



# Increased Incidence of Inflammatory Bowel Disease After Hirschsprung Disease: A Population-based Cohort Study

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**Objective** To determine the frequency with which inflammatory bowel disease (IBD) is diagnosed in persons with Hirschsprung disease in population-based datasets from 3 Canadian provinces.

**Study design** In study I, Ontario data were used to assess the incidence of IBD in a birth cohort of children with Hirschsprung disease relative to children without Hirschsprung disease. In study II, a case-control design was used in Alberta and Manitoba to determine the frequency of previously diagnosed Hirschsprung disease in persons with IBD, compared with the frequency of Hirschsprung disease in matched controls. Validated algorithms for Hirschsprung disease and IBD were applied to each provincial health registry.

**Results** In study I, of the 716 children diagnosed with Hirschsprung disease in Ontario since 1991, 18 (2.5%) ultimately developed IBD (168.8 per 100 000 person-years), compared with 7109 of 3 377 394 children without Hirschsprung disease (0.2%, 14.2 per 100 000 person-years). The percentage of males with post-Hirschsprung disease IBD was 77.8%. The incidence rate ratio was 11.9 (95% CI, 7.5-18.8). In study II, the OR of having had Hirschsprung disease before a diagnosis of IBD compared with controls was 74.9 (95% CI, 17.1-328.7) in Alberta and 23.8 (95% CI, 4.6-123) in Manitoba. Crohn's disease was more common after Hirschsprung disease than ulcerative colitis.

**Conclusions** IBD can emerge in more than 2% of patients with Hirschsprung disease and, like Hirschsprung disease itself, is more common in males. IBD is much more common after a diagnosis of Hirschsprung disease than in the general population. (*J Pediatr* 2021;233:98-104).

Hirschsprung disease is a congenital condition resulting from aganglionosis of the colon affecting approximately 1 in 5000 live births, which leads to impaired colonic motility and treatment involves surgical resection of the involved segment typically with a pull-through of the remaining normal colon down to the anus.<sup>1</sup> The condition is limited typically to the rectosigmoid; however, up to 10% of affected individuals have total colonic aganglionosis.<sup>2</sup> Most diagnoses and surgeries are undertaken within the first year of life. Hirschsprung disease-associated enterocolitis (HAEC) presents in about one-half of patients preoperatively, and up to 50% postoperatively.<sup>2</sup> HAEC that occurs postoperatively most typically occurs within months of surgery, and it is therefore uncommon after age 5 years.

Inflammatory bowel disease (IBD) affects approximately 0.7% of the Canadian population, with similar rates of affected Americans and northern Europeans.<sup>3-6</sup> Although IBD is emerging worldwide, incidence rates are plateauing in Western countries.<sup>7-9</sup> However, childhood onset-IBD and especially very early onset IBD (IBD diagnoses before age 6 years) are increasing.<sup>10,11</sup>

Because there are no biomarkers or specific diagnostic tests for HAEC and the diagnosis of IBD requires a clinical constellation of features, it is possible that HAEC and IBD as diagnostic entities could be confused in young people who have been treated for Hirschsprung disease. However, case series have emerged of persons with diagnoses much more typical of IBD that responded to treatments used in IBD and not in HAEC, such as immunomodulators and biologics.<sup>12,13</sup> In this study, we determined the frequency with which IBD is diagnosed in persons

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Funding and conflicts of interest statement available at [www.jpeds.com](http://www.jpeds.com).

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<https://doi.org/10.1016/j.jpeds.2021.01.060>

HAEC	Hirschsprung disease-associated enterocolitis
HR	Hazard ratio
IBD	Inflammatory bowel disease
NPV	Negative predictive value
PPV	Positive predictive value
RR	Relative risk
UC	Ulcerative colitis

with Hirschsprung disease in population-based datasets from 3 Canadian provinces.

## Methods

We conducted 2 retrospective studies using population-based provincial health administrative data from Ontario, Manitoba and Alberta, Canada. In the first study (study I), Ontario data were used to assess the incidence of IBD in a birth cohort of children with Hirschsprung disease relative to children without Hirschsprung disease. In a replication study (study II), a case-control design was used in Alberta and Manitoba to determine the frequency of previously diagnosed Hirschsprung disease in a population of patients with IBD, compared with the frequency of Hirschsprung disease in matched controls. Study I was approved by the Research Ethics Board of the Children's Hospital of Eastern Ontario. Study II in Manitoba was approved as a part of the Research Ethics Board of the University of Manitoba approval of Manitoba IBD Longterm Outcomes Study. Study II in Alberta was approved by the Research Ethics Board of the University of Calgary as part of The Alberta IBD Surveillance Cohort: Current and Future IBD Care.

