community paediatric gastroenterology, 5 adult gastroenterology, 1 consultant general paediatrics). With chart review, 599 patients were confirmed to have IBD, of which 593 could be linked to administrative data (342 with CD, 226 with UC, 26 with IBD-U). 551/593 (92.9%) underwent diagnostic sigmoidoscopy/colonoscopy. Of patients without IBD, 1251 charts were reviewed, of which 1241 could be linked to administrative data. Of these, 370 (29.8%) had sigmoidoscopy/colonoscopy. Based on chart review at 11/12 participating centres, the most common non-IBD diagnosis given was gastroesophageal reflux disease (18.2%), with other common diagnoses including idiopathic/functional abdominal pain (15.7%), irritable bowel syndrome (10.3%) and chronic constipation (9.4%). The diagnostic properties achieved for each algorithm using chart information from the different centers is provided in Tables 1 and 2. The two step algorithm achieved a sensitivity of 91.1% (95% CI 88.4-93.2%), specificity of 99.5% (95% CI 98.9-99.8%), LR+ of 188.3 (95% CI 84.7-418.6), and LR- of 0.0898 (95% CI 0.0694-0.116).

The most recent seven available physician billing claims accurately determined a diagnosis of CD (AUROC 0.9618). CD patients were distinguished from UC patients if five of their last seven diagnoses were for CD (sensitivity 95.1%, specificity 86.0%, PPV 92.0%, NPV 91.2%). Conversely, UC patients were labelled such if five of their last seven physician claims had a diagnosis of UC. Otherwise, patients were labelled unclassifiable. Using this strategy, 5.4% of patients diagnosed with CD or UC were inaccurately deemed to be unclassifiable compared with their charts. If patients did not have record of seven physician contacts, they were labelled CD if all of their diagnostic codes were for CD, UC if all of their diagnoses were UC, or unclassifiable.
2.4.4 Estimates of incidence and prevalence

Table 2.3 describes prevalence and incidence among children <18 years by year of diagnosis. Table 2.4 presents crude incidence and prevalence stratified by sex, age group and diagnosis (total IBD, CD or UC). Figures 2.1 and 2.2 illustrate trends over time from 1994 to 2005. Age- and sex-standardized prevalence of IBD per 100,000 population has increased from 42.1 (95% CI 39.6-44.8) in 1994 to 56.3 (95% CI 53.6-59.1) in 2005 (p<0.0001). Prevalence of CD has increased from 23.9 (95% CI 22.0-25.9) to 31.6 (95% CI 29.6-33.7) (p<0.0001). Prevalence of UC has increased from 16.2 (95% CI 14.6-17.8) to 19.7 (95% CI 18.1-21.4) (p<0.0001).

The OCCC contains 3169 incident cases of paediatric IBD diagnosed between 1994-2005. The incidence of IBD per 100,000 population has increased from 9.5 (95% CI 8.4-10.8) in 1994 to 11.4 (95% CI 10.2-12.7) in 2005 (p=0.03). The incidence of CD has changed from 5.0 (95% CI 4.1-5.9) to 6.0 (95% CI 5.2-7.0) (p=0.19). The incidence of UC has remained comparatively unchanged from 4.1 (95% CI 3.3-5.0) to 4.2 (95% CI 3.5-5.1) (p=0.55).

Results of the adjusted regression models stratified by age group and diagnosis (CD or UC) are presented in Table 2.5. Significant increases in incidence are seen in IBD patients in 6 month to 4 year olds (5.0% per year, p=0.03) and 5-9 year olds (7.6% per year, p<0.0001). When stratified by age group and diagnosis, the only group with a statistically significant increase in incidence was CD patients aged 5-9 (8.7% per year, p<0.0001). No statistically significant interaction existed between sex and year of diagnosis. Table 2.5 also describes the male predominance of CD patients in the younger age groups (5-9 years and 10-14 years), with a balanced incidence between males and females in 15-17 year olds. UC is more likely in males at younger ages (<10 years), while it is more common in females in pre-adolescents and adolescents.
2.5 Discussion

Canadian health administrative data provide an outstanding resource for population-based chronic disease surveillance. We developed a novel algorithm for identifying children with IBD within Ontario's administrative data. The strengths of our algorithms include an accurate determination of PPV in light of the population-based sample with accurate estimation of prevalence in Toronto, specific applicability to children and its validation across paediatric age ranges, in both ambulatory and hospitalized populations, in multiple geographic regions and across different practice types. The higher PPVs seen in younger patients emphasize the need to validate algorithms in all age groups to which they will be applied. Our development and validation of a definition specific for children and youth should allow for better case ascertainment in Canada and other jurisdictions with comparable physician claims and hospitalization data.

To our knowledge, the OCCC is the largest population-based cohort of paediatric IBD patients in the world. We found an increased prevalence and incidence over the 12 years of surveillance. This is in keeping with population-based studies from other jurisdictions which have reported increased rates of IBD in children, particularly in CD (23, 63, 64). A recent Norwegian study demonstrated a doubling of the incidence of IBD over 15 years in children <16 years old compared to a historical cohort (79). One other study reported incidence trends by age in paediatric IBD. Armitage et al. (80, 81) reported significantly increased incidence rates between 1981 and 1995 in both CD and UC, with females 7-11 years and both sexes 12-16 years at higher risk in later years. Our study was sufficiently powered to examine incidence trends in all age groups including the youngest children, despite the rarity of IBD in that population. We were also able to determine the ages at which gender ratio and CD:UC ratio changes and found no difference in the rate of increase in incidence by sex. The preponderance of male children with IBD has been well-documented, and we demonstrated that an adult pattern, in which females are slightly more likely to develop IBD, occurs after the onset of puberty. Changes in gender ratio after puberty has previously been demonstrated in other immune-mediated conditions such as myasthenia gravis (82) and type 1 diabetes (83).
Ontario appears to have higher rates of IBD than those reported in other large and well-designed population-based studies from the United States (15), Scotland (81) and other parts of the United Kingdom (80). The incidence and prevalence rates for children <18 years are lower than those reported for some other Canadian provinces, although those provinces reported rates for <20 year olds (3). Given the peak ages of occurrence of IBD, inclusion of 18 and 19 year olds would be expected to increase rates for any "paediatric" cohort that includes these older adolescents. Additionally, the observed difference may be influenced by environmental factors, migration patterns or the accuracy of the diagnostic algorithm, which was validated primarily in adults (30) and may have performed differently in the <20 year age group.

It is noteworthy that the increased incidence demonstrated by this study appears to have occurred primarily after 2001 (see Figure 2.2). This may be explained by an as yet undetermined environmental change or by evolving immigration patterns in recent years. In fact, the proportion of immigrants to Ontario from South Asia (India, Pakistan, Sri Lanka, etc.) has more than doubled between 1981 and 2000 (57), and this group was reported to have increased rates of IBD following arrival to Canada (84). The proportion of immigrants to Ontario from other regions of the world including China, the Middle East, Europe and Africa has remained stable or decreased (57). This changing pattern of immigration may explain the stable rates of paediatric IBD in other jurisdictions (with smaller proportions of South Asian patients).

A number of limitations to this study exist. These include the lack of medication data to aid in the identification of IBD patients. We were unable to determine whether medication data improved the test properties of our algorithm, and we would encourage jurisdictions with such data to assess whether it improves identification of children with IBD. We were able to identify that a physician billing for colonoscopy improves the confidence with which we can identify children with IBD within health administrative data. Published guidelines allow for the diagnosis of IBD without colonoscopy (using radiology or surgical pathology) (33), however the vast majority of young patients in Ontario underwent colonoscopy. However, should the investigation of IBD change in the future (and the frequency of colonoscopy decrease), the two-step algorithm may no longer apply. As such, we have reported the accuracy of algorithms excluding colonoscopy (Table 2.2). Unlike other studies validating IBD diagnostic algorithms,
we accurately reported PPV values because we attempted to identify all patients with and without IBD within a jurisdiction using administrative data. The lower PPVs seen in older patients from the Toronto cohort can be explained in a number of ways. Our algorithm may be less robust in older adolescents, however this was not observed in the chart validation portion of this study. More likely, the reference standard SickKids IBD database contains a lower percentage of mid-adolescent IBD patients residing in Toronto than had previously been documented (74). We feel this is more likely because no matter how restrictive our algorithm, we were unable to achieve a PPV of greater than 59.8% in <15 year olds. To be certain of the accuracy of our algorithm, we therefore confirmed it with a second reference standard: patient charts from multiple practices across the province. We achieved excellent accuracy in this sample, providing reassurance that the algorithm would accurately identify children with IBD when applied to administrative data.

It is important to view our data as physician-identified prevalence. It is possible that the reported increase in IBD may not be due to more prevalent disease but rather due to improved physician detection of the disease due to changes in physician practice patterns, improved access to diagnostic procedures or more awareness of the possibility of early-onset IBD. However, if our findings were due to earlier diagnosis of IBD (without increased overall incidence), we would expect that the incidence trends in the >10 year old groups would have decreased as they increased in the <10 year old groups, which was not the case.

In summary, we have reported on the development and rigorous validation of an algorithm to allow accurate identification of a population-based cohort of Ontario children with IBD using health administrative data from multiple sources. We report a significant rise in the prevalence and incidence of IBD, especially in children under the age of 10 years. Overall, the quality and availability of health administrative data is improving in North America and elsewhere. We encourage researchers to apply this algorithm to administrative data from other jurisdictions after validation, which will allow for future collaborative research examining paediatric IBD internationally. The population-based nature of the OCCC makes it ideal to act as an IBD surveillance program in order to track trends over time and answer important epidemiologic and health services questions about patients with childhood-onset IBD.
2.6 Acknowledgements

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Table 2.1: Examples of test characteristics of multiple two-step algorithms to ascertain children with IBD using physician claims and hospitalization data. The selected algorithm is highlighted in grey.

<table>
<thead>
<tr>
<th>Patients with Scope Claim</th>
<th>Patients without Scope Claim</th>
<th>Duration (years)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Sens</th>
<th>Spec</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 contacts or 1 hosp.</td>
<td>5 contacts or 2 hosp.</td>
<td>2</td>
<td>91.2%</td>
<td>&gt;99.9%</td>
<td>66.7%</td>
<td>&gt;99.9%</td>
<td>90.2%</td>
<td>&gt;99.9%</td>
<td>51.2%</td>
<td>&gt;99.9%</td>
<td>92.9%</td>
<td>98.5%</td>
<td>60.7</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>91.8%</td>
<td>&gt;99.9%</td>
<td>65.8%</td>
<td>&gt;99.9%</td>
<td>91.3%</td>
<td>&gt;99.9%</td>
<td>50.8%</td>
<td>&gt;99.9%</td>
<td>93.9%</td>
<td>98.4%</td>
<td>58.3</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>92.5%</td>
<td>&gt;99.9%</td>
<td>65.4%</td>
<td>&gt;99.9%</td>
<td>92.4%</td>
<td>&gt;99.9%</td>
<td>50.8%</td>
<td>&gt;99.9%</td>
<td>94.3%</td>
<td>98.4%</td>
<td>58.5</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>93.2%</td>
<td>&gt;99.9%</td>
<td>65.2%</td>
<td>&gt;99.9%</td>
<td>92.9%</td>
<td>&gt;99.9%</td>
<td>50.6%</td>
<td>&gt;99.9%</td>
<td>94.4%</td>
<td>98.4%</td>
<td>58.6</td>
<td>0.057</td>
</tr>
<tr>
<td>4 contacts or 2 hosp.</td>
<td>7 contacts or 3 hosp.</td>
<td>3</td>
<td>90.5%</td>
<td>&gt;99.9%</td>
<td>76.0%</td>
<td>&gt;99.9%</td>
<td>89.6%</td>
<td>&gt;99.9%</td>
<td>59.2%</td>
<td>&gt;99.9%</td>
<td>91.1%</td>
<td>99.5%</td>
<td>188.3</td>
<td>0.090</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>92.5%</td>
<td>&gt;99.9%</td>
<td>76.0%</td>
<td>&gt;99.9%</td>
<td>91.8%</td>
<td>&gt;99.9%</td>
<td>57.8%</td>
<td>&gt;99.9%</td>
<td>91.7%</td>
<td>99.3%</td>
<td>126.5</td>
<td>0.083</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>92.5%</td>
<td>&gt;99.9%</td>
<td>74.7%</td>
<td>&gt;99.9%</td>
<td>91.8%</td>
<td>&gt;99.9%</td>
<td>57.9%</td>
<td>&gt;99.9%</td>
<td>91.9%</td>
<td>99.5%</td>
<td>190.1</td>
<td>0.081</td>
</tr>
<tr>
<td>5 contacts or 2 hosp.</td>
<td>7 contacts or 3 hosp.</td>
<td>3</td>
<td>86.4%</td>
<td>&gt;99.9%</td>
<td>75.2%</td>
<td>&gt;99.9%</td>
<td>84.2%</td>
<td>&gt;99.9%</td>
<td>57.7%</td>
<td>&gt;99.9%</td>
<td>89.4%</td>
<td>99.5%</td>
<td>148.9</td>
<td>0.107</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>85.7%</td>
<td>&gt;99.9%</td>
<td>75.5%</td>
<td>&gt;99.9%</td>
<td>84.2%</td>
<td>&gt;99.9%</td>
<td>59.5%</td>
<td>&gt;99.9%</td>
<td>88.9%</td>
<td>99.5%</td>
<td>183.8</td>
<td>0.112</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>88.4%</td>
<td>&gt;99.9%</td>
<td>77.4%</td>
<td>&gt;99.9%</td>
<td>88.5%</td>
<td>&gt;99.9%</td>
<td>59.8%</td>
<td>&gt;99.9%</td>
<td>89.5%</td>
<td>98.3%</td>
<td>123.5</td>
<td>0.105</td>
</tr>
</tbody>
</table>

N.B. "Contacts" refers to physician contacts with diagnostic code for IBD. "Hosp." refers to hospitalizations with diagnostic code for IBD. "Scope" refers to either sigmoidoscopic or colonoscopic examination of the large bowel.
Table 2.2: Examples of test characteristics of multiple single-step algorithms to ascertain children with IBD using physician claims and hospitalization data. The selected single-step algorithm is highlighted in grey.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>&lt;12y old (n=147 with IBD, n=771,534 controls)</th>
<th>&lt;15y old (n=183 with IBD, n=936,514 controls)</th>
<th>&lt;18y old (validation) (n=593 with IBD, n=1241 controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (years)</td>
<td>Sens</td>
<td>Spec</td>
<td>PPV</td>
</tr>
<tr>
<td>Any contact or hosp. for IBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>99.3%</td>
<td>99.8%</td>
<td>7.7%</td>
</tr>
<tr>
<td>3</td>
<td>91.8%</td>
<td>&gt;99.9%</td>
<td>51.1%</td>
</tr>
<tr>
<td>4</td>
<td>93.2%</td>
<td>&gt;99.9%</td>
<td>48.9%</td>
</tr>
<tr>
<td>5</td>
<td>93.9%</td>
<td>&gt;99.9%</td>
<td>47.8%</td>
</tr>
<tr>
<td>3 contacts or 1 hosp.</td>
<td>94.6%</td>
<td>&gt;99.9%</td>
<td>46.8%</td>
</tr>
<tr>
<td>3 contacts or 2 hosp.</td>
<td>92.5%</td>
<td>&gt;99.9%</td>
<td>46.3%</td>
</tr>
<tr>
<td>4</td>
<td>95.2%</td>
<td>&gt;99.9%</td>
<td>45.3%</td>
</tr>
<tr>
<td>5</td>
<td>95.2%</td>
<td>&gt;99.9%</td>
<td>44.6%</td>
</tr>
<tr>
<td>5 contacts</td>
<td>82.3%</td>
<td>&gt;99.9%</td>
<td>50.8%</td>
</tr>
<tr>
<td>3 contacts or 1 hosp.</td>
<td>92.9%</td>
<td>&gt;99.9%</td>
<td>49.3%</td>
</tr>
<tr>
<td>4</td>
<td>95.2%</td>
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</tr>
<tr>
<td>5</td>
<td>95.2%</td>
<td>&gt;99.9%</td>
<td>47.0%</td>
</tr>
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<td>5 contacts</td>
<td>88.4%</td>
<td>&gt;99.9%</td>
<td>70.3%</td>
</tr>
<tr>
<td>3 contacts or 1 hosp.</td>
<td>86.4%</td>
<td>&gt;99.9%</td>
<td>70.9%</td>
</tr>
<tr>
<td>4</td>
<td>84.4%</td>
<td>&gt;99.9%</td>
<td>71.4%</td>
</tr>
<tr>
<td>5</td>
<td>88.4%</td>
<td>&gt;99.9%</td>
<td>70.3%</td>
</tr>
<tr>
<td>5 contacts</td>
<td>89.1%</td>
<td>&gt;99.9%</td>
<td>64.8%</td>
</tr>
<tr>
<td>3 contacts or 1 hosp.</td>
<td>90.5%</td>
<td>&gt;99.9%</td>
<td>64.6%</td>
</tr>
<tr>
<td>4</td>
<td>91.2%</td>
<td>&gt;99.9%</td>
<td>64.7%</td>
</tr>
<tr>
<td>5</td>
<td>91.8%</td>
<td>&gt;99.9%</td>
<td>63.7%</td>
</tr>
<tr>
<td>5 contacts</td>
<td>84.4%</td>
<td>&gt;99.9%</td>
<td>69.7%</td>
</tr>
<tr>
<td>3 contacts or 1 hosp.</td>
<td>87.8%</td>
<td>&gt;99.9%</td>
<td>70.1%</td>
</tr>
<tr>
<td>4</td>
<td>89.8%</td>
<td>&gt;99.9%</td>
<td>70.6%</td>
</tr>
<tr>
<td>5</td>
<td>90.5%</td>
<td>&gt;99.9%</td>
<td>69.3%</td>
</tr>
</tbody>
</table>
Table 2.3: Age-sex adjusted prevalence and incidence rates of inflammatory bowel disease in children and youth in Ontario (Fiscal Years 1994-2005).

