Epidemiology of Pediatric Inflammatory Bowel Disease: A Systematic Review of International Trends

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Background: Temporal trends in the incidence of pediatric-onset inflammatory bowel disease (IBD) are controversial and a wide range of estimates have been reported worldwide. We conducted a systematic review of research describing the epidemiology of childhood-onset IBD to assess changes in incidence rates over time and to evaluate international differences.

Methods: The following electronic databases were searched for articles published 1950–2009: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane IBD/Functional Bowel Disorders Group Specialised Trial Register. All included studies reported incidence or prevalence of IBD, Crohn's disease (CD) or ulcerative colitis (UC). Two authors independently completed the data extraction form for each eligible study. Choropleth maps demonstrated the international incidence of IBD, CD, and UC. Incidence of CD and UC was graphed using data from studies reporting rates in multiple time periods.

Results: The search yielded 2209 references and review resulted in 139 included studies from 32 countries. A wide range of incidence was reported internationally; however, rates of IBD were not described in most countries. Twenty-eight studies (20.1%) used statistical analysis to assess trends over time, and 77.8% reported statistically significantly increased incidence of pediatric IBD. Of studies calculating statistical trends in CD incidence, 60% reported significantly increased incidence. Of similar UC studies, 20% reported significantly increased incidence.

Conclusions: Globally rising rates of pediatric IBD (due primarily to the rising incidence of CD) was demonstrated in both developed and developing nations; however, most countries lack accurate estimates. Analyzing incidence trends may help identify specific environmental and genetic risk factors for pediatric IBD.

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Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, pediatrics, epidemiology

As recently reviewed,[1] the incidence and prevalence of Crohn's disease (CD) and ulcerative colitis (UC) varies greatly around the globe. In the absence of large genetic background shifts (through migration), changing rates of inflammatory bowel disease (IBD) incidence within a country's borders highlight the importance of environmental factors in the pathogenesis of disease. It is postulated that "Westernization" of society accounts for recent increases in the incidence in Asian countries, where IBD was once considered rare. Similarly, the increased occurrence of IBD in families who have emigrated from regions where IBD is very rare to areas of high incidence reminds us of the urgent need to identify the as-yet elusive environmental triggers.

IBD develops during childhood or adolescence in up to 25% of patients.[2] Unique to pediatric-onset disease is the potential for linear growth impairment as a complication of undertreated inflammation. As among adults, the phenotypic spectrum of chronic IBD observed in young patients is wide. Nevertheless, specific demographic and phenotypic differences characterize early-onset versus later-onset IBD.[3] Specifically, the colon is the most common macroscopic site of disease in very young children and differentiation of UC from colonic CD may be difficult. Childhood-onset UC is typically extensive, whereas adults are equally likely to develop UC confined to the distal colon. CD occurring prior to puberty affects a preponderance of males, whereas adult females are more commonly affected. Despite such phenotypic differences and the recognition that heritability is greater with earlier onset in complex disorders, genome-wide association studies demonstrate that the multiple genes conferring susceptibility are shared between cohorts with predominantly adult-onset and exclusively pediatric-onset IBD.[4,5] The development UC and CD during childhood may be influenced by a

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TABLE 1. Detailed MEDLINE Search Strategy for Article Retrieval (1950 to December 31 2009)

1. Inflammatory bowel diseases/ or colitis, ulcerative/ or crohn disease/ or ((ulcerative adj2 colitis) or (inflammatory adj2 bowel) or crohn*).mp.
2. Morbidity/ or incidence/ or prevalence/
3. 1 and 2
4. Inflammatory bowel diseases/ep or colitis, ulcerative/ep or crohn disease/ep or (((ulcerative adj2 colitis) or (inflammatory adj2 bowel) or crohn*).mp. and ep.fs.)
5. 3 or 4
6. Limit 5 to "all child (0 to 18 years)"
7. (infan* or child* or teen* or adolescen* or pediatric* or paediatric*).ti,ab.
8. 7 and 5
9. 8 or 6

greater total number of susceptibility genes and/or to earlier exposure to environmental triggers.

There has yet to be a comprehensive review of trends of the epidemiology of pediatric-onset IBD. We conducted a systematic review of the literature to describe worldwide rates of pediatric IBD and specifically examined trends in the incidence of childhood-onset disease in order to summarize the literature, highlighting similarities and differences by geographic region. Ultimately, the goal of this study is to generate hypotheses that will inspire future research to investigate the etiology, environmental factors, and geographic differences of pediatric-onset IBD.

MATERIALS AND METHODS

Search Strategy and Study Selection

We conducted an electronic search of the online bibliographic databases MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialised Trial Register to identify potentially relevant studies published in print or online before January 1, 2010. Our detailed search strategy is outlined in Table 1.