### Study I

We used Ontario health administrative data, which include all legal residents who qualify for universal single-payer healthcare (>99% of the population). Data are maintained by a health data repository, International Credential Evaluation Services, via an agreement with the Ontario Ministry of Health and Long-Term Care, with the data available to researchers in an uncleaned and unedited format.<sup>14</sup> Multiple databases were deterministically linked using a unique encrypted identification number based on the Ontario health card number assigned to each Ontario resident. We included all children born in Ontario on or after April 1, 1991, identified from the Registered Persons Database. We used the Ontario Health Insurance Plan database to identify all outpatient physician contacts; the Canadian Institute for Health Information-Discharge Abstract Database to identify all hospitalizations; and the National Ambulatory Care Reporting System and Emergency Room Claims to identify emergency department visits. In Ontario, prescription drug data are not population based and, therefore, were not used for this study.

We used a validated algorithm to identify children living in Ontario who were <18 years old diagnosed with Hirschsprung disease between April 1, 1991, and March 31, 2016. This algorithm identified children with Hirschsprung disease with a sensitivity of 93.5%, specificity of >99.9%, a positive predictive value (PPV) of 89.6%, and a negative predictive value (NPV) of >99.9%. Exclusion criteria included those not continuously eligible for Ontario Health Insurance Plan for 3 years after birth, those with missing information on sex or date of birth, and children who were diagnosed with IBD before being diagnosed with Hirschsprung disease. Children were followed until IBD diagnosis, loss of Ontario

Health Insurance Plan eligibility, death, or the end of the study (March 31, 2019).

Children with and without Hirschsprung disease were followed forward in time to determine whether they were diagnosed with IBD. We classified people as having or not having IBD based on validated algorithms. These algorithms accurately identified children <18 years of age with incident IBD with the following diagnostic accuracies: sensitivity of 89.6%-91.1%, specificity of 99.5%-100%, PPV of 59.2%-76.0%, and NPV of 99.9%-100%.<sup>15</sup> The algorithms identified adult-onset IBD with the following diagnostic accuracies: sensitivity of 76.8%, specificity of 96.2%, PPV of 81.4%, and NPV of 95.0%.<sup>16</sup> No lookback period was applied to distinguish incident from prevalent cases, because all data were available on all patients from birth. All IBD diagnostic codes within the first 6 months were excluded owing to the risk of misclassification with HAEC and food protein enterocolitis. A validated algorithm was used to classify IBD as being Crohn's disease or ulcerative colitis (UC) based on the diagnoses assigned at the latest 5 of 7 outpatient visits for children <18 years of age and 5 of 9 outpatient physician visits for adults, which accurately assigned IBD type in 91.1% of cases.<sup>15,16</sup>

### Analysis

We determined the crude incidence of IBD, Crohn's disease, and UC after diagnosis of Hirschsprung disease per 100 000 person-years of follow-up time. The crude incidence of IBD (and subtypes) were compared in individuals with and without Hirschsprung disease using relative risk (RR) with a Gamma distribution. Kaplan-Meier survival curves were created to demonstrate risk of IBD over time in people born with and without Hirschsprung disease. Poisson and Cox proportional hazards regression analyses were used to compare the risk of IBD (including subtypes) in individuals with and without Hirschsprung disease; results are summarized as RR and hazard ratio (HR), respectively, with 95% CIs comparing the incidence of IBD (including subtypes) in patients with Hirschsprung disease compared with those without Hirschsprung disease. All multivariable regression models controlled for rural/urban household and mean neighborhood income quintile because these variables have been demonstrated to be confounders in the relationship between IBD, access to care, and health services utilization in previous studies.<sup>17,18</sup> In all cases, cells with a sample size of <6 people were suppressed owing to privacy regulations. All analyses were conducted using SAS version 9.4 (SAS Institute).

### Study II

A replication study was designed to evaluate the association between Hirschsprung disease and IBD using 2 separate study populations (ie, Alberta and Manitoba) and a case control study design.

Patients were identified with a validated algorithm where they would have 2 hospitalizations using Canadian Institute for Health Information-Discharge Abstract Database, 2 outpatient procedure or emergency visit contacts using

National Ambulatory Care Reporting System, or 4 physician claims with *International Classification of Disease-9 or -10* codes for IBD using the Alberta Physicians' Claims Database within 2 years; this algorithm has a sensitivity of 78.0%, a specificity of 99.8%, a PPV of 97.2%, and a NPV of 98.0%.<sup>19</sup> Additionally, Crohn's disease, UC, and those where IBD subtype was unclassifiable based on administrative data were identified using an algorithm validated in Alberta for consistency in both provincial case-control studies, and patients with UC and IBD type unclassifiable were combined. Ten age- and sex-matched controls were included for each IBD case (314 850 controls). Two sets of IBD cases were analyzed: (1) cases of IBD who were continuously eligible for provincial health coverage from birth to IBD diagnosis (born between 2002 and 2016); and (2) incident cases (a 3-year wash-out period for those <18 years of age, diagnosed between 2005 and 2016, and an 8-year wash-out period for those ≥18 years of age, diagnosed between 2010 and 2016) with IBD.

