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Inflammatory Bowel Disease Increases the Risk of Venous Thromboembolism in Children: A Population-Based Matched Cohort Study

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Abstract

Background and Aims: Although venous thromboembolism [VTE] is a well-known complication of inflammatory bowel disease [IBD] in adults, limited data exist on the risk in children. We report the incidence of VTE among children with and without IBD.

Methods: We conducted a matched cohort study within a distributed network of population-based Canadian provincial health administrative databases. Children <16 years diagnosed with IBD were identified using validated algorithms from administrative data in Alberta, Manitoba, Nova Scotia, Ontario and Québec and compared to age- and sex-matched children without IBD. Hospitalizations for VTE within 5 years of IBD diagnosis were identified. Generalized linear mixed-effects models were used to pool province-specific incidence rates and incidence rate ratios [IRR] with 95% confidence intervals [CI]. Hazard ratios [HR] from Cox proportional hazards models were pooled with fixed-effects meta-analysis.

Results: The 5-year incidence of VTE among 3593 children with IBD was 31.2 [95% CI 23.7–41.0] per 10 000 person-years [PY] compared to 0.8 [95% CI 0.4–1.7] per 10 000 PY among 16 289 children without IBD [unadjusted IRR 38.84, 95% CI 16.59–90.83; adjusted HR 22.91, 95% CI 11.50–45.63]. VTE was less common in Crohn's disease than ulcerative colitis [unadjusted IRR 0.47, 95% CI 0.27–0.83; adjusted HR 0.52, 95% CI 0.29–0.94]. The findings were similar for deep vein thrombosis and pulmonary embolism when comparing children with and without IBD.

Conclusions: The risk of VTE is much higher in children with IBD than controls without IBD. While the absolute risk is low, we found a higher incidence rate than previously described in the pediatric literature.

1. Introduction

Inflammatory bowel disease [IBD] is a complex systemic inflammatory condition associated with intestinal and extra-intestinal complications. Among the most devastating extra-intestinal complications of IBD is the development of venous thromboembolism [VTE]. VTE is a well-recognized complication of IBD in adults, particularly in the setting of active inflammation or in the post-operative period.[1–4] Current clinical practice guidelines on the use of VTE prophylaxis recommend adults with IBD who are hospitalized or have active disease with a previous VTE event receive chemoprophylaxis but recommend against chemoprophylaxis in children with IBD who are hospitalized and have not had a previous VTE event.[5] VTE prophylaxis is also recommended in children with ulcerative colitis [UC] in the post-operative setting or in those with acute severe UC in the presence of other factors known to increase the risk of VTE.[6,7]

The risk of VTE in children with IBD is not well described. The only population-based study of VTE incidence in patients under 20 years of age found a significantly lower rate of VTE in this age group compared to adults, but higher rates than in children and adolescents without IBD.[8] Because VTE events remain rare, the authors concluded that the risks and cost of VTE prophylaxis may not outweigh the benefits in children in the absence of other risk factors. Some clinical practice guidelines on the management of paediatric IBD recommend VTE prophylaxis in children requiring surgery or in patients who are otherwise at an increased risk of VTE, while others make no mention of VTE

prophylaxis.[6,7,9–11] Recent updates to these guidelines currently recommend VTE prophylaxis in all hospitalized IBD patients, regardless of age, due to the additional pro-thrombotic risk associated with COVID-19.[12,13] The mixed recommendations regarding thromboprophylaxis in children with IBD are primarily due to a lack of evidence, low perceived absolute risk and absence of risk–benefit analysis in the literature. Further understanding the absolute and relative rates of VTE in children with IBD may help provide guidance on whether thromboprophylaxis should be considered in selected patients.

Canada has amongst the highest incidence of paediatric IBD in the world.[14] The availability of validated, population-based cohorts of IBD patients derived from health administrative data allows for the evaluation of rare disease complications. We used these cohorts to report rates of VTE events among children with IBD using data from five provinces, comprising 79% of the Canadian population.[15]

2. Materials and Methods

This study was approved by the Research Ethics Boards at the Children's Hospital of Eastern Ontario, IWK Health Centre, Montreal Jewish General Hospital, University of Alberta, University of Calgary and University of Manitoba. This study was reviewed for privacy concerns by Alberta Health Services, Manitoba Health's Information Privacy Committee, Health Data Nova Scotia, ICES and the Commission d'Accès a l'Information du Québec.

