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CLINICAL AT

Twenty-first Century Trends in the Global Epidemiology of Pediatric-Onset Inflammatory Bowel Disease: Systematic Review

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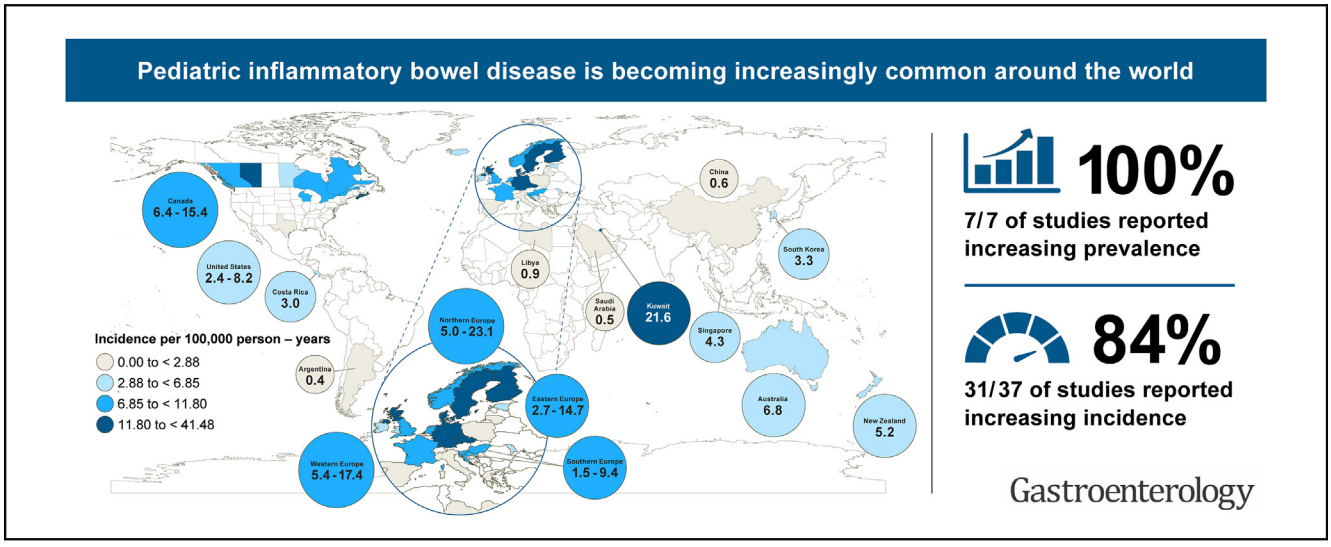

BACKGROUND & AIMS: The incidence of inflammatory bowel disease (IBD) is increasing internationally, particularly in nations with historically low rates. Previous reports of the epidemiology of pediatric-onset IBD identified a paucity of data. We systematically reviewed the global trends in incidence and prevalence of IBD diagnosed in individuals <21 years old over the first 2 decades of the 21st century. **METHODS:** We systematically reviewed studies indexed in MEDLINE, EMBASE, Airiti Library, and SciELO from January 2010 to February 2020 to identify population-based studies reporting the incidence and/or prevalence of IBD, Crohn's disease, ulcerative colitis, and/or IBD-unclassified. Data from studies published before 2000 were derived from a previously published systematic review. We described the geographic distribution and trends in

children of all ages and limiting to very early onset (VEO) IBD. **RESULTS:** A total of 131 studies from 48 countries were included. The incidence and prevalence of pediatric-onset IBD is highest in Northern Europe and North America and lowest in Southern Europe, Asia, and the Middle East. Among studies evaluating trends over time, most (31 of 37, 84%) studies reported significant increases in incidence and all (7 of 7) reported significant increases in prevalence. Data on the incidence and prevalence of VEO-IBD are limited to countries with historically high rates of IBD. Time trends in the incidence of VEO-IBD were visually heterogeneous. **CONCLUSIONS:** Rates of pediatric-onset IBD continue to rise around the world and data are emerging from regions where it was not previously reported; however, there remains a paucity of data on VEO-IBD and on pediatric IBD from developing and recently developed countries.

Keywords: Crohn's Disease; Ulcerative Colitis; Childhood; Incidence; Prevalence.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Rates of inflammatory bowel disease are increasing worldwide, but data on trends in children are lacking, particularly from developing and newly developed nations.

NEW FINDINGS

The incidence and prevalence of pediatric inflammatory bowel disease are continuing to climb, and data are emerging from regions where rates were previously not reported. There remains a paucity of population-based studies.

LIMITATIONS

The availability, quality, and heterogeneous nature of population-based studies limited the full description of the international epidemiology of inflammatory bowel disease in children.

IMPACT

Growing global rates of inflammatory bowel disease will place increasing pressure on children, their families, and health care systems, and understanding the burden of pediatric inflammatory bowel disease is important to helping understand its pathogenesis.

Inflammatory bowel disease (IBD) diagnosed in childhood is different from IBD diagnosed during adulthood.[1,2] Children are more often diagnosed before disease-related complications arise. For example, pediatric-onset Crohn's disease (CD) is most often diagnosed with an inflammatory behavior, before fibrostenotic or penetrating complications develop.[1,3] However, being diagnosed with IBD during childhood presents unique challenges, such as the psychological effects of chronic disease on the patient and family, missed school, and linear growth delay.[4] The cost of caring for children with IBD surpasses that of older individuals, and children face a lifetime of health care.[4] Studying IBD in children provides unique opportunities to study environmental exposures in IBD because those diagnosed early in life have experienced fewer environmental factors.

Previous systematic reviews described increasing incidence and prevalence of IBD among both children and adults.[5–9] IBD is most common among Westernized countries, but there is a paucity of data on the epidemiology of IBD in industrializing and newly industrialized countries. More recent systematic reviews of adult-onset IBD have reported data from an increasing number of countries, where IBD is emerging and/or rapidly accelerating in incidence.[6,8] The global epidemiology of IBD in children and adolescents remains a knowledge gap.

Recent studies have demonstrated rapid growth in the incidence of very early onset IBD (VEO-IBD) in countries with long-standing high rates of IBD among children and adults.[10,11] VEO-IBD, often defined as IBD diagnosed before 6 years of age, is associated with a different clinical phenotype, treatment response, and outcomes relative to children diagnosed at older ages.[12–14] Previous systematic reviews on the incidence and prevalence of pediatric-onset IBD have not explicitly described the epidemiology of VEO-IBD.

We systematically reviewed the literature to provide an updated landscape of the incidence and prevalence of pediatric-onset IBD, including VEO-IBD. We describe geographic variation and how the epidemiology has evolved over time.

Methods

This systematic review is based on a previously registered protocol[15] (PROSPERO CRD42019125193) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[16]

Study Identification and Selection

We searched MEDLINE, EMBASE, CNKI, Airiti Library, and SciELO from 2010 to February 2020 to using MeSH terms and keywords for IBD, CD, and ulcerative colitis (UC) combined with MeSH terms and keywords for epidemiology, incidence, and prevalence. We searched for pediatric papers published since 2010 and for papers of all ages published since 2017. Studies published before this were identified from previous systematic reviews on the incidence and prevalence of IBD.[5,7,8] The full search strategy is outlined in Supplementary Table 1. Additional studies published since the end of the literature

Abbreviations used in this paper: **CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease type unknown or unclassifiable; UC, ulcerative colitis; VEO-CD, very early onset Crohn's disease; VEO-IBD, very early onset inflammatory bowel disease; VEO-IBDU, very early onset inflammatory bowel disease type unknown or unclassifiable; VEO-UC, very early onset ulcerative colitis.**

Most current article

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search were identified through active surveillance of the published literature.

Eligible studies were population-based observational studies describing the incidence and/or prevalence of IBD, CD, UC, or IBD type unknown or unclassifiable in the source data (IBDU) among individuals <21 years of age. IBD type unknown refers to an inability to distinguish between CD and UC based on clinical, endoscopic, radiologic, or histologic criteria, whereas IBD unclassifiable refers to an inability to distinguish between CD and UC based on diagnostic codes in routinely collected health data (ie, an individual has diagnostic codes for both CD and UC). Population-based studies were those providing estimates of incidence and/or prevalence for the population within a well-defined jurisdiction (ie, studies identifying all individuals living with IBD in a given region qualified by the total population or person-time at risk). Studies reporting the incidence and/or prevalence of IBD (or any subtype) in people of all ages were included if they also reported pediatric-specific data. We excluded any studies in which the incidence or prevalence of IBD in a region was calculated based on fewer than 5 cases. No eligibility restrictions were placed on date of publication, language, or region.