In Manitoba, we used the University of Manitoba IBD Epidemiology Database.<sup>20</sup> This database contains all Manitobans diagnosed with IBD from April 1, 1984, through March 31, 2018, using a validated administrative algorithm.<sup>20</sup> We identified all outpatient contacts and inpatient hospitalizations until 2004 for IBD by *International Classification of Disease-9* codes 555 and 556 and all inpatient hospitalizations after 2004 by *International Classification of Disease-10* codes K50 and K51. An IBD case was defined as having ≥5 health system contacts (either outpatient or hospitalization) if residing in the province for >2 years or ≥3 health system contacts if residing in the province for <2 years. This validated administrative definition was shown to be 90% sensitive and ≥99% specific for identifying persons with IBD and can differentiate between cases of Crohn's disease and UC with approximately 90% accuracy. In cases where codes for both Crohn's disease and UC were present, patients were classified according to the diagnosis in the majority of the 9 most recent healthcare contacts.<sup>20</sup> Of the 1.3 million Manitobans there are 11 495 persons with IBD identified in the database and 110 000 matched controls, matched 10:1 by age, sex, and region of residence using postal codes. In this analysis, we assessed only persons born after 1984, because those born before 1984 may have had a Hirschsprung disease diagnosis in early life that did not appear in later records, leading to an underestimate of prevalence.

In both Alberta and Manitoba, we used the validated algorithm for Hirschsprung disease developed in Ontario to compare the frequency of Hirschsprung disease in persons with IBD compared with matched controls.<sup>1</sup>

## Analysis

Stratified logistic regression was used to compare the odds of having Hirschsprung disease in IBD cases as compared with controls. Strata were individual IBD cases and their associated age- and sex-matched controls. In Alberta and Manitoba, we did not adjust for income and rurality as we did in the Ontario study, because the sample sizes were too small

to adjust for these covariates. In Alberta, cells with sample size <7 people were suppressed owing to privacy regulations. In Manitoba, cell sizes <6 were suppressed.

## Results

### Study I

There were 4 743 309 children born in Ontario between April 1, 1991, and March 31, 2016. Of these, 3 378 152 were continuously eligible for healthcare in Ontario for 3 years after birth. We excluded 42 patients from the study because they were missing sex, were diagnosed with IBD before Hirschsprung disease, or had a date of death incorrectly listed as before their birthdate.

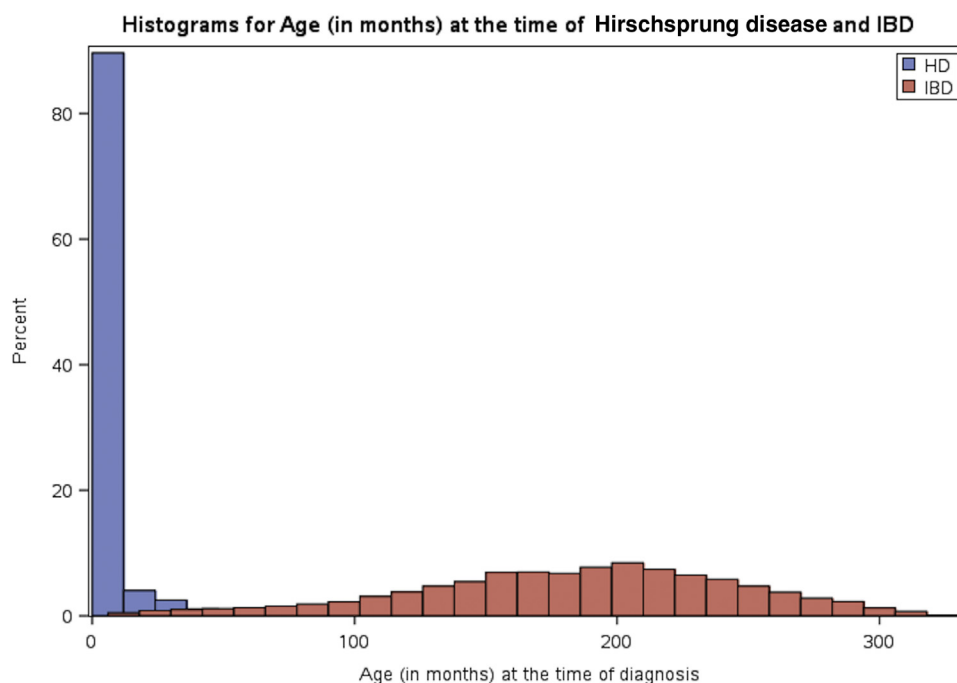
Of 716 children diagnosed with Hirschsprung disease in Ontario since 1991, 18 (2.5%) ultimately developed IBD, compared with 7109 of 3 377 394 children without Hirschsprung disease (0.2%). Seventy-six percent of Hirschsprung disease cases were males and 77.8% of post-Hirschsprung disease IBD were males. The incidence of IBD in patients with Hirschsprung disease was 168.8 per 100 000 person-years compared with 14.2 per 100 000 person-years in children without Hirschsprung disease (incidence rate ratio, 11.9; 95% CI, 7.5-18.8). On multivariable Poisson regression analysis, patients with Hirschsprung disease had a higher risk of developing IBD than controls (RR, 12.0; 95% CI, 7.5-19.0). This was also true for subtypes, namely, Crohn's disease (RR, 16.1; 95% CI, 9.3-27.8) and UC (RR, 6.6; 95% CI, 2.5-17.6). The age distribution of Hirschsprung disease diagnosis and of IBD diagnosis are presented in [Figures 1 and 2](#), respectively.