2.1. Data sources

We used health administrative data from five Canadian provinces: Alberta, Manitoba, Nova Scotia, Ontario and Québec. Each province has universal healthcare coverage. Data include demographic information [age, sex, eligibility for provincial healthcare coverage, location of residence, mean neighbourhood income quintile] and all healthcare encounters [outpatient visits, hospitalizations] for all residents of each province eligible to receive health services [>99% of the population]. Mean neighbourhood income quintile is a validated proxy for individual-level income.[16] Supplementary Table 1 provides a detailed description of the data sources in each province. Data are linked deterministically using a unique encrypted identifier. In Ontario, all databases are maintained by ICES according to an agreement with the Ontario Ministry of Health and Ministry of Long-Term Care. In Manitoba, all administrative health data are maintained by Manitoba Health and the study utilized the population-based cohort of persons with IBD with matched controls in the University of Manitoba IBD Epidemiology Database. In Nova Scotia, the administrative health data were made available through Health Data Nova Scotia. In Alberta, the administrative health data were made available through Alberta Health Services. In Québec, data were made available through the Commission d'Accès du Québec. Databases are available to researchers in an uncleaned and unedited format.[17]

2.2. Identifying children with IBD

Children <16 years of age diagnosed with IBD were identified from health administrative data using previously validated province-specific algorithms [Supplementary Table 1].[18–21] Validated classification systems based on International Classification of Diseases [ICD]-9 and ICD-10 codes for Crohn's disease [CD, ICD-9 555, ICD-10 K50] and UC [ICD-9 556, ICD-10 K51] were used to differentiate between children with CD and UC. Children were identified as IBD-type unclassifiable when classification systems could not differentiate between CD and UC; these children were included in the overall analyses but not in any disease-specific analyses. The date of IBD diagnosis was considered to be a child's first healthcare encounter with a diagnostic code for IBD that qualified them as an IBD case. We included cases diagnosed during the following fiscal years: Alberta, 2005–2015; Manitoba, 2004–2014; Nova Scotia, 2001–2011; Ontario, 2002–2014; Québec, 2006–2008. These dates correspond to the introduction of ICD-10 coding in each province. The start of ICD-10 coding was selected as the beginning of the study due to improved ability to identify VTE events using ICD-10 codes relative to ICD-9 codes.

In all provinces, data were available for at least 3 years prior to the start of the study to facilitate the 3-year lookback period required to distinguish incident from prevalent cases.[18] Thus, all children included in the study were required to be continuously eligible for provincial healthcare coverage for 3 years prior to their IBD diagnosis without a diagnostic code for IBD. Children diagnosed with IBD prior to their third birthday were included in the study if they were continually eligible for provincial healthcare coverage from birth until their date of IBD diagnosis. All children were followed into adulthood, until death, end of eligibility for provincial health care [i.e. migration out of the province in which they were diagnosed] or the end of the study period [Alberta: 2017; Manitoba: 2018; Nova Scotia: 2016; Ontario: 2017; Québec: 2010]. Study end dates varied across provinces due to differing data availability.

2.3. Study design

We conducted a retrospective matched cohort study. Children with IBD were matched to five children without IBD based on birth date, sex, and duration of eligibility for provincial healthcare coverage in Alberta, Manitoba, Nova Scotia and Ontario; controls in Manitoba were additionally matched based on the first three digits of a child's postal code. Eligible controls were selected at random from all children eligible for universal provincial healthcare coverage in their respective province. Data on children without IBD were not available from Québec. Children without IBD were assigned an index date corresponding to the diagnosis date of their matched child with IBD.

Due to provincial privacy regulations, individual-level data cannot be shared across provincial borders. Therefore, a distributed network analysis was conducted in which the same analytical code was used to run analyses in each province and provincial results were then meta-analysed to produce overall national estimates.[14,22] Validation of this method has demonstrated that meta-analysis of pooled estimates produces similar results to individual-level data analysis in multi-variable regression models.[23]

2.4. Identifying children with venous thromboembolism

Hospitalizations lasting ≥48 h on or after the date of IBD diagnosis [children with IBD] or index date [children without IBD] involving a VTE were identified using ICD-10 codes for deep vein thrombosis [DVT], pulmonary embolism [PE] and cerebral sinovenous thrombosis [Supplementary Table 2], adapted from a previously validated code list.[24] We report the incidence of each outcome within 1 and 5 years of diagnosis in children with IBD and, due to rarity of events, within 5 years of index date in children without IBD. We analysed all types of VTE events as a combined outcome, and DVT and PE events individually. There was an insufficient number of cerebral sinovenous thrombosis events to evaluate these separately from other types of VTE. Only the first relevant thrombotic event was included in each analysis. That is, if a child experienced both a DVT and a PE, these would both be counted in the analyses specific to each subtype of VTE but only the first of these events would contribute to the overall count of VTE events.