Studies reporting incidence and/or prevalence of IBD, CD, and/or UC were included. All included articles were required to meet the following four criteria. First, they must have reported the methods used to obtain the diagnosis, such as (but not limited to) clinical characteristics, historical findings, histology, radiologic findings, or (in the case of health administrative databases) physician diagnosis. Second, if incidence was reported, studies were required to follow patients with IBD forward from diagnosis (inception cohort). Third, included studies must have provided population-based prevalence/incidence estimates of patients <21 years old, with a denominator for total population estimate of the relevant age groups. Lastly, the study must have been published in full manuscript form. Study exclusion criteria included review articles or meta-analyses, studies that based their incidence estimates on fewer than five pediatric cases of IBD, CD, or UC, and studies that reported left-sided colitis or proctitis rates only, without reporting incidence or prevalence of total UC cases. The reference lists of review articles were searched for studies meeting inclusion criteria.

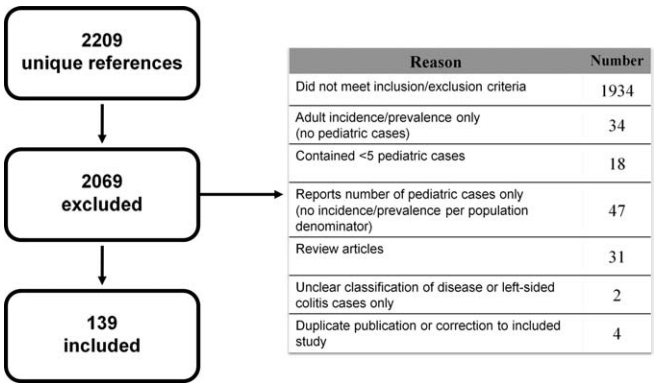
Abstracts of all articles meeting the above search strategy were screened for eligibility. Full-text studies were retrieved if they were potentially eligible for inclusion or if they were relevant review articles (for a manual reference search). The retrieved full-text articles were then independently reviewed by E.I.B. and K.J.F. for eligibility, and the decision to include or exclude was by consensus. Any disagreement was solved by consultation with the content expert (A.M.G.).

Data Extraction

Two authors (E.I.B. and K.J.F.) independently completed a data extraction form for each eligible study. Forms were then reviewed to assure consistency of data extraction. A third author (J.V.L.) aided with article language translation. Disagreement was solved after review of the article by the content expert (A.M.G.). All data extracted from the studies were entered into Access 2007 (Microsoft Corporation, Redmond, WA).

Summarization of Data

Description of the studies were summarized using proportions. Geographic maps of incidence (from studies reporting incidence after 1990) of IBD, CD, and UC were created using ArcGIS v. 9.3 (ESRI, Redlands, CA). Choropleth (shaded) maps used here represent rate values using color intensity (darker color indicates higher rate). The value ranges shown on maps were derived using Jenk's natural breaks classification method[6] and rounded to the nearest decimal value. Rate values in local jurisdictions are shown only for Australia, Canada, France, the United Kingdom (UK) and the United States of America (USA). For other countries where rates existed for local jurisdictions, the highest rate value within the given country was assigned to all of the country's jurisdictions where rates were not reported and then mapped. This ensured that incidence for these countries will be visible despite the fact that the jurisdictions with reported rates may occupy a small geographic region of the country. Incidence reported by studies at multiple timepoints were plotted onto line graphs for both CD and UC using Excel 2007 (Microsoft Corporation, Redmond, WA), with rates plotted representing either raw or age- and sex-adjusted incidence per 100,000 population. Where incidence was reported for a multiyear time period, this was plotted as the incidence in the final year of that time period.



Reason	Number
Did not meet inclusion/exclusion criteria	1934
Adult incidence/prevalence only (no pediatric cases)	34
Contained <5 pediatric cases	18
Reports number of pediatric cases only (no incidence/prevalence per population denominator)	47
Review articles	31
Unclear classification of disease or left-sided colitis cases only	2
Duplicate publication or correction to included study	4

FIGURE 1. Flow diagram of included and excluded studies.

RESULTS

Search Results

A total of 2209 references were reviewed, resulting in 139 included studies[7–145] from 32 countries (Fig. 1). Of included articles, 39 (28.1%) reported IBD incidence and/or prevalence in children only[8,12–14,16–18,29,31,48,49,51,53,65,68,71,72,77,79,83,84,86,92,107–109,111–113,115–117,124,129,134,136,137,141,145], while the remaining 100 (71.9%) reported rates of pediatric IBD within cohorts of children and adults. The methods used for case ascertainment varied significantly between studies. Of included studies, 104 (74.8%) used one method of case ascertainment, 29 studies (20.9%) used two methods of case ascertainment, and six studies (4.3%) used three methods of case ascertainment. These consisted of retrospective chart review ($n = 62$), active prospective surveillance, including disease registries ($n = 62$), health administrative data or large epidemiologic databases ($n = 33$), surveys of practitioners or patients ($n = 16$), and other methods such as birth/death registries and laboratory/pathology databases ($n = 7$). Figure 2 shows incidence rates by jurisdiction for studies reporting incidence after 1990. Table 2 summarizes included studies.