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>Number of children (&lt;18 years) with IBD living in Ontario†</th>
<th>Age-/sex-standardized prevalence rate per 100,000 (95% CI)</th>
<th>Number of children and youth with new diagnosis of IBD</th>
<th>Age-/sex-standardized incidence rate per 100,000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>1034</td>
<td>42.1 (39.6 – 44.8)</td>
<td>235</td>
<td>9.54 (8.4 – 10.8)</td>
</tr>
<tr>
<td>1995</td>
<td>1117</td>
<td>44.8 (42.2 – 47.5)</td>
<td>229</td>
<td>9.17 (8.0 – 10.4)</td>
</tr>
<tr>
<td>1996</td>
<td>1194</td>
<td>46.9 (44.3 – 49.7)</td>
<td>246</td>
<td>9.65 (8.5 – 10.9)</td>
</tr>
<tr>
<td>1997</td>
<td>1278</td>
<td>49.2 (46.6 – 52.0)</td>
<td>264</td>
<td>10.15 (9.0 – 11.5)</td>
</tr>
<tr>
<td>1998</td>
<td>1398</td>
<td>52.8 (50.1 – 55.7)</td>
<td>264</td>
<td>9.95 (8.8 – 11.2)</td>
</tr>
<tr>
<td>1999</td>
<td>1448</td>
<td>53.8 (51.1 – 56.7)</td>
<td>252</td>
<td>9.36 (8.2 – 10.6)</td>
</tr>
<tr>
<td>2000</td>
<td>1478</td>
<td>53.8 (51.1 – 56.7)</td>
<td>270</td>
<td>9.85 (8.7 – 11.1)</td>
</tr>
<tr>
<td>2001</td>
<td>1498</td>
<td>53.6 (50.9 – 56.7)</td>
<td>267</td>
<td>9.57 (8.5 – 10.8)</td>
</tr>
<tr>
<td>2002</td>
<td>1519</td>
<td>53.7 (51.0 – 56.4)</td>
<td>248</td>
<td>8.76 (7.7 – 9.9)</td>
</tr>
<tr>
<td>2003</td>
<td>1510</td>
<td>53.1 (50.5 – 55.9)</td>
<td>270</td>
<td>9.51 (8.4 – 10.7)</td>
</tr>
<tr>
<td>2004</td>
<td>1553</td>
<td>53.4 (51.7 – 57.1)</td>
<td>297</td>
<td>10.42 (9.3 – 11.7)</td>
</tr>
<tr>
<td>2005</td>
<td>1621</td>
<td>56.3 (53.6 – 59.2)</td>
<td>327</td>
<td>11.43 (10.2 – 12.7)</td>
</tr>
</tbody>
</table>

† Represents the number of children and youth (<18 years old) with IBD alive and living in Ontario, Canada on July 1 of the noted year. This number does not include patients with childhood-onset IBD who turned 18 years of age before July 1 of the noted year, and therefore does not represent the cumulative prevalence.
Table 2.4: Crude incidence and prevalence (per 100,000 population) of paediatric IBD by age group and sex for Ontario in 2005.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age Group</th>
<th>TOTAL IBD Incidence</th>
<th>TOTAL IBD Prevalence</th>
<th>CD Incidence†</th>
<th>CD Prevalence†</th>
<th>UC Incidence‡</th>
<th>UC Prevalence‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>6 mo – 4 years</td>
<td>0.6</td>
<td>3.3</td>
<td>0.3 – 0.4</td>
<td>0.9 – 1.1</td>
<td>0 – 0.2</td>
<td>1.8 – 2.2</td>
</tr>
<tr>
<td></td>
<td>5-9 years</td>
<td>4.5</td>
<td>18.5</td>
<td>2.9</td>
<td>8.7 – 10.5</td>
<td>1.6</td>
<td>7.1 – 8.0</td>
</tr>
<tr>
<td></td>
<td>10-14 years</td>
<td>16.0</td>
<td>64.5</td>
<td>7.1 – 8.9</td>
<td>32.1 – 37.4</td>
<td>6.1 – 7.0</td>
<td>24.5 – 27.2</td>
</tr>
<tr>
<td></td>
<td>15-17 years</td>
<td>26.3</td>
<td>146.7</td>
<td>13.5 – 15.2</td>
<td>78.7 – 85.2</td>
<td>10.3 – 11.1</td>
<td>58.2 – 61.4</td>
</tr>
<tr>
<td></td>
<td>TOTAL</td>
<td>10.9</td>
<td>51.7</td>
<td>5.5 – 6.3</td>
<td>26.4 – 29.7</td>
<td>4.1 – 4.6</td>
<td>20.2 – 22.0</td>
</tr>
<tr>
<td>M</td>
<td>6 mo – 4 years</td>
<td>2.9</td>
<td>6.7</td>
<td>0.3 – 0.4</td>
<td>1.5 – 1.7</td>
<td>2.3 – 2.5</td>
<td>4.4 – 5.0</td>
</tr>
<tr>
<td></td>
<td>5-9 years</td>
<td>8.7</td>
<td>24.8</td>
<td>4.9 – 5.2</td>
<td>12.3 – 13.3</td>
<td>3.3 – 3.5</td>
<td>11.0 – 11.5</td>
</tr>
<tr>
<td></td>
<td>10-14 years</td>
<td>16.8</td>
<td>84.0</td>
<td>10.7 – 11.8</td>
<td>54.2 – 59.0</td>
<td>4.4 – 5.0</td>
<td>22.6 – 25.1</td>
</tr>
<tr>
<td></td>
<td>15-17 years</td>
<td>24.6</td>
<td>170.7</td>
<td>12.9 – 14.1</td>
<td>103.8 – 113.7</td>
<td>9.7 – 10.4</td>
<td>52.1 – 57.0</td>
</tr>
<tr>
<td></td>
<td>TOTAL</td>
<td>12.6</td>
<td>64.7</td>
<td>7.0 – 7.7</td>
<td>38.9 – 42.5</td>
<td>4.6 – 5.0</td>
<td>20.4 – 22.3</td>
</tr>
<tr>
<td>Both sexes</td>
<td>6 mo – 4 years</td>
<td>1.8</td>
<td>5.1</td>
<td>0.3 – 0.4</td>
<td>1.2 – 1.4</td>
<td>1.2 – 1.4</td>
<td>3.1 – 3.6</td>
</tr>
<tr>
<td></td>
<td>5-9 years</td>
<td>6.6</td>
<td>21.7</td>
<td>3.9 – 4.1</td>
<td>10.5 – 11.9</td>
<td>2.5 – 2.6</td>
<td>9.1 – 9.8</td>
</tr>
<tr>
<td></td>
<td>10-14 years</td>
<td>16.4</td>
<td>74.5</td>
<td>9.0 – 10.4</td>
<td>43.4 – 48.5</td>
<td>5.3 – 6.0</td>
<td>23.6 – 26.1</td>
</tr>
<tr>
<td></td>
<td>15-17 years</td>
<td>25.4</td>
<td>159.0</td>
<td>13.2 – 14.6</td>
<td>91.6 – 99.8</td>
<td>10.0 – 10.7</td>
<td>55.1 – 59.2</td>
</tr>
<tr>
<td>BOTH SEXES</td>
<td>All AGE GROUPS</td>
<td>11.8</td>
<td>58.3</td>
<td>6.2 – 7.0</td>
<td>32.8 – 36.2</td>
<td>4.4 – 4.8</td>
<td>20.3 – 22.1</td>
</tr>
</tbody>
</table>

† Lower number in range represents incident/prevalent cases of CD excluding unclassifiable patients. Upper range of incidence/prevalence represents incident/prevalent of CD including 2/3 of unclassifiable patients (except in 6mo – 4 year age group, where 1/3 of unclassifiable patients are included as possible CD cases).
‡ Lower number in range represents incident/prevalent cases of UC excluding unclassifiable patients. Upper range of incidence/prevalence represents incident/prevalent of UC including 1/3 of unclassifiable patients (except in 6mo – 4 year age group, where 2/3 of unclassifiable patients are included as possible UC cases).
Table 2.5: Time trends in incidence stratified by age group. "Year" refers to the year of diagnosis.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Variable</th>
<th>Estimate</th>
<th>95% CI of the Estimate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IBD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo – 4 y</td>
<td>Year</td>
<td>0.050</td>
<td>0.0048 – 0.1051</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.256</td>
<td>0.0628 – 0.4499</td>
<td>0.009</td>
</tr>
<tr>
<td>5-9 y</td>
<td>Year</td>
<td>0.076</td>
<td>0.0436 – 0.1083</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.091</td>
<td>-0.026 – 0.209</td>
<td>0.13</td>
</tr>
<tr>
<td>10-14 y</td>
<td>Year</td>
<td>0.0063</td>
<td>-0.0086 – 0.0213</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.1339</td>
<td>0.0776 – 0.1903</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>15-17 y</td>
<td>Year</td>
<td>-0.0021</td>
<td>-0.013 – 0.009</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.0174</td>
<td>-0.025 – 0.0598</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>CD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo - 4 y</td>
<td>Year</td>
<td>0.009</td>
<td>-0.048 – 0.066</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.207</td>
<td>-0.011 – 0.425</td>
<td>0.06</td>
</tr>
<tr>
<td>5-9 y</td>
<td>Year</td>
<td>0.087</td>
<td>0.047 – 0.127</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.173</td>
<td>0.027 – 0.320</td>
<td>0.02</td>
</tr>
<tr>
<td>10-14 y</td>
<td>Year</td>
<td>0.006</td>
<td>-0.008 – 0.020</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.235</td>
<td>0.182 – 0.289</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>15-17 y</td>
<td>Year</td>
<td>-0.006</td>
<td>-0.024 – 0.011</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.048</td>
<td>-0.017 – 0.114</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>UC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo - 4 y</td>
<td>Year</td>
<td>0.037</td>
<td>-0.019 – 0.093</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.207</td>
<td>-0.012 – 0.425</td>
<td>0.06</td>
</tr>
<tr>
<td>5-9 y</td>
<td>Year</td>
<td>0.045</td>
<td>-0.007 – 0.098</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>0.028</td>
<td>-0.165 – 0.221</td>
<td>0.78</td>
</tr>
<tr>
<td>10-14 y</td>
<td>Year</td>
<td>-0.027</td>
<td>-0.060 – 0.007</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>-0.047</td>
<td>-0.173 – 0.079</td>
<td>0.47</td>
</tr>
<tr>
<td>15-17 y</td>
<td>Year</td>
<td>-0.007</td>
<td>-0.026 – 0.011</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Sex (M)</td>
<td>-0.047</td>
<td>-0.116 – 0.022</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Figure 2.1: Age- and sex-standardized prevalence of IBD, CD, UC and unclassifiable IBD per 100,000 population in Ontario, Canada. Vertical whisker lines represent 95% CI using Gamma distribution. P values presented are from age- and sex-controlled Poisson models without stratification by age group.
Figure 2.2: Age- and sex-standardized incidence of IBD, CD, UC and unclassifiable IBD per 100,000 population in Ontario, Canada. Vertical whisker lines represent 95% CI using Gamma distribution. P values presented are from age- and sex-controlled Poisson models without stratification by age group.
Appendix 2.1: Responses to peer review

REVIEW #1

GUT/2009/188383
Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data
Eric Ian Benchimol, Astrid Guttmann, Anne M Griffiths, Linda Rabeneck, David R. Mack, Herbert Brill, John Howard, Jun Guan, and Teresa To
Decision: Accept for Online First; Decision Date: 21 Jul 2009
Date Received: 16 May 2009
Previous manuscript ID: GUT/2009/188383
Article Type: Paper
Corresponding Author: Eric Ian Benchimol
Keywords: EPIDEMIOLOGY; HEALTH SERVICE RESEARCH; INFLAMMATORY BOWEL DISEASE; PAEDIATRIC GASTROENTEROLOGY
Supplemental Files: 0

Reviewer 1 Comments for the Author...
The manuscript presented by Benchimol et al. focus on validation of case ascertainment definition of pediatric onset IBD using administrative data and describes prevalence and incidence of pediatric IBD in Ontario. The original interest of these data is the use of health services and outcomes to get data mimicking a population-based study like those a Registry may get.

#1 The first part regarding the method for development and validation of a diagnostic algorithm using health administrative data is adequate and suffers no criticism.

#2 In a second part this diagnostic algorithm is used to estimate incidence and prevalence of pediatric IBD in Ontario. In Table 2.3 as the first column reports the number of children with IBD for every year it must represent a prevalence. The fourth column reports the number of children newly diagnosed per year: thus it is the incidence. As mentioned in the manuscript in the results section the OCCC contains 3169 incident cases. Indeed when summing the incident values per year from 1994 to 2005 from column 4 of table 2.3, the result is well 3169. As prevalence is incidence x duration of the disease it is difficult to explain why the total incidence over the 12 year period (n=3169) is largely over the prevalence at the end of the 12 year period (n=1621). This major discrepancy point should be thoroughly explained or amended. Indeed if these values were exact, then we may evocate either an over estimation of incidence or an under estimation of prevalence (or both). In any case the validity of the algorithm would be questioned.

#3 On figures 1 and 2 it would be necessary to perform linearity tests to objectivate either a stability or an increase. Likewise p values should be mentioned for every test used in the manuscript. i.e. « age and sex standardized prevalence of IBD per 100,000 has increased from 42.1 to 56.3 ». Significant results would then strengthen the conclusions of authors.
#4 Numbering pages of the manuscript would have been useful.

#5 For a better statistical power it is possible to pool by 3 year period.

#6 We agree with the importance of colonoscopy in IBD diagnosis that is pivotal in the algorithm. However diagnosis using enteroscanner and/or entero IRM in children may decrease the frequency of colonoscopy. Thus in some years the algorithm could become obsolete and would require modifications. This should be discussed.

#7 Statistical procedures of estimation of incidence and prevalence should be largely explained. Indeed in the present version of the manuscript it is not clear how were performed the evolutions over time.

#8 What is the meaning of « FY » at the end of methods section.

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**Reviewer 2 Comments for the Author...**

Benchimol et al. analyze in this study incidence and prevalence of pediatric IBD in the Ontario area. They observe when comparing the data from 1994 to 2005 a marked increase in prevalence and incidence of pediatric IBD, mainly in the younger age groups, below the age of 10 years.

This is a very nicely designed and performed study. The major strength is the development of an accurate design, allowing to minimize the risk to consider non-IBD patients having IBD. Therefore, the data presented are very clear cut and most relevant.

I have only some minor points:

In the abstract the authors indicate as age limit < 15 years, but in the text a group of 15-17 is also included (as validation group ?). This is not clear and should be better explained. What is the rationale to limit to < 15 years ?

Could the authors comment on the different sensitivity/specificity/PPV/NPV results according to age ? It is quite surprising to see such a big difference in PPV between the different age groups – what could be the explanation ?

In Table 1 are indicated the PPV and NPV. In the right (third) part, is indicated LR+ LR- instead of PPV, NPV , what does this mean ?

Table 2.5 does not add relevant additional information and could be omitted.

**RESPONSES TO REVIEWERS #1:**

Reviewer 1

Thank you for taking the time to review our manuscript.

Comment #1: Thank you for your comment.
Comment #2: We apologize for the confusion over this prevalence estimate. Both the raw number shown in Table 2.3 and the age- and sex-standardized prevalence rates do not represent cumulative prevalence. Instead, we meant these to represent the number of children (<18 years) living in Ontario in that year with IBD. As such, adolescents who turn 18 prior to July 1 of the year displayed in Table 2.3 are not included in the estimate. For example, you will note that the number of children living with IBD decreases from 2002 to 2003. This is because more children turned eighteen in that year than were newly diagnosed IBD patients. We have added a footnote to Table 2.3 to attempt to clarify this issue.

Comment #3: We presume when you refer to "linearity tests" you are referring to the trend of the regression line. We did in fact perform Poisson regression for trend over time on the incident cohort, are reported these results (stratified by age group) in Table 2.5. We did not report unstratified results on Figures 1 and 2 because of statistically significant interaction terms between year of diagnosis and age group. This interaction makes any Beta/Estimate difficult to interpret when reported on the entire cohort.

Since the reviewer felt strongly that overall P-values should be reported, we have added them to the text (for overall prevalence and incidence estimates) and to Figures 1 and 2. It should be clearly understood that these P values are for the Poisson regression unstratified by age group and are therefore difficult to interpret. As such, we have not reported the estimates or confidence intervals for the overall cohort.

Should the editors wish for the full results of the Poisson regression stratified by age group for the prevalence estimate (such as that presented in Table 2.5 for incidence), we would happily provide this as an extra table to be included as a supplemental.

Comment #4: Our apologies for the lack of numbering – we assumed that the Bench>Press system used by Gut/BMJ would automatically number the manuscript upon conversion to PDF.

Comment #5: We felt that pooling by 2-3 year groups was not necessary in light of the large cohort size. The Poisson regression was indeed powered to show significance even in our smallest incident age group (the 6 month to 4 year age group). We might have pooled years for the subgroup analyses of Crohn's and UC, however since we did not decide to do this a priori that it might represent data mining. Therefore, we have elected not to pool years.

Comment #6: We have added a line in the discussion to address this issue.

Comment #7: Clarification of the statistical methods used to estimate incidence and prevalence of time. Details of the Poisson regression models were updated in the methods section (Methods, Estimates of incidence and prevalence). We hope that the regression model (which includes "year of diagnosis" as the main independent variable) is now clear.

Comment #8: As requested by the journal, we have added a listing of abbreviations to the cover page.
Reviewer 2

Thank you for your kind words, and for your insightful review.

Comment #1: Re: Abstract - Age groups for algorithm development, validation and cohort samples.
The abstract does state that the algorithm was developed in an <15y old cohort (Toronto), and validated in the <18y old cohort (12 medical practices across Ontario). We stated the diagnostic accuracy of the Toronto cohort (for <12 and <15y old) as well as for the Ontario-wide chart cohort (for <18y old). We used the <15y cut-off for the true-positive SickKids IBD Database because it was shown by a survey of adult gastroenterologists, that the database contained approximately 90% of children <15y with IBD in Toronto (see reference 22). Conversely, children >15y may have been followed by adult gastroenterologists and therefore not contained within the database. Therefore, we chose 15y as the cut-off for reliability of the database to represent almost all children with IBD in Toronto. We reworded this point in the methods section of the manuscript to make it more clear. In order to be certain the algorithm performed adequately in all children <18y the Ontario-wide cohort, we used chart validation methods. Since the algorithm was validated and performed well in the <18y group, we felt it could be applied to all children <18y in the province.

Comment #2: Re: PPV values in different age groups.
We have addressed possible reasons for the differing PPVs in the different age groups in the Discussion section of the manuscript (Discussion, Paragraph 5, beginning with "A number of limitations to this study exist").

Comment #3: Re: Table 2.1
We included likelihood ratios for the algorithm validation (<18 year olds) group (and not PPV/NPV) because of the artificially elevated prevalence of IBD in our chart-validation study. We extracted one IBD chart (n=593) for every 2-3 non-IBD charts (n=1241), making the prevalence of IBD in our validation sample approximately 0.48. Since PPV and NPV are dependent on prevalence, any predictive values quoted for the validation sample would be artificially elevated due to the artificial elevation of prevalence in our sample. As such, PPV and NPV should not be reported. We felt that likelihood ratios were a more applicable way of reporting the diagnostic accuracies for this sample. In the algorithm development samples (using a presumed 90% of IBD patients living in Toronto and the entire remaining population of Toronto <15 years of age), we attempted to achieve a true prevalence estimate of IBD within Toronto. Therefore, reporting PPV/NPV can be accomplished in this case (see Discussion section, paragraph 5).

Comment #4: Re: Table 2.5
We disagree with the comment that Table 2.5 does not add relevant additional information. In fact, we feel this Table is likely the most important information in the manuscript with respect to incidence trends. It reports the slope trends in incidence over time (by Poisson regression) with magnitude (Estimate/Beta), confidence intervals and P-values reported for each age group and each diagnosis (as requested by Reviewer 1). This Estimate is important because the overall
Estimate using Poisson regression (unstratified by age group) is unreliability due to a statistically significant interaction between age and year of diagnosis. Additionally, Table 2.5 quantifies the importance of the sex differences in incidence over time and by age group. We feel that it should remain in the manuscript, but we will comply with the wishes of the editorial staff.