Identified abstracts were assessed for eligibility through 2 methods: (1) independently by at least 3 independent individuals using the InsightScope crowdsourcing platform,[17,18] or (2) 2 study authors (MEK and EIB). Abstracts identified through InsightScope for inclusion by ≥2 individuals were retained for full-text review and studies identified for inclusion by 1 individual and excluded by ≥2 individuals were additionally assessed for inclusion by MEK. The full text of identified studies were similarly assessed using 2 approaches: (1) independently by 3 independent reviewers using the same platform with eligibility confirmed by a member of the study team (MEK, SGF, EIB), and (2) study authors (MEK and EIB). A previous validation study of the InsightScope platform reported a sensitivity of 100% and specificity of 48.6% at the abstract-screening stage and sensitivity of 100% and specificity of 73.9% at the full-text screening stage.[18] Conflicts arising during the full-text stage of the review were resolved by consensus discussion. Cohen's kappa was used to calculate agreement between studies assessed by 2 study authors.

Before being added to the study team, all individuals participating in the crowdsourced InsightScope team were required to complete a test set of 100 abstracts assessed for eligibility by MEK and EIB with a sensitivity of ≥80%.[17]

Data Extraction and Risk of Bias

Data from identified studies were extracted by 1 author and verified independently by a second (MEK, SGF, LM, and EIB) using a piloted data extraction form in REDCap electronic data capture tools hosted at the Children's Hospital for Eastern Ontario.[19] Data presented in figures were extracted using WebPlotDigitizer.[20] Extracted data included geographic region(s); method of case identification and ascertainment; year(s) of data collection; incidence and/or prevalence of IBD, CD, UC, or IBDU; and changes in the incidence and/or prevalence of IBD, CD, UC, or IBDU over time in all age-reported pediatric age groups (ie, where the maximum age at diagnosis was <21 years). Incidence rates were extracted as the (1) number of new diagnoses of IBD per specified number of people or person-years; and/or (2) number of new diagnoses of IBD and the number of people or person-time at risk within a defined geographic region and time frame. Prevalence rates were extracted as the (1) number of people living with IBD per specified number of people, and/or (2) number of people living with IBD and the number of people living within a defined geographic region. We extracted incidence and prevalence at all time points for all available sex- and age-specific subgroups reported in the manuscript. When studies evaluated trends over time, we extracted the effect measure and associated confidence interval, *P* value, and statistical test used to evaluate the trend. When data were not clear, authors of included studies were contacted.

To obtain complete data on the global incidence and prevalence of IBD in the 21st century, we additionally extracted data on the incidence and prevalence of pediatric-onset IBD, CD, UC, and/or IBDU from a previous systematic review.[5] We limited these data extraction to (1) studies in which data were reported on or after 2000 (including studies that reported data for a range of years that included time points on or after 2000), and (2) did not duplicate data already included in this review. Extracted data included the incidence and/or prevalence of IBD in both the overall age group and VEO-IBD, as described previously.

The risk of bias in individual studies was assessed using a version of the Newcastle-Ottawa Scale[21] adapted to assess for bias in the identification and representativeness of IBD cases in the population. The risk of bias was assessed independently by 2 study authors (MEK, EIB). Conflicts were resolved through consensus.

Data Synthesis

Incidence rates are summarized as the number of new cases per 100,000 person-years, and prevalence as the total number of cases per 100,000 at-risk population. When studies reported numerators and denominators, incidence and prevalence were calculated with exact confidence intervals. Incidence rates and prevalence for each study are summarized for each age group and time point reported in the paper.

Age categorizations. We included data on the incidence and prevalence of IBD, CD, UC, and/or IBDU among all age groups reported in each included manuscript. For our primary synthesis of incidence and prevalence (trends over time and geographic variation, described later in this article), we included studies that combined male and female individuals and included both childhood- and adolescent-onset IBD, CD, UC, and IBDU (ie, had a lower age limit <2 years and upper age limit >10 but <21 years). When studies reported multiple eligible age groups, we selected the highest upper age limit (ie, included the largest number of cases).

We also described the incidence and prevalence of VEO-IBD, VEO-CD, and VEO-UC. Our study protocol defined VEO-IBD as IBD diagnosed at <6 years of age. Because of the heterogeneity in the literature, we expanded our definition of VEO-IBD to IBD diagnosed at <5, <6, or <7 years. We planned to report incidence and prevalence of infantile-onset IBD (ie, diagnosed at <2 years of age). However, infantile-onset IBD was not reported in any study identified in our review. In addition, we had planned to stratify by the age categorizations described in the Paris Classification.[22] However, the epidemiology of IBD in the A1b age categorization (10–16 years at diagnosis) was reported

in only 2 studies: 1 describing incidence[3] and 1 describing prevalence.[23]

Trends over time. Trends in the incidence and prevalence of IBD, CD, and UC from 2000 to present day were plotted to describe temporal patterns in the 21st century using all available time points. Studies reporting multiple time points were connected to depict trends in the same population. When incidence and prevalence data were only available as an aggregate estimate over a range of years, incidence was plotted at the midpoint of the interval. If the midpoint of this interval predated the year 2000 but included data aggregated after 2000, data were plotted at the year 2000. When multiple studies reported incidence or prevalence for the same country, national data were plotted with the following exceptions: (1) data from each Canadian province and American state were plotted separately; (2) data from each country in the United Kingdom were plotted separately; and (3) regional data (when available) were plotted instead of national data that were reported as a single time point but aggregated over a wide time frame that included $\geq$5 years before 2000. If national data were not available, regional data were plotted. When multiple studies included data for the same country (or region within a country), studies were included if there was limited overlap between the time intervals included in the studies. When there was an overlap of time points, we included the study with the largest number of unique time points.

Trends in incidence rates over time were plotted for children diagnosed at any age and for those with VEO-IBD (defined previously). Trends in prevalence over time were only plotted for children diagnosed at any age due to a limited number of studies describing the prevalence of VEO-IBD. Unique colors are used for each continent for our plot of trends of incidence and prevalence among all ages and for each country for our plots of trends in incidence and prevalence of VEO-IBD. To account for potential differences in incidence and prevalence rates arising from our combination of 3 age groups in the VEO-IBD plot, we used shapes to identify age-specific estimates.

Geographic variation. Choropleth maps were created to visualize global patterns in the incidence and prevalence of pediatric-onset IBD, CD, and UC. Colors were assigned based on quartile of incidence or prevalence. When there were multiple estimates of incidence or prevalence for a given country, we selected the most recent national estimate. If national estimates were not available, we selected the most recent regional estimate and extrapolated this to the entire country, with the following exceptions: (1) American data were mapped at the state level; (2) Canadian data were mapped at the province level; and (3) data from Scotland, England, and Wales were mapped using country-specific data, with data from the whole of the United Kingdom mapped to Northern Ireland. Maps were created for the following age groups: (1) incidence and prevalence of IBD diagnosed during childhood and adolescence as defined previously; and (2) incidence of VEO-IBD. Prevalence of VEO-IBD was not mapped due to sparsity of data.

Comparison of CD and UC. When studies described the epidemiology of CD and UC, we compared the relative incidence and prevalence of one subtype to the other by calculating the ratio of CD to UC (CD:UC). We plotted trends in the CD:UC ratio to visualize changes in the relative incidence of the 2 subtypes over time and created maps to describe geographic variation in this ratio. These analyses were restricted to studies reporting combined incidence or prevalence of childhood- and adolescent-onset IBD, as described previously.