Temporal Trends in Incidence

Of included articles, 28 (20.1%) used statistical analysis to assess trends over time in incidence of pediatric-onset CD, UC, or both. The most common statistical test used was Poisson regression analysis ($n = 11$). In the case of five studies, *P*-values were quoted; however, the study methods reported no details of the statistical test used to obtain these results. Of nine articles which tested statistical trends in pediatric IBD overall, seven (77.8%) reported increased incidence over time and no study reported decreased incidence. Of 25 studies that calculated temporal trends in CD incidence, 15 (60.0%) reported significant

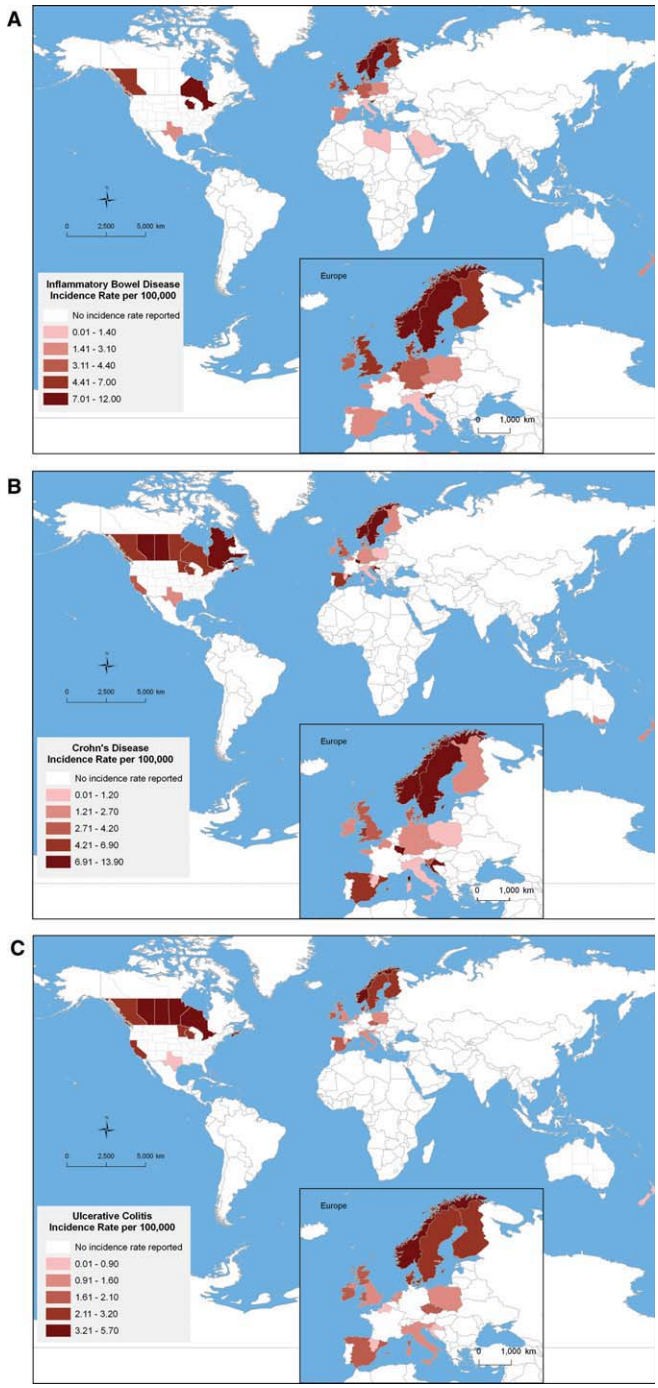


FIGURE 2. (A) Worldwide IBD incidence rate quintiles for countries reporting incidence after 1990. (B) Worldwide Crohn's disease incidence rates quintiles for countries reporting incidence after 1990. (C) Worldwide UC incidence rates quintiles for countries reporting incidence after 1990. Note: Except in the cases of Canada, the United States, the United Kingdom, France, Spain and Australia where a jurisdiction is reported (e.g., city, province, region), the incidence is extrapolated to the country level.