Using data from Ontario only, we determined the proportion of children experiencing a VTE event who had an IBD-related surgery [intestinal resection or colectomy; see Supplementary Table 3 for a list of validated IBD surgical codes[25,26]] either during the same hospitalization or in the 60 days prior to their VTE hospitalization. This analysis was restricted to Ontario since it was the largest provincial paediatric IBD cohort and the only one with a sufficient number of children developing a VTE during the course of the study to report the number of children with surgery around the time of their VTE.

2.5. Statistical analysis

For each province, age at diagnosis is described using means and standard deviations; sex, type of IBD, living in a rural or urban household at the date of diagnosis [using the Statistics Canada definition], and mean neighbourhood income quintile are described using percentages.

The incidence rates of VTE, DVT and PE were calculated using the total number of events occurring in children with and without IBD divided by the total person-years of follow-up in each group. We report the incidence rates of VTE, DVT and PE for all types of IBD combined, and separately for CD and UC. When there were between one and five children experiencing a given outcome in Manitoba, Nova Scotia and Québec, the exact number of events could not be shared within the study team due to privacy regulations. When this occurred, we assigned a random number between one and five to represent the number of events. This random number of events was then used with

the known person-time to calculate province-specific incidence rates. In all other provinces [Alberta and Ontario], the exact number of events could be shared for meta-analysis but not published.

The relative and absolute differences in 5-year incidence rates of VTE and DVT among children with IBD, CD and UC were compared to children without IBD, as well as between children with CD vs UC. They are expressed as events per 10 000 person-years [PY] and compared using incidence rate ratios [IRR] and incidence rate differences [IRD] with 95% confidence intervals [CI]. The 5-year incidence rates of PE were also compared in children with IBD vs their matched controls; analyses stratified by disease sub-type could not be conducted due to the small numbers of PE events.

Generalized linear mixed-effects models [GLMMs] were used to pool province-specific incidence rates.[27] Unconditional fixed-effects GLMMs were used to estimate IRRs.[27] IRDs were pooled using fixed-effects Mantel–Haenszel methods.[28] Heterogeneity across provinces was described using the I^2 statistic; this describes the percentage of variability that results from between-province differences.

In provinces where the number of events was sufficient to ensure model convergence, we estimated the association between IBD and risk of VTE, DVT and PE using [1] multivariable modified Poisson regression for binary outcomes to estimate the relative rate [RR] of VTE events across groups[29] and [2] multivariable Cox proportional hazards models to compare the time-to-VTE using hazard ratios [HR]. Models were adjusted for age at diagnosis/index date, sex, mean neighbourhood income quintile and living in a rural household. The number of provinces included in each pooled analysis varied based on the event [i.e. VTE, DVT or PE] and comparison [i.e. children with vs without IBD or children with CD vs UC]. Fixed effects were used to pool RRs and HRs estimated from province-specific models; inverse-variance weights were used to weight the contribution of individual provinces to the overall pooled estimate. Statistical analyses were conducted using the GENMOD and PHREG procedures in SAS 9.4 [SAS Institute Inc.]. Meta-analyses were conducted using the meta[30] and metafor[31] packages in R.[32]

2.5.1. Sensitivity analysis

We conducted two sensitivity analyses. The first sensitivity analysis excluded Québec from the calculation of 1- and 5-year incidence rates of VTE, DVT and PE since data from Québec were not available for children without IBD. The second sensitivity analysis re-calculated incidence rates, IRRs and IRDs using extreme values [i.e. either one or five] when privacy regulations prevented the sharing of the actual number of events. For the comparison of children with and without IBD, we compared IRRs and IRDs assuming: [1] one event in both those with and without IBD, [2] one event in those with IBD and five events in those without IBD, [3] five events in those without IBD and one event in those with IBD, and [4] five events in those with and without IBD.

3. Results

3.1. Participant characteristics

A total of 3593 children with IBD [CD: 2201; UC: 1131] and 16 284 age- and sex-matched children without IBD were included in the study [Table 1].

3.2. Venous thromboembolism

The 1- and 5-year incidence rates of VTE among children with IBD were 81.16 [95% CI 56.40–116.80] and 31.18 [95% CI 23.69–41.02] per 10 000 PY, respectively [Table 2]. Within 5 years, there were 0.78 [95% CI 0.35–1.74] VTE events per 10 000 PY among

children without IBD. VTE events were more common in children with vs without IBD [IRR 38.84, 95% CI 16.59–90.93; IRD 29.59 95% CI 20.79–38.39 per 10 000 PY] [Table 3]. Findings were similar when adjusting for age, sex, income and rurality.