Kaplan-Meier survival curves demonstrating the risk of IBD in patients with Hirschsprung disease and controls are presented in [Figure 3](#). Cox proportional hazard models demonstrated an increased hazard of IBD (HR, 11.8; 95% CI, 7.4-18.7), Crohn's disease (HR, 15.9; 95% CI, 9.3-27.5), and UC (HR, 6.5; 95% CI, 2.5-17.4) in patients with Hirschsprung disease compared with controls.

### Study II

In Alberta, 15 cases of IBD in the birth cohort were previously diagnosed with Hirschsprung disease compared with <7 controls (OR, 74.9; 95% CI, 17.1-328.7). For the Crohn's disease birth cohort the OR was 24.6 (95% CI, 4.7-127.5) and the OR for UC could not be calculated owing to collinearity. The overall median (IQR) age for Hirschsprung disease diagnosis in the IBD birth cohort was 0 ± 1.71 years (IQR, 0-2 years). In the incident cohort, there were 13 individuals diagnosed with Hirschsprung disease before IBD (median age, 4; IQR 2-6) and <7 individuals were diagnosed with Hirschsprung disease before IBD, were in the birth cohort and were incident cases.

In Manitoba, there were 7 cases of Hirschsprung disease identified among all IBD cases. Cell sizes were too small to allow reporting of subgroups. The odds of having Hirschsprung disease in an IBD case vs control was significantly higher (OR, 23.8; 95% CI, 4.6-123). For Crohn's disease, the OR for having Hirschsprung disease was 38.4 (95% CI,



**Figure 1.** From study I, age distribution in months of diagnosis of Hirschsprung disease and of diagnosis of IBD in persons with Hirschsprung disease.

4.3-34.4) and for UC it was 9.48 (95% CI, 0.59-152). For persons born after April 1984, the odds of having had Hirschsprung disease in persons with IBD was higher compared with controls (OR, 29.2; 95% CI, 3.0-281). The OR could not be calculated for Crohn's disease or UC owing to small cell sizes, resulting in a lack of model convergence. Because of the small sample size, the mean age at IBD diagnosis could not be reported for those subsequently diagnosed with IBD.