**REVIEW #2**

GUT/2009/188383  
Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data  
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**Reviewer 1 Comments for the Author...**

I thank the authors for their corrections but i have other points to comment:

Comment # 1  
The authors performed statistical tests to confirm or not the increase of whole IBD (and CD and UC) incidences between 1994 and 2005. They reported overall P-values in the text (at the end of the & “Results”) and on the figures 1 (for prevalence) and 2 (for incidence). I did not understand the discordance between the P-value in the text about the evolution of CD incidence (5.0 to 6.0; p=0.008) whereas in the figure 2 this P-value was 0.19? Giving the distribution of the CD incidence in 1994 (5.0 95%CI 4.1-5.9) and that of the CD incidence in 2005 (6.0; 95%CI 5.2-7.00), it seems that p=0.19 is the good number. These numbers must be corrected.

Comment # 2  
As CD and UC incidences did not increase during the studied period (1994-2005), it was not statistically permit to divide the whole cohort according to age and/or sex. Moreover the absence of significant interaction between sex and year of diagnosis reinforce my comment. Your conclusion must be more nuanced. You cannot advance "there is an accelerated increase in incidence in younger children" in your conclusion.
RESPONSES TO REVIEWERS #2:

Reviewer 1

Comment #1: Thank you for you for bringing this typographical error to our attention. Indeed the correct P-value should be 0.19. The value of 0.008 actually reflects the Estimate/Beta value and was incorrectly transcribed as the P-value. This has been corrected in the manuscript.

Comment #2: We respectfully disagree with the reviewer regarding the significance of interaction terms. The reviewer states that "As CD and UC incidences did not increase during the studied period (1994-2005), it was not statistically permit to divide the whole cohort according to age and/or sex". In fact, the P-value stated for the overall model (excluding the interaction term) IS NOT interpretable in light of a significant interaction between age group and year of diagnosis. When an interaction occurs between two confounding variables, interpretation of the estimate (or P-value as a reflection of the estimate and confidence measures) can lead to a Type 2 error. This is particularly true when the older age groups (which are not significantly changing) add greater weight to the model in light of their greater numbers within the cohort. Therefore, it has been clearly stated in the statistical literature that estimates and P-values should not be interpreted in light of a significant interaction term (Jaccard J, Turrisi R, and Wan C (1990). Interaction Effects in Multiple Regression. Newbury Park, CA: Sage).

To our knowledge, two methods have been used to create interpretable results from regression models with significant interaction terms. The method we used was to stratify the models by the significant interaction term (see example Table 2 of Llorca J and Delgado-Rodriguez, M. A new way to estimate the contribution of a risk factor in populations avoided nonadditivity. J Clin Epidemiol 2004; 57:479-83). We used this method so as to present the results in table format (Table 2.5 of manuscript) and so the effect of sex on each age group could be viewed by readers. The only disadvantage to using this method would be that stratification would lead to insufficient subjects to create a multivariable model, which was not an issue in our case of a large sample size.

The other method of creating interpretable results from a model with a significant interaction term is more complex (Pages 16-43 of Jaccard J, Turrisi R (2003). Interaction Effects in Multiple Regression (2nd ed.). Thousand Oaks, CA: Sage). This method would entail calculating the individual Betas (or estimates) for each interaction term and adding them separately. For example,
Overall model: \( \log(\mu) = B_0 + B_1(\text{year}) + B_2(\text{AgeGrp}) + B_3(\text{year} \times \text{AgeGrp}) \)

For AgeGrp=-0 (the 0-4 year olds):
\[
\log(\mu) = B_0 + B_1(\text{year}) + B_2(0) + B_3(\text{Year} \times 0) \\
= B_0 + B_1(\text{year}) \\
= -65 + 0.03354(\text{year})
\]
(numbers taken from output of Poisson model for incidence of IBD over time)

Therefore, the rate of increase using this method in the 0-4 yr age group is 3.35%/year (95%CI 1.8%-4.9%)

For AgeGrp=1 (the 5-9 year olds):
\[
\log(\mu) = B_0 + B_1(\text{year}) + B_2(1) + B_3(\text{Year} \times 1) \\
= (B_0+B_2) + (B_1+B_3)\text{Year} \\
= (-65 – 78.8\text{year}) + (0.0335 + 0.0391)\text{Year}
\]

Therefore, the rate of increase using this method in the 5-9 year age group is (0.0335 + 0.0391) = 0.0726 = 7.26%/year

The results utilizing this more complex method should approximate the results of our stratified analysis (which they do) (Austin P, personal communication). The reason for the slight discrepancies is that for the stratified analysis, sex is controlled within each age group, whereas for the latter analysis, sex is controlled only for the overall model. Because we felt that readers would be interested in the effect of sex across different age groups (as displayed in Table 2.5), we elected for the stratified method of interpreting the regression.

The absence of a significant interaction between sex and year of diagnosis simply means that the effect of sex on incidence over time is interpretable. Due to the lack of interaction between sex and year of diagnosis, we did not need to stratify by sex or control for it using the Jaccard and Turrisi method.

We hope that this has clarified our methods. Thank you for your comments.
Chapter 3
Surgical and Health Services Outcomes of Childhood-onset Inflammatory Bowel Disease by Socio-economic Status: Findings From a Universal Access Healthcare System

Published in abstract form:

Benchimol EI, To T, Griffiths AM, Rabeneck L, Guttmann A. Low income children with inflammatory bowel disease have higher surgical and hospitalization rates in a universal health care system. *Inflammatory Bowel Diseases* 2009; 15(Supp 2): S20.
3.1 Abstract

BACKGROUND & AIMS: Canada's single-payer health system provides all residents of Ontario with publicly-funded healthcare. Nonetheless, there are income-based disparities in health outcomes in children with chronic diseases. We examined variation in healthcare utilization and surgical rates according to neighbourhood household income in children with inflammatory bowel disease (IBD).

METHODS: We used a validated algorithm to identify all children <18 years diagnosed 1994-2004 with IBD within Ontario's health administrative databases. Patients were grouped into the lowest and highest two mean neighbourhood income quintile. Multivariable models tested the association between income group and physician and emergency department (ED) visits, hospitalizations, or surgery.

RESULTS: IBD-related health services use was highest in the three years following diagnosis and then stabilized. Care providers (gastroenterologists, surgeons) were similar between income groups. Lower income children were more likely to be hospitalized at least once (hazard ratio (HR) 1.17, 95% confidence intervals (CI) 1.05-1.30) or visit the ED (HR 1.21, 95% CI 1.09-1.35) and had more IBD-related physician visits (odds ratio (OR) 3.73, 95% CI 1.05-13.27). Lower income children with Crohn's disease (not ulcerative colitis) were more likely to undergo intra-abdominal surgery within 3 years of diagnosis (OR 1.22, 95% CI 1.01-1.49), especially if diagnosed after 2000 (OR 1.79, 95% CI 1.27-2.53)

CONCLUSIONS: Lower income was associated with greater health services utilization rates in children with IBD and a higher risk of surgery in children with Crohn’s. These were not associated with differences in specialist healthcare provision, suggesting other risk factors may play a role.

3.2 Introduction

Low socioeconomic status (SES) is a well-established risk factor for poor health outcomes in children (49). In Canada, all legal residents have universal access to primary and acute health services. Despite this, disparities in the health outcomes of children exist in neonatal complex
chronic diseases (53), asthma (54), type 1 diabetes and seizure disorders (55). Although there is some evidence of inequities in access to healthcare, especially specialized care in adults (85-87) and children (88) in Canada, it is not clear how much of the relationship between poor health outcomes and low socio-economic status in children with chronic diseases is due to issues of healthcare delivery.

Inflammatory bowel disease (IBD) is a chronic gastrointestinal condition with increased prevalence in relatively affluent Westernized nations (89). Both Crohn's disease (CD) and ulcerative colitis (UC) have been reported to differentially affect people of higher SES (90). In France, adults of lower SES had similar IBD severity to those of higher SES but were more likely to be hospitalized and less likely to undergo surgery (9). Although children with IBD have been noted to utilize the health system more frequently, resulting in higher attributable health care costs compared with adults (8, 91), the relationship to SES has not been examined. Ontario, Canada's largest province, has among the highest rates of paediatric IBD in the world (92). The high burden of disease, coupled with the universal access single-payer health system makes Ontario the ideal setting in which to examine the effect of SES on the health services utilization and surgical rates among children with IBD.

Rates of hospitalization, emergency department use and surgery are outcomes that may be considered markers of failure of outpatient medical management in IBD. Assuming clinical characteristics and disease severity of patients are similar across socioeconomic groups, these markers should be similar across household income if medical care is provided equally and universally for all children. The goals of our study were to describe healthcare use in patients with childhood-onset IBD and to test the relationship between neighbourhood income and these measures. We considered emergency department visits, hospitalization and surgery to be reflective of morbidity as potential markers of failure of outpatient medical management. We used a large population-based cohort of childhood-onset IBD patients derived from health administrative data over a 14 year period. In so doing, we were able to address the hypothesis that lower SES was associated with greater health care resource use in childhood-onset IBD.
3.3 Methods

Ethics approval for this study was received from the research ethics boards of the University of Toronto, The Hospital for Sick Children and Sunnybrook Health Sciences Centre.

3.3.1 Study Cohort
The Ontario Crohn’s and Colitis Cohort is a cohort of paediatric-onset (six months to 18 years) IBD patients derived from health administrative data. Patients are identified using a validated algorithm as previously described (92): if patients underwent colonoscopy, they required at least four physician contacts or two hospitalizations on different days over a maximum of three years with associated International Classification of Diseases, Ninth Revision (ICD-9) code for CD (555.x) or UC (556.x) or ICD, Tenth Revision (ICD-10) code for CD (K50.x) or UC (K51.x), while patients who did not undergo colonoscopy required at least seven physician visits or three hospitalizations over three years. This algorithm achieved a sensitivity of 89.6-91.1% and a specificity of 99.5-100% for identifying children with IBD within Ontario's health administrative databases (92).

3.3.2 Data Sources
The administrative databases are maintained by the Institute for Clinical Evaluative Sciences (ICES) through a comprehensive data sharing agreement with the Ontario Ministry of Health and Long Term Care. ICES is an independent, not-for-profit organization that conducts health services research for the province of Ontario. To report on hospitalizations, we used discharge abstract data mandatorily collected from all hospitals and reported to the Canadian Institute for Health Information (CIHI), with diagnostic codes found to be 92-99% accurate (93). Outpatient physician visits, surgical procedures and emergency department (ED) usage were obtained from physician billing information obtained from the Ontario Health Insurance Plan (OHIP) database. The ICES Physician Database was used to classify the type of provider: family physician, general paediatrician, general internist, general surgeon, adult gastroenterologist (internists with reported or certified specialty in gastroenterology, internists who performed >25 colonoscopies per year and whose practices were made up primarily of adults), or paediatric gastroenterologist.
(paediatricians with reported or certified specialty in gastroenterology, paediatricians who performed colonoscopies on >5 children per year, or adult gastroenterologists whose practices were made of >70% children <18 years of age). Demographic information including postal code was obtained from the Registered Persons Database, a registry of all residents eligible for health care in Ontario. We linked postal codes recorded at birth and IBD diagnosis to 1996 and 2001 Canadian Census data using Postal Code Conversion Files Plus (PCCF+) (94) to obtain the mean neighbourhood income quintile and community size (rural versus urban residence) of individual children with IBD. For patients diagnosed in 1994-1998, we used the 1996 PCCF+ which assigned quintiles at the enumeration area level, comprising approximately 125 dwellings in rural communities, and 440-650 dwellings in urban communities. For patients diagnosed in 1999-2004, we used the 2001 PCCF+ which assigned quintiles at the dissemination area level, comprising a geographic block area which contained 400-700 residents. The quintiles are adjusted for household and community size. As such it is impossible to report the mean income of a quintile as it varies across areas. Quintiles were not calculated independently for rural and urban communities, thereby allowing for urban/rural residence to be assessed as an independent variable in multivariable models. Canada does not define a “poverty level” as in the United States however these income quintiles are operationalized by Statistics Canada to represent “low income cutoffs” with an emphasis on relative cost of living and household size (94). Income quintiles for areas with unstable populations (such as chronic care institutions or universities) are not reported by Statistics Canada and are designated here as missing.

3.3.2 Study Design and Population
This study assessed all children (6 months to 18 years) diagnosed with IBD within Ontario from fiscal years (FY) 1994-2004. The date of diagnosis was defined as the date of first contact with a physician or first hospitalization with associated diagnostic code for IBD. All subjects were followed for a minimum of three years from diagnosis using administrative data. Analyses were stratified by diagnosis (overall IBD, CD or UC). Classification of diagnosis (CD, UC or unclassifiable) was accomplished with a validated algorithm that distinguished CD from UC with an area under the receiver operating characteristic curve of 0.9618 as previously described (92). We tested the association of income quintile and health services utilization by comparing
patients in the lowest two income quintile groups at the time of diagnosis to those in the highest two quintile groups.

### 3.3.3 Categories of Health Services Utilization

The number of physician visits, hospitalizations, and ED visits are described as means (with standard deviations [SD]) for each year following diagnosis. The likelihood of hospitalization, ED visit, surgical resection, and any IBD-related surgery are presented using Kaplan-Meier hazard rates. Surgeries were classified as intestinal or peri-anal by OHIP billing code (see Supplemental Table 3.1). All descriptions and analyses of health services utilization (physician visits, hospitalizations, ED visits) were classified by the reason for the visit using the associated ICD code: all reasons, IBD-specific visits, or all IBD-related visits (see Supplemental Table 2.2). For associated diagnoses, OHIP utilizes a shortened three-digit version of ICD-9 while the CIHI discharge abstract database uses a four-digit ICD-9 code (prior to 2002) or seven-digit ICD-10 (after 2002).

### 3.3.5 Statistical Analysis

Descriptive statistics are presented as proportions or means (with standard deviations). Comparison between low and high income groups were conducted using Wilcoxon Rank Sum for continuous variables or chi-square analysis for categorical variables. The association between income and the likelihood of hospitalization, surgery or ED visit within three years of diagnosis was analyzed using logistic regression models. The association between income and number of physician visits, hospitalizations and ED visits within three years of diagnosis was analyzed using linear regression models. The association between income and the likelihood of hospitalization, surgery or ED visit over the full follow-up period was analyzed using Cox proportional hazard multivariable survival models. All hypothesis tests were two-sided and determined to be significant at P<0.05. All multivariable analyses included income quintile group (lowest two quintiles vs. highest two quintiles) as the major predictor, as well as sex and age at diagnosis because of their known association with greater disease severity and specific disease phenotypes (10, 95). Confounding with other variables (decade of diagnosis [1994-1999 vs. 2000-2004], rural residence at birth, rural residence at diagnosis) was assessed by the 10
percent change in the odds ratio estimate method (96), with variables included in the model if they met this criterion as confounders. The cut-off for decade of diagnosis (FY 2000) was determined a priori and chosen as a marker of important changes in the treatment of children with IBD (1). In Ontario after 2000, usage of azathioprine, 6-MP or methotrexate within three years of diagnosis increased from 12% to 39% in children on social assistance (OCCC data, unpublished), perhaps related to the publication of the first trial of immunosuppression for maintenance of remission in children newly diagnosis with CD (1). Additionally, since 2000 infliximab was available on compassionate release as the first biologic therapy in paediatric CD. Irrespective of whether covariates met the 10% change in estimate criterion for confounding, the interaction between the covariate and income quintile group was evaluated for statistical significance using the Wald chi-square statistic. If the interaction term was significant (p<0.05), the covariate with interaction term were included in the final model if their inclusion improved the goodness-of-fit test by >10%. For goodness-of-fit testing, we used the -2 log likelihood ratio for Cox proportional hazard models, the R² statistic for linear regression models and the c-statistic for logistic regression models. Collinearity of covariates was assessed with threshold tolerance >0.4 and variance inflation <2.5 in all final models. All statistical analyses were performed using SAS® version 9.1.3 (SAS Institute Inc., Cary, U.S.A.).

3.4 Results

The Ontario Crohn's and Colitis Cohort contained 3404 children diagnosed with IBD in FY 1994-2006. Of these, 446 children were excluded because they did not have three years of follow-up data, 716 were excluded because they lived in neighbourhoods of the middle income quintile and 12 were excluded because of missing neighbourhood income quintile. At diagnosis, 944 patients lived in neighbourhoods with the lowest two mean income quintiles and 1286 were in neighbourhoods of the highest two mean income quintiles. Characteristics of the cohorts are presented in Table 3.1. Children of higher income families were more likely to be diagnosed with CD, while those of lower income families were more likely to be diagnosed with UC (P=0.0002). Higher income patients was also less likely to live in a rural region at the time of diagnosis compared with lower income patients (P=0.01). The number of visits to adult or paediatric gastroenterologists and the proportion of outpatient visits to gastroenterologists
compared with generalists were not significantly different between low and high income patients (P>0.05).

3.4.1 Overall Health Services Utilization

Physician visit, hospitalization, and ED visit rates are presented in Figures 3.1, 3.2 and 3.3 by year since diagnosis. For CD patients, cumulative 1-year, 5-year and 10-year likelihoods of undergoing at least one intra-abdominal surgery were 7.5%, 21.1% and 28.8% respectively. When peri-anal surgeries were included, the cumulative rates of CD surgeries increased to 8.8%, 23.5% and 31.8% respectively. For UC patients, likelihood of colectomy at 1, 5 and 10 years was 6.5%, 16.4% and 20.6% respectively. The likelihood of IBD-related hospitalization in CD patients was 41.2%, 59.9% and 65.7% within 1-year, 5-years and 10-years respectively. For UC patients, the likelihood of hospitalization was 37.7%, 52.1% and 55.9% within 1-year, 5-years and 10-years respectively. The likelihood of at least one IBD-related ED visit was 33.4%, 57.0% and 67.3% (in CD patients) and 28.8%, 53.1% and 64.4% (in UC patients) within 1-year, 5-years and 10-years respectively.

3.4.2 Health Services Utilization by Income Quintile Group

Results of multivariable regression models are presented in Table 3.2 with the hazard and odds ratios of various health utilization in lower income IBD patients compared with higher income patients. No income disparities existed when examining the number of physician visits for any reason, the number of ED visits for any reason or the likelihood of ED visit for any reason within three years of diagnosis with IBD. In general, hospitalization (for any reason) was more likely in lower income patients. When examining only IBD-related reasons for health care utilization, patients with IBD of lower household income had a greater: 1) number of IBD-related physician visits (OR 3.73, P=0.04), 2) hazard of IBD-related hospitalization over the full follow-up period (HR 1.17, P=0.004, Figure 3.4a), 3) likelihood of IBD-related hospitalization within three years of diagnosis (OR 1.30, P=0.002), 4) number of IBD-related hospitalizations over three years (OR 1.26, P=0.0009), 5) hazard of IBD-related ED visit over the full follow-up period (HR 1.21, P=0.0003, Figure 3.4b), 6) number of IBD-related ED visits within three years of diagnosis (OR 1.41, P<0.0001), and 7) likelihood of IBD-related ED visit within three years of diagnosis (OR
1.33, \( P=0.001 \). Similar increased utilization patterns existed in lower income patients when assessing IBD-specific visits (data not shown) and when patients were stratified by diagnosis (CD or UC).