Among the 26 children with IBD experiencing a VTE event in Ontario within 5 years of IBD diagnosis, seven [26.9%] underwent intestinal resection or colectomy during the same admission as their VTE event or in the previous 60 days.

The incidence of VTE was elevated in children with CD and UC compared with children without these conditions [Table 3]. Before adjusting for potential confounders, children with CD were less likely to have a VTE event than children with UC [IRR 0.47, 95% CI 0.27–0.83; IRD –26.62, 95% CI –47.95 to –5.30 per 10 000 PY]. After adjusting for age, sex, rurality and income, the association between IBD type and the risk of VTE was similar in magnitude [Table 3].

3.3. Deep vein thrombosis

Among children with IBD, the incidence rate of DVT was 75.57 [95% CI 51.82–110.19] and 24.42 [95% CI 17.91–33.29] per 10 000 PY within 1 and 5 years of diagnosis, respectively [Table 2]; children without IBD had an incidence of 0.52 [95% CI 0.20–1.39] per 10 000 PY [IRR 45.39, 95% CI 16.15–127.52; IRD 23.20, 95% CI 15.44–30.97 per 10 000 PY] [Table 3]. The association between IBD and DVT was consistent when adjusting for age, sex, rurality and income [Table 3].

CD and UC were both consistently associated with an increased risk of DVT compared with children without IBD [Table 3]. The 5-year incidence of DVT was lower among children with CD compared to children with UC [IRR 0.46, 95% CI 0.25–0.87; IRD –21.54, 95% CI –40.72 to –2.37 per 10 000 PY]. The magnitude of this association was slightly attenuated and no longer significant when adjusting for age, sex, rurality and income.

3.4. Pulmonary embolism

The incidence of PE was 8.40 [95% 2.71–26.03] per 10 000 PY within the first year of IBD diagnosis [Table 2]. Within 5 years of IBD diagnosis/index date, the incidence of PE was 3.05 [95% CI 1.27–7.32] per 10 000 PY in children with IBD and 0.26 [95% CI 0.07–1.04] per 10 000 PY in children without IBD. PEs were significantly more common in children with IBD compared to children without IBD [IRR 12.51, 95% CI 2.43–64.49; IRD 3.02, 95% CI 0.12–5.92 per 10 000 PY] [Table 3]. The adjusted association between IBD and risk of PE was attenuated but remained statistically significant. Due to the small number of events, we were not able to separately analyse children with CD and UC or compare between the two types of IBD.

3.5. Sensitivity analyses

Incidence rates of VTE, DVT and PE among children with IBD were similar when excluding Québec [Supplementary Table 4]. Pooled incidence rates of VTE among children with IBD within 5 years of diagnosis varied slightly when replacing the random number of events [between one and five, and therefore not sharable for meta-analysis between provinces] with either extreme [i.e. one or five], ranging from 25.68 to 33.01 VTE events per 10 000 PY [Supplementary Table 5]. The risk of VTE remained significantly elevated when compared to controls.

4. Discussion

In this population-based Canadian study, we report substantially higher rates of VTE in children diagnosed with IBD as compared to children without IBD. Within 5 years of diagnosis, the incidence

Table 1. Characteristics of study children with and without inflammatory bowel disease, stratified by province