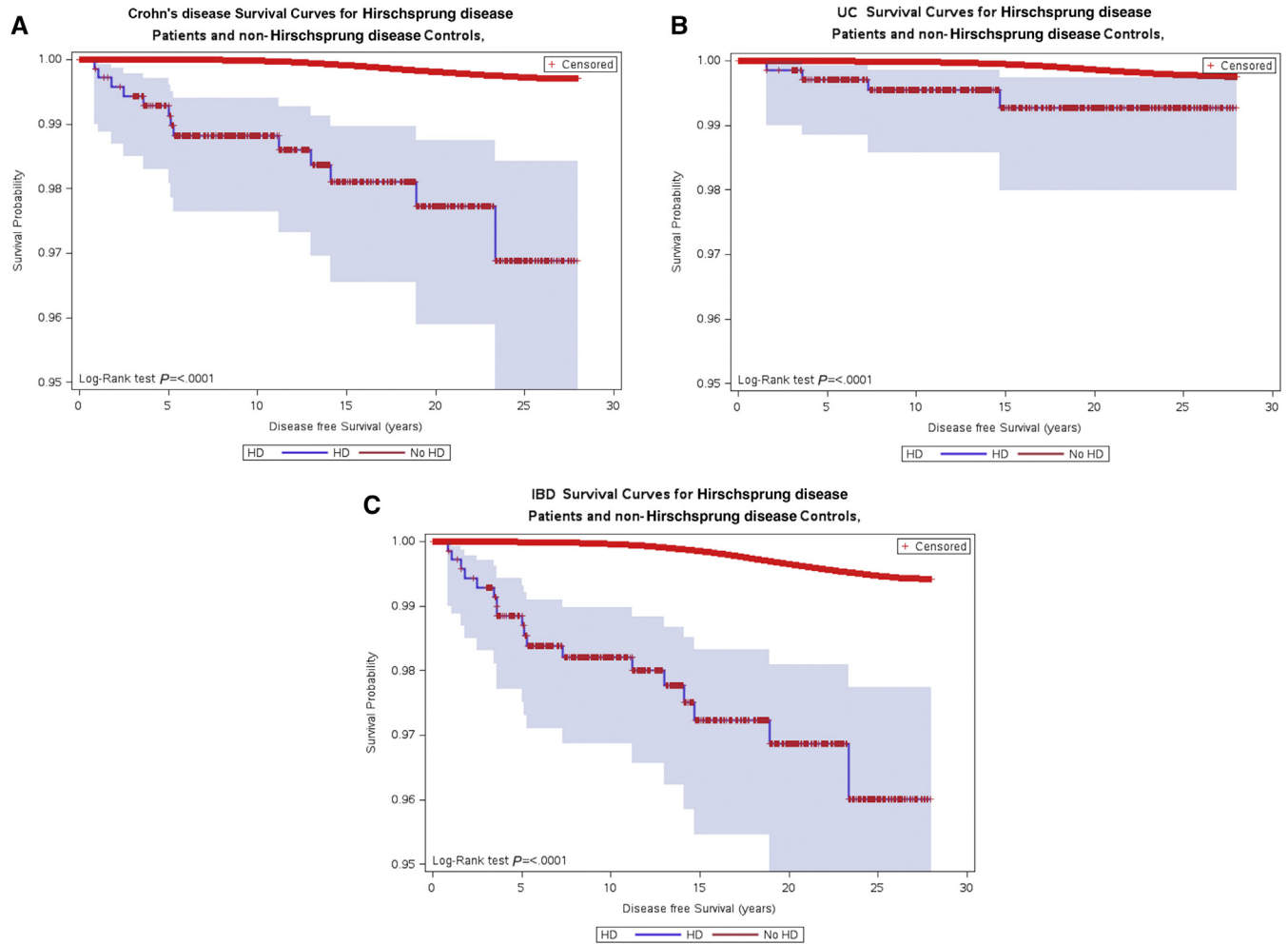
## Discussion

We determined that, in Ontario, Canada, being diagnosed with Hirschsprung disease resulted in a 12-fold increased risk of subsequently being diagnosed with IBD. In case control studies from Alberta and Manitoba we found that persons with IBD were 24-40 times more likely to have had Hirschsprung disease than matched controls. Hence, we have demonstrated a strong association between Hirschsprung disease and IBD in a large Canadian province and we corroborated the findings in 2 other Canadian provinces. This finding raises the question as to whether the IBD diagnosed post Hirschsprung disease is the same disease process as the typical pediatric-onset IBD.

Hirschsprung disease is well-known to result in HAEC, a different form of intestinal inflammation than that seen in IBD. There are several features that distinguish HAEC from IBD. Hirschsprung disease is most typically diagnosed within the first year of life and HAEC is most typically diagnosed either before Hirschsprung disease surgery or within 1 year after Hirschsprung disease surgery which suggests age of first diagnosis will occur before age 2 years in the vast majority of cases.

The median age of presentation of HAEC in a large series of 2030 persons was 50 days.<sup>21</sup> Further, congenital neurologic abnormalities and central nervous system infections were risk factors for HAEC post Hirschsprung disease.<sup>21</sup> These are not known risk factors for IBD. In Ontario, to decrease the risk of misclassification bias, we removed healthcare contacts with associated diagnosis codes for IBD from the identification algorithms if they occurred within the first 6 months of life.<sup>15</sup> The mean age of first presentation of IBD in our study was 7.5 years in Ontario, much different than that seen for HAEC. Hirschsprung disease is more common in persons with trisomy 21 and trisomy 21 is a risk factor for developing HAEC.<sup>2,22</sup> Trisomy 21 is not typically associated with IBD.<sup>23</sup>