RStudio Software version 1.2.5033 with the epiR, countrycode, ggplot2, rnaturalearth, RColorBrewer, and tmap packages, was used for all analyses and figures.[24–30]

Results

Description of Included Studies

Our database search yielded 12,807 records; an additional 3 records were identified after reviewing references of previous systematic reviews on the incidence and/or prevalence of IBD (Supplementary Figure 1). After removing duplicates, 8096 records remained and the full texts of 376 articles were assessed. Seven additional studies were identified after the formal literature search was completed. Our review yielded a total of 117 studies from 42 countries that reported the incidence and/or prevalence of pediatric-onset IBD, CD, UC, and/or IBDU. An additional 14 studies from 11 countries were included in the systematic review by Benchimol et al.,[5] bringing the total number of countries with incidence and/or prevalence data in childhood IBD to 47. Agreement between reviewers was 98.4% (kappa: 0.65) for abstracts and 98.0% (kappa: 0.96) for full texts of manuscripts. Most studies were at low risk of both selection and misclassification bias (Supplementary Table 2). The characteristics of included studies are described in Supplementary Table 2. A list of studies excluded following full-text review, including reasons for exclusion, is provided in Supplementary Table 3. All extracted data and interactive maps are available at https://cangiec.shinyapps.io/PIBD_epi/ and online at https://osf.io/bujrt/?view_only=a5a8f060cd7f4754bec2d39deb4dabf3.

Incidence of IBD

The incidence of IBD, CD, UC, and/or IBDU in children and/or adolescents was described in 112 studies from 42 countries (99 studies from the current review and 13 studies from Benchimol et al.[5]). Reginal incidence rates are reported in Table 1. The earliest and most recent estimates from each study are summarized in Supplementary Table 4. Overall, age-, and sex-specific incidence rates at additional time points are available for download and at https://cangiec.shinyapps.io/PIBD_epi/.

Geographic distribution. The incidence of pediatric-onset IBD is highest in Canada, Northern Europe, and New Zealand and lowest in Southern Europe, Africa, Asia, and South America (Figure 1). Incidence per 100,000 person-years ranged from 0.5 to 21.6 in Asia, 0.4 to 3.0 in Central and South America, 0 to 21.3 in Europe (excluding the Faroe Islands, which had an incidence of 41.5 per 100,000 person-years), 2.4 to 15.4 in North America, and 5.2 to 6.8 in Oceania (Table 1). The geographic distribution of regions with high and low incidence rates were similar when combining all IBD types and when stratifying by subtype.

Trends over time. Trends in the incidence of IBD, CD, UC, and/or IBDU were reported in 39 studies from 20 countries (Supplementary Table 4). Plots of trends over time

Table 1. Most Recent Regional Incidence and Prevalence of Pediatric-Onset IBD, CD, and UC

	Incidence per 100,000 person-years			Prevalence per 100,000		
Region	IBD	CD	UC	IBD	CD	UC
Africa	0.9			3.6		
Asia						
Eastern Asia	0.6 to 3.3	0.3 to 2.8	0.1 to 0.6		7.2	15.0
Southeastern Asia	4.3	2.1	1.0			
Southern Asia						
Western Asia (Middle East)	0.5 to 21.6	0.3 to 15.3	0.2 to 6.0	5.0 to 52.2	9.32	
Caribbean				23.9	7.0	10.9
Central and South America	0.4 to 3.0	0.2	0.2		0.0005	0.0009
Europe						
Eastern Europe	2.7 to 14.7	0.2 to 9.8	1.3 to 4.0			
Northern Europe[a]	0 to 23.1	0 to 8.3	0 to 14.8	75.0	29.0	30.0
Southern Europe	0 to 9.4	0 to 6.1	0 to 9.1	31.0	15.5	15.5
Western Europe	5.4 to 17.4	2.1 to 15.3	1.5 to 8.4	58.9 to 66.3	37.7 to 39.5	12.5 to 23.7
North America						
Canada	6.4 to 15.4	4.3 to 11.2	1.2 to 5.7	28.3 to 63.6	17.8 to 47.5	7.9 to 20.6
United States of America	2.4 to 8.2	1.3 to 15.3	0.5 to 4.0			
Oceania	5.2 to 6.8	3.5 to 5.9	1.0 to 1.6	21.7 to 46.0	16.5	3.3

NOTE. Additional age groups, time points, and study-specific are included in Supplementary Tables 4 (incidence) and 5 (prevalence), as well as for download and at https://cangiec.shinyapps.io/PIBD_epi/.
[a]Excluding Faroe Islands, with an IBD incidence of 41.5 per 100,000 person-years.

in the incidence of pediatric-onset IBD among children of all ages (ie, combining childhood and adolescent-onset IBD) are generally increasing (Figure 2). Most (31 [84%] of 37) of included studies that statistically evaluated trends in incidence over time reported increasing incidence rates in at least some age and disease-specific subgroups. Notable differences in trends across ages at diagnosis were observed across studies, with some studies reporting decreasing or stable incidence rates in the youngest children but increasing incidence rates in older children (eg, Saudi Arabia,[31] Finland,[32] France,[33] and the United Kingdom[34]) and others reporting increasing rates in the youngest children but stable incidence rates in older children (eg, Canada[10,11,35]).

Some data suggest that incidence rates may be starting to plateau in some regions. The incidence in Wessex, England, increased significantly from 2002 to 2017, with no statistically significant increase noted from 2013 to 2017.[36] Similarly, the incidence of IBD in Slovenia increased between 2002 and 2004, and 2008 and 2010, but the incidence in 2005 to 2007 was similar to that of 2008 to 2010[37]; however, the flattening of incidence rates in recent years was not universally observed. The incidence of UC in France was relatively stable from 1988 to 1999 then increased significantly from 2000 to 2011.[3]

Relative incidence of CD and UC. Among the 82 studies from 38 countries where the incidence of both CD and UC was reported, the incidence of CD was higher than UC in almost all regions with available data (Figure 3*A*). The ratio of CD to UC was highest in Québec, Canada (approximately 9:1). The ratio of CD to UC was lowest in Moldova, Malta, Italy, Poland, and the Faroe Islands (approximately 0.1–0.4:1). In most studies, the ratio was approximately 2 to 3:1. Trends in the CD:UC ratio were stable over time (Supplementary Figure 2).

Prevalence of IBD

Thirty-six studies (31 from the current review and 5 from Benchimol et al.[5]) reported the prevalence of IBD, CD, UC, and/or IBDU in children in 22 countries. The most recent regional prevalence rates are reported in Table 1. The earliest and most recent estimates of the prevalence of pediatric-onset IBD, CD, UC, and IBDU are summarized in Supplementary Table 5. Prevalence at all time points reported in each study, including those stratified by sex, are available for download and at https://cangiec.shinyapps.io/PIBD_epi/.

Trends over time. Trends in the prevalence of childhood-onset IBD were described in 7 studies from 3 countries and evaluated statistically in 6 (Supplementary Table 5). Prevalence of IBD, CD, and UC were increasing over time (Supplementary Figure 3). This was consistent with studies evaluating the statistical significance of any trends over time, in which all 6 studies reported increasing prevalence of pediatric IBD over time in most age- and disease-specific subgroups.[10,23,35,38–40] Heterogeneity in trends was noted among studies reporting trends in the age-specific prevalence of IBD. For example, the prevalence of CD in Israel increased among all age groups (<6, 6–9, and 10–17), whereas the prevalence of UC decreased

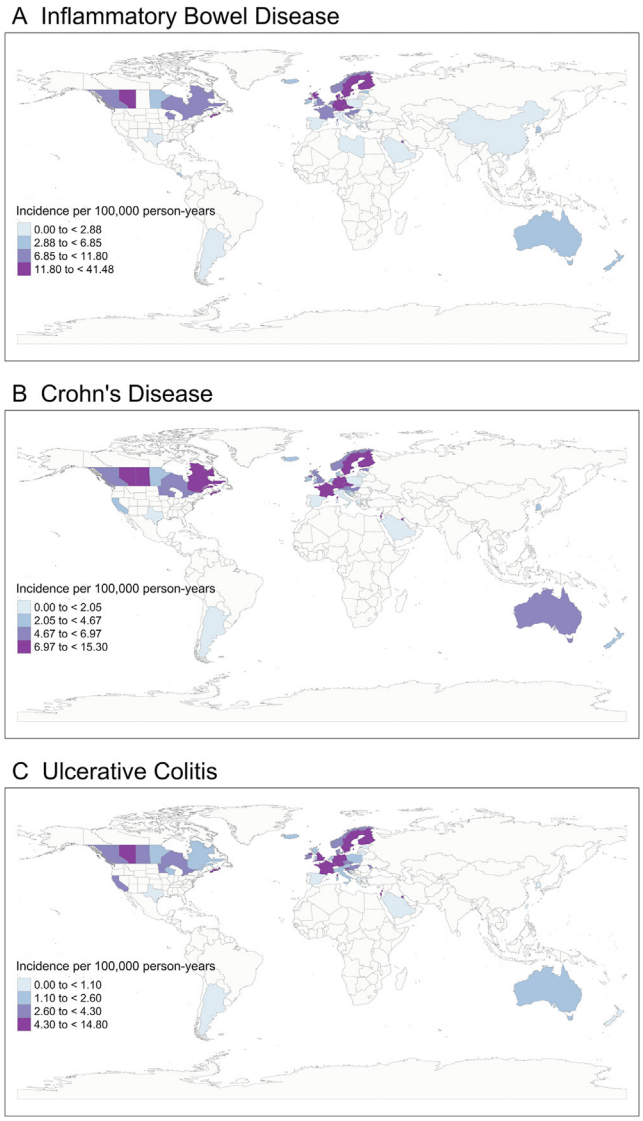

Figure 1. Maps depicting the global incidence of pediatric-onset (*A*) IBD, (*B*) CD, and (*C*) UC.