Characteristics	Alberta		Manitoba		Nova Scotia		Ontario		Québec[a]	Overall	
	With IBD [N = 703]	Without IBD [N = 3515]	With IBD [N = 163]	Without IBD [N = 814]	With IBD [N = 255]	Without IBD [N = 1275]	With IBD [N = 2136]	Without IBD [N = 10,680]	With IBD [N = 336]	With IBD [n = 3593]	Without IBD [n = 16284]
Age*, years, mean [SD]	10.8 [4.1]	10.8 [4.1]	11.8 [2.8]	11.9 [2.8]	11.6 [3.7]	11.6 [3.7]	11.4 [3.4]	11.5 [3.4]	12.9 [2.7]	11.7 [0.3][b]	11.4 [0.2][b]
Female, n [%]	307 [43.7]	1535 [43.7]	71 [43.6]	354 [43.5]	112 [43.9]	560 [43.9]	899 [42.1]	4495 [42.1]	150 [44.6]	1539 [42.8]	6944 [42.6]
Type of IBD, n [%]											
Crohn's disease	407 [57.9]	—	103 [63.2]	—	159 [62.4]	—	1247 [58.4]	—	285 [84.8]	2201 [61.3]	
Ulcerative colitis	217 [30.9]	—	60 [36.8]	—	80 [31.4]	—	738 [34.6]	—	36 [10.7]	1131 [31.5]	
IBD unclassifiable[c]	79 [11.2]	—	—	—	16 [6.3]	—	151 [7.1]	—	15 [4.5]	261 [7.3]	
Rural[*,d], n [%]	140 [19.9]	866 [24.6]	38 [23.3]	180 [22.1]	75 [29.4]	461 [36.2]	223 [10.4]	1276 [11.9]	60 [17.9]	536 [14.9]	2783 [17.1]
Mean neighbourhood income quintile[*,d], n [%]											
Q1	115 [16.4]	734 [20.9]	15 [9.2]	75 [9.2]	63 [24.7]	292 [22.9]	277 [13.0]	2104 [19.7]	45 [13.4]	515 [14.3]	3205 [19.7]
Q2	142 [20.2]	721 [20.5]	23 [14.1]	133 [16.3]	47 [18.4]	257 [20.2]	374 [17.5]	2011 [18.8]	62 [18.4]	648 [18.0]	3122 [19.2]
Q3	141 [20.1]	611 [17.4]	34 [20.9]	136 [16.7]	50 [19.6]	262 [20.6]	429 [20.1]	2191 [20.5]	49 [14.6]	703 [19.6]	3200 [19.7]
Q4	115 [16.4]	626 [17.8]	37 [22.7]	197 [24.2]	43 [16.9]	244 [19.1]	501 [23.5]	2219 [20.8]	105 [31.2]	801 [22.3]	3286 [20.2]
Q5	180 [25.6]	714 [20.3]	52 [31.2]	259 [31.8]	52 [20.4]	218 [17.1]	550 [25.7]	2095 [19.6]	70 [20.8]	904 [25.2]	3286 [20.2]
VTE event, n [%]											
Within 1 year of IBD diagnosis or index date	9 [1.3]	1—5[e] [0.03–0.1]	1—5[e] [0.6–3.1]	0 [0]	1—5[e] [0.4–2.0]	0 [0]	16 [0.7]	0 [0]	0 [0]	27–35 [0.8–1.0][e]	1–5 [0.006–0.03]
Within 5 years of IBD diagnosis or index date	13 [1.8]	1—5[e] [0.03–0.1]	1—5[e] [0.6–3.1]	0 [0]	1—5[e] [0.4–2.0]	0 [0]	26 [1.2]	1—5[e] [0.009–0.05]	1—5[e] [0.3–1.5]	42–54 [1.2–1.5][e]	2–10 [0.01–0.06][e]

Abbreviations: IBD, inflammatory bowel disease; VTE, venous thromboembolism.

[a]No data on children without IBD were available in Québec.

[b]Province-specific means were pooled using a random effects model.

[c]Only available in some provinces [see Supplementary Table 1].

[d]Totals may not add to 100% due to missing data for some children.

[e]Actual number of events suppressed due to privacy regulations and replaced with the range. Ranges for overall estimates account for the possible number of events in each province where these numbers were suppressed.

*Defined based on date of IBD diagnosis [children with IBD] or index date [children without IBD].

Table 2. The 1- and 5-year incidence rates of venous thromboembolism, deep vein thrombosis and pulmonary embolism in children with and without inflammatory bowel disease. Data are reported as incidence rates per 10 000 person-years and are stratified by disease type

Type of thrombosis	Within 1 year of IBD diagnosis		Within 5 years of IBD diagnosis or index date			
	With IBD		With IBD		Without IBD	
	IR per 10 000 PY [95% CI]	Between-province heterogeneity [I²]	IR per 10 000 PY [95% CI]	Between-province heterogeneity [I²]	IR per 10 000 PY [95% CI]	Between-province heterogeneity [I²]
Inflammatory bowel disease						
VTE	81.16 [56.40–116.80]	0.0%	31.18 [23.69–41.02]	18.1%	0.78 [0.35–1.74]	0.0%
DVT	75.57 [51.82–110.19]	29.6%	24.42 [17.91–33.29]	34.1%	0.52 [0.20–1.39]	0.0%
PE	8.40 [2.71–26.03]	0.0%	3.05 [1.27–7.32]	0.0%	0.26 [0.07–1.04]	68.5%
Crohn's disease						
VTE	59.41 [34.50–102.32]	0.0%	25.13 [16.98–37.19]	34.5%	0.68 [0.22–2.10]	17.3%
DVT	54.84 [31.15–96.57]	0.0%	18.08 [11.39–28.70]	0.0%	0.23 [0.03–1.60]	0.0%
PE	0 events	—	0 events	—	0.45 [0.11–1.80]	68.0%
Ulcerative colitis						
VTE	115.35 [66.98–198.66]	0.0%	49.58 [33.76–72.82]	45.1%	1.17 [0.38–3.64]	0.0%
DVT	75.57 [51.82–110.19]	29.6%	39.97 [26.06–61.30]	41.6%	1.17 [0.38–3.64]	0.0%
PE	17.75 [4.44–70.95]	0.0%	7.59 [2.85–20.22]	0.0%	0 events	—

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; IBD, inflammatory bowel disease; IR, incidence rate; PE, pulmonary embolism; PY, person-years; VTE, venous thromboembolism.
There were no VTE events within 1 year among children without IBD.