TABLE 2. Summary of Included Articles, Sorted by Continent and Country of Origin

Reference	Country	Jurisdiction / Region	Years of Data Collection	Age Range*	Method of Case Ascertainment	IBD Incidence (Cases/10^5)	CD Incidence (Cases/10^5)	UC Incidence (Cases/10^5)	Other Age Groups Reported	Comments
NORTH AMERICA										
Benchimol, 2009 (18)	Canada	Ontario	1994–2005	0–17	HAD	9.54 (1994) 11.43 (2005)	6.2–7.0	4.4–4.8	0–4, 5–9, 10–14, 15–17	MTP, Prev
Bernstein, 1999 (20)	Canada	Manitoba	1989–1994	0–19	HAD		AGO	AGO	0–9, 10–19	Prev
Bernstein, 2006 (21)	Canada	Alberta, British Columbia, Manitoba, Nova Scotia, Saskatchewan	1998–2000	0–19	HAD		9.4 (Alberta) 5.4 (BC) 6.9 (Manitoba) 12.0 (NS) 7.9 (Sask)	4.1 (Alberta) 3.2 (BC) 4.5 (Manitoba) 5.7 (NS) 4.2 (Sask)		Prev
Grieci, 2009 (51)	Canada	Ontario (Southwest)	1997–2006	0–17	RCR	13.3	4.9	8.1		MTP
Lowe, 2009 (91)	Canada	Quebec	1993–2002	0–19	HAD		13.9		0–14	
Pinchbeck, 1988 (114)	Canada	Alberta (North)	1977–1981	0–19	HAD		PO	PO		Prev
Pinsk, 2007 (115)	Canada	British Columbia	1985–2005	0–16	RCR	5.19	3.69	0.96		
Edouard, 2005 (35)	French West Indies		1997–1999	0–19	APS	AGO	AGO	AGO	0–9, 10–19	Reports 'South Asian' and 'non-South Asian' incidence–non-South Asian rate quoted here
Appleyard, 2004 (10)	U.S.A.	Puerto Rico	1996–2000	0–19	RCR	PO	PO	PO		Prev
Calkins, 1984 (28)	U.S.A.	Baltimore, MD	1977–1979	0–19	RCR		AGO	AGO	0–9, 10–19	MTP Reports for 'whites' and 'nonwhites'
Garland, 1981 (43)	U.S.A.		1973	0–19	HAD		AGO	AGO	0–9, 10–19	
Gollop, 1988 (47)	U.S.A.	Olmsted County, MN	1943–1982	0–14	HAD		0.75			MTP
Herrinton, 2008 (57)	U.S.A.	San Francisco Bay area, Sacramento, California	1996–2002	0–18	RCR + HAD		3.0	2.9	0–4, 5–9, 10–14, 15–19	Prev
Kappelman, 2007 (67)	U.S.A.		2003–2004	0–19	HAD	PO	PO	PO		Prev
Kugathasan, 2003 (72)	U.S.A.	Wisconsin	2000–2001	0–17	APS	7.05	4.56	2.14		
Loftus, 1998 (88)	U.S.A.	Olmsted County, MN	1940–1993	0–19	RCR + HAD		2.5			MTP

TABLE 2. (*Continued*)

Reference	Country	Jurisdiction / Region	Years of Data Collection	Age Range*	Method of Case Ascertainment	IBD Incidence (Cases/10^5)	CD Incidence (Cases/10^5)	UC Incidence (Cases/10^5)	Other Age Groups Reported	Comments
Loftus, 2000 (89)	U.S.A.	Olmsted County, MN	1940–1993	0–19	RCR + HAD			1.8		MTP
Loftus, 2007 (87)	U.S.A.	Olmsted County, MN	1940–2000	0–19	RCR + HAD		3.4	2.4		MTP
Malaty, 2010 (92)	U.S.A.	Texas	1991–2002	0–17	APS	1.1 (1991–1996)	0.66 (1991–1996)	0.34 (1991–1996)	0–4, 5–9, 10–14, 15–17	MTP
						2.44 (1997–2002)	1.33 (1997–2002)	0.45 (1997–2002)		Reports for incidence for 'White', 'African-American', 'Hispanic'
Ogunbi, 1998 (107)	U.S.A.	Georgia	1986–1995	0–19	RCR		8.8*	5.3*		* Reports incidence in Afrcan-Americans only, MTP
Stowe, 1990 (130)	U.S.A.	Rochester, NY	1940–1989	0–19	RCR + HAD		AGO	AGO	0–9, 10–19	MTP
Torres, 2003 (131)	U.S.A.	Puerto Rico	1996	0–19	HAD		PO	PO		Prev
EUROPE										
Sincic, 2006 (125)	Croatia	Primorsko-Goranska County	2000–2004	0–14	APS		8.69	0.86		
Kolek, 2004 (71)	Czech Republic		1990–2001	0–15	RCR	2.24	0.97	1.12		MTP
Pozler, 2006 (117)	Czech Republic		1990–2001	0–14	APS		0.25 (1990) 1.26 (2001)			MTP
Bonnevie, 1968 (24)	Denmark	Copenhagen County	1961–1967	0–19	RCR			AGO	0–9, 10–19	Prev
Fonager, 1997 (42)	Denmark		1981–1992	0–14			0.75	2.5		
Hoj, 1973 (62)	Denmark	Copenhagen County	1960–1970	0–19	RCR		AGO		0–9, 10–19	
Jacobsen, 2006 (64)	Denmark	North Jutland County	1978–2002	0–14	HAD		1.45	2.65		
Jakobsen, 2008 (65)	Denmark	Eastern Denmark, Copenhagen County	1998–2000, 2002–2004	0–14	HAD + S	4.3 (1998–2000)	2.3 (1998–2000)	1.8 (1998–2000)		MTP
						6.1 (2002–2004)	3.1 (2002–2004)	2.7 (2002–2004)		
Langholz, 1991 (78)	Denmark	Copenhagen County	1962–1987	0–19	APS			6.1 (1962–1969) 8.56 (1970–1979) 13.29	0–9, 0–15, 15–20	Prev, MTP