Differences in surgical rates by income quintile group are presented in Table 3.3 for intra-abdominal surgeries (in the IBD, CD and UC groups) and for all IBD-related surgeries including peri-anal (for IBD and CD groups). In the Cox proportionate hazard models (for IBD and CD patients), the decade of diagnosis (1990s vs. 2000s) qualified as a confounder and therefore was included in the models. However, due to a significant interaction between decade of diagnosis and income quintile group (in IBD and CD patients, not in UC patients), results are presented stratified by decade of diagnosis. We found no significant difference between low and high income patients in those diagnosed prior to 2000, however CD patients diagnosed after 2000 were more likely to undergo any surgery (HR 1.56, \( P=0.006 \)) or intra-abdominal surgery (HR 1.79, \( P=0.0009 \)) if they lived in low income neighbourhoods (Figure 3.5a). There was no significant interaction between decade of diagnosis and income group for the logistic regression models examining likelihood of undergoing surgery within three years of diagnosis. Again, CD patients (but not UC patients) were more likely to undergo either intra-abdominal (OR 1.66, \( P=0.0009 \)) or any surgery (OR 1.57, \( P=0.002 \)) within three years of diagnosis if they were in the lower income group.

### 3.4.3 Influence of Age and Sex on Health Services Utilization

Since age of diagnosis and sex were included in all multivariate models, significant associations between these variables and health services utilization are noted here. Females were more likely to be hospitalized for IBD-related reasons through the full follow-up period (HR 1.20, 95% CI 1.08-1.34, \( P=0.0006 \)) and had more hospitalizations within three years of diagnosis (OR 1.26, 95% CI 1.06-1.49, \( P=0.008 \)). This was consistent with a higher rate of hospitalization in female patients for any reason, and higher rates of hospitalization were present for both female CD and UC patients. Female patients were also more likely to utilize the ED at least once over the follow-up period for IBD-related reasons (HR 1.33, 95% CI 1.20-1.48, \( P<0.0001 \)) and had a higher number of IBD-related ED visits within three years (OR 1.33, 95% CI 1.16-1.53, \( P<0.0001 \)). Additionally, increasing age at diagnosis was associated with increased likelihood to
utilize the ED at least once over the follow-up period for IBD-related reasons (HR 1.06, 95% CI 1.04-1.08, \( P<0.0001 \)) and older age was associated with a higher number of IBD-related ED visits within three years of diagnosis (OR 1.10, 95% CI 1.07-1.13, \( P<0.0001 \)).

Increasing age was associated with increased likelihood of surgery over the full follow-up (HR 1.07, 95% CI 1.04-1.10, \( P<0.0001 \)) and within three years of diagnosis (OR 1.15, 95% CI 1.10-1.19, \( P<0.0001 \)). This association was present in both CD and UC patients, and was also present when peri-anal surgeries were included for CD patients. There was no association between sex and surgical rates in any group.

### 3.5 Discussion

To our knowledge, this is the first population-based study to assess the association between socioeconomic status, health services utilization and surgical rates in paediatric IBD. With a follow-up period of up to 14 years, we documented a high number of IBD related and unrelated health care contacts for IBD patients in the year following diagnosis, with stabilization thereafter. Five and ten-year surgical rates were approximately 25% and 30% in CD, which were significantly lower than in older studies (97, 98) but consistent with more recent paediatric cohorts from the UK (99) and Europe (100, 101). This change could be due to improved medical treatments, earlier diagnosis (resulting in improved response to medical therapy) or improved comfort of medical practitioners with medical treatments for IBD. UC colectomy rates were similar to a recent paediatric cohort from Finland (101). Our finding that females had increased health services utilization compared with males may reflect greater disease severity in females as was suggested in earlier paediatric (10) and adult studies (102).

Low income children had higher IBD-related physician visit rates, hospitalization rates and ED usage than higher income patients. The higher all-cause hospitalization rates in low income children is consistent with other Canadian studies across a number of medical conditions (54, 57, 103, 104). However, we also document higher surgical rates in low income children with CD, and more so in those diagnosed after 2000. This may be explained in a number of ways. It is possible that disease severity or phenotype (not measurable with health administrative data) may be different depending on SES. However, a recent study demonstrated no association between
social deprivation and disease severity in French adults with CD (9). Access to specialized medical care may play a role in changing outcomes and health services utilization, and lower income patients may have less access to specialized services (105, 106). However, we found no significant difference by income group in the number of outpatient physician visits to surgeons, adult and paediatric gastroenterologists or the proportion of outpatient care provided by adult/paediatric gastroenterologists. Although this does not prove that all aspects of quality of care are the same for low and high income children, it does imply that basic access to care, including specialized care is unlikely to explain the differences in outcomes. However, access to medications may be particularly important when explaining the differences between CD patients diagnosed between 1994-1999 to those diagnosed between 2000-2004. In the early 2000s, landmark studies in maintenance of remission in CD demonstrated the efficacy of 6-mercaptopurine in children (1) and the efficacy of infliximab (12). It is possible that our finding of greater disparities in surgical outcomes in CD patients after 2000 relates to access to these medications as Ontario does not universally fund prescription medications in residents, but rather only for those on social assistance. Funding approval for biologics may be more difficult to obtain from government bodies for patients on social assistance than for more affluent patients with private drug coverage. The finding of an income disparity only in those diagnosed after 2000 may be due to longer follow-up length of those diagnosed between 1994-1999 and the narrowing of the differential when patients were followed for long periods (see Figure 3.5a). The majority of the income differential in surgical outcomes is noted between two and seven years following diagnosis, with the difference narrowing after the seventh year, and a smaller proportion of those diagnosed after 2000 have seven years of longitudinal data. This was consistent with the finding that all low income CD patients (whether diagnosed before or after 2000) had higher surgical rates when three year outcome was assessed.

A number of social factors may explain the greater use of health care resources in low income children with IBD. Firstly, medication adherence may play a role in disease outcome. Studies on medication adherence in adults with IBD have not demonstrated an association between income and medication adherence (107-109), however studies in children with asthma suggest low income children are less adherent to treatment (110) largely mediated by differences in medication insurance coverage (111, 112). Disease severity and surgical resection rates have
been noted to be associated with tobacco smoking in patients with CD (113), and smoking rates are 2-3 higher in low compared with high income Canadians (114, 115).

Although some of the strengths of our study, such as its large and representative sample and long follow-up period are related to its administrative data sources, these data have their limitations. These include lack of clinical information, including phenotypic disease details, as well as pharmacy data which could elucidate the relationship of income and outcome that we have documented. We also lacked individual level income for our patient population. However, neighbourhood income has been validated as a proxy for household income and social deprivation in previous studies (116-118) and this method has been widely used.

In summary, the reported rates of physician visits, hospitalization, ED usage and surgical intervention can provide important prognostic information for families of children diagnosed with IBD. Even in a universal access system, there are disparities in outcomes of IBD related to socio-economic status. Further work needs to be done to explore the causes of these inequities in order to improve outcomes and the quality of care provided to children with IBD.

3.6 Acknowledgements

This research was funded by a Clinical Research Award from the American College of Gastroenterology and was made possible with the support of the Institute for Clinical Evaluative Sciences which receives funding from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The results and conclusions are those of the authors; no official endorsement by the Ontario MOHLTC should be inferred. Eric Benchimol is a Canadian Institutes of Health Research (CIHR) training fellow in the Canadian Child Health Clinician Scientist Program, in partnership with SickKids Foundation and the Child & Family Research Institute of British Columbia, and was also supported by fellowships from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition-Children's Digestive Health and Nutrition Foundation, and the Clinician Scientist Training Program of the Research Institute of the Hospital for Sick Children. Astrid Guttmann was supported by a CIHR New Investigator Award.
Table 3.1: Descriptive statistics of overall cohort and of groups by income quintile.

<table>
<thead>
<tr>
<th></th>
<th>Overall Cohort (n=3404)</th>
<th>Lowest Two Income Quintiles (n=944)</th>
<th>Highest Two Income Quintiles (n=1286)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td>1568 (46.1%)</td>
<td>419 (44.4%)</td>
<td>575 (44.7%)</td>
</tr>
<tr>
<td><strong>Age at Diagnosis (years ± SD)</strong></td>
<td>14.4 ± 3.9</td>
<td>13.6 ± 3.7</td>
<td>14.0 ± 3.3</td>
</tr>
<tr>
<td><strong>Fiscal Year of Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-1999</td>
<td>1813 (53.3%)</td>
<td>479 (50.7%)</td>
<td>708 (55.1%)</td>
</tr>
<tr>
<td>2000-2004</td>
<td>1591 (46.7%)</td>
<td>465 (49.3%)</td>
<td>578 (44.9%)</td>
</tr>
<tr>
<td><strong>Length of Follow-up (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>8.4 ± 3.2</td>
<td>8.2 ± 3.1</td>
<td>8.5 ± 3.1</td>
</tr>
<tr>
<td>MIN</td>
<td>1.9</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>MAX</td>
<td>14.0</td>
<td>14.0</td>
<td>14.0</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Crohn’s</td>
<td>1967 (57.8%)</td>
<td>514 (54.5%)</td>
<td>801 (62.3%)</td>
</tr>
<tr>
<td>UC</td>
<td>1190 (35.0%)</td>
<td>363 (38.4%)</td>
<td>387 (30.1%)</td>
</tr>
<tr>
<td>IBD-U</td>
<td>247 (7.3%)</td>
<td>67 (7.1%)</td>
<td>98 (7.6%)</td>
</tr>
<tr>
<td><strong>Deaths Since Diagnosis</strong></td>
<td>20 (0.59%)</td>
<td>5 (0.39%)</td>
<td>5 (0.53%)</td>
</tr>
<tr>
<td><strong>Rural Resident at Diagnosis</strong></td>
<td>445 (13.1%)</td>
<td>143 (15.2%)</td>
<td>147 (11.4%)</td>
</tr>
<tr>
<td><strong>Outpatient Adult GI visits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 1y</td>
<td>0.5 ± 1.8</td>
<td>0.5 ± 1.6</td>
<td>0.44 ± 1.7</td>
</tr>
<tr>
<td>Within 3y</td>
<td>0.9 ± 3.2</td>
<td>0.8 ± 2.9</td>
<td>0.8 ± 2.9</td>
</tr>
<tr>
<td><strong>Outpatient Paediatric GI visits</strong></td>
<td>2.3 ± 3.4</td>
<td>2.9 ± 3.8</td>
<td>3.1 ± 3.6</td>
</tr>
<tr>
<td>Within 1y</td>
<td>4.5 ± 6.5</td>
<td>5.9 ± 7.6</td>
<td>6.1 ± 7.0</td>
</tr>
<tr>
<td><strong>Mean percentage of outpatient visits to any gastroenterologist</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 1y</td>
<td>36.3% ± 37.3%</td>
<td>39.2% ± 37.3%</td>
<td>42.4% ± 38.1%</td>
</tr>
<tr>
<td>Within 3y</td>
<td>32.0% ± 33.1%</td>
<td>34.8% ± 32.8%</td>
<td>37.7% ± 34.0%</td>
</tr>
</tbody>
</table>
Figure 3.1. Number of outpatient physician visits for IBD cohort by year since diagnosis.
Figure 3.2. Number of hospitalizations for IBD cohort by year since diagnosis.
Figure 3.3. Number of emergency department visits for IBD cohort by year since diagnosis.
Figure 3.4. Likelihood of IBD-related hospital admission (A) and emergency department visit (B) by income quintile group by year since diagnosis.
Figure 3.5. Likelihood of intra-abdominal or resective surgery by income quintile group for patients with Crohn's (A) or UC (B) by year since diagnosis.
Table 3.2. All cause and IBD-related health services utilization and adjusted odds/hazard ratios by neighbourhood income quintile group. All-cause health services utilization includes diagnostic codes for IBD-specific and IBD-related usage in addition to all other causes. IBD-related usage includes IBD-specific usage, IBD signs and symptoms and extra-intestinal manifestations of IBD (see Supplemental Table 3.2).

<table>
<thead>
<tr>
<th></th>
<th>Low Income (IBD: n=944) (Crohn's: n=514) (UC: n=363)</th>
<th>High Income (IBD: n=1286) (Crohn's: n=801) (UC: n=387)</th>
<th>Adjusted Regression Model* Odds/Hazard Ratios (95% CI) (low vs. high income)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause health services utilization:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># physician visits within 3y of diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>42.6 ± 27.1</td>
<td>42.5 ± 26.6</td>
<td>1.23 (0.13-11.63)†‡</td>
</tr>
<tr>
<td>Crohn's</td>
<td>44.8 ± 27.3</td>
<td>44.8 ± 28.1</td>
<td>1.02 (0.05-22.19)‡</td>
</tr>
<tr>
<td>UC</td>
<td>39.3 ± 25.7</td>
<td>39.5 ± 23.2</td>
<td>0.85 (0.03-28.56)‡</td>
</tr>
<tr>
<td>Hazard of hospital admission (% hospitalized by 10y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>70.8%</td>
<td>67.0%</td>
<td>1.15 (1.04-1.28)</td>
</tr>
<tr>
<td>Crohn's</td>
<td>73.4%</td>
<td>71.8%</td>
<td>1.11 (0.98-1.26)‡</td>
</tr>
<tr>
<td>UC</td>
<td>68.6%</td>
<td>59.4%</td>
<td>1.33 (1.11-1.59)</td>
</tr>
<tr>
<td>Hospitalization within 3y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>570 (60.4%)</td>
<td>684 (53.2%)</td>
<td>1.36 (1.15-1.61)</td>
</tr>
<tr>
<td>Crohn's</td>
<td>317 (61.7%)</td>
<td>453 (56.6%)</td>
<td>1.25 (0.99-1.56)</td>
</tr>
<tr>
<td>UC</td>
<td>213 (58.7%)</td>
<td>184 (47.6%)</td>
<td>1.62 (1.21-2.17)</td>
</tr>
<tr>
<td># hospitalizations within 3y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>1.59 ± 1.99</td>
<td>1.27 ± 1.83</td>
<td>1.39 (1.18-1.62)</td>
</tr>
<tr>
<td>Crohn's</td>
<td>1.63 ± 1.94</td>
<td>1.29 ± 1.75</td>
<td>1.40 (1.15-1.72)</td>
</tr>
<tr>
<td>UC</td>
<td>1.18 ± 1.60</td>
<td>1.01 ± 1.65</td>
<td>1.18 (0.94-1.50)</td>
</tr>
<tr>
<td>Hazard of ED visit (% with visit by 10y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>89.7%</td>
<td>85.3%</td>
<td>1.21 (1.10-1.32)</td>
</tr>
<tr>
<td>Crohn's</td>
<td>88.9%</td>
<td>85.9%</td>
<td>1.12 (0.99-1.26)‡</td>
</tr>
<tr>
<td>UC</td>
<td>90.4%</td>
<td>84.2%</td>
<td>1.28 (1.10-1.49)</td>
</tr>
<tr>
<td><strong>IBD-related utilization:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># physician visits within 3y of diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>20.1±16.5</td>
<td>18.7±14.0</td>
<td>3.73 (1.05-13.27)</td>
</tr>
<tr>
<td>Crohn's</td>
<td>21.5±14.9</td>
<td>19.9±14.3</td>
<td>4.79 (0.96-23.7)</td>
</tr>
<tr>
<td>UC</td>
<td>18.2±17.0</td>
<td>16.7±12.0</td>
<td>3.58 (0.44-29.1)</td>
</tr>
<tr>
<td>Hazard of hospital admission (% hospitalized by 10y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>64.5%</td>
<td>59.8%</td>
<td>1.17 (1.05-1.30)</td>
</tr>
<tr>
<td>Crohn's</td>
<td>67.7%</td>
<td>66.3%</td>
<td>1.10 (0.96-1.26)‡</td>
</tr>
<tr>
<td>UC</td>
<td>61.7%</td>
<td>50.4%</td>
<td>1.40 (1.16-1.70)</td>
</tr>
<tr>
<td></td>
<td>IBD</td>
<td>Crohn's</td>
<td>UC</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Hospitalization within 3y</td>
<td>521 (55.2%)</td>
<td>630 (49.0%)</td>
<td>1.30 (1.10-1.54)</td>
</tr>
<tr>
<td></td>
<td>293 (57.0%)</td>
<td>430 (53.7%)</td>
<td>1.15 (0.92-1.44)</td>
</tr>
<tr>
<td></td>
<td>192 (52.9%)</td>
<td>161 (41.6%)</td>
<td>1.62 (1.21-2.17)</td>
</tr>
<tr>
<td># hospitalizations within 3y</td>
<td>1.30 ± 1.66</td>
<td>1.07 ± 1.58</td>
<td>1.26 (1.10-1.44)</td>
</tr>
<tr>
<td></td>
<td>1.40 ± 1.71</td>
<td>1.13 ± 1.56</td>
<td>1.30 (1.09-1.56)</td>
</tr>
<tr>
<td></td>
<td>1.18 ± 1.60</td>
<td>1.01 ± 1.65</td>
<td>1.18 (0.94-1.50)</td>
</tr>
<tr>
<td>Hazard of ED visit (% with visit by 10y)</td>
<td>65.7%</td>
<td>59.6%</td>
<td>1.21 (1.09-1.35)</td>
</tr>
<tr>
<td></td>
<td>68.3%</td>
<td>64.2%</td>
<td>1.14 (0.997-1.31)</td>
</tr>
<tr>
<td></td>
<td>63.9%</td>
<td>51.7%</td>
<td>1.42 (1.18-1.72)</td>
</tr>
</tbody>
</table>

* All models adjusted for sex and age at diagnosis. Where indicated, model also adjusted for decade of diagnosis, rural residence at birth, rural residence at diagnosis based on whether these variables acted as confounders (see Methods for model-building strategy). Bolded odds/hazard ratios represent p<0.05.
Table 3.3. Likelihood of surgery by neighbourhood income quintile group.