among those <6 but increased among older children (6–9 and 10–17).[41] In contrast, data from Ontario, Canada, suggested prevalence is increasing among all age groups but most rapidly among those <10,[35] and a study combining data from multiple Canadian provinces suggested prevalence was rising fastest among those <5, followed by those 5 to 9 years of age.[10] This same study reported increased prevalence of IBD and CD among those 10 to 13 years but no changes in the prevalence of UC in this age group and no changes in the prevalence among those 14 to 15 years of age.

Geographic distribution. Most studies describing prevalence of IBD are those with historically high rates (Supplementary Figure 4). The prevalence of IBD was highest in Germany, Sweden, Scotland, and Nova Scotia (Canada), with the lowest prevalence in Saudi Arabia and Libya. Prevalence per 100,000 people ranged from 5.0 to 52.2 in Asia, 31.0 to 75.0 in Europe, 28.3 to 63.6 in Canada, and 21.7 to 46.0 in Oceania (Table 1). Similar geographic patterns were observed in the prevalence of CD, with the additional observation of very low prevalence of CD in Colombia and South Korea. The prevalence of UC was highest in Northern and Central Europe and lowest in Colombia, Québec (Canada), Manitoba (Canada), and New Zealand. Korea had an intermediate prevalence of UC.

Relative prevalence of CD and UC. Among the 28 studies from 18 countries reporting the prevalence of both CD and UC, the prevalence ratio of CD:UC was highest in Québec, Canada (approximately 6:1), and New Zealand (approximately 5:1), indicating that CD was much more common than UC in these regions (Figure 3*B*). In contrast, this ratio was below 1 in Colombia, Japan, Puerto Rico, and Sweden, indicating that UC was more common than CD in these regions.

Very-Early Onset IBD

Incidence. The incidence of VEO-IBD and subtypes was described in 27 studies from 18 countries (Table 2, Supplementary Table 4). Most of the data on the incidence was primarily reported by countries with historically high rates of IBD (Figure 4). The highest incidence of VEO-IBD was observed in Denmark, the Czech Republic, Alberta (Canada), and Wisconsin (United States), with lowest rates in France, Texas (United States), New Zealand, and Saudi Arabia. The incidence of VEO-IBD per 100,000 person-years ranged from 0.2 to 1.4 in Asia, 0.4 to 3.3 in Europe, and 0.5 to 3.6 in Canada. There were no new VEO-IBD cases in New Zealand. The geographic distribution of VEO-CD was similar to that of overall IBD, whereas VEO-UC was higher in North America than in Europe and lowest in Asia and Italy.

Plots depict heterogeneous trends over time, likely due to the small number of cases diagnosed each year in each study (Figure 5). Four studies statistically evaluated trends over time. In both Canadian studies, the incidence of VEO-IBD increased significantly, while increases in CD and UC were observed but were not statistically significant.[10,11] A French study reported no changes in the incidence of VEO-IBD,[33] whereas Saudi Arabia reported no changes in the incidence of VEO-IBD or VEO-UC but a significant decrease in the incidence of VEO-CD.[31]

Prevalence. The prevalence of VEO-IBD and subtypes was described in 6 studies from 5 countries (Table 2, Supplementary Table 5). The prevalence of VEO-IBD ranged from 1.9 (British Columbia, Canada) to 5.8 (Scotland) cases per 100,000. The prevalence of VEO-IBD, CD, and UC all increased significantly in Canada.[10] The prevalence of VEO-CD increased in Israel, whereas the prevalence of VEO-UC decreased.[41] Because of the small number of countries reporting prevalence and the limited number of time points reported in these studies, we did not plot trends over time or create maps.

Discussion

The incidence and prevalence of pediatric-onset IBD continues to increase in most countries around the world. Countries with historically high rates of IBD[5] continue to

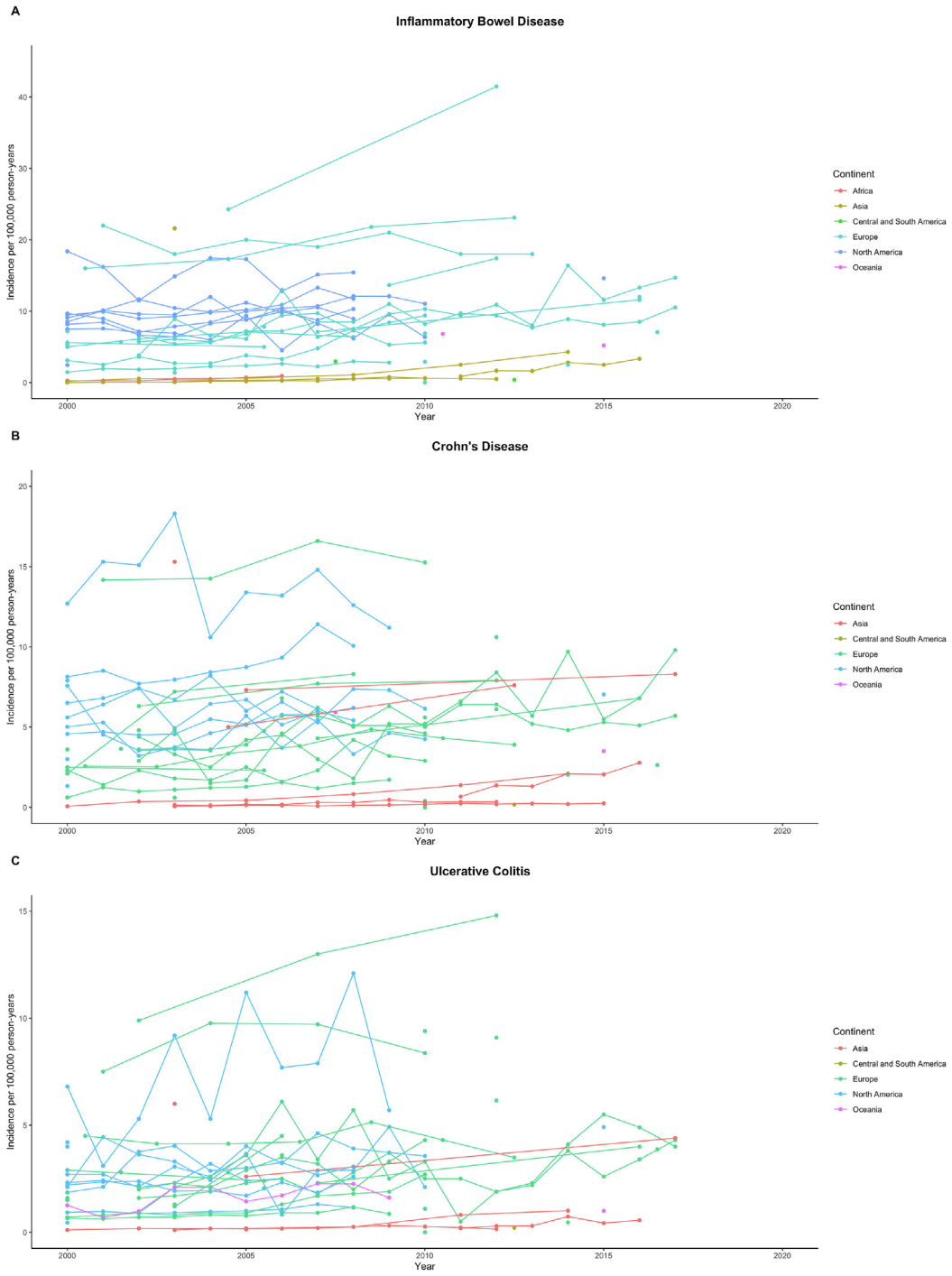

Figure 2. Trends in the global incidence of pediatric-onset (*A*) IBD, (*B*) CD, and (*C*) UC during the 21st century.

have the highest incidence and prevalence. The most recent data indicate its emergence in regions where it was previously unreported. Although our knowledge of the global IBD epidemiology has greatly improved, there remains a paucity of population-based studies reporting the epidemiology of childhood-onset IBD.