TABLE 2. (*Continued*)

Reference	Country	Jurisdiction / Region	Years of Data Collection	Age Range*	Method of Case Ascertainment	IBD Incidence (Cases/10^5)	CD Incidence (Cases/10^5)	UC Incidence (Cases/10^5)	Other Age Groups Reported	Comments
								(1980–1987)		
Langholz, 1997 (79)	Denmark	Copenhagen County	1962–1987	0–14	APS + S		0.7	2.2		
Munkholm, 1992 (98)	Denmark	Copenhagen County	1962–1987	0–14	RCR + HAD		0.2			
Urine, 2002 (136)	Denmark	Vestsjellands County	1998–2000	0–14	HAD	4.3	1.8	2.3		
Vind, 2006 (138)	Denmark	Copenhagen County	2003–2004	0–17	APS		4.4	5.0	0–15	
Linden, 1971 (85)	Finland		1967	0–19	HAD			1.92	10–19	
Turenen, 2006 (136)	Finland		1987–2003	0–17	RCR	3.9 (1987)	1.7 (1987)	2.2 (1987)		
						4.7 (1994)	1.3 (1995)	1.9 (1995)		
						7.0 (2003)	2.6 (2003)	3.2 (2003)		
Abakar-Mahamat, 2007 (7)	France	Corsica	2002–2003	0–19	APS + S		12.36	2		
Auvin, 2005 (16)	France	Nord-Pas de Calais, Somme, Seine-Maritime	1998–1999	0–16	APS	3.1	2.3	0.8	0–4, 5–9, 10–14, 15–16	
Colombel, 1990 (30)	France	Nord-Pas de Calais	1988	0–19	APS		AGO	AGO	0–9, 10–19	
Gottrand, 1991 (48)	France	Nord-Pas de Calais	1988	0–16	APS	3.13	2.07	0.46		
Gower-Rousseau, 1994 (50)	France	Nord-Pas de Calais, Somme	1988–1990	0–19	APS		AGO	AGO	0–9, 10–19	
Gower-Rousseau, 2009 (49)	France	Nord-Pas de Calais, Somme, Seine-Maritime	1988–2002	0–16	APS			0.8		
Nerich, 2006 (100)	France		2000–2002	0–19	HAD		AGO	AGO	0–4, 5–9, 10–14, 15–19	
Tourtelier, 2000 (132)	France	Bretagne	1994–1997	0–16	APS	3.0	1.7	0.97		MTP, note correction published in separate reference (156)
Dirks, 1994 (34)	Germany	Western Ruhr	1980–1984	0–19	APS			AGO	0–4, 5–9, 10–14, 15–19	
Goebell, 1994 (46)	Germany	Essen, Oberhausen, Mülheim, Duisberg	1980–1984	0–19	APS		AGO		0–9, 10–19	Prev
Ott, 2008 (110)	Germany	Oberpfalz	2004–2006	0–15	APS	3.96	2.44	1.11		
Ladas, 2005 (75)	Greece	Trikala	1990–1994	0–19	APS			AGO	10–19	

TABLE 2. (*Continued*)