<table>
<thead>
<tr>
<th>Intra-Abdominal Surgeries</th>
<th>Low Income (IBD: n=944)</th>
<th>High Income (IBD: n=1286)</th>
<th>Stratum (by year of diagnosis)</th>
<th>Adjusted Regression Models* Odds/Hazard Ratios (95% CI) (low vs. high income)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IBD</td>
<td>CD</td>
<td>UC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Crohn's: n=514)</td>
<td>(Crohn's: n=801)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(UC: n=363)</td>
<td>(UC: n=387)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard of Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% with surgery by 10y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>26.1%</td>
<td>24.6%</td>
<td>Full Cohort†</td>
<td>1.11 (0.94-1.31)</td>
</tr>
<tr>
<td></td>
<td>1994-1999</td>
<td></td>
<td></td>
<td>0.92 (0.75-1.13)</td>
</tr>
<tr>
<td></td>
<td>2000-2004</td>
<td></td>
<td></td>
<td>1.55 (1.18-2.05)</td>
</tr>
<tr>
<td>CD</td>
<td>31.7%</td>
<td>28.0%</td>
<td>Full Cohort†</td>
<td>1.22 (1.01-1.49)</td>
</tr>
<tr>
<td></td>
<td>1994-1999</td>
<td></td>
<td></td>
<td>1.00 (0.79-1.28)</td>
</tr>
<tr>
<td></td>
<td>2000-2004</td>
<td></td>
<td></td>
<td>1.79 (1.27-2.53)</td>
</tr>
<tr>
<td>UC</td>
<td>19.0%</td>
<td>20.2%</td>
<td>Full Cohort</td>
<td>0.97 (0.71-1.35)†</td>
</tr>
<tr>
<td></td>
<td>1994-1999</td>
<td></td>
<td></td>
<td>0.82 (0.54-1.23)†</td>
</tr>
<tr>
<td></td>
<td>2000-2004</td>
<td></td>
<td></td>
<td>1.28 (0.76-2.17)†</td>
</tr>
<tr>
<td>Likelihood of Surgery within 3y of diagnosis</td>
<td>15.8%</td>
<td>12.7%</td>
<td>Full Cohort</td>
<td>1.34 (1.05-1.71)</td>
</tr>
<tr>
<td>IBD</td>
<td>20.0%</td>
<td>13.2%</td>
<td>Full Cohort</td>
<td>1.66 (1.23-2.25)</td>
</tr>
<tr>
<td>CD</td>
<td>10.7%</td>
<td>12.7%</td>
<td>Full Cohort</td>
<td>0.87 (0.56-1.37)</td>
</tr>
<tr>
<td>UC</td>
<td>34.2%</td>
<td>31.3%</td>
<td>Full Cohort†</td>
<td>1.17 (0.97-1.42)</td>
</tr>
<tr>
<td>All Surgeries (Including Peri-Anal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard of Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% with surgery by 10y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>34.2%</td>
<td>31.3%</td>
<td>Full Cohort†</td>
<td>1.17 (0.97-1.42)</td>
</tr>
<tr>
<td></td>
<td>1994-1999</td>
<td></td>
<td></td>
<td>1.00 (0.79-1.27)</td>
</tr>
<tr>
<td></td>
<td>2000-2004</td>
<td></td>
<td></td>
<td>1.56 (1.14-2.15)</td>
</tr>
<tr>
<td>Likelihood of Surgery within 3y of diagnosis</td>
<td>22.2%</td>
<td>15.5%</td>
<td>Full Cohort</td>
<td>1.57 (1.18-2.10)</td>
</tr>
</tbody>
</table>

* All models adjusted for sex and age at diagnosis. †Where indicated, model also for rural residence at diagnosis. Bolded odds/hazard ratios represent p<0.05.
†Due to a significant interaction between income group and decade of diagnosis covariates, these hazard ratios are unreliable when unstratified by decade of diagnosis.
Supplemental Table 3.1: Billing codes used to identify intestinal, rectal and peri-anal surgeries within the OHIP physician billing database.

1) INTRA-ABDOMINAL/RESECTIVE SURGERIES
a) Enterotomy:
   S149 - Ileostomy
   S150 - Small intestine - including excision of polyps or biopsy
   S151 - Insertion of feeding enterostomy
   S154 - Large intestine - including excision of polyps
   S155 - Colonoscopy with laparotomy
   S156 - Exteriorization of intestine (Mickulicz)
   S157 - Colostomy
   S158 - Cecostomy
   S160 - Entero-enterostomy
b) Fistula excision (intestine):
   E714 - repair of entero-cutaneous fistula in conjunction with bowel resection
c) Resection (small bowel):
   S164 - duodenum
   S165 – other
d) Resection (small bowel + colon):
   S166 - Small and large intestine terminal ileum, cecum and ascending colon (right hemicolecotomy)
e) Resection (colon):
   S167 - Large intestine - any portion
   S169 - Total colectomy with ileo-rectal anastomosis
   S172 - Total colectomy with mucosal proctectomy with ileal pouch, ileoanal anastomosis and loop ileostomy
   S171 - Left hemicolectomy with anterior resection or proctosigmoidectomy (anastomosis below peritoneal reflection & mobilization of splenic flexure)
   S188 - Bowel resection without anastomosis (colostomy and mucous fistula)
d) Ileostomy:
   S168 - subtotal colectomy
   S170 - plus total colectomy plus abdomino-perineal resection
   S173 – abdominal
   S174 – perineal
   E718 - bowel resection following previous resection with anastomosis

2) PERI-ANAL/RECTAL SURGERIES:
   S213 - Anterior resection or proctosigmoidectomy (anastomosis below peritoneal reflection)
   S214, S215, S216 - Abdomino-perineal resection or pull through
   S217 - Hartmann procedure
   S218 - Colon reconstruction following Hartmann procedure
   S222 - Presacral or trans-sacral proctotomy and excision of lesion
   S223 - Anastomosis of rectum
   S246 - Excision of fissure(s)
   S247 - Haemorrhoidectomy, with or without sigmoidoscopy or repair of fissure(s) and/or sphincterotomy and/or anal dilation
   Z565 - Complete haemorrhoidectomy using cryotherapy and/or Barron ligation(s) including rectal dilation
   Z546 - Barron ligation(s) (not to exceed 6 in any one year)
   Z566 - Barron ligation(s) plus cryotherapy (not to exceed 6 in any one year)
   S249 - Local excision for malignancy
   Z757 - Excision of benign anal lesion(s)
   S251 - Fistula-in-ano
Supplemental Table 3.2: Classification of health services use. Note that description of IBD-related diagnoses in the text refer to all diagnostic codes classified IBD-specific, IBD signs/symptoms and extra-intestinal manifestations.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ICD-9</th>
<th>OHIP diagnostic code</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD-SPECIFIC:</td>
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<td></td>
</tr>
<tr>
<td>Crohn's</td>
<td>555.x</td>
<td>555</td>
<td>K50.x</td>
</tr>
<tr>
<td>UC</td>
<td>556.x</td>
<td>556</td>
<td>K51.x</td>
</tr>
<tr>
<td>IBD SIGNS/SYMPTOMS:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>783.0</td>
<td>787</td>
<td>R63.0</td>
</tr>
<tr>
<td>Abnormal Weight Gain</td>
<td>783.1</td>
<td></td>
<td>R63.5</td>
</tr>
<tr>
<td>Abnormal Weight Loss</td>
<td>783.2</td>
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<td>R63.4</td>
</tr>
<tr>
<td>Underweight</td>
<td>783.22</td>
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<td>R62.8</td>
</tr>
<tr>
<td>Failure to thrive, child</td>
<td>783.41</td>
<td></td>
<td>R62.8</td>
</tr>
<tr>
<td>Failure to thrive, adult</td>
<td>783.7</td>
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<td>R62.9</td>
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<td>Symptoms involving digestive system, including:</td>
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<td>787</td>
<td>R11.x</td>
</tr>
<tr>
<td>(787.0) Nausea and vomiting</td>
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<td></td>
<td>R12.x</td>
</tr>
<tr>
<td>(787.01) Nausea w/vomiting</td>
<td></td>
<td></td>
<td>R13.x</td>
</tr>
<tr>
<td>(787.02) Nausea, alone</td>
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<td></td>
<td>R14.x</td>
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<tr>
<td>(787.03) Vomiting, alone</td>
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<td>R15.x</td>
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<td>(787.1) Heartburn</td>
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<td>R19.x</td>
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<tr>
<td>(787.2) Dysphagia</td>
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<td></td>
</tr>
<tr>
<td>(787.3) Gas/bloating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(787.6) Encopresis, fecal incontinence</td>
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</tr>
<tr>
<td>(787.9) Other symptoms involving digestive system</td>
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<td></td>
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<tr>
<td>(787.91) Diarrhea, NOS</td>
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<tr>
<td>Abdominal pain</td>
<td>789.0</td>
<td>787</td>
<td>R10.x</td>
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<td>Dyspepsia</td>
<td>536.8</td>
<td>536</td>
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<td>Cachexia</td>
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<td>Esophagitis</td>
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<td>GERD</td>
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<td>K21.x</td>
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<td>531</td>
<td>K25.x</td>
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<td>Duodenal ulcer</td>
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<td>532</td>
<td>K26.x</td>
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<tr>
<td>Peptic ulcer</td>
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<td>K27.x</td>
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<td>534</td>
<td>534</td>
<td>K28.x</td>
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<tr>
<td>Gastritis/duodenitis</td>
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<td>535</td>
<td>K29.x</td>
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<td>Intestinal obstruction</td>
<td>560.8</td>
<td>560</td>
<td>K31.5</td>
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<tr>
<td>Intestinal obstruction</td>
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<td>K56.6</td>
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<tr>
<td>Rectal/anal hemorrhage</td>
<td>569.3</td>
<td>569</td>
<td>K62.5</td>
</tr>
<tr>
<td>Other disorder of</td>
<td>569.4</td>
<td>569</td>
<td>K62.6</td>
</tr>
</tbody>
</table>
rectum/anus, including:
(569.41) Ulcer
(569.42) Pain
(569.43) Sphincter tear (healed)
(569.44) Dysplasia
(569.45) Other specified, including proctitis, inflamm.

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<td>(569.82) Ulcer of intestine</td>
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<td>(569.83) Perforation</td>
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<td>(569.84) Angiodysplasia, no hemorrhage</td>
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**EXTRA-INTESTINAL MANIFESTATIONS:**

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<td>Venous embolism/thrombosis</td>
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Chapter 4
Changes in surgical and hospitalization rates in paediatric inflammatory bowel disease in Ontario, Canada (1994-2007)
4.1 Abstract

**BACKGROUND & AIMS:** Over the past decade, significant advances have been made in the care of children with inflammatory bowel disease. We aimed to describe changes in hospitalization, outpatient visit and surgical rates, as well as changes in specialist care provision and immunomodulator use in children with IBD since 1994.

**METHODS:** We used a validated algorithm to identify all children <18 years diagnosed 1994-2004 with IBD within Ontario's health administrative databases. Patients were grouped by era of diagnosis (1994-1997, 1998-2000, 2001-2004). Multivariable models tested the association between era of diagnosis and physician visits, hospitalizations, or surgery. Rates of immunomodulator use, rates of biologic use and the proportion of outpatient care provided by medical specialists were also described.

**RESULTS:** IBD-related outpatient health services were increasingly provided by paediatric gastroenterologists, with decreasing care provided by adult gastroenterologists and surgeons. Children diagnosed in 2001-2004 with Crohn’s were more likely to use an immunomodulator within three years of diagnosis (P = 0.0001). The number of hospitalizations and physician visits remained stable over the study period. Although children diagnosed between 2001-2004 were less likely to be hospitalized within three years than those diagnosed earlier, after adjusting for age at diagnosis, the odds of being hospitalized within three years was higher for Crohn’s (hazard ratio [HR] 3.22, 95% confidence intervals [CI] 2.15-4.83) and ulcerative colitis (UC) (HR 2.83 95% CI 1.55-5.19). Intra-abdominal surgical rates within three years of diagnosis decreased from 18.8% in children diagnosed in 1994-1997 to 13.6% in those diagnosed in 2001-2004 (P = 0.035). When stratified by age at diagnosis, this decrease was significant in multivariable analysis in children diagnosed ≥10 years old (odds ratio 0.67, 95% CI 0.48-0.93). No significant change was demonstrated in UC patients.

**CONCLUSIONS:** The care of children with IBD has changed over the past two decades. These changes included increased specialist care provided by paediatric gastroenterologists, and increased immunomodulator use. Changes were associated with reduced surgical rates in children with Crohn’s, but not ulcerative colitis.
4.2 Introduction

Inflammatory bowel disease (IBD) develops during childhood or adolescence in up to 25% of patients (62). In efforts to avoid the deleterious effects of chronic corticosteroid therapy in young patients, paediatric gastroenterologists pioneered the early introduction of immunomodulators in newly diagnosed children with Crohn’s disease (CD) (119). In this population a randomized placebo-controlled clinical trial demonstrated high efficacy of maintenance therapy with 6-mercaptopurine with 18 month remission rates in excess of those demonstrated in adult trials (1). More recently infliximab, a chimeric antibody to tumour necrosis factor alpha (anti-TNF) induced and maintained clinical remission in children with otherwise chronically active steroid-dependent CD (13). The superior remission rates in this paediatric trial are likely attributable to the overall shorter duration of disease at initiation of anti-TNF therapy in comparison to adult studies (120). These two paediatric clinical trials signal a change in paediatric IBD therapy over the past decade, which in turn holds promise for improving outcomes.

We previously developed and validated an algorithm for identification of children and adolescents with IBD using Ontario health administrative data (92). The Ontario Crohn’s and Colitis Cohort (OCCC) can be used to track incidence and prevalence, and to assess practices and changes in health services utilization. The main aim of this study was to describe trends over time (1994-2007) in drug utilization, hospitalization and surgical rates for children with IBD in Ontario. We hypothesized that changes in medical therapy (particularly since the publication of a trial demonstrating the efficacy of 6-MP to maintain remission in paediatric CD in 2000 (1)) have altered rates of immunomodulator usage surgery and hospitalization in children with IBD. We also describe trends in physician care provision as there were increases in the number of paediatric gastroenterologists which we hypothesized would have an impact on care provision.
4.3 Methods

Ethics approval for this study was received from the research ethics boards of the University of Toronto, The Hospital for Sick Children and Sunnybrook Health Sciences Centre.

4.3.1 Study Cohort
The OCCC is a cohort of paediatric-onset (six months to 18 years) IBD patients derived from health administrative data. Children with IBD are identified using a validated algorithm (92). To be included in the cohort, patients who underwent colonoscopy required at least four physician contacts or two hospitalizations on separate days over a maximum of three years with associated International Classification of Diseases, Ninth Revision (ICD-9) code for CD (555.x) or UC (556.x) or ICD, Tenth Revision (ICD-10) code for CD (K50.x) or UC (K51.x). Patients who did not undergo colonoscopy required at least seven physician visits or three hospitalizations over three years. This algorithm achieved a sensitivity of 89.6-91.1% and a specificity of 99.5-100% for identifying children with IBD within Ontario's health administrative databases (92).

4.3.2 Data Sources
Ontario’s administrative databases are maintained by the Institute for Clinical Evaluative Sciences (ICES) through a comprehensive data sharing agreement with the Ontario Ministry of Health and Long Term Care. ICES is an independent, not-for-profit organization that conducts health services research for the province of Ontario. For hospitalizations, we used discharge abstract data mandatorily collected from all hospitals and reported to the Canadian Institute for Health Information (CIHI), with diagnostic codes found to be 92-99% accurate (93). Outpatient physician visits and surgical procedures were obtained from physician billing information obtained from the Ontario Health Insurance Plan (OHIP) database. The ICES Physician Database was used to classify the type of provider. This database contains certification status and self-reported specialty of physicians practicing in Ontario. Prior to initiation of examinations for paediatric and adult gastroenterology by the Royal College of Physicians of
Canada, not all practicing gastroenterologists were examination-certified. We therefore used customized definitions combined with certification status to identify functional physician specialty: family physician, general paediatrician, general internist, surgeon (general or paediatric), adult gastroenterologist (internists with reported or certified specialty in gastroenterology, or internists who performed >25 colonoscopies per year and whose practices were made up primarily of adults), or paediatric gastroenterologist (paediatricians with reported or certified specialty in gastroenterology, paediatricians who performed colonoscopies on >5 children per year, or adult gastroenterologists whose practices were made of >70% children under 18 years per year). To calculate physician supply per 100,000 children in Ontario, we used the Canadian censuses from 1991, 1996, 2001 and 2006 to calculate annual intercensal population estimates of children <18 years (66). Demographic information including postal code was obtained from the Registered Persons Database, containing all residents eligible for health care in Ontario. We linked postal codes recorded at IBD diagnosis to 1996 and 2001 Canadian Census data using Postal Code Conversion Files Plus (94) to obtain the mean neighbourhood income quintile and community size (rural versus urban residence) of individual children with IBD at the enumeration area (1996) or dissemination area (2001) level. Prescription drug claims in Ontario are only tracked for residents >65 years old or those on social assistance. We used the Ontario Drug Benefit (ODB) claims database to obtain prescription information for children on social assistance. Drug identification number was used to identify prescriptions for azathioprine, 6-mercaptopurine (6-MP), methotrexate (MTX), infliximab and adalimumab. To assess the proportion of patients using an immunomodulator or biologic medication, we divided the number of patients with any prescription for the above medications by the total number of patients with IBD who had an ODB claim for any medication (and therefore qualified for ODB coverage).

4.3.3 Study Design
This study assessed all children (6 months to 18 years) diagnosed with IBD within Ontario from fiscal years (FY) 1994-2004. The date of diagnosis was defined as the date of first contact with a physician or first hospitalization with associated diagnostic code for IBD. We followed subjects for a minimum of three years from diagnosis using administrative data. To describe health services utilization (physician visits, hospitalizations, surgery within three years of diagnosis), yearly inception cohorts were used with each group representing patients diagnosed within a
fiscal year (FY). For univariable and multivariable analyses, three comparison groups were used
to determine the association between era of diagnosis and use of health services: 1) subjects
diagnosed in FY 1994-1997, 2) subjects diagnosed in FY 1998-2000, 3) subjects diagnosed in
FY 2001-2004. These eras were chosen \textit{a priori} to evenly divide the cohort and to assess
changes in care since the 2000 publication of a trial showing the efficacy of 6-MP in paediatric
CD (1). Analyses were conducted to determine whether era of diagnosis was associated with
physician visit and hospitalization rates, likelihood of hospitalization within three years of
diagnosis and likelihood of intra-abdominal surgery within three years of diagnosis. We tested
the association of era and health services utilization by comparing patients in the latter two era
groups to the earliest (reference) group. Admissions and surgeries within six months of
diagnosis may be less a function of the medical care provided to children with IBD, and more a
function of disease phenotype and severity at diagnosis. Therefore as a secondary analysis, we
tested the association between era group and hospitalizations and surgeries excluding the first six
months after diagnosis. Analyses were stratified by diagnosis (CD or UC). Classification of
diagnosis (CD, UC or unclassifiable) was accomplished with a validated algorithm that
distinguished CD from UC with an area under the receiver operating characteristic curve of
0.9618 (92).

4.3.4 Description and Classification of Health Services Utilization
The number of physician visits and hospitalizations are described as means (with standard
deviations [SD]) for each year following diagnosis. The likelihood of hospitalization, or surgical
resection are presented as proportions. Surgeries were classified as intra-abdominal/resective by
OHIP billing code (see Supplemental Table 3.1). A list of IBD-related health services utilization
ICD codes was developed (see Supplemental Table 3.2), and these codes were used to determine
IBD-related physician visits and hospitalizations. For associated diagnoses, OHIP utilizes a
shortened three-digit version of ICD-9 while the CIHI discharge abstract database uses a four-
digit ICD-9 code (prior to 2002) or seven-digit ICD-10 (after 2002). Health services contacts
and surgeries prior to the date of diagnosis were excluded.
4.3.5 Statistical Analysis

Descriptive statistics are presented as proportions or means (with standard deviations). Comparison between the three groups were conducted using Kruskal-Wallis analysis of variance for continuous variables or chi-square analysis (or Mantel-Haenszel test where appropriate) for categorical variables. The association between era group and hospitalization or surgery within three years of diagnosis was analyzed using logistic regression models. The association between era group and number of physician visits and hospitalizations within three years of diagnosis was analyzed using Poisson regression models. All hypothesis tests were two-sided and determined to be significant at \( P < 0.05 \). All multivariable analyses included era group (1994-1997, 1998-2000 or 2001-2004) as the major predictor. Confounding with other variables (age at diagnosis, sex, rural residence at diagnosis and mean neighbourhood income quintile) was assessed by the 10 percent change in the odds ratio estimate method (96), with variables included in the model if they met this criterion as confounders. These variables were chosen a priori due to their known impact on disease course/severity or health services utilization and surgical rates in our cohort (121) or other studies (8, 10). Interaction between covariates and year of diagnosis was evaluated for statistical significance using the Wald chi-square statistic. If the interaction term was significant \( P < 0.05 \), analysis was stratified by categories of that variable. Poisson regression models were assessed for overdispersion using the scaled Pearson chi-square statistic, and all models resulted in normal dispersion (1.0). Collinearity of covariates was assessed with threshold tolerance >0.4 and variance inflation <2.5 in all final models. All statistical analyses were performed using SAS® version 9.1.3 (SAS Institute Inc., Cary, U.S.A.).