Table 3. Comparison of 5-year incidence rates of venous thromboembolism, deep vein thrombosis and pulmonary embolism in children with and without inflammatory bowel disease

Type of thrombosis	Unadjusted				Adjusted					
	IRR [95% CI]	Between-province heterogeneity [I²]	IRD per 10 000 PY [95% CI]	Between-province heterogeneity [I²]	RR* [95% CI]	Between-province heterogeneity [I²]	Number of provinces	HR† [95% CI]	Between-province heterogeneity [I²]	Number of provinces
Inflammatory bowel disease vs control [reference]										
VTE	38.84 [16.59–90.93]	0.0%	29.59 [20.79–38.39]	10.8%	22.72 [11.40–45.26]	0.0%	2 [AB, ON]	22.91 [11.50–45.63]	0.0%	2 [AB, ON]
DVT	45.39 [16.15–127.52]	0.0%	23.20 [15.44–30.97]	62.9%	31.86 [12.07–84.13]	—	1 [ON]	31.69 [12.31–81.61]	—	1 [ON]
PE	12.51 [2.43–64.49]	67.5%	3.02 [0.12–5.92]	12.5%	—	—	—	6.72 [2.10–21.53]	—	1 [ON]
Crohn's disease vs control [reference]										
VTE	32.64 [9.70–109.87]	0.0%	21.70 [11.87–31.54]	0.0%	23.86 [8.26–68.88]	—	1 [ON]	20.76 [7.72–55.84]	0.0%	2 [AB, ON]
DVT	83.21 [11.07–625.29]	0.0%	18.79 [9.74–27.84]	0.0%	41.84 [9.41–185.96]	—	1 [ON]	41.60 [9.56–181.04]	—	1 [ON]
Ulcerative colitis vs control [reference]										
VTE	42.73 [12.93–141.18]	0.0%	49.50 [29.98–69.02]	63.5%	19.23 [6.17–59.91]	—	1 [ON]	19.18 [6.39–57.59]	—	1 [ON]
DVT	34.62 [10.33–116.08]	0.0%	39.72 [22.18–57.25]	58.3%	21.39 [5.84–78.29]	—	1 [ON]	21.29 [6.04–75.05]	—	1 [ON]
Crohn's disease vs ulcerative colitis [reference]										
VTE	0.47 [0.27–0.83]	0.0%	−26.62 [−47.95 to −5.30]	30.1%	0.68 [0.35–1.32]	—	1 [ON]	0.52 [0.29–0.94]	36.0%	3 [AB, NS, ON]
DVT	0.46 [0.25–0.87]	0.0%	−21.54 [−40.72 to −2.37]	0.0%	0.76 [0.37–1.56]	—	1 [ON]	0.58 [0.30–1.11]	70.2%	2 [AB, ON]

Abbreviations: AB, Alberta; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; IRD, incidence rate difference; IRR, incidence rate ratio; NS, Nova Scotia; ON, Ontario; PE, pulmonary embolism; PY, person-years; RR, relative rate; VTE, venous thromboembolism.

Because of the small number of PE events, the modified Poisson models comparing children with and without IBD did not converge and we could not present disease-specific analyses.

*Modified Poisson models for binary outcomes adjusted for age, sex, rural/urban household and median neighbourhood income quintile.

†Cox proportional hazards models adjusted for age, sex, rural/urban household and median neighbourhood income quintile.

rates of any VTE, DVT or PE among children with IBD were 31.18, 24.42 and 3.05 per 10 000 PY, respectively. These rates were 12- to 45-fold higher than controls. While incidence was elevated in both CD and UC, the risk of VTEs in children with UC was nearly double the risk in children with CD. Only a quarter of VTE events were associated with an IBD-related surgery. In addition, we noted that the majority of VTE events occurred in the first year following diagnosis for patients with both CD and UC, a time when they are more likely to have severe, active disease. These findings confirm that VTE is an important complication of IBD in children.