Reference	Country	Jurisdiction / Region	Years of Data Collection	Age Range*	Method of Case Ascertainment	IBD Incidence (Cases/10^5)	CD Incidence (Cases/10^5)	UC Incidence (Cases/10^5)	Other Age Groups Reported	Comments
Lakatos, 2003 (76)	Hungary	Veszprem County	1977–2001	0–20	APS + RCR		AGO	AGO	0–10, 11–20	
Bjornsson, 1998 (23)	Iceland		1990–1994	0–19	APS		AGO	AGO	0–9, 10–19	
Bjornsson, 2000 (22)	Iceland		1980–1989	0–19	O (biopsy specimens)		AGO	AGO	0–9, 10–19	
Castro, 2008 (29)	Italy		1996–2003	0–17	APS	0.89 (1996) 1.39 (2003)				MTP
Cottone, 1991 (32)	Italy	Sicily	1987–1989	0–19	RCR		AGO		0–9, 10–19	
Ranzi, 1996 (119)	Italy	Lombardia	1990–1993	0–14	APS		1.18	1.18		
Tragnone, 1996 (133)	Italy		1989–1992	0–19	APS		AGO	AGO	0–9, 10–19	
Cachia, 2008 (27)	Malta		1993–2005	0–15	RCR		0.62	1.85		
Romberg-Camps, 2009 (121)	Netherlands	South Limberg	1991–2002	0–19	APS			AGO	0–9, 10–19	
Russel, 1998 (123)	Netherlands	South Limberg	1991–1995	0–19	APS		AGO	AGO	0–4, 5–9, 10–14, 15–19	
Van der Zaag-Loonen, 2004 (137)	Netherlands		1999–2001	0–17	APS	5.2	2.1	1.6		
Bentsen, 2002 (19)	Norway	South-East	1990–1993	0–15	APS	4.15	2.00	1.67	0–14, 0–12, 13–15	
Gjone, 1966 (45)	Norway		1956–1963	0–19	S		AGO		0–9, 10–19	
Haug, 1988 (54)	Norway	Rogaland, Hordaland, Sogn and Fjordane	1984–1985	0–19	APS			AGO	0–4, 5–9, 10–14, 15–19	
Haug, 1989 (55)	Norway	Rogaland, Hordaland, Sogn and Fjordane	1984–1985	0–14	APS		2.5		0–9, 10–19	
Kildebo, 1989 (69)	Norway	Nordland, Troms, Finnmark	1983–1986	0–19	APS		AGO		0–9, 10–19	
Kildebo, 1990 (70)	Norway	Nordland, Troms, Finnmark	1983–1986	0–19	APS			AGO	0–9, 10–19	
Moum, 1995 (97)	Norway	Telemark, Aust-Agder, Østfold, Oslo	1990	0–14	APS	3.0	1.2	0.6		
Moum, 1996 (96)	Norway	Telemark, Aust-Agder, Østfold, Oslo	1990–1993	0–14	APS		0.94			
Moum, 1996 (95)	Norway	Telemark, Aust-Agder, Østfold, Oslo	1990–1993	0–14	APS			1.28		
Myren, 1971 (99)	Norway		1964–1969	0–19	S		AGO	AGO	0–9, 10–19	
Olafsdottir, 1989 (108)	Norway	Rogaland, Hordaland, Sogn and Fjordane	1984–1985	0–15	APS	6.8	2.5	4.3		Prev

TABLE 2. (*Continued*)

Reference	Country	Jurisdiction / Region	Years of Data Collection	Age Range*	Method of Case Ascertainment	IBD Incidence (Cases/10^5)	CD Incidence (Cases/10^5)	UC Incidence (Cases/10^5)	Other Age Groups Reported	Comments
		Counties								
Perminow, 2006 (112)	Norway	Akershus	1993–2004	0–15	APS + RCR	5.65	2.8	2.8	0–5, 6–12, 13–15	MTP
Perminow, 2009 (111)	Norway	South-east	2005–2007	0–17	APS	10.9	6.8	3.6	0–15	
Stordal, 2004 (129)	Norway	South-east	1990–1993	0–15	APS + RCR	4.7	2.7	2.0		
Karolewska-Bochenek, 2009 (68)	Poland		2003–2004	0–18	APS	2.7	0.6	1.3	0–16, 0–2, 3–5, 0–5, 6–10, 11–18	
Orel, 2009 (109)	Slovenia	Central, Western regions	1994–2005	0–17	RCR	4.03	2.42	1.14		MTP
Arin Letamendia, 2008 (11)	Spain	Navarra	2001–2003	0–14	APS	2.6	1.74	0.87		
Brullet, 1998 (26)	Spain	North, South	1991–1993	0–14	APS + HAD + O		1.6	0.2		
Fernandez, 1994 (41)	Spain	Cantabria, Basque, Navarra, La Rioja, Aragon	1975–1991	0–14	RCR	0.57	0.38	0.19		
Fernandez Gonzalez, 2004 (40)	Spain	Asturias	1993–2000	0–14	APS + RCR	0.25	0.15	0.10		
Lopez Miguel, 1999 (90)	Spain	Aragon	1992–1995	0–14	APS + RCR + S		0.44	0.33		
Rodrigo, 2004 (120)	Spain	Oviedo	2000–2002	0–14	APS		5.76	1.63		
Ruiz Ochoa, 1984 (122)	Spain	Galicia	1976–1983	0–19	S		AGO		0–9, 10–19	
Askling, 1999 (15)	Sweden	North Stockholm County	1990–1998	0–16	RCR	6.9	3.8	2.1		MTP
Brahme, 1975 (25)	Sweden	Malmo	1958–1973	0–19	RCR		AGO	AGO	0–9, 10–14, 15–19	
Ekbom, 1991 (36)	Sweden	Uppsala Health Care Region	1965–1983	0–19	RCR + HAD		5.91 (1965) 5.00 (1970) 4.77 (1975) 5.45 (1980) 3.18 (1983)	5.23 (1965) 4.77 (1970) 3.86 (1975) 4.09 (1980) 2.73 (1983)		MTP
Hellers, 1979 (56)	Sweden	Stockholm County	1955–1974	0–14	RCR + HAD		0.4 (1955–1959) 1.1 (1960–1964) 1.3 (1965–1969)			MTP