Although HAEC is quite commonly associated with Hirschsprung disease in a retrospective study of 880 persons with Hirschsprung disease, only 9 (1%) later developed IBD.<sup>12</sup> In a cases series from pediatric hospitals in Toronto and Helsinki, 8 patients out of an estimated 700 treated for Hirschsprung disease were diagnosed with IBD of >20 years.<sup>13</sup> In a meta-analysis of 14 studies of 66 patients reported as having IBD after being diagnosed with Hirschsprung disease, the mean age of diagnosis of Crohn's disease was 7.7 years, similar to our results from Ontario, and 47% of those diagnosed with IBD had past diagnoses of HAEC.<sup>24</sup> In a recent population-based study of Hirschsprung disease diagnosed in Sweden from 1964 to 2013, the cumulative incidence of IBD was 2.7% in patients with Hirschsprung disease, with a calculated OR of 4.99 (95% CI, 2.85-8.45).<sup>25</sup> The ratio of Crohn's disease to UC was 3:1 and the median age at IBD diagnosis was 19 years, compared with 21 years in controls without Hirschsprung disease (not significant).



**Figure 3.** Survival curves for development of, **A**, Crohn's disease, **B**, UC, and **C**, IBD in Hirschsprung disease cases vs controls.

There are histologic changes that are more consistent with HAEC, such as crypt dilation and mucin retention, and some more consistent with Crohn's disease, such as granulomas and fibrosis; however, the histopathology of both diseases may be nonspecific and there is certainly overlap between the histopathology of HAEC and UC.<sup>26</sup> HAEC is also treated much differently than IBD. Therapies for HAEC include antibiotics, rectal irrigations, laxatives if constipation is a major symptom, anal dilations, botulinum toxin injections to the internal anal sphincter, posterior myectomy of the internal anal sphincter, colostomy placement, and redo anorectal pull-through, none of which are typical therapies in IBD.<sup>27,28</sup> However, there may be some mechanistic similarities between HAEC and IBD. One paper reported an association of HAEC after Hirschsprung disease surgery with high serum levels of anti-*Saccharomyces cerevisiae* immunoglobulin A and anti-outer membrane porin-C, both of which are highly associated with Crohn's disease.<sup>29,30</sup> There has been emerging research on the alteration of the gut microbiome in HAEC.<sup>31</sup> It may be that surgically altering a bowel that may have other undiagnosed neural alterations leads to stasis of a proinflammatory gut microbiome. Increased proteobacteria

and decreased firmicutes in the gut microbiome is a signature of IBD and recently also reported in HAEC.<sup>31,32</sup>

There are other forms of IBD-like diseases that present in childhood. In post-neonatal necrotizing enterocolitis stricture development is common.<sup>33</sup> Although post-neonatal necrotizing enterocolitis strictures may be difficult to distinguish from Crohn's disease, their onset is typically by 6 months of age, a rare age for Crohn's disease to present. Single gene mutations have been associated with chronic enterocolitis that is often severe but potentially curable with a stem cell transplant.<sup>34</sup> Other immunodeficiency disorders can also present with conditions that mimic IBD.<sup>35</sup> These diseases would not have an age of presentation as shown in **Figure 1**.

The strengths of our study are its population-based nature, use of validated algorithms for defining Hirschsprung disease and IBD, and the use of different methods in different jurisdictions. The main limitation is that the administrative data did not include full details on the phenotype and course of the IBD. It will require further study to determine to what extent persons with post-Hirschsprung disease IBD share phenotypes with sporadic IBD, are being treated with IBD-related drugs, and to what extent they respond to these drugs. Another limitation is the risk

of misclassification bias, especially from misdiagnosis or miscoding of IBD in patients with HAEC. However, we used validated algorithms to identify patients with IBD. In addition, as mentioned, the age of IBD onset noted in patients with Hirschsprung disease was older than we would expect for HAEC. Although the accuracy of the administrative coding for IBD and Hirschsprung disease have been validated separately, the validity of coding for both IBD and Hirschsprung disease in the same individual is not known and, thus, may be associated with a reduction in the overall sensitivity and PPV of the study. A final limitation is the limited follow-up time available for data from Ontario and Alberta. The birth cohort, in particular, represented a younger onset of IBD than typically observed in the general population. We could not follow patients into later adulthood to determine whether this trend in IBD risk among patients with Hirschsprung disease continued, or whether the risk of adult-onset IBD was lower in patients with Hirschsprung disease. However, considering the changes to Hirschsprung disease surgeries and their success rates, patients with longer follow-up time may have been fundamentally different from patients born more recently with Hirschsprung disease. Therefore, the truncated follow-up time may have decreased the heterogeneity among the Hirschsprung disease population.