4.4 Results

The Ontario Crohn's and Colitis Cohort contained 2838 children diagnosed with IBD in FY 1994-2004. Of these, 37 children were excluded because they did not have three years of follow-up data, and 208 were excluded because they were not classifiable as CD or UC patients. This resulted in 2593 patients (1642 CD, 951 UC) available for stratified analysis. Descriptive statistics of the cohorts are presented in Table 4.1. Characteristics of era groups were similar, except patients diagnosed more recently were younger at diagnosis \( P = 0.02 \) and more often
resided in urban communities (P <0.0001). These observations are consistent with the rising incidence of IBD in <10 year olds in Ontario (92) and the increasing urbanization of the population (122).

4.4.1 Care Provision to Children with IBD
The trend over time in number of outpatient visits to various medical specialties for IBD-related care is shown in Figure 4.1. Over time, there was a rise in the number of visits to paediatric gastroenterologists within 1 year (P <0.0001) and three years (P < 0.0001) of diagnosis, with corresponding decrease in the number of visits to adult gastroenterologists within one year (P <0.0001) and three years (P <0.0001) of diagnosis. The number of outpatient IBD-related visits to generalists within one year of diagnosis significantly decreased over time (P = 0.04), but the number of visits within three years was statistically stable (P = 0.07). Similarly, the number of outpatients visits to general and paediatric surgeons was stable within one year (P = 0.40) and three years (P = 0.09) of diagnosis. The proportion of outpatient IBD-related care by various specialties over time is shown in Figure 4.2. Similar to the overall number, the proportion of care provided by paediatric gastroenterologists increased, while the proportion of care from adult gastroenterologists decreased (within one and three years of diagnosis, all P values <0.0001). The proportion of care provided by surgeons within three years of diagnosis decreased (P = 0.03), as did the proportion of care provided by generalists (P = 0.0002).

Changing care patterns may be related to changes to overall physician human resources in the province. Based on our definitions of medical specialty, the number of paediatric gastroenterologists working in Ontario has increased from 0.38 per 100,000 population of children <18 years old in 1994 to 0.90 per 100,000 in 2006. The number of adult gastroenterologists rose from 8.1 to 10.5 per 100,000 children between 1994 and 2006. The number of general surgeons was 25.7 per 100,000 children in 1994 and 24.4 per 100,000 children in 2006. The number of generalists (paediatricians, internists and family doctors) also remained stable (482.0 per 100,000 children in 1994 and 481.1 per 100,000 children in 2006).
4.4.2 Immunomodulator and Biologic Use in Children on Social Assistance

Of the full IBD cohort, 20.4% of CD patients (n=335) and 14.9% of UC patients (n=142) had at least one ODB claim within three years of diagnosis. In these patients with CD, the likelihood of at least one prescription claim for an immunomodulator (azathioprine, 6-MP or MTX) within three years of diagnosis rose from 19.6% in those diagnosed 1994-1997 to 43.7% in those diagnosed 2001-2004 (P = 0.0001). In ODB-eligible patients with UC, the likelihood of an immunomodulator claim was 17.0% in those diagnosed 1994-1997 and 33.3% in those diagnosed 2001-2004 (P = 0.09). No eligible patient with CD diagnosed 1994-1997 was prescribed an anti-TNF therapy (infliximab or adalimumab) within three years of diagnosis, while fewer than five patients of the 1998-2000 group and nine (7.6%) of the 2001-2004 group received a biologic within three years of diagnosis (P = 0.004). Fewer than five patients with UC in the cohort received a biologic via an ODB claim, and the number of patients receiving a biologic did not increase over time (P = 0.22).

4.4.3 Outpatient Visit, Hospitalization and Surgical Rates

The number of outpatient visits and hospitalizations within three years of diagnosis (and the number excluding the first six months following diagnosis) have not changed over time (see Table 4.2). Despite an overall decrease in likelihood of hospitalization within three years of diagnosis, odds of hospitalization increased in those diagnosed in 2001-2004 when rates were adjusted by age at diagnosis (which decreased over time). This increase was not restricted to hospitalizations within six months of diagnosis.

As shown in Table 4.3, overall surgical rates decreased in CD patients diagnosed more recently compared with those diagnosed in 1994-1997. The likelihood of intra-abdominal surgery within three years of diagnosis was 13.6% in those diagnosed in 2001-2004 compared with 18.8% in those diagnosed in 1994-1997 (chi-square P = 0.035). This trend was also present when surgeries within six months of diagnosis were excluded, although not significant on univariate analysis (9.4% vs. 13.7%, chi-square P = 0.055). A significant interaction existed between age at diagnosis and year of diagnosis, and therefore the CD cohort was split between those <10 years old at diagnosis and those ≥10 years at diagnosis and the analysis repeated. This resulted in a non-significant interaction term when re-assessed in each group. Although the number of <10
year old patients with surgery within three years of diagnosis was very small, there was no significant difference in the odds of surgery over time. However, patients ≥10 years old at diagnosis were less likely to undergo intra-abdominal surgery if diagnosed in 2001-2004 compared with 1994-1997 (OR 0.67, 95% CI 0.48 to 0.93). When surgeries within six months of diagnosis were eliminated, there was no statistical interaction with age of diagnosis and those diagnosed in 2001-2004 were significantly less likely to undergo surgery than those diagnosed in 1994-1997 (OR 0.69, 95% CI 0.48 to 0.99). During the two time periods studied, there was no significant change in likelihood of surgery in UC patients and no significant interaction existed with age at diagnosis.

4.5 Discussion

This study demonstrates a number of changes to the care and health services utilization patterns of children with IBD in Ontario between 1994 and 2007. Utilization rates were relatively stable over the 14 year longitudinal course of this study. Patients diagnosed in later years had similar rates of outpatient physician visits and hospitalizations as those diagnosed in the 1994-1997 time period. In fact, the likelihood of hospitalization within three years of diagnosis decreased in CD patients, and therefore the per-patient hospitalization burden on the health system decreased over time. However, when age at diagnosis was included in a multivariable model, the adjusted odds of hospitalization within three years was higher in those diagnosed in 2001-2004 compared with those diagnosed in 1994-1997. It was not surprising that age confounded the relationship between year and hospitalization; we previously demonstrated that the incidence of CD is increasing only in children under 10 years old in Ontario (92), and older age at diagnosis was associated with increased risk of hospitalization (121). We demonstrated decreased surgical rates in CD patients, but not UC patients in our cohort. Age also confounded the relationship between risk of surgery and year of diagnosis in both CD and UC patients. When we stratified by age group, only patients >10 years old at diagnosis with CD diagnosed in 2001-2004 demonstrated a reduced surgical rate. Because surgery within three years was a rare outcome in patients diagnosed under 10 years old, no conclusions can be drawn from our data. However, the reduced surgical rates in CD >10 years old and not UC patients may have resulted from changes to medication use or specialist care provision.
Outpatient care was increasingly provided by paediatric gastroenterologists rather than adult gastroenterologists. This change likely reflects the increased availability of paediatric gastroenterologists. Moreover, outpatient care by adult gastroenterologists and generalists decreased significantly in our cohort, despite the stable numbers of these physicians in Ontario. We cannot deduce whether the lower proportion of outpatient care provided by surgeons was the precedent or antecedent factor in reduced surgical rates. However the trend of reduced care by surgeons was present for both UC and CD patients while the reduced likelihood of surgery was only demonstrated in CD patients. The changing patterns of outpatient care demonstrate an increasing recognition of childhood-onset IBD as a specific disease, different from the adult-onset variety, and potentially best handled by paediatricians with specialized training. This is consistent with a statement from the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition recommendation that paediatric gastroenterologists care for all children with IBD with linear growth potential (123). Nevertheless, the optimal age of transition from paediatric to adult care IBD providers has not been well delineated, and further study is required to determine whether the increased care by paediatric gastroenterologists is truly associated with improved health care quality.

Our assessment of changing patterns of drug use were limited to patients dependent of social assistance. ODB claims data in this population revealed increased immunomodulator use during the time periods under study. This was particularly evident in children with CD whose use of immunomodulators doubled and who had a significantly increased use of anti-TNF medications. This finding is consistent with a survey conducted of North American paediatric gastroenterologists which demonstrated an increased willingness to prescribe immunomodulators to young children with IBD (119). Use of anti-TNF medications was uncommon even in those diagnosed in the most recent years, most likely because use in children was off-label and not approved by Health Canada or the Food and Drug Administration until 2006 (124). Because of low usage, changes to hospitalization and surgical rates cannot be attributed to anti-TNF therapy. Our observations are based on the relatively small number of patients who are on social assistance and may not be broadly applicable. Patients on the ODB plan tend to be of lower socioeconomic status, and we have previously demonstrated disparities in health care use and
surgical outcomes based on income in children with IBD (121). Information on prescription rates of immunomodulators is sparse for children with IBD. A small Dutch study of 43 children with CD from general and tertiary care hospitals demonstrated one year rates of immunomodulator use of 37% (125). Another study, which excluded mildly active CD patients, demonstrated two-year prescription rates of 86% in children with IBD treated at tertiary care centers in North America (126). The three-year rate of 43.7% in our CD patients diagnosed in 2001-2004 is substantially lower than the two-year rate of 76% in adults in the conventional therapy arm of a 'top-down or step-up' open label trial (127). This difference may be due to the population-based nature of our study, with patients treated in community practices, general hospitals and academic paediatric centers. Alternatively, it may exemplify incongruity between true medical practice and research scenarios.

Trends in health services use and surgical rates reported in the literature are controversial. A French retrospective cohort study of adult IBD patients found a large increase in immunomodulator use over 25 years, and a trend toward usage earlier in disease course, but no change in intestinal excision rates (14). This study was framed as assessing the effectiveness (rather than efficacy) of immunosuppressive medications for reducing intestinal resections, however did not account for other changes to care provision over the follow-up period. A larger study from California (128) used health administrative data to assess trends and found a significant decline in surgical rates in adult UC patients, but not adult CD patients. This coincided with significant increased use of immunomodulators and anti-TNF therapies. They also found a decreased hospitalization rate and a shift in outpatient visits away from gastroenterologists and toward primary care providers. There was significant variation in health services and medication utilization across centers. We were unable to control for center of care or clustering in our models due to the rarity of surgical outcomes in children with IBD.

In Ontario, reorganization of the health system and funding restrictions has resulted in lower physician visit rates for preventative and primary care (129) and decreased hospitalization rates for a number of paediatric conditions (130-132). In contrast, physician visit rates were stable in our population and although crude hospitalization rates decreased, rates adjusted for age of diagnosis increased in recent years. This may be due to the changing profile of care providers.
(paediatric gastroenterologists may be more likely to admit patients), changing medication use (children started on immunomodulators may visit physicians or be hospitalized more frequently), or changing disease severity in recent years. Alternatively, another unmeasurable systemic, procedural or patient-based factor may have changed resulting in health services utilization trends in our patients which contrasted with the overall paediatric population in Ontario.

Despite our study's strengths, including its population-based nature and large numbers of paediatric cases, the use of health administrative data has limitations. Firstly, we had no access to clinical information on patients in our cohort, including genotype and phenotype. If stricturing or penetrating CD has decreased in prevalence over time, this may partly explain the reduced surgical rates. Additionally, we had limited access to pharmacy data. Although we were able to detect prescriptions in patients on social assistance, we are not able to deduce the length of treatment or adherence. The ODB does not contain qualification dates, so we are unable to deduce whether a patient qualified for benefits and then left the program. As such, we used a single prescription for an immunomodulator or anti-TNF medication as a proxy for ongoing treatment. This study was not powered to detect differences in patterns on a yearly basis or to control for time trends. We therefore split the cohort into three larger groups. When physician visit, hospitalization rates and surgical rates are plotted on a yearly basis, no sudden change occurred in utilization or surgical rates based on year of diagnosis (data not shown). We feel that this indicates gradual changes to outcomes and that no single event (such as the 2000 publication of a trial showing the efficacy of 6-MP in paediatric CD (1)) drove trends. Although some of the decrease in surgical rates were in the era of immunomodulator use for paediatric IBD, it is likely that overall outpatient care has improved with more specialized physician contact. This underlines the importance of assessing systemic changes to patient care when evaluating the impact of interventions in a longitudinal study.

In summary, we have demonstrated significant changes to the care provided to children with IBD associated with altered health services utilization patterns and lower surgical rates in CD patients. In our population of patients with childhood-onset IBD, more care is being provided by paediatric gastroenterologists but health services utilization has remained relatively stable. Patients with CD diagnosed after 2001 are at significantly lower risk of surgery than those
diagnosed between 1994-1997, particularly if they are diagnosed above the age of 10 years. This may indicate that changes to medical care and prescribing patterns have altered the natural history of paediatric CD over the past two decades.

4.6 Acknowledgements
The authors are grateful to Andrew Wilton for providing programming and data analyst support. This research was funded by a Clinical Research Award from the American College of Gastroenterology and was made possible with the support of the Institute for Clinical Evaluative Sciences which receives funding from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The results and conclusions are those of the authors; no official endorsement by the Ontario MOHLTC should be inferred. Eric Benchimol is a Canadian Institutes of Health Research (CIHR) training fellow in the Canadian Child Health Clinician Scientist Program, in partnership with SickKids Foundation and the Child & Family Research Institute of British Columbia, and was also supported by a fellowship from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition-Children's Digestive Health and Nutrition Foundation. Astrid Guttmann was supported by a CIHR New Investigator Award.
Table 4.1: Descriptive statistics of overall cohort and of groups by era of diagnosis.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td>443 (45.9%)</td>
<td>352 (45.7%)</td>
<td>465 (43.7%)</td>
</tr>
<tr>
<td><strong>Age at Diagnosis (years ± SD)</strong></td>
<td>13.9 ± 3.5</td>
<td>14.1 ± 3.3</td>
<td>13.6 ± 3.6</td>
</tr>
<tr>
<td><strong>Length of Follow-up (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>11.8 ± 1.7</td>
<td>8.6 ± 1.2</td>
<td>5.2 ± 1.2</td>
</tr>
<tr>
<td>MIN</td>
<td>3.1</td>
<td>3.6</td>
<td>3.1</td>
</tr>
<tr>
<td>MAX</td>
<td>14.6</td>
<td>10.7</td>
<td>7.5</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s</td>
<td>564 (58.4%)</td>
<td>449 (58.2%)</td>
<td>629 (59.1%)</td>
</tr>
<tr>
<td>UC</td>
<td>341 (35.3%)</td>
<td>270 (35.0%)</td>
<td>340 (32.0%)</td>
</tr>
<tr>
<td>IBD-U</td>
<td>61 (6.3%)</td>
<td>52 (6.7%)</td>
<td>95 (8.9%)</td>
</tr>
<tr>
<td><strong>Rural Resident at Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>144 (14.9%)</td>
<td>118 (15.3%)</td>
<td>100 (9.4%)</td>
</tr>
<tr>
<td><strong>Income Quintile at Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First (Lowest)</td>
<td>133 (13.9%)</td>
<td>119 (15.5%)</td>
<td>165 (15.5%)</td>
</tr>
<tr>
<td>Second</td>
<td>174 (18.1%)</td>
<td>138 (18.0%)</td>
<td>196 (18.4%)</td>
</tr>
<tr>
<td>Third</td>
<td>196 (20.4%)</td>
<td>152 (19.8%)</td>
<td>248 (23.3%)</td>
</tr>
<tr>
<td>Fourth</td>
<td>208 (21.7%)</td>
<td>180 (23.4%)</td>
<td>226 (21.3%)</td>
</tr>
<tr>
<td>Fifth (Highest)</td>
<td>249 (25.9%)</td>
<td>179 (23.3%)</td>
<td>228 (21.5%)</td>
</tr>
</tbody>
</table>
Figure 4.1. Number of IBD-related outpatient visits within three years of diagnosis by physician specialty. GI = gastroenterologist
Figure 4.2. Proportion of IBD-related outpatient care within three years of diagnosis by physician specialty. GI = gastroenterologist
Table 4.2. IBD-related health services utilization and adjusted odds ratios by year of diagnosis

<table>
<thead>
<tr>
<th></th>
<th>CROHN’S (n=1641)</th>
<th>UC (n=951)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number ± SD or Number (Proportion)</td>
<td>Adjusted Odds Ratio* (95% CI)</td>
</tr>
<tr>
<td># physician visits within 3y of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-1997</td>
<td>20.7 ± 15.6</td>
<td>REF</td>
</tr>
<tr>
<td>1998-2000</td>
<td>20.7 ± 13.8</td>
<td>1.02 (0.97-1.07)\textsuperscript{d}</td>
</tr>
<tr>
<td>2001-2004</td>
<td>19.5 ± 13.0</td>
<td>0.96 (0.92-1.01)\textsuperscript{d}</td>
</tr>
<tr>
<td>Hospitalization within 3y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-1997</td>
<td>319 (56.6%)</td>
<td>REF</td>
</tr>
<tr>
<td>1998-2000</td>
<td>257 (57.2%)</td>
<td>1.84 (1.26-2.7)\textsuperscript{a}</td>
</tr>
<tr>
<td>2001-2004</td>
<td>317 (50.4%)</td>
<td>3.22 (2.15-4.83)\textsuperscript{a}</td>
</tr>
<tr>
<td># hospitalizations within 3y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-1997</td>
<td>1.43 ± 1.91</td>
<td>REF</td>
</tr>
<tr>
<td>1998-2000</td>
<td>1.27 ± 1.62</td>
<td>1.01 (0.93-1.10)\textsuperscript{a}</td>
</tr>
<tr>
<td>2001-2004</td>
<td>1.00 ± 1.35</td>
<td>0.97 (0.90-1.05)\textsuperscript{a}</td>
</tr>
<tr>
<td>Hospitalization within 3y (excluding hospitalizations with 6 mo of diagnosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-1997</td>
<td>227 (40.3%)</td>
<td>REF</td>
</tr>
<tr>
<td>1998-2000</td>
<td>166 (37.0%)</td>
<td>1.22 (0.89-1.69)\textsuperscript{a}</td>
</tr>
<tr>
<td>2001-2004</td>
<td>185 (29.4%)</td>
<td>2.20 (1.54-3.14)\textsuperscript{a}</td>
</tr>
<tr>
<td># hospitalizations within 3y (excluding hospitalizations with 6 mo of diagnosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994-1997</td>
<td>0.80 ± 1.38</td>
<td>REF</td>
</tr>
<tr>
<td>1998-2000</td>
<td>0.70 ± 1.26</td>
<td>0.98 (0.88-1.10)\textsuperscript{a}</td>
</tr>
<tr>
<td>2001-2004</td>
<td>0.50 ± 0.99</td>
<td>1.06 (0.95-1.19)\textsuperscript{a}</td>
</tr>
</tbody>
</table>