TABLE 2. (*Continued*)

Reference	Country	Jurisdiction / Region	Years of Data Collection	Age Range*	Method of Case Ascertainment	IBD Incidence (Cases/10^5)	CD Incidence (Cases/10^5)	UC Incidence (Cases/10^5)	Other Age Groups Reported	Comments
							1.0 (1970–1974)			
Hildebrand, 1991 (61)	Sweden		1984–1985	0–15	APS	4.8	1.7	1.7		Prev
Hildebrand, 1994 (59)	Sweden	Bohuslän, Halland, Malmöhus	1983–1987	0–15	APS	5.3	2.7	2.6	0–14, 0–9, 0–4, 5–9, 10–14	
Hildebrand, 2003 (60)	Sweden	Stockholm County	1990–2001	0–15	APS	7.4	4.9	2.2	0–4, 5–9, 10–15	MTP
Lapidus, 1997 (80)	Sweden	Stockholm County	1955–1989	0–14	HAD + S		4.09		0–4, 5–9, 10–14	MTP
Lindberg, 1991 (82)	Sweden		1963–1987	0–14	RCR + S		1.4 (1963–1967) 1.3 (1968–1972) 0 (1973–1977) 6.4 (1978–1982) 0.7 (1983–1987			MTP
Lindberg, 2000 (83)	Sweden		1984–1995	0–15	APS	4.6 (1984–1986) 7.0 (1993–1995)	1.2 (1984–1986) 1.3 (1993–1995)	1.4 (1984–1986) 3.2 (1993–1995)		MTP
Lindberg, 2008 (84)	Sweden		1961–2005	0–18	RCR			1.6		
Lindquist, 1984 (86)	Sweden	Orebro County	1971–1980	0–16	RCR		6.1			
Nordenvall, 1985 (103)	Sweden	Stockholm County	1955–1979	0–19	RCR + HAD			5.05	0–4, 5–9, 10–14, 15–19	
Norlen, 1970 (104)	Sweden	Uppsala, Västmanland Counties	1956–1967	0–19	RCR		AGO		0–4, 5–9, 10–14, 15–19	
Nyhlin, 1986 (105)	Sweden	Norrbotten, Västerbotten Counties	1974–1981	0–19	RCR + HAD		2.70–2.79		0–9, 10–19	Reports incidence in North Sweden with or without Umeå Health District
Stewenius, 1995 (128)	Sweden	Malmö	1958–1982	0–19	RCR			AGO	0–9, 10–19	
Tysk, 1992 (135)	Sweden	Örebo	1963–1987	0–19	S			5.98	0–9, 10–19	
Ahmed, 2006 (9)	U.K.	South Wales	1996–2003	0–15	APS	5.4	3.6	1.5		
Armitage, 1999 (12)	U.K.	Scotland	1981–1992	0–16	RCR		1.91 (1981–83) 2.91 (1990–92)		0–6, 7–11, 12–16	MTP
Armitage, 2001 (13)	U.K.	Scotland	1981–1995	0–16	RCR		2.6	1.3	0–6, 7–11, 12–16	MTP, Prev
Armitage, 2004 (14)	U.K.	Scotland	1981–1995	0–15	RCR	3.4	2.3	1.2		MTP
Barton, 1989 (17)	U.K.	Scotland	1968–1983	0–16	HAD		0.66 (1968)	1.91 (1968)		MTP

TABLE 2. (*Continued*)