A 4-stage model has recently been proposed to describe the evolution of IBD epidemiology: (1) emergence, (2) acceleration in incidence, (3) compounding prevalence, and (4) prevalence equilibrium.[42] Many countries in the Western world are currently in the "compounding prevalence" phase in the evolution of IBD among adults.[8] This phase is characterized by stable incidence and low mortality rates, resulting in continually increasing prevalence. The evolution in the epidemiology of pediatric-onset IBD has lagged behind that of adult-onset IBD. Studies reporting childhood-onset IBD epidemiology indicate that most countries are in the "emergence" or "acceleration in incidence" phases. Studies from Western countries continue to describe increasing IBD incidence, and recent data indicate

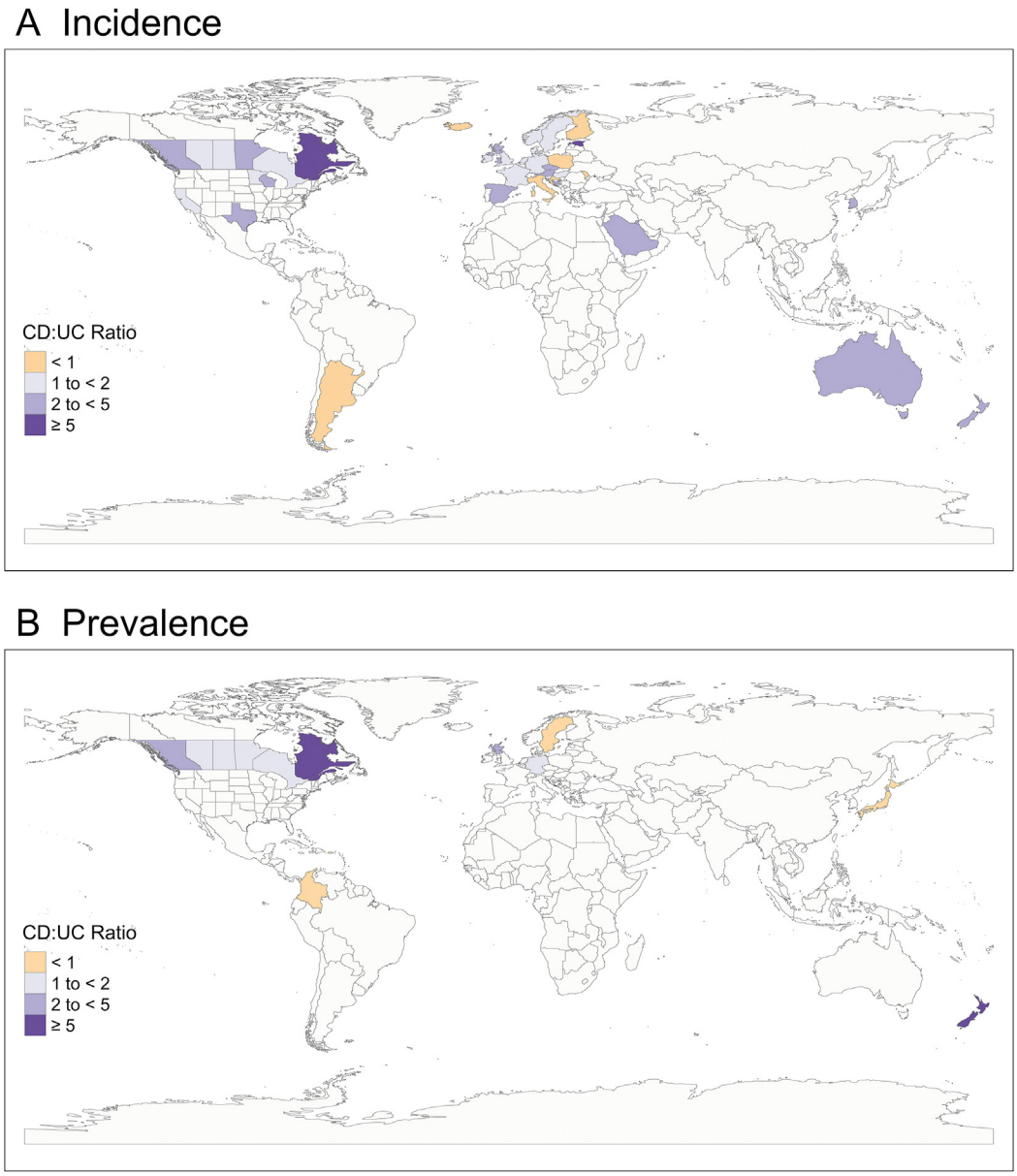

Figure 3. Maps depicting the ratio of the (*A*) incidence and (*B*) prevalence of pediatric-onset CD and UC (CD:UC) around the world.

growing numbers of new diagnoses in regions where IBD was not previously reported. However, we may be on the cusp of reaching the "compounding prevalence" phase in some geographic regions. Both Slovenia[37,43] and England[36] have seen recent plateaus in the incidence of pediatric IBD. In contrast, incidence rates in France were relatively stable between 1988 and 1999, but increased between 2000 and 2011.[3] Continued global surveillance of the trends in the incidence and prevalence of IBD in children and adolescents is needed to fully understand the comparative evolution of IBD in children and adults.

Changes over time in age-specific incidence rates were inconsistent across studies, with some specifically noting increases in young children and others noting increases in adolescents and teenagers. Causes of these changes in epidemiology are multifactorial and likely include changes in environmental risk factors (eg, increasing Westernization in regions with previously low incidence rates of pediatric-onset IBD), better recognition that young children can develop IBD (resulting in earlier diagnosis), and better diagnostic capabilities (eg, availability of pediatric gastroenterology specialists, endoscopy, and radiologic imaging). The role of improved awareness and better access to specialist care[4,44] may result in earlier diagnoses, and may be supported by an increasing proportion of newly diagnosed children with CD presenting with an inflammatory phenotype.[1,3]

In most regions of the world, CD is notably more common than UC. Regions with more CD than UC in children also had more CD than UC in adults.[45] The CD:UC ratio in adults was changing over time in regions where UC was previously the predominant form of IBD, trending to parity of the 2 IBD types. Changes in environmental risk factors (eg,

Table 2. Most Recent Regional Incidence and Prevalence of Very Early-Onset Inflammatory Bowel Disease, Crohn's Disease, and Ulcerative Colitis

	Incidence per 100,000 person-years			Prevalence per 100,000		
Region	IBD	CD	UC	IBD	CD	UC
Asia						
Eastern Asia		0	0			
Western Asia	0.2 to 1.4	0.05 to 0.9	0.14 to 0.5	2.9	1.9	1.0
Europe						
Eastern Europe	1.5 to 3.3	0.2 to 2.1	0.4 to 1.0			
Northern Europe	0.9 to 2.8	0.7 to 1.2	1.0			
Southern Europe		0.7	0			
Western Europe	0.4 to 2.6	0.1 to 0.4	0.07 to 2.2	5.2 to 5.8	0.4	3.7
North America						
Canada	0.5 to 3.6	0.4 to 1.6	0.9 to 1.0	1.9 to 11.2	0.7 to 4.3	0.7 to 2.5
United States of America	0.5 to 3.7	1.0 to 1.9	0.7 to 0.9			
Oceania	0	0	0			

NOTE. Additional age groups, time points, and study-specific are included in Supplementary Tables 4 (incidence) and 5 (prevalence), as well as for download and at https://cangiec.shinyapps.io/PIBD_epi/.