To our knowledge, this is the first population-based North American study to report the risk of VTE in paediatric IBD. The only other population-based study used Danish health administrative data to demonstrate VTE risk in all ages; while the absolute risk was lower in patients less than 20 years old than in older age groups, the relative risk compared to controls was highest in paediatric patients.[8] Another study was conducted using data from an international prospectively collected safety registry where data were collected using a monthly survey of >150 gastroenterologists from 26 countries.[33] Of note, we found that the incidence of VTEs in Canadian children was approximately three-fold higher than rates reported in Danish children and more than six-fold higher than rates reported in the safety registry. For example, we found that overall VTE risk in our patients was 31.18 per 10 000 PY, while the Danish cohort had rates of 8.9 per 10 000 PY and the safety registry reported rates of 4.86 per 10 000 PY. Similarly, risk of DVT in IBD patients in our study was 24.42 per 10 000 PY, compared to 5.4 per 10 000 PY in Denmark. Risk of PE was similar in Canada and Denmark [3.05 vs 3.4 per 10 000 PY]. The incidence of VTEs in children without IBD was similar in Canada and in the Danish study.[8] Adjusted hazard ratios were therefore much higher in Canada compared to Denmark for IBD [22.9 vs 6.6], CD [20.8 vs 6.0] and UC [19.2 vs 6.4]. We restricted our cohort to incident cases only while the Danish study included both prevalent and incident cases, potentially contributing to the differences between the two studies. The incidence of VTE in the safety registry is probably underreported due to non-response among participating gastroenterologists and recall bias [i.e. physicians only report the most severe VTE events to the registry].

We demonstrated a higher incidence of VTEs in the first year following diagnosis, suggesting a role of bowel and systemic inflammatory burden in the pathophysiology of VTE development. Stabilization of disease activity after the first year may have also accounted for the reduced overall risk of developing VTE beyond 1 year in our cohort. Another population-based study primarily of adult patients from the UK found similar incidence of VTE in their IBD population [2.6 per 1000 PY], with much higher rates during hospitalizations [25.2 per 1000 PY], disease flares [9.0 per 1000 PY] or chronically active disease states [5.4 per 1000 PY], even in the ambulatory setting.[2] It is noteworthy that the incidence of VTE in our study during the first year of diagnosis [81.2 per 10 000 PY or 8.12 per 1000 PY] was very similar to the incidence noted in UK adults in the setting of disease flare [9.0 per 1000 PY], reinforcing the importance of disease activity in the risk of VTEs. Therefore, the absolute risk of VTEs in children with active disease may be similar to rates in adult IBD patients.

Canadian clinical practice guidelines recommend VTE prophylaxis in hospitalized adult IBD patients even when in remission, extrapolating from recommendations for non-IBD hospitalized patients.[5] However, thromboprophylaxis was not recommended in hospitalized children with IBD in the absence of a previous VTE event. This was a weak recommendation, based on low certainty of

evidence according to GRADE criteria. The decision was based primarily on the lower absolute risk of VTE in children compared to adults, as demonstrated from a single population-based study,[8] and the discomfort of subcutaneous injection.[5] More recent European and Canadian paediatric practice guidelines did not address the use of prophylaxis against VTE in paediatric CD.[10,11] However, European practice guidelines recommended prophylaxis in children with severe UC with one or more risk factors, such as smoking, oral contraceptive use, complete immobilization, central venous catheters, obesity, concurrent infection, known prothrombotic disorder, previous VTE and family history of VTE.[7] Guidelines published during the current COVID-19 pandemic recommend all patients hospitalized for moderate-to-severe IBD receive prophylaxis.[12,13] Paediatric gastroenterologists, although aware of the increased risk of VTE in children with IBD, are hesitant to provide prophylaxis for their patients based on the current lack of literature [e.g. clinical practice guidelines].[34] Our data suggest that VTE prophylaxis in children could be clinically appropriate, especially in a context of hospitalization for active inflammation or surgical intervention. Updated clinical practice guidelines may be needed.