* Where indicated, model also adjusted for \textsuperscript{(a)} age of diagnosis, \textsuperscript{(b)} sex \textsuperscript{(c)} rural residence at birth, \textsuperscript{(d)} income quintile based on whether these variables acted as confounders (see Methods for model-building strategy). Bolded odds ratios represent \(P\) values <0.05.
Table 4.3. Likelihood of surgery within three years of diagnosis by year of diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>Stratum (by age of diagnosis)</th>
<th>(1) Diagnosed 1994-1997</th>
<th>(2) Diagnosed 1998-2000</th>
<th>(3) Diagnosed 2001-2004</th>
<th>Adjusted Regression Model Odds Ratios (95% CI) (2) vs. (1)</th>
<th>Adjusted Regression Model Odds Ratios (95% CI) (3) vs. (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CROHN'S</strong></td>
<td>Full Cohort* (n=1642)</td>
<td>106 (18.8%)</td>
<td>69 (15.4%)</td>
<td>84 (13.6%)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>&lt;10y old (n=173)</td>
<td>&lt;10 patients</td>
<td>&lt;10 patients</td>
<td>&lt;10 patients</td>
<td></td>
<td>2.61 (0.23-30.1)ac</td>
<td>4.74 (0.56-40.0)ac</td>
</tr>
<tr>
<td>≥10y old (n=1469)</td>
<td>105 (20.4%)</td>
<td>67 (16.4%)</td>
<td>77 (14.1%)</td>
<td></td>
<td>0.77 (0.55-1.09)ac</td>
<td>0.67 (0.48-0.93)ac</td>
</tr>
<tr>
<td><strong>UC</strong></td>
<td>Full Cohort (n=951)</td>
<td>37 (10.9%)</td>
<td>40 (14.8%)</td>
<td>44 (12.9%)</td>
<td>1.40 (0.87-2.27)a</td>
<td>1.22 (0.76-1.94)a</td>
</tr>
<tr>
<td><strong>CROHN'S</strong></td>
<td>Full Cohort (n=1642)</td>
<td>77 (13.7%)</td>
<td>47 (10.5%)</td>
<td>59 (9.4%)</td>
<td>0.74 (0.50-1.10)a</td>
<td><strong>0.69 (0.48-0.99)a</strong></td>
</tr>
<tr>
<td><strong>UC</strong></td>
<td>Full Cohort (n=951)</td>
<td>30 (8.8%)</td>
<td>34 (12.6%)</td>
<td>36 (10.6%)</td>
<td><strong>1.46 (0.87-2.46)abc</strong></td>
<td>1.22 (0.73-2.03)abc</td>
</tr>
</tbody>
</table>

*Due to a significant interaction between era group and age at diagnosis covariates, these odds ratios are unreliable when unstratified by age at diagnosis. Where indicated, model also adjusted for 
(a) age of diagnosis, 
(b) sex 
(c) rural residence at birth, 
(d) income quintile based on whether these variables acted as confounders (see Methods for model-building strategy). Bolded odds ratios represent *P* values <0.05.
CHAPTER 5
DISCUSSION

5.1 Summary of Research

The preceding studies describe the development and validation of an algorithm to identify Ontario residents with onset of inflammatory bowel disease (IBD) prior to the age of 18 years, and the application of the algorithm to Ontario's health administrative data to develop the Ontario Crohn's and Colitis Cohort (OCCC). The development phase used a clinical database housed at the Hospital for Sick Children (SickKids), containing children <15 years with IBD diagnosed from 1991-1995. The algorithm was validated using the charts of patients from 12 diverse medical practices across the province in order to be certain of the algorithm's accuracy using different practice patterns and in different geographic regions, in recent years and in older children. Additionally, an algorithm to differentiate patients with Crohn's disease (CD) from ulcerative colitis (UC) was validated using information from patients' medical records. The OCCC was used to describe differences in health services utilization and surgical outcomes. Rates of physician visits, emergency department (ED) visits and hospitalizations were higher in children with IBD of lower compared with higher socioeconomic status. Most worrying was the finding that low income children with CD were more likely to undergo intra-abdominal surgery than those from higher income families. This association was not present in those with UC, implying differences in either disease course or medical care in children with CD of lower income. The final study in the series of three examined changes in treatment patterns of children with IBD in Ontario over the past two decades. Increased immunomodulator use, increased care by paediatric gastroenterologists, decreased care by surgeons and adult gastroenterologists was noted. These changes were accompanied by lower health services utilization and lower surgical rates in recent years, particularly in patients with CD.

Upon its introduction, I had the privilege of presenting details of the OCCC's development and these results at numerous local, national and international rounds, meetings and conferences. Perhaps most surprising was the national-level media attention received by the studies. One of
the challenges of effective epidemiology and health services research is the translation of knowledge to improve the care of our patients. Traditionally, patients with IBD have been left out of the policy and planning discussions in the ministries of Canadian provincial and national governments, despite an estimated prevalence of 0.5% in Canada (the highest in the world) (3). For example, the Ontario Ministry of Health and Long-Term Care has developed a framework on preventing and managing chronic diseases, with discussion of asthma, diabetes, arthritis, cancer and kidney disease but no mention of IBD (133). One of my goals as an IBD researcher is to improve public awareness of IBD and its implications in children, thereby driving policy-makers to improve the care received by patients with IBD and the funding to investigate its etiologies. To that end, the Crohn's and Colitis Foundation of Canada used data derived from the OCCC and this thesis as a central component of their "Get Gutsy" Crohn's and Colitis Awareness Month 2009 (134), which focused on improving public awareness of paediatric IBD and the steps needed to address the issue from a research point of view.

In the following pages, I will review the literature on the use of health administrative data for chronic disease surveillance as well as the changing epidemiology of paediatric IBD worldwide. I will discuss the implications of developing the OCCC, highlighting challenges, weaknesses and possible solutions. I will then discuss my planned future projects which will build on the OCCC, expanding it to adult patients, answering new questions and integrating clinical with the health administrative. In doing so, I will highlight the career I hope to build using and expanding upon the methods described in this thesis.

5.2 Administrative Data as a Tool for Chronic Disease Surveillance

Health services and epidemiologic research is best conducted with population-level data. This helps to ensure the minimization of referral bias, the appropriate estimation of incidence rates and the overall generalizability of the study conclusions to the population in question. Since prospective clinical registries and retrospective chart review comprising all residents of a province are impractical, health administrative data are an alternative for population-based chronic disease surveillance. Health administrative data are defined as information passively
collected, often by government and health care providers, for the administrative purpose of managing the health care of patients (135). These data often comprise all residents within a given jurisdiction, are readily available and relatively inexpensive to access. Canadian privacy regulations allow linkage of patients using encrypted identifiers across visits and databases, allowing for longitudinal data accrual and long follow-up periods. However, administrative data are not collected with a priori determined research questions and are therefore subject to a number of limitations and biases. Firstly, research conducted with these data is limited in scope and hypotheses must be limited to those answerable using the data collected. For chronic disease surveillance, administrative data is sometimes supplemented with clinical information in order to overcome this weakness (136). Another major limitation of health administrative data is the quality and accuracy of the data itself, especially the diagnosis codes. A large gradient in data quality exists, with some being of higher quality (e.g. hospitalization discharge recording) than others (e.g. physician billing information). As such, validation of the codes used to identify patients with chronic diseases is essential in order to avoid misclassification bias (137). In fact, validation of health administrative data has been identified as a priority in the health services research by an international consortium funded by the Canadian Institutes for Health Research (CIHR) (29). Despite this realization, a recent systematic review conducted for the comprehensive component of this thesis found nearly 40% of studies identifying patients within health administrative data did so without any validation at all or validated against another administrative data source (138). The search strategy used would have preferentially identified studies with some form of validation, likely excluding many studies which clearly had no validation, implying that a far greater number are conducted using health administrative data without any validation of their identification methods. As the number of studies using these databases increases, a focus must be placed on the accuracy and quality of their identification methods. However, when researchers employ rigorously validated methods, health administrative data represent a unique opportunity to monitor the incidence, outcomes and surveillance of patients with chronic diseases. As well, health administrative data represent an excellent resource for assessing health services utilization patterns and quality of care received by patients within a given jurisdiction.
The Institute for Clinical Evaluative Sciences (ICES) has been extremely successful in developing chronic disease surveillance programs using health administrative data. Ontario's health administrative databases are housed within ICES, which was established in 1992 as an independent, not-for-profit organization by the Ontario Ministry of Health and Long-Term Care with a mandate to "conduct research that contributes to the effectiveness, quality, equity and efficiency of health care and health services in Ontario" (139). Since its inception, chronic disease surveillance programs have used ICES data following validation of identification methods. The diseases currently being monitored by ICES researchers include asthma (68), diabetes (25, 140), myocardial infarction (141), chronic obstructive pulmonary disease (28), and hypertension (26). ICES has become a leader in the use of administrative data, and the improvement in the quality of care provided to patients with chronic conditions. Until this project, however, no researcher has embarked on surveillance of IBD in Ontario.

Health administrative data have been used to monitor IBD in other Canadian provinces, as well as in the United States. Bernstein et al. (30) validated an algorithm to identify adults with IBD within Manitoba's databases. They found that to be accurately classified as having physician-diagnosed IBD, patients required five physician contacts or one hospitalization (with International Classification of Disease (ICD) diagnostic codes for IBD) over the course of their lives. Alternatively, if a patient only resided within the province for three or fewer years, they required three physician contacts over that period. These algorithms achieved a 90% sensitivity and 90% specificity to accurately classify a patient as afflicted with IBD. The algorithms were applied to the administrative databases of five Canadian provinces (Ontario was not included) to describe the incidence and prevalence of IBD in Canada (3). The three-year algorithm was also applied (without further validation) to an American administrative database of health maintenance organizations (HMOs) to describe the prevalence and health services utilization of adult and paediatric IBD patients in the United States (8, 33). Another study using the administrative databases of the Kaiser Permanente health maintenance organization in northern California found that patients required two physician contacts or two hospitalizations (with associated ICD codes for IBD), which achieved a sensitivity of 86% and positive predictive value (PPV) of 95% for accurately identifying IBD (142).
A number of factors prevent the application of these algorithms to Ontario health administrative data to describe paediatric IBD in the province. Firstly, previous studies have described the differing diagnostic accuracies of administrative data algorithms when applied to different age groups (31). Since these algorithms were validated primarily with the charts of adult IBD patients, we could not be certain of their accuracy when identifying children with IBD. Secondly, the long time allowance to qualify for the diagnosis (the Manitoba algorithm allowed 11 years for patients to qualify, while the Kaiser algorithm allowed an unlimited time to qualify) makes them less useful to identify children. Both the Manitoba (30) and Kaiser (142) algorithms allowed unlimited time for the patients to qualify, and the Manitoba algorithm was validated with charts from an 11 year time span. Since paediatric care in chronic diseases differs from adult care, and children with IBD are typically diagnosed in their adolescence, patterns of care are expected to change once they reach adulthood. Allowing 11 or more years for an algorithm to qualify a patient as having IBD would clearly not mimic paediatric clinical practice (in which the diagnosis is typically made within one year), and the child would have outgrown the period of paediatric care. This makes algorithms allowing unlimited time for patients to qualify less useful for surveillance of changes in care, incidence and prevalence in children. Similarly, we were uncertain as to how the algorithms would perform in Ontario when validated in other jurisdictions. In fact, we found that neither the Manitoba algorithm nor the Kaiser algorithm performed adequately in our population. More specifically, we found requiring two codes for an IBD-specific hospitalization improved the PPV by 6% compared to requiring only a single code for hospitalization (as was required by the Manitoba algorithm) to accurately identify an IBD patient. The accuracy of the Canadian Institute for Health Information (CIHI) Discharge Abstract Database has been reported to have a 92-99% accuracy in a validation study of adult patients (93). The lower accuracy found in our study again implies that validation studies of administrative data codes do not necessarily apply across all age groups.

Finally, the validation cohort populations of the Manitoba and Kaiser algorithms comprised primarily IBD patients. The only non-IBD patients' charts against which the algorithms were validated were those that qualified as false positives for IBD. As such, the prevalence of IBD in their populations was falsely elevated, thereby falsely elevating any estimates of PPV and negative predictive value (NPV). Predictive values have been identified as the most important
diagnostic accuracy markers in epidemiological studies (32, 143-145). They define the likelihood of false positive test results (resulting in over-estimation of incidence and prevalence by misclassification of unaffected subjects as diseased) and false negative test results (resulting in an underestimation of burden of illness due to misclassification of diseased patients as unaffected). Without accurate estimations of the PPV and NPV, it is impossible to estimate the true quality of a diagnostic algorithm. Despite this, my aforementioned systematic review of the literature found that the majority of studies validating algorithms to identify patients within administrative databases quoted PPV or NPV values without using a validation cohort with a disease prevalence similar to the population to which the algorithm was applied (138). In a disease as uncommon as paediatric IBD (prevalence 50 per 100,000 or 0.05%), the importance of accurate estimations of PPV and NPV is compounded. This concept is demonstrated in Figure 5.1. In Figure 5.1a, a diagnostic test (or in the case of this project, an algorithm) that performs poorly due to a low PPV is demonstrated. The true prevalence of the disease in a given population is 500 per 100,000. Since the PPV is low (55.1%), the estimated prevalence (890 per 100,000) is much higher than the true prevalence. Figure 5.1b demonstrates the same algorithm when applied to a population where the prevalence of the disease is higher (with the same proportion of false positives to true negatives, i.e. 1:2500). The true positive (diseased) population is of similar magnitude, but the true negative (normal) population is smaller. Investigators who abstract charts as part of a validation sample may be falsely reassured by the high markers of diagnostic accuracy (in this example, PPV 99.8%, NPV 99.6%), and the estimated prevalence of disease is similar to the true prevalence. When the test or algorithm is then applied to a larger population of non-diseased patients, the prevalence of the disease decreases and the estimated prevalence (590 per 100,000) is higher than the true prevalence (500 per 100,000). When the test or algorithm is applied to an even larger population (Figure 5.1d), it vastly overestimates the prevalence of the disease in the population. This example demonstrates the importance of accurately determining predictive values using a validation cohort in which the disease is of the same prevalence as in the general population. Since neither the Manitoba nor the Kaiser IBD algorithms had a population of non-IBD patients of the magnitude required to accurately estimate PPV and NPV, their performance when applied to a large provincial population was uncertain. The algorithm described in this thesis was initially developed using the SickKids IBD Database as a full representation of the IBD patients <15 years diagnosed in
Toronto. As such, the full population <15 years of the city of Toronto (not contained within the SickKids IBD Database and therefore assumed not to have IBD) could be applied as the true negative population. This allowed for an accurate estimation of the algorithms' PPV and NPV to identify IBD. Unfortunately, it is likely that the number of children <15 years diagnosed with IBD and missing from the SickKids IBD Database was underestimated, because those patients were being treated by community adult gastroenterologists and never seen at SickKids. We concluded this was likely the source of the lower PPV because no matter how restrictive the algorithm, a PPV above 59.8% in the <15 year old group could not be achieved. When the same algorithm was applied to <12 year olds, it functioned much better implying that fewer <12 year olds were being treated outside of SickKids. When the various algorithms were tested in the chart abstraction cohort, there were no significant differences in PPV in different age groups, implying the reduced PPV in the <15 year group was likely due to artifactual error rather than true test performance.

In summary, health administrative databases represent valuable tools to monitor rates and burden of chronic diseases. Due to inaccuracies and biases within the data, rigorous validation is required to ensure accurate identification of patients and minimization of misclassification. An understanding of the accuracy of the algorithms used to identify patients with a disease within the data is required prior to application for research purposes. Factors involved in the functioning of these algorithms include their accuracies when applied to various age groups, jurisdictions and populations. Of vital importance are the predictive values, particularly in the case of rare diseases such as childhood-onset IBD. This thesis describes the development and rigorous validation of an algorithm specifically designed to identify patients with childhood-onset IBD within Ontario's health administrative data. This algorithm will continue to be used to monitor paediatric IBD in Ontario, and could be applied to other jurisdictions following re-validation.
Figure 5.1. Example of the importance of PPV in determining the prevalence of a rare disease.
5.3 The Rising Incidence and Prevalence of Paediatric IBD in Ontario

Crude prevalence of childhood-onset IBD has increased by nearly 50% over 12 years (1994-2005) in Ontario. Additionally, the incidence of IBD is increasing in patients <10 years old. When stratified by diagnosis, this increase seems primarily due to an increased risk of CD in patients 5-9 years old. This general trend (of increased CD but not UC rates) seems consistent with world rates of paediatric IBD. A systematic review to be published in *Inflammatory Bowel Diseases* found 139 studies which quoted incidence and/or prevalence of paediatric IBD from a variety of jurisdictions worldwide (preliminary results, manuscript in preparation). Of these, 28 studies statistically tested trends in incidence over time in paediatric patients. Fifteen studies (60.0% of studies assessing CD trends) found significant increases in rates of CD over time, while four (20.0% of studies assessing UC trends) found increases in UC. Three studies found a significantly decreased incidence of UC, while one study found a decrease in both CD and UC (but only in the 10-19 year age group) (146). Only two other studies reported incidence trends by age group in paediatric IBD. Armitage et al. (18) reported significantly increased incidence rates between 1981 and 1995 in both CD and UC, with females 7-11 years and both sexes 12-16 years at higher risk in later years. A recent reported from Texas demonstrated significantly increased incidence of IBD in children aged 10-14 and 15-17 with stable incidence in children under 10 (147). Our study was sufficiently powered to examine incidence trends in all age groups including the youngest children, despite the rarity of IBD in that population.

IBD is a disease whose full etiology is unknown at present. It results from an interaction between genetic predisposition and environmental factors. A number of explanations exist for the increased incidence in Ontario's youngest residents. Based on the rising incidence of CD internationally, environmental changes seem a likely contributory factor. IBD is a disease with increased prevalence in Western, industrialized countries which may contribute to increased international rates (with increased industrialization of countries in eastern Europe and Asia) but does not explain increased rates in Ontario over only 12 years. Environmental etiologies postulated to contribute to the rising prevalence of IBD include a shift in T cell immunity due to improved hygiene and lower overall exposure to infectious agents (148), as well as altered
exposures to specific enteric infections such as mycobacterium, salmonella and campylobacter (149, 150). A major environmental shift would have to occur for such a sharp rise in rates, and none has been noted in Ontario over the past two decades. Since administrative data can only describe physician-identified IBD (and not patients who have not sought medical attention), a change to the care provided to Ontario residents may be responsible. Increased awareness of paediatric IBD by the population (leading to visits to a health care provider earlier in the course of disease) or by health care providers (leading to earlier investigation) may have resulted in earlier diagnosis and thus a perceived increased incidence of paediatric IBD. This thesis describes an increased number of paediatric gastroenterologists practicing in the province over two decades, which may have improved access to care and time to diagnosis in children with IBD. However, there was not a decreasing incidence in children diagnosed at 10-18 years old to accompany the increased incidence in 0-9 year olds. This would imply a truly increased incidence in paediatric IBD and not earlier identification in the paediatric cohort. However, earlier identification may still be responsible, with an overall shift in diagnoses from the early adult groups (>18 years old) to the adolescents and pre-adolescent groups. We were unable to assess whether this shift occurred because we did not have data from adult age groups. Future studies will assess adult incidence and prevalence rates in Ontario. If rates are not decreasing in adults, this would imply a true increased rate of disease in Ontario (and not earlier identification).