We have found that IBD can emerge in >2% of patients with Hirschsprung disease and is more frequently classified as Crohn's disease than UC. Post-Hirschsprung disease IBD is 3-fold more common in males, but Hirschsprung disease itself is 3-fold more common in males (vs the typical 2-fold risk for males in typical pediatric IBD). More research is required to better define which patients with Hirschsprung disease are at risk for IBD and the pathophysiologic link between Hirschsprung disease and chronic small and large bowel inflammation after an aganglionic segment is removed. This may provide more insights into the origins of sporadic IBD. However, clinicians should be aware of the link between Hirschsprung disease and onset of IBD in childhood and young adulthood. ■

Submitted for publication Oct 14, 2020; last revision received Jan 8, 2021; accepted Jan 26, 2021.

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## 50 Years Ago in *THE JOURNAL OF PEDIATRICS*

### DNA Antibody Testing for Childhood Systemic Lupus Erythematosus (cSLE): Going Far(r)

Pincus T, Hughes GRV, Pincus D, Tina LU, Bellanti JA. Antibodies to dsDNA in childhood systemic lupus erythematosus. *J Pediatr* 1971;78:981-4.

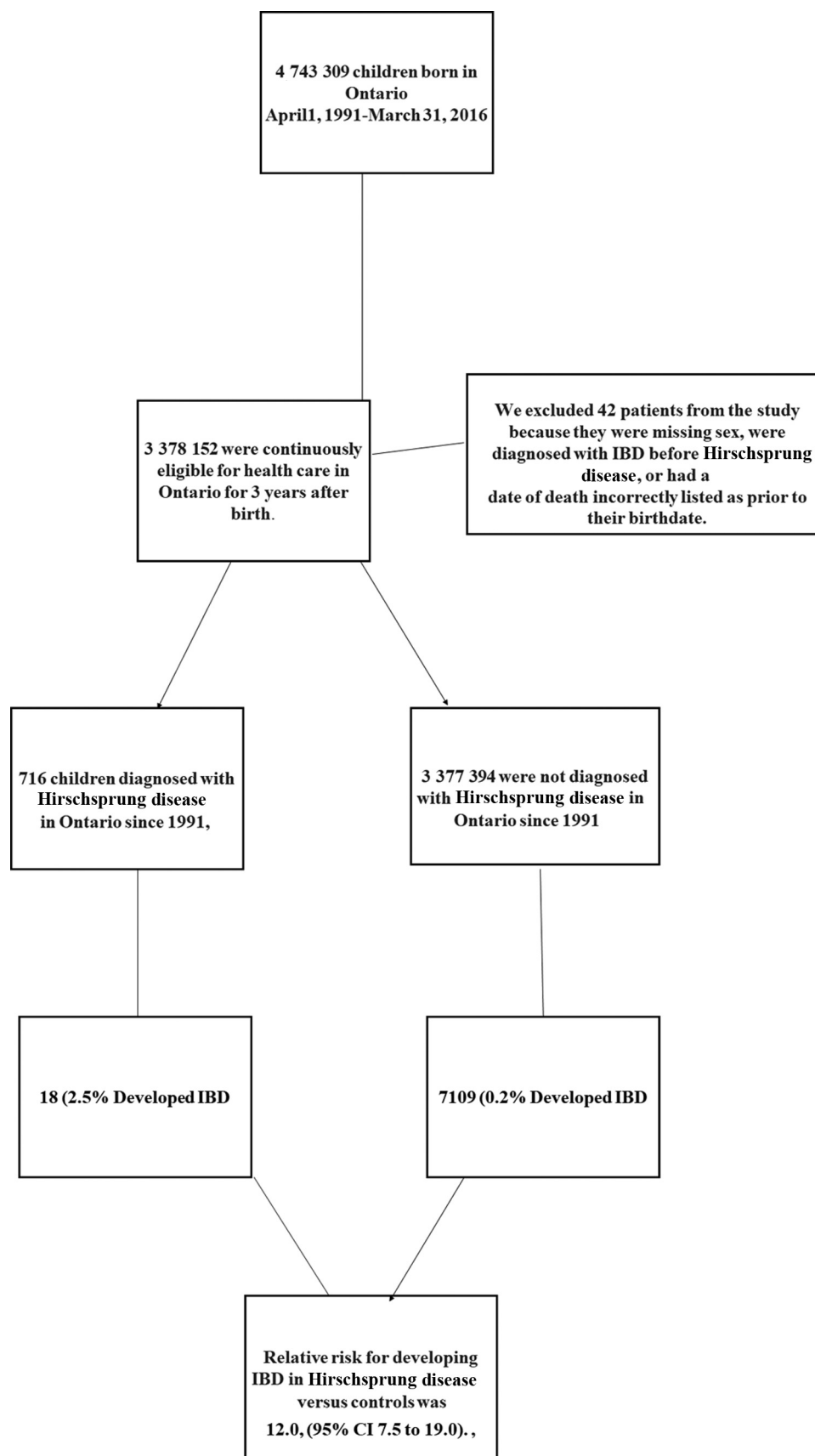
The authors described the utility of measuring dsDNA antibodies in diagnosing childhood systemic lupus erythematosus (cSLE) and the ability to differentiate from juvenile rheumatoid arthritis associated with positive antinuclear antibodies and glomerulonephritis associated with low complement levels. They also showed the utility of following dsDNA antibody levels in monitoring disease activity and the response to treatment.