The strengths of this study include its large sample of paediatric IBD patients, population-based nature and the ability to assess the risk of VTEs longitudinally in an inception cohort. However, as with all studies that use health administrative data, there are limitations. There is always a risk of misclassification bias; however, we used validated algorithms to identify both diagnosis of paediatric-onset IBD and VTE. Since the algorithm to identify VTE events was only validated in Canadian hospitalization data from the province of Alberta,[24] it is possible we missed some cases diagnosed in the ambulatory setting. However, it is unlikely that a child with IBD diagnosed with VTE would remain an outpatient. In addition, it is unlikely that children with a VTE would be hospitalized for less than 48 h [and therefore missed by our algorithm], since all children would receive consultation from a haematologist, undergo investigation for an underlying pro-thrombotic condition, be counselled and started on appropriate therapy, and monitored for response to therapy with bloodwork, including thrombosis measures. The algorithm we used to identify VTE events did not include mesenteric thrombosis or thrombotic events related to an indwelling catheter [e.g. PICC line]. The magnitude of the comparison between children with and without IBD may have been biased if the threshold for admitting a child with a DVT differed between those with and without IBD. The codes used to identify VTE had a sensitivity of 75%, which may have additionally resulted in an underestimate of the incidence of VTE in our study.[24] Health administrative data do not contain information on risk factors for VTE. This includes disease phenotype or activity and prescription medication in either the inpatient or the outpatient setting [e.g. corticosteroids, anticoagulants]. In addition, we did not have data on other chronic conditions among children with and without IBD in our study. It has been previously estimated that 2.5% of children in Ontario are living with a chronic condition[35] and we would expect this proportion to be similar among the randomly selected children without IBD included in our study. The follow-up periods were slightly different in each province due to data availability. There were no paediatric clinical practice guidelines that recommend prophylaxis in children with IBD that were published during the time period of this study, so we anticipate that rates of prophylaxis were very low and did not change over the course of the study. Improvements in the treatment of IBD in children have occurred over the study period; however, we were not able to determine if the risk of VTE events has changed

over time due to the small number of VTE events. We could not determine whether VTE was associated with treatment or disease severity. We included VTE events that occurred during a hospitalization [i.e. the patient was admitted to hospital prior to their VTE event] and events that occurred outside of the hospital for which patients were later admitted to hospital. Because we had so few VTE events in our study, were not able to differentiate between these two types of VTE. The rarity of VTE outcomes limited our ability to provide adjusted rates for all participating provinces. This decrease may have contributed to adjusted analyses being no longer significant, despite effect estimates similar in magnitude to the unadjusted analysis. In addition, privacy regulations prevented the sharing of data when there were small numbers of events. The data from Québec did not contain a cohort of non-IBD children, and we could therefore only report absolute risks from that province. The rarity of outcome rates prevented our ability to assess cerebral sinovenous thrombosis rates. Previous studies have reported a high proportion of cerebral sinovenous thrombosis among thrombotic events in children with IBD; however, both studies may have been subject to reporting biases with more severe thrombotic events more likely to be published as case series/reports or reported to a safety registry.[33,36] Finally, we did not have a sufficient number of VTE events to report the incidence of VTE events separately for medical and surgical admissions, among individuals with co-occurring pro-thrombotic conditions, or among those experiencing the VTE event during a hospital admission or in an ambulatory setting requiring subsequent hospitalization.

In summary, we have demonstrated that the risk of VTE was much higher in children with IBD compared to controls. In addition, while the absolute risk was low, it was much higher than the previous Danish population-based study and in the study conducted from a prospectively collected safety registry, and similar to the risk reported in adults with IBD. VTE rates were highest in UC patients, and in the first year following diagnosis. Future research should assess the risks and benefits of thromboprophylaxis in this population, as well as identify patients at greatest risk based on clinical, biological and demographic criteria with the goal of informing clinical practice guidelines on the use of VTE prophylaxis in paediatric IBD.

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Conflict of Intereast

M.E.K., A.B., M.W.C., G.C.N., T.A.S., J.L.J., S.K.M., L.M.L., J.N.P.S., D.R.M., T.J.B.D., S.G.F., S.S., Z.N., D.T., Y.C., C.F., S.C. and S.S. have no known conflicts of interest. G.G.K. has received honoraria for speaking or consultancy from Abbvie, Janssen, Pfizer and Takeda. He has received research support from Janssen, Abbvie, GlaxoSmith Kline, Merck and Shire. He shares ownership of a patent: TREATMENT OF INFLAMMATORY DISORDERS, AUTOIMMUNE DISEASE, AND PBC. UTI Limited Partnership, assignee. Patent 62/ 555,397. A.R.O. has been on advisory boards of AbbVie Canada, Janssen Canada and Nestle. He has received unrestricted educational grants from AbbVie Canada and Janssen Canada. His site is involved with clinical trials for AbbVie, Pfizer, Takeda, Eli Lily and Celgene. H.S. has consulted to Amgen Canada, Bristol-Myers Squibb Canada, Sandoz Canada, Roche Canada, Takeda Canada and Guardant Health. A.M.G. has been a consultant for Abbvie, Amgen, BristolMyersSquibb, Janssen, Lilly, Pfizer and Roche; has received speaker fees from Abbvie, Janssen, Nestle and investigator-initiated grant support from Abbvie. L.E.T. has received investigator initiated funding from Janssen Canada, and served on advisory boards for AbbVie Canada,

Author Contributions

Data Availability Statement

Acknowledgments

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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