Westernization) and their subsequent impact on the microbiome are likely substantial contributors to this shift in type of IBD being diagnosed. In adults, smoking is a well-established risk factor, with a paradoxical impact on the risks of CD and UC: smoking increases the risk of CD, and quitting smoking increases the risk of UC. It is conceivable that other environmental factors that are less well described but potentially more influential in the pathogenesis of pediatric IBD share similar paradoxical associations. For example, a study conducted in the United Kingdom reported that NO_2 exposure (marker of traffic-related air pollution) was associated with a significant increase in the risk of CD and a numerical decrease in the risk of UC in children and young adults.[46] It is therefore conceivable that shifts in environmental exposures associated with Westernization will not only cause continued increases in the incidence of IBD, but may also influence future changes the relative incidence of pediatric CD and UC (similar to current trends in adults).

The contribution of genetic susceptibility and the interaction between genetics and the environment may be different in pediatric- and adult-onset IBD. For example, in a study examining *NOD2*-smoking interactions, the penetrance of *NOD2* and cigarette smoking followed different trajectories across the age spectrum: the penetrance of the 1007fs single nucleotide polymorphism was highest among those diagnosed at ≤16 years and decreased with increasing age, whereas a history of smoking increased with increasing age.[47] Similarly, the genetic burden of disease (as defined by genetic risk scores) has been demonstrated to decrease with age (particularly for CD).[48] This changing genetic risk profile may partly account for the change in the CD:UC ratio in newly diagnosed patients, with two-thirds of children being diagnosed with CD, whereas those diagnosed in adults are equally likely to have UC and CD.

Immigration studies provide valuable insight regarding the global evolution of pediatric IBD. Individuals migrating from regions with low to high rates of IBD remain at decreased risk of IBD.[49–51] However, those migrating at younger ages may be less protected by their region of birth than individuals migrating at older ages.[49] Second-generation immigrants to Canada also confer some benefit from their mother's country of birth, although this protective effect was greater for CD than UC.[49] Differences in the risk of IBD among immigrants also depend on the region of emigration. Specifically, children born to parents emigrating from East Asia were the least likely to develop IBD, whereas children born to parents emigrating from the Middle East, South Asia, Sub-Saharan Africa, and other Western nations had a similar risk of IBD to those whose mothers were born in Canada.[49] The reduction in the risk of IBD among second-generation immigrants to Sweden was not universally observed, but also varied by region of origin.[51] These findings support the importance of both genetic susceptibility and environmental factors in the risk of developing IBD and its phenotype and can provide insight to regions that may be on the cusp of rapid growth in IBD with increasing Westernization.

Our conclusions are limited by the methods, quality, and completeness of the studies included in our systematic review. Included studies were heterogeneous in the reported age groups. We were, therefore, limited in our ability to describe the epidemiology of IBD, CD, UC, and IBDU in some of our prespecified age groups, including infantile-onset IBD (diagnosed at <2 years) and those defined by the Paris Classification (diagnosed at <10 years and at 10–16 years). Included studies also varied in how they reported changes in incidence and/or prevalence over time, with statistical analyses consisting of regression analyses to determine an annual percentage change, correlation

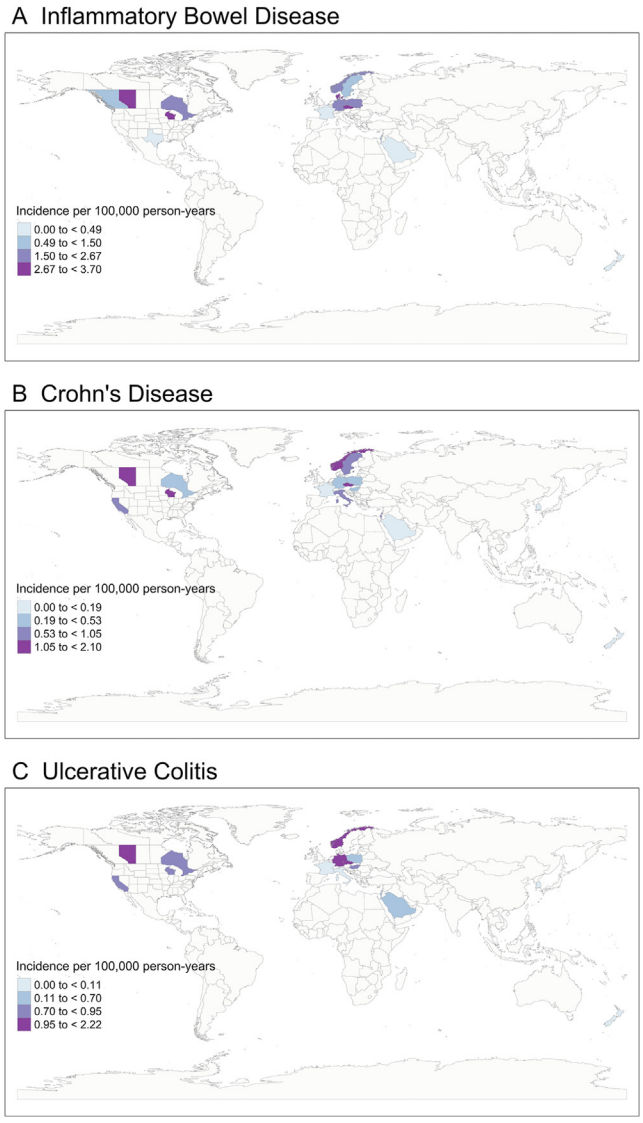

Figure 4. Maps depicting the global incidence of VEO (*A*) IBD, (*B*) CD, and (*C*) UC.

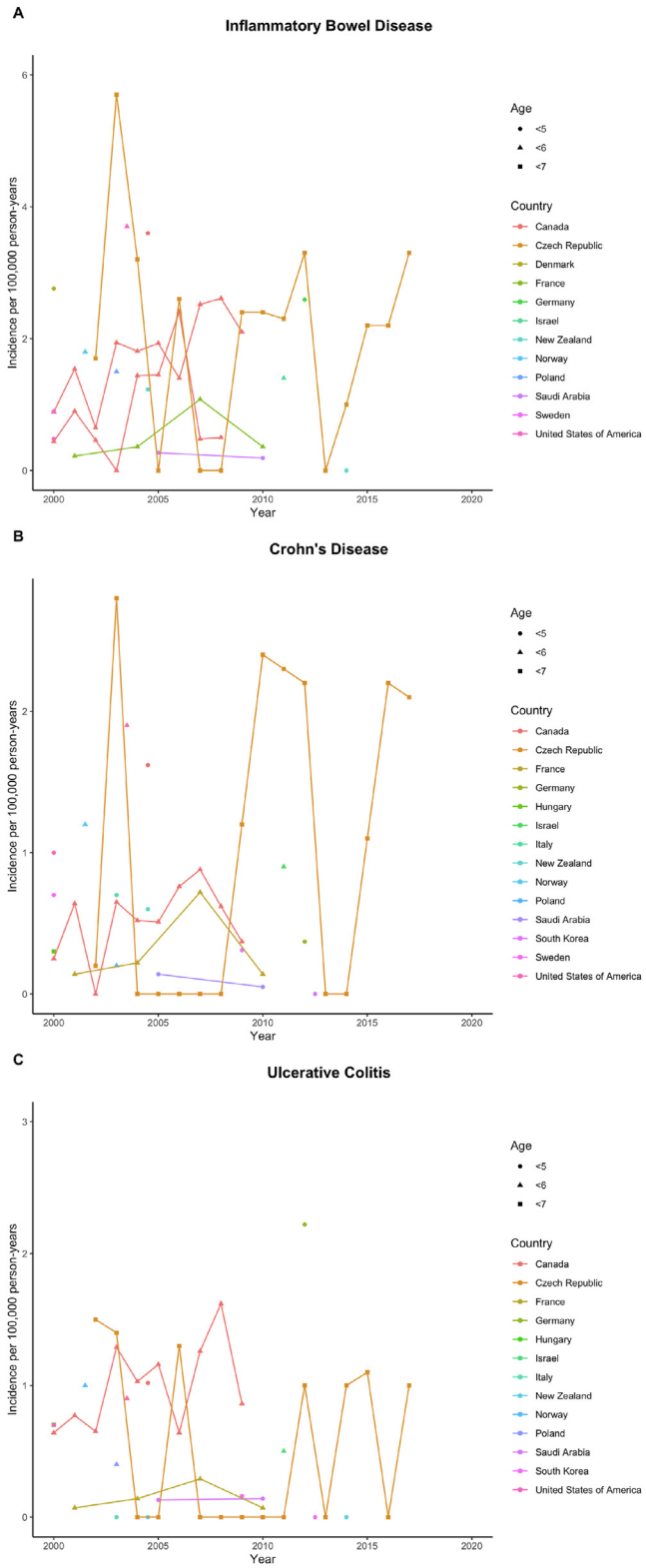

Figure 5. Trends in the global incidence of VEO (*A*) IBD, (*B*) CD, and (*C*) UC.