Reference	Country	Jurisdiction / Region	Years of Data Collection	Age Range*	Method of Case Ascertainment	IBD Incidence (Cases/10^5)	CD Incidence (Cases/10^5)	UC Incidence (Cases/10^5)	Other Age Groups Reported	Comments
							2.29 (1983)	1.56 (1983)		
Cosgrove, 1996 (31)	U.K.	South Glamorgan	1983–1993	0–15	RCR + HAD + O	PO	2.21	0.71	5–9, 10–15	MTP, Prev
Devlin, 1980 (33)	U.K.	North Tees Health District	1971–1977	0–19	RCR		AGO	AGO	0–9, 10–19	
Evans, 1965 (38)	U.K.	Oxford, England	1951–1960	0–14	RCR + S + HAD			0.95		Prev
Fellows, 1990 (39)	U.K.	Derby	1951–1975	0–19	APS + RCR		AGO		0–9, 10–19	MTP
Hassan, 2000 (53)	U.K.	Wales	1995–1997	0–15	APS	2.6	1.36	0.75		
Humphreys, 1975 (63)	U.K.	Northern Ireland	1966–1973	0–19	S		AGO		0–9, 10–19	
Jayanthi, 1992 (66)	U.K.	Leicestershire, England	1972–1989	0–20	RCR + HAD		AGO		0–5, 6–10, 11–15, 16–20	
Kyle, 1971 (73)	U.K.	Northeast Scotland	1955–1969	0–19	APS + RCR		PO		0–9, 10–19	
Kyle, 1992 (74)	U.K.	Northeast and Northern Isles, Scotland	1955–1988	0–19	APS + RCR		AGO		0–9, 10–19	MTP
Lee, 1985 (81)	U.K.	Blackpool, England	1968–1980	0–20	RCR	PO			0–10, 11–20	Prev
Mayberry, 1979 (93)	U.K.	Cardiff	1934–1977	0–14	RCR		0.50 (1931–1970) 1.75 (1971–1977)			MTP
Morris, 1984 (94)	U.K.	Cardiff	1968–1977	0–19	RCR + S			AGO	0–9, 10–19	
Probert, 1992 (118)	U.K.	Leicestershire	1972–1989	0–15	RCR			AGO	0–10, 11–15	Reports 'South Asian' and 'European' incidence
Sawczenko, 2001 (124)	U.K., Ireland		1998–1999	0–16	APS	5.2	3.1	1.4		Reports incidence for the U.K., Engalnd, Scotland, Wales, Northern Ireland and the Republic of Ireland
Smith, 1975 (126)	U.K.	Clydesdale, Scotland	1961–1970	0–19	HAD		AGO		0–9, 10–19	MTP
Srivastava, 1992 (127)	U.K.	Cardiff	1968–1987	0–15	RCR + S			AGO	0–9, 10–19	MTP
Watson, 2002 (141)	U.K.	Grampian Region, Scotland	1980–1999	0–16	RCR		2.2 (1980–1989) 4.4 (1990–1999)	0.7 (1980–1989) 1.5 (1990–1999)		MTP
Vucelic, 1991 (140)	Yugoslavia	Zagreb	1980–1989	0–14	APS + RCR		1.76			
Vucelic, 1991 (139)	Yugoslavia	Zagreb	1980–1989	0–14	APS + RCR			3.09		
ASIA										
Grossman, 1989 (52)	Israel	Tel Aviv-Yafo	1970–1980	0–19	APS			0.91		

TABLE 2. (*Continued*)

Reference	Country	Jurisdiction / Region	Years of Data Collection	Age Range*	Method of Case Ascertainment	IBD Incidence (Cases/10^5)	CD Incidence (Cases/10^5)	UC Incidence (Cases/10^5)	Other Age Groups Reported	Comments
Landau, 2008 (77)	Israel		1998–2003	0–17	O (Army Screening)	PO				Prev, MTP
Niv, 1999 (101)	Israel	269 Kibbutz settlements	1987–1997	0–19	S + RCR		PO, AGO		0–4, 5–14, 15–19	
Niv, 2000 (102)	Israel	269 Kibbutz settlements	1987–1997	0–14	S + RCR			PO, AGO	0–4, 5–14	
Odes, 1994 (106)	Israel	Southern	1968–1992	0–19	RCR + S		3.65			
Higashi, 1988 (58)	Japan		1969–1985	0–19	HAD		PO	PO		
Yao, 2000 (144)	Japan		1986–1998	0–19	HAD		PO		0–9, 10–19	Prev
Ahmaida, 2009 (8)	Libya	Eastern	1997–2006	0–14	RCR	0 (1997) 0.24 (2002) 0.91 (2006)				Prev
El Mouzan, 2006 (37)	Saudi Arabia	Riyadh	1993–2002	0–17	RCR	0.5				Prev
Yang, 2000 (142)	South Korea	Song Pa-Kang Dong District, Seoul	1986–1997	0–19	APS + RCR + S			AGO	0–9, 10–19	MTP
Yang, 2008 (143)	South Korea	Seoul	1986–2005	0–19	RCR + S		AGO	AGO	0–9, 10–19	
OCEANIA										
Phavichitr, 2003 (113)	Australia	Victoria	1971–2001	0–16	RCR		0.06 (1970–1975) 0.18 (1976–1980) 0.85 (1981–1985) 1.06 (1986–1990) 1.88 (1991–1995) 2.09 (1996–2001)			MTP
Ponsonby, 2009 (116)	Australia	Victoria	1983–1998	0–15	APS		2.01		0–5	MTP
Gearry, 2006 (44)	New Zealand	Canterbury	2004–2005	0–19	APS + RCR	AGO	AGO	AGO	0–4, 5–9, 10–14, 15–19	Prev
Yap, 2008 (145)	New Zealand		2002–2003	0–15	APS	2.9	1.9	0.5		

*Age range reported is inclusive (e.g., 0–16 includes children less than 17 years old). Methods of case ascertainment: APS, active prospective surveillance; RCR, retrospective chart review; S, retrospective survey; HAD, health administrative data or large-area epidemiologic database; O, other; PO, reports prevalence only; AGO, reports incidence rates by age groups only, no overall pediatric incidence quoted; Comments: MTP, reports multiple time periods; prev, reports prevalence.