A third explanation for the rising rates of IBD are changing genetic background and demographics in Ontario. Immigrants from low-incidence countries were reported to have increased risk of developing IBD upon arrival to western nations (151). Ontario receives approximately 125,000 immigrants yearly, the largest number of any Canadian province (152). Ontario immigration patterns have changed significantly over the past two decades. Since 1991, people from South Asia (India, Pakistan, Sri Lanka, Bangladesh, etc.) represent the largest immigration group, with nearly 25% of immigrants arriving from these countries (153). Additionally, immigration from regions with known lower rates of IBD risk (such as East Asia and Africa) have decreased (153). This may be partially driving the increased incidence and high prevalence of IBD seen in Canada. Incidence and prevalence rates of IBD development in Canada's immigrant communities have not been well discerned. One previous study reported
that children of South Asian descent (ancestry from India, Pakistan, Sri Lanka, Bangladesh, etc.) had triple the rate of developing IBD as those of non-South Asian ancestry (84). Increased rates have also been reported in small studies of adults from South Asia who emigrate to the U.K. (154, 155). A recent systematic review of the literature reported a wide range of incidence in patients from Asia and South Asia, as well as Hispanics, depending on their region of residence. This review confirmed low rates in Asian and high rates in South Asian populations who live in Westernized countries, but an overall increase in the rates of incidence in all ethnic populations studied (156). Future studies should more clearly characterize the risk of IBD to immigrants and their Ontario-born children to fully assess whether changing demographics may have caused the increased prevalence in children.

In summary, we have described the rising incidence and prevalence of paediatric IBD in Ontario. We have speculated on the reasons for this increase, but cannot discern the etiology using health administrative data alone. At present, a large Canadian prospective cohort study is recruiting unaffected siblings of patients with CD to determine environmental factors which may be contributing to disease development (157). My hope would be that future studies would link these clinical cohorts to health administrative data, allowing for researchers to follow patients throughout a jurisdiction for long periods of time at reasonable costs and minimizing loss to follow-up. With such linkage between clinical and administrative data, we may begin to find the reasons for the increased incidence over the past two decades.

5.4 Children of Low Income Neighbourhoods Have Higher Health Services Utilization and Surgical Rates

5.4.1 The Use of Neighbourhood Income As a Proxy for Individual/Household Income

The second study in this thesis demonstrated that lower income patients are more likely to visit physicians, become hospitalized, and visit the emergency department (ED) than higher income patients. Additionally, low income CD patients had higher surgical rates (both intra-abdominal and all IBD-related surgeries) than high income patients, specifically if diagnosed after 2000. It should be noted that mean neighbourhood income quintile was used as a proxy for individual-
level income. There are a number of important methodological considerations with using neighbourhood-level markers for individual income. Census-level income measures have been shown to correlate with individual income in the United States (116) and Canada (158). Neighbourhood income was significantly correlated with Carstairs index of deprivation in one study from Scotland (159). The association between poverty and health outcomes is well-established. In order to use neighbourhood-level income as a proxy for individual income in assessing health outcomes, one must ensure that the association between neighbourhood-level data and health outcomes is demonstrated without attenuation of the strength of the association between individual income and health. When assessing Canadian neighbourhood-level income compared with individual-level income, some studies have shown no attenuation in the relationship between income and health outcomes or utilization, while others have demonstrated less correlation (160). Mustard et al. (161) produced a well-designed study to assess both urban and rural ecological proxies for individual income. There was consistent correlation between neighbourhood and individual income in predicting health outcomes for six conditions. The authors cautiously recommend using neighbourhood-level data if individual income is unavailable, although they highlight some inconsistencies in the strength of the association between neighbourhood income and health outcomes. Nevertheless, most Canadian studies have been able to demonstrate a strong correlation between neighbourhood-level and health outcomes (162-164).

One reason for this controversy may be the level at which neighbourhood income is measured. In Canada, the units of measurement tracked by the census are as follows (165):

1) Census Metropolitan Area (CMA): a minimum urban population of at least 100,000
2) Census Agglomeration (CA): a minimum urban population of at least 10,000
3) Census Subdivision (CSD): municipalities or their equivalent
4) Forward Sortation Area (FSA): comprises residents with the same first three digits of their postal code; in urban regions, this comprises approximately 20,000-40,000 people.
5) Census Tract (CT): small, relatively stable geographic region with a population of 2500 to 8000 which can be located within CAs or CMAs
6) Enumeration Area (EA): the small geographic region canvassed by one census representative, composed of one or more adjacent blocks, comprising 125 dwellings in rural areas and 440-650 dwellings in urban areas.

7) Dissemination Area (DA): a small and relatively stable geographic unit composed of one or more blocks, composed of 400-700 people. In the 2001 census, the DA replaced the EA as the basic unit of dissemination.

The unit at which neighbourhood income acts as an accurate proxy for individual income and/or is associated with health outcomes is controversial. A study from Montreal found significant misclassification in household income when examining EAs used with the higher-level CT income (166). In Alberta, a study by Southern et al. found that EA-derived income levels were more accurate for any given FSA-derived income quintile and they recommended using EA-derived measures when individual data are not available (167). Some misclassification can be introduced with inaccurate addresses and postal codes, however this appears not to be a significant source of bias in Ontario (158). It should be noted that geocoding classification of neighbourhoods is less precise in rural areas, and this can result in misclassification of neighbourhood income and a bias towards the null hypothesis. Most patients with IBD in Ontario reside within urban neighbourhoods, and the size of our population-based administrative databases are large enough to minimize the effect of this random misclassification error (53). In general, use of EA or smaller-level neighbourhood income as a proxy for individual income is accepted, although one must be cognizant of the potential biases introduced when using large-area income markers (160, 168). In this study, EA-level data was used for 1996 and the more specific DA for 2001 Canadian Census data. In the 2001 Canadian Census, dissemination areas had 400 to 700 residents (169), and are likely to be more accurate and stable than EA-level data. We can therefore safely assume that using neighbourhood income quintile in our study introduced little or no bias in our conclusions.

Although neighbourhood income correlates with individual income, it may also play an independent role in determining the health of residents within that neighbourhood. The aforementioned Scottish study found both neighbourhood and individual-level incomes contributed independently to the cardiovascular health of residents and concluded that using only one income measure may not fully account for the impact of social deprivation on a person’s
Other studies have also correlated neighbourhood income with health outcomes, indicating the importance of patients' living environment when assessing access and outcomes of health care, suggesting that a person’s neighbourhood plays an independent role in determining health (170-174). However, since mean neighbourhood income is derived from individual-level census data, the two measures are highly correlated and collinear. This presents a challenge to analyze statistically, even with the use of multi-level modeling (175). We did not have access to individual-level income data and therefore could not determine the proportion of our findings that were due to income at the neighbourhood level as opposed to income at the household/family level.

5.4.2 The Role of Socioeconomic Status in Patients with Inflammatory Bowel Disease

Few studies have examined the role of SES in the clinical course of IBD and health care utilization of CD patients. Nahon et al. (9) used the Evaluation of Precarity and Inequalities in Health Examination Centers (EPICES) score of social deprivation (176) to assess clinical characteristics and surgical rates in adult patients with IBD in a prospective multicentre study from France. They found no difference in disease severity based on social deprivation, but found that lower SES patients were less likely to undergo surgery (9). This study did not assess health services utilization and did not contain children or UC patients. Nevertheless, it is, to our knowledge, the only study to directly assess the role of SES in the prognosis of CD. A study from Sweden examined educational level and occupational status in adults with CD and UC and found that patients with more than 12 years of education had lower rates of hospitalization (177). A number of occupations were found to carry an increased risk of hospitalization due to CD or UC, however the authors did not link these findings to income (177). Patients of lower SES (in the form of mean neighbourhood income quintile) had more physician visits and ED visits in the three years following diagnosis. Additionally, children of lower income families with CD were more likely to be hospitalized and more likely to undergo surgery (particularly if diagnosed after 2000) than those of higher income. Access to specialized medical care (in the form of gastroenterologist outpatient care) is unlikely to be the main cause given the similar visit rates between income group. One of the explanations for the income disparities discussed in the study manuscript was that there may be barriers in access to newer, more expensive medications.
Although this is speculative in our study (as we did not have access to patient insurance status nor could we monitor medication usage), one study found that adult IBD patients underwent significant difficulty getting medical insurance in the Netherlands (178), which may contribute to difficulty paying for expensive medications.

5.4.3 The Link Between Income, Healthcare Provision and Health Outcomes in Children with Chronic Diseases

The link between income and health outcomes in American children is well established (49, 179-181). Canada's universal health system should theoretically eliminate disparities in health care access and outcomes that are sensitive to healthcare based on SES. Nevertheless, disparities in infant mortality and in infant chronic disease outcomes based on income are recognized (53, 182, 183). These disparities continue for at least nine years following birth in Canadian children for ambulatory care-sensitive conditions, and may be due in part to differences in the methods of care provision (such as appropriate primary care or access to specialized care) (57, 104).

Ambulatory care-sensitive conditions are those for which appropriate primary medical care will prevent complications (184, 185). Although IBD has not been scientifically demonstrated to be an ambulatory care-sensitive condition as yet, it certainly falls in the realm of chronic conditions which are primarily treated in the ambulatory setting. For example, Crohn’s disease is likely to begin as inflammatory disease in most cases. When left untreated, this inflammation can result in stricturing or penetrating disease, at which point medical management is unlikely to be successful and surgical intervention is required. It stands to reason that appropriately timed qualified medical care could prevent the complications of IBD, which include hospitalization, and need for surgical intervention. In our study, we demonstrated worse health outcomes (hospitalizations, surgeries) in children with IBD despite equal specialist visit rates and only minimally higher overall IBD-related physician visit rates in the lower income group. A group at risk of worse health outcomes should be seen more frequently and intensely than those who are at lower risk, which was not the case in lower income children with IBD. Our study generates hypotheses regarding the role of income on healthcare provision and outcomes in children with IBD.
In general, the link between poverty and poor health outcomes in children with other chronic diseases has been well described (49). Low income in Canadian children has been associated with worse birth outcomes (163), higher rates of paediatric cardiovascular events (55), as well as worse health outcomes (including emergency department visits and hospitalizations) in paediatric chronic diseases such as asthma (112, 186-188), epilepsy (189), and migraines (188). In the United States, lower socioeconomic status has been associated with poor access to specialist care for children with chronic diseases (51, 52), which may account for some of the disparities in health outcomes. There was no association between specialist healthcare provision and outcomes in low income children with IBD. We hypothesized that access to medications (either access or adherence) may play a role in these outcomes, as they do in children with asthma (112). Unfortunately due to limitations in the health administrative data, we could not control for SES-related social factors such as exposure to environmental tobacco smoke, medication adherence, or patient help-seeking behaviours may have contributed to the disparity. Future studies will assess whether these factors, access to medications or access to specialist care (while controlling for disease severity) play roles in the income disparities demonstrated in children with IBD in Ontario. By identifying the etiologies of the disparities in health outcomes seen in children with IBD, we can better advocate for at-risk children and youth and improve the health and social systems in our province thereby reducing disease complication rates and health services utilization rates and improving patients’ quality of life.

5.5 Assessing Effectiveness of Recent Changes to Medical Treatment in IBD

The third and final study within this thesis described rates of hospitalization and surgeries in children with IBD over time. This study was designed to assess whether changes to medical therapy in paediatric IBD after 2000 had altered outcomes. It was therefore constructed as an ecological analysis of the real-world effectiveness of medications that were shown efficacious in clinical trials. Efficacy is defined as the demonstrated benefit of a treatment over a control under ideal circumstances, such as randomized controlled clinical trials. Effectiveness is defined as the benefit of a treatment in the conditions in which it is typically used in medical care (190).
Agency for Healthcare Research and Quality (AHRQ) has defined six criteria for distinguishing effectiveness from efficacy trials when conducting systematic reviews (191):

1) Populations in primary care
2) Less stringent eligibility criteria
3) Assessment of health outcomes (e.g. functional capacity, quality of life, mortality)
4) Long study duration; clinically relevant treatment modalities (e.g. no fixed-dose designs, equivalent dosages for head-to-head comparisons)
5) Assessment of adverse events
6) Adequate sample size to assess a minimally important difference from a patient perspective
7) Intention-to-treat analysis

Azathioprine has been demonstrated efficacious for maintenance of remission of CD in children (1) and adults (192), as well as in adults with UC (193). Additionally, there is evidence from randomized controlled trials that anti-TNF therapy (infliximab and adalimumab) may decrease the need for surgery (12, 194, 195). All of these studies meet criteria as efficacy studies. Effectiveness studies examining the effectiveness of immunomodulators (azathioprine, 6-MP and methotrexate) and anti-TNF therapy have been less promising. A systematic review of population-based studies published in 2004 failed to demonstrate significant improvements in disease outcome over the preceding four decades (196). The use of immunomodulators in CD patients also did not reduce the complication or surgical rates in a population based study from France (14). Two recent unpublished studies (from the United States and Spain) compared calendar cohorts of patients who were diagnosed before or after 2000 and showed that the availability of infliximab had no impact on the occurrence of stricturing and penetrating complications and did not reduce surgical rates (197). In fact, an American study recently demonstrated a significant increase in hospitalization rates of adults with CD and UC between 1998 and 2005 using an unvalidated algorithm to identify IBD patients within health administrative data. They demonstrated no change in surgical rates (198).

Our ecological study used health administrative data to demonstrate significant reductions in the crude hospitalization and surgical rates in children with CD but not UC diagnosed between 1994
and 2005. Multivariable analyses which controlled for age at diagnosis demonstrated an increased odds of hospitalization in recent years, while the odds of surgery decreased in those diagnosed above 10 years old. Outpatient care was increasingly provided by paediatric gastroenterologists, with decreased care provided by adult gastroenterologists and surgeons in recent years. We concluded that improved outcomes were most likely due to the overall changes to care provision rather than medication changes, as no significant inflection point in physician visit, hospitalization or surgical rates existed at the time of publication of a clinical trial demonstrating the efficacy of immunomodulators in children with CD. These findings emphasize that effectiveness studies at the population-based level should also assess changes to other aspects of the health system and care provision in order to be certain that outcomes were affected by the intervention in question and not other factors.

5.6 Limitations of the Ontario Crohn’s and Colitis Cohort

The limitations of the OCCC are primarily related to its reliance on health administrative data to follow patients longitudinally. Although administrative databases represent a strong resource for population-based epidemiologic and health services studies, questions answered by researchers are limited to the data content. For example, the role of clinical phenotype in the changing frequencies of hospitalization and surgeries could not be assessed as no clinical information is available within the data. Similarly, while there was an increasing incidence and prevalence of childhood-onset IBD in Ontario, the reason for this increase remains elusive within the confines of the current databases. However, linkage to new databases (such as the Landed Immigrant Data Set) may allow us to determine the etiology of this increase (see Future Directions). It is also important to remember that we described only patients with physician-identified IBD. The number of patients with either subclinical disease or those that have not sought treatment from a physician could not determined, as they would not be identified as having IBD within the databases. We therefore may only be observing the ‘tip of the iceberg’ of the increase in paediatric IBD, or we may have observed the portion of the iceberg that was ‘below the water’ (i.e. unidentified children with IBD) becoming smaller due to improved investigation by physicians or access to specialists. Finally, although there were changes to treatment of children with IBD over time, we could not assess medication usage in all patients, nor could we deduce
adherence. This limits our conclusions to overall trends in outcomes of interest, and we are unable to assign causality to a single factor such as medications or specialist care.

It is important to emphasize that the algorithm validated in this thesis to identify children with IBD is limited in its applications. Since it was validated in children in Ontario, it should not be applied to other jurisdictions without consideration of similarities in data types, patterns of care and access to care issues, or without further validation for those databases. In addition to 159 studies which did not validate identification algorithms, our systematic review of the methods used to identify patients within health administrative data found seven studies which utilized algorithms validated in a different cohort/jurisdiction than the one to which it was applied (138). It is impossible to predict how our algorithm would function when applied to age group or another jurisdiction’s health administrative databases. However, a paediatric-specific algorithm is an excellent first step to highlighting the importance of validation for each application, and may lead to collaborative studies in which we validate the algorithm in other cohorts. While the OCCC will be updated yearly by ICES in order to continue surveillance of paediatric IBD in Ontario, we are uncertain whether the algorithm will perform with similar accuracy in the future. We validated the algorithm using two different time periods (1991-1995 in Toronto, 2001-2005 in Ontario), however changes to physician billing patterns or to CIHI coding may result in altered accuracy of the algorithm in the future. We would recommend re-validation of algorithms at regular time periods in order to ensure continued accuracy.

Despite its limitations, the OCCC represents the largest cohort of paediatric IBD patients in the world. The advantages of using health administrative data (feasibility, linkability, long longitudinal follow-up periods, etc.) far outweigh the disadvantages. Researchers should be aware of the limitations of using the OCCC (and health administrative data in general) prior to forming their research questions. However, with properly crafted hypotheses and an advanced knowledge of the characteristics of health administrative data, the OCCC is a powerful tool to examine paediatric IBD in Ontario.
5.7 Futures Directions

A number of steps will be taken over the next few years to further expand, strengthen and reinforce research conducted with the OCCC. My first endeavour will be to expand the cohort to include adult patients with IBD. I will use similar methods to validate an algorithm to identify patients with onset of IBD >18 years old. I will use this algorithm to describe the incidence and prevalence of adult-onset IBD in Ontario and assess burden of disease on the health system. In so doing, the OCCC will become the largest cohort of patients with IBD in North America. Additionally, describing the incidence trends of adult-onset CD will allow us to assess whether the increase in paediatric incidence is due to earlier identification or an overall increase in CD in the province. If decreased incidence in young adults is found, the increased rates in young children may be due to earlier diagnosis, with ‘bracket-shift’ occurring. However, if the rates of CD are stable or increasing in adults (as has been described in other jurisdictions), this would confirm a true recent increase in incidence in Ontario. Similarly, I anticipate expanding the OCCC beyond Ontario’s borders with validation of the algorithm in other provinces. I will also address our hypothesis that immigration trends may have played a role in the increased incidence by linkage of the OCCC to Citizenship and Immigration Canada’s Landed Immigrant Dataset to assess risk of IBD in immigrants and their Ontario-born children. I will assess whether earlier age of immigration is associated with a higher risk of developing IBD, generating new hypotheses regarding environmental exposures and the etiology of IBD.

Countless other questions can be answered using the OCCC. These include questions of appropriate use of radiologic investigations in children with IBD, the transition from paediatric to adult care and comparisons of children to adults for outcomes and health services use. The OCCC will be strengthened with linkage of clinical to administrative data. In order to accurately answer questions of access to medications, specialists and investigations (in order to improve health care quality), the administrative data should be supplemented with medication data, phenotypes, and disease severity. In the future, I hope to link some clinical information to the OCCC administrative data to expand the number of types of questions that can be answered. For example, assessing disease severity and disease phenotype at the time of symptom onset may
predict outcomes years after diagnosis. Rather than creating a clinical inception cohort and following patients for years or decades in the future, I could link inception data to the administrative data and use the latter to follow patients longitudinally with better cost-efficiency. The OCCC could also be used to assess variations in care province-wide and eventually create evidence for improving quality of care and outcomes. By combining data sources, linking across databases and supplementing the administrative data, I hope that the OCCC can be used to generate hypotheses, answer important research questions and improve the care received by children with IBD in Ontario and beyond.
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