coefficient, or rate ratio comparing specific time frames. Others reported *P* values without clearly specifying the statistical approach used to evaluate trends over time. This prevented meta-analyses to calculate region-specific rates of change. Wide confidence intervals were common among studies failing to identify significant trends in incidence over time, suggesting that these studies may have been underpowered to detect such changes. Some studies reported data at only a single time point, and we were therefore prevented from using these studies to interpret changes over time in these regions. In 2021, many regions of the world still lack data on the incidence and prevalence of pediatric IBD. In an effort to reduce the risk of selection and ascertainment bias, we included only population-based studies. Many of these studies relied on comprehensive efforts using active surveillance methods to identify all cases within a region. It is therefore possible that the reported epidemiology from some jurisdictions may be biased. Studies using passive surveillance methods typically identified cases using routinely collected health data. However, some did not use validated case identification methods, potentially resulting in misclassification bias. Of these, most studies were the only reports from their jurisdiction. However, in countries where both

unvalidated and validated case finding algorithms were used, we noted a difference in incidence estimates. For example, the incidence described by Jung et al.[52] for Korea, which did not use a validated algorithm, was lower than incidence reported by other Korean national studies.[53–55] Without information on the accuracy of case finding methodology, we are limited in our ability to draw conclusions about the true global patterns in the epidemiology.

In summary, the incidence and prevalence of pediatric IBD is increasing globally. Although there are some initial indications of plateauing incidence in some regions, this is overshadowed by continued increases in regions with already high rates of pediatric IBD and emerging data from other regions of the world. There remains a paucity of data on the incidence and prevalence of childhood-onset IBD, particularly from underdeveloped and developing nations. Future research should design population-based cohorts that can be used to describe the epidemiology of IBD in these regions and understand the role of changing environmental risk factors on the risk of IBD in children.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.12.282.

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Data Availability
Data extracted from studies included in this systematic review will be available for download online. Interactive versions of the maps included in this manuscript are available at https://cangiec.shinyapps.io/PIBD_epi/. This site also includes a searchable database with the incidence and prevalence estimates from all studies included in the review, including at all time points and age groups reported in these studies.

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Conflict of interest
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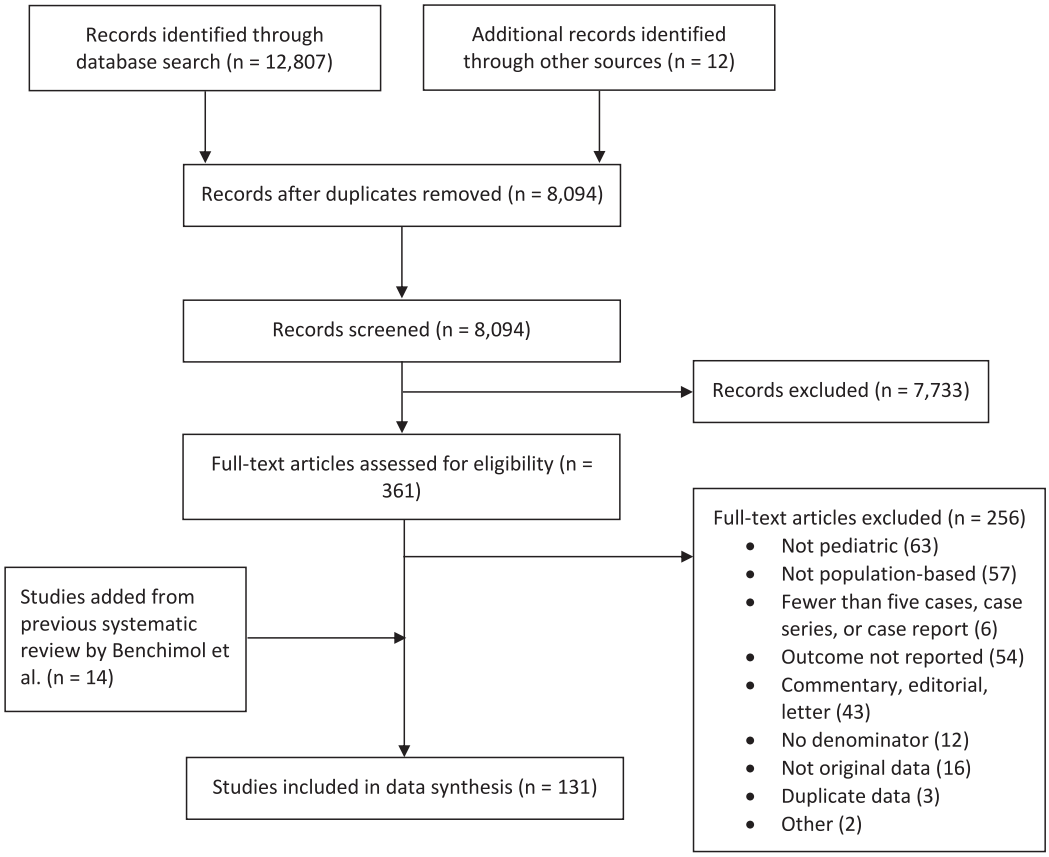
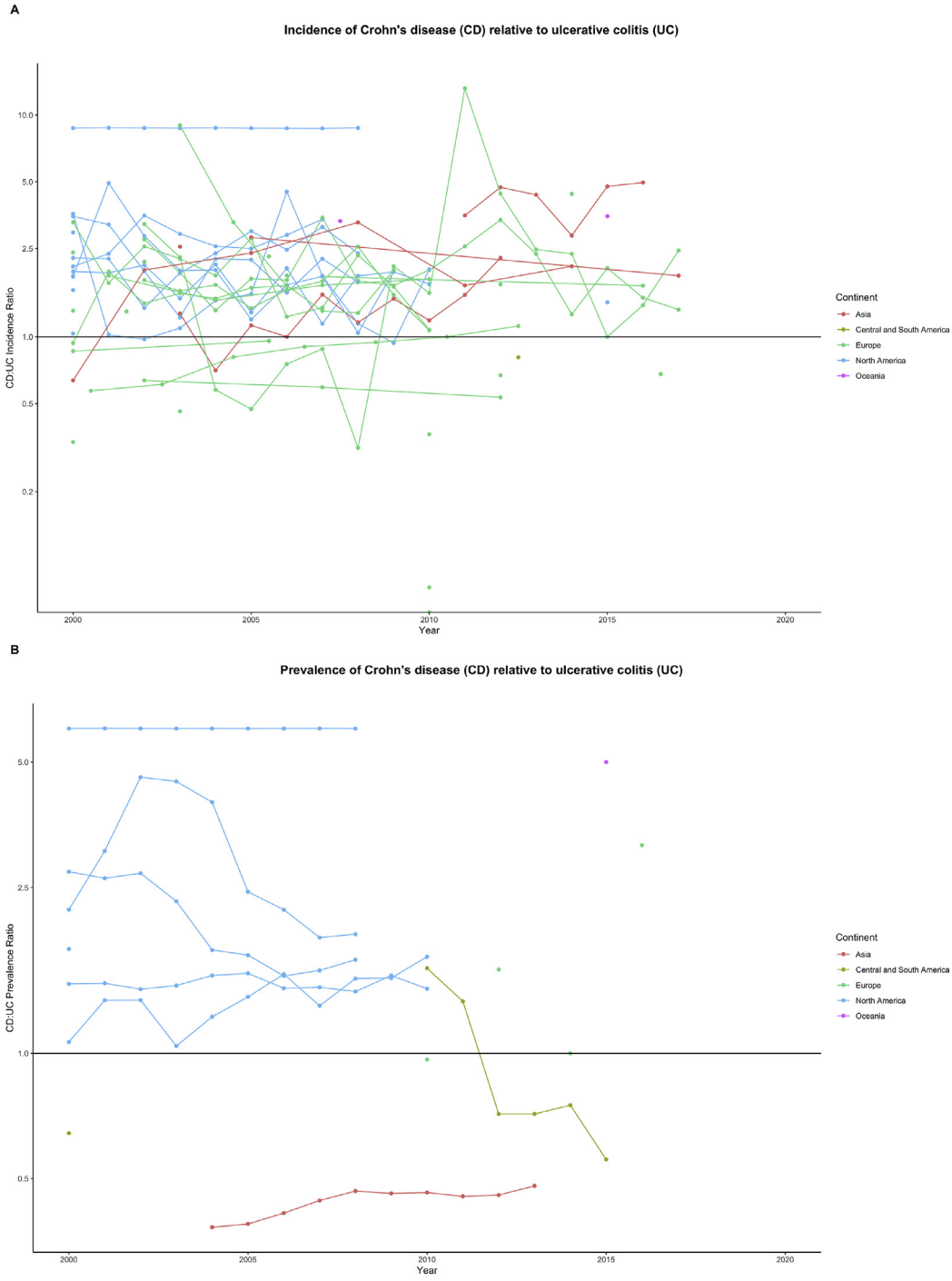
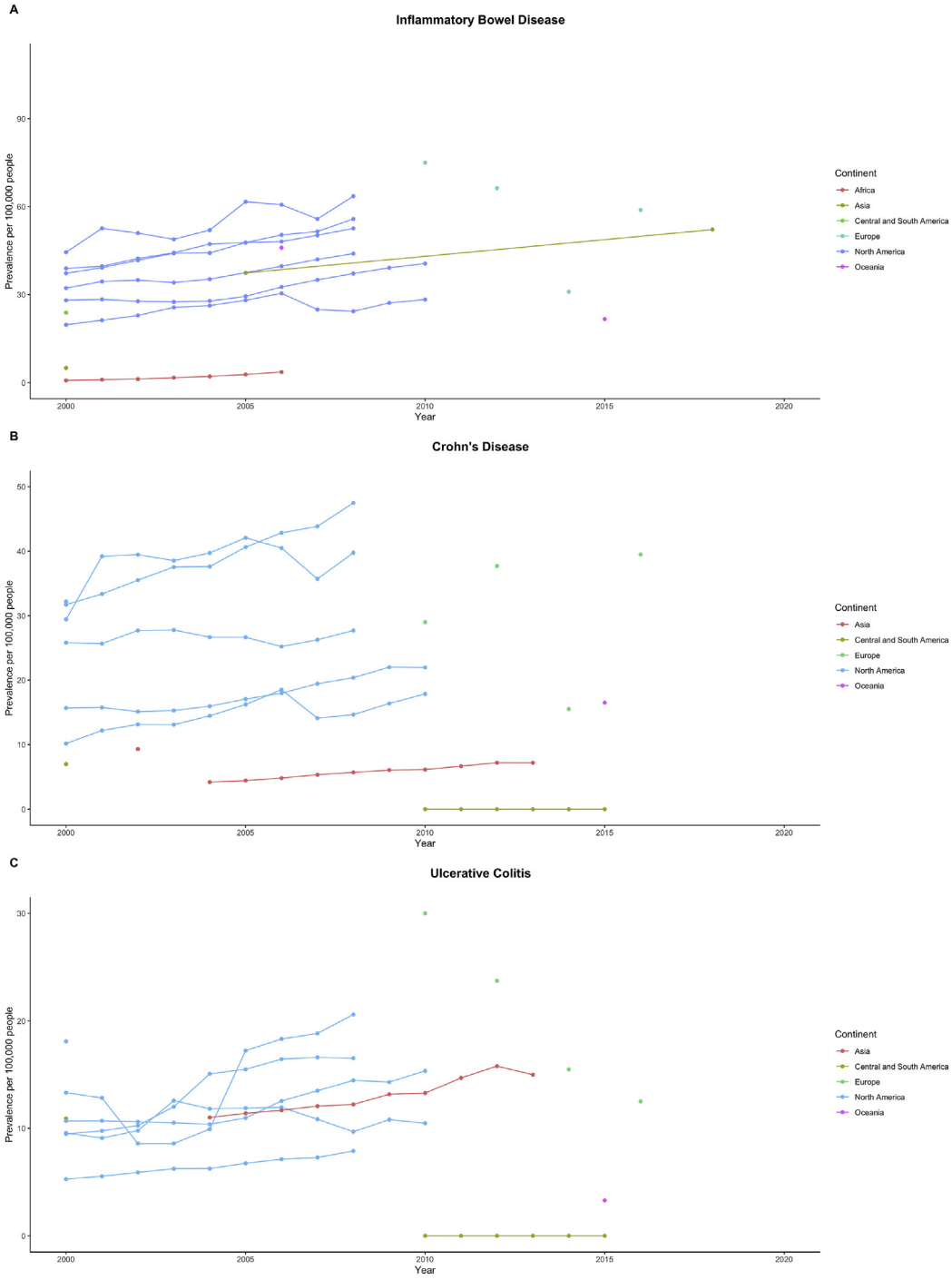