The diagnosis of cSLE is based on an array of criteria, one of which is the presence of dsDNA antibodies. Even today, assessing dsDNA antibodies is a crucial part of diagnosing and monitoring cSLE.

The novelty of the Farr technique, introduced in children through this report, is that it is a quantitative method for assessing dsDNA antibodies that provides greater sensitivity than previously used techniques. The Farr technique is based on the precipitation of radioactively labeled DNA-DNA antibody complexes, rendered insoluble, in a half-saturated ammonium sulfate solution. Due to the need for radioactive facilities, the Farr method is currently used less. Nonradioactive Farr methods are being tested and implemented. Other methods currently used include the following: (1) enzyme-linked immunosorbent assay using wells of a microtiter plate coated with dsDNA. This method is cheaper but less accurate than the Farr technique. (2) Fluorescent beads—flow cytometry analysis of dsDNA coupled to fluorescent microspheres, incubated with patient serum, and with an antiserum directed against human immunoglobulin. (3) *Crithidia luciliae* immunofluorescent semiquantitative assay, testing serial dilutions of serum on the hemoflagellate substrate consisting of only dsDNA. It is highly specific and may be preferred for the initial diagnosis of SLE whereas other techniques are preferred for assessing disease activity.

As in many important papers in pediatric rheumatology from 50 years ago, none of the authors are pediatric rheumatologists. What is more remarkable is that the 3 senior authors are still highly active practitioners and researchers. Dr Ted Pincus is active at Rush University, particularly in research of disease activity assessment tools in rheumatology. Prof Graham Hughes is a consultant in London and discovered the antiphospholipid antibody syndrome, which used to be called “Hughes syndrome.” Dr Joseph Bellanti is an immunologist in Georgetown University and is the Editor in Chief of *Allergy & Asthma Proceedings*.

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**Figure 2.** Study I outline.



## Funding and Conflicts of Interest

Supported by a Foundation Grant from the Canadian Institutes of Health Research (CIHR) and a CIHR Operating Grant Reference Number PJT 162393. C.B. is supported in part by the Bingham Chair in Gastroenterology. E.B. was supported by a New Investigator Award from the Canadian Institutes of Health Research, Canadian Association of Gastroenterology and Crohn's and Colitis Canada and by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program. M.K. was supported by a Mitacs Elevate Post-Doctoral Fellowship. The study sponsor (CIHR) had no role in any of (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication. C.B. has served on the advisory boards of Abbvie Canada, Janssen Canada, Pfizer Canada, Takeda Canada, Roche Canada; has served as a consultant for Takeda and Mylan Pharmaceuticals; has served on the speaker's bureau for Abbvie Canada, Janssen Canada, Takeda Canada, and Medtronic Canada; has

received unrestricted educational grants from Abbvie Canada, Janssen Canada, Pfizer Canada, and Takeda Canada; and has done contract research with Abbvie, Janssen, Pfizer, Celgene, Boehringer Ingelheim, and Roche. W.E-M. served as an advisory board member of Abbvie Canada, Janssen Canada and Merck Canada and received honoraria for speaking from Abbvie Canada. H.S. has served on advisory boards or as a consultant for Amgen Canada, Sandoz Canada, Roche Canada, Takeda Canada, Pendopharm, Ferring Canada, Merck Canada, and Guardant Health, Inc; has received an educational grant from Ferring Canada; and research funding from Merck Canada for an independent investigator grant. G.K. has received honoraria for speaking or serving as a consultant for Abbvie, Janssen, Pfizer, and Takeda; has received research support from Ferring, Janssen, Abbvie, GlaxoSmith Kline, Merck, and Shire; has served as a consultant for Gilead; and shares ownership of a patent: TREATMENT OF INFLAMMATORY DISORDERS, AUTOIMMUNE DISEASE, AND PBC. UTI Limited Partnership, assignee. Patent WO2019046959A1. PCT/CA2018/051098. 7 Sept. 2018. The other authors declare no conflicts of interest.