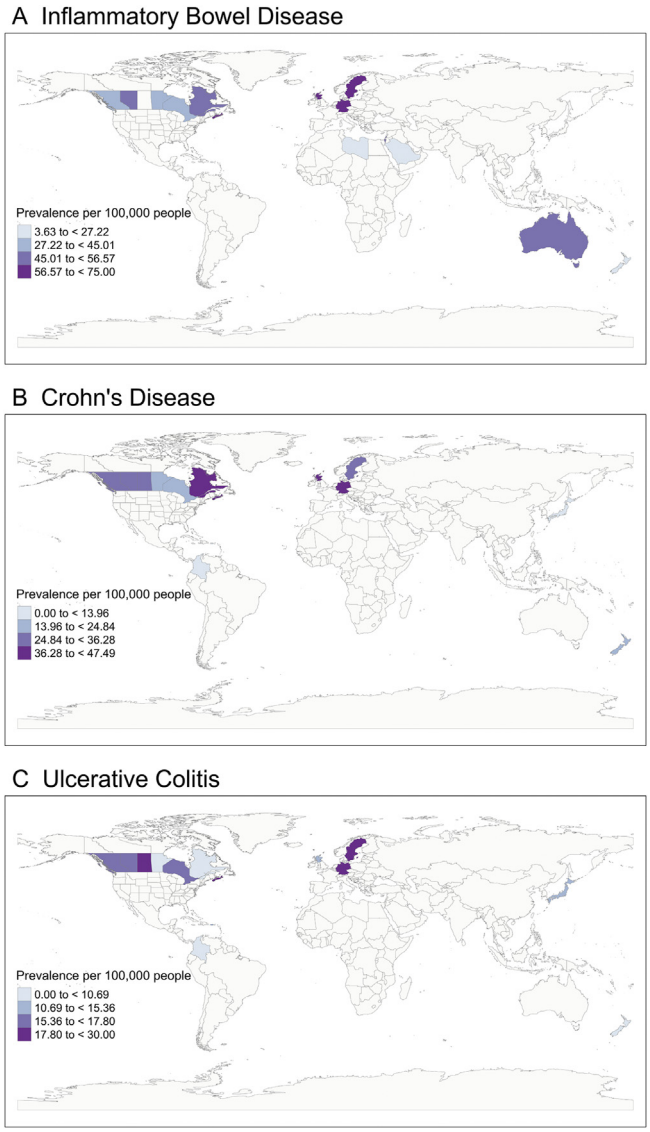
Supplementary Figure 1. Flow diagram describing the study selection process.



Supplementary Figure 2. Trends in the ratio of the (*A*) incidence and (*B*) prevalence of pediatric-onset CD and UC (CD:UC) around the world.



Supplementary Figure 3. Trends in the global prevalence of pediatric-onset (*A*) IBD, (*B*) CD, and (*C*) UC during the 21st century.



Supplementary Figure 4. Maps depicting the global prevalence of pediatric-onset (*A*) IBD, (*B*) CD, and (*C*) UC during the 21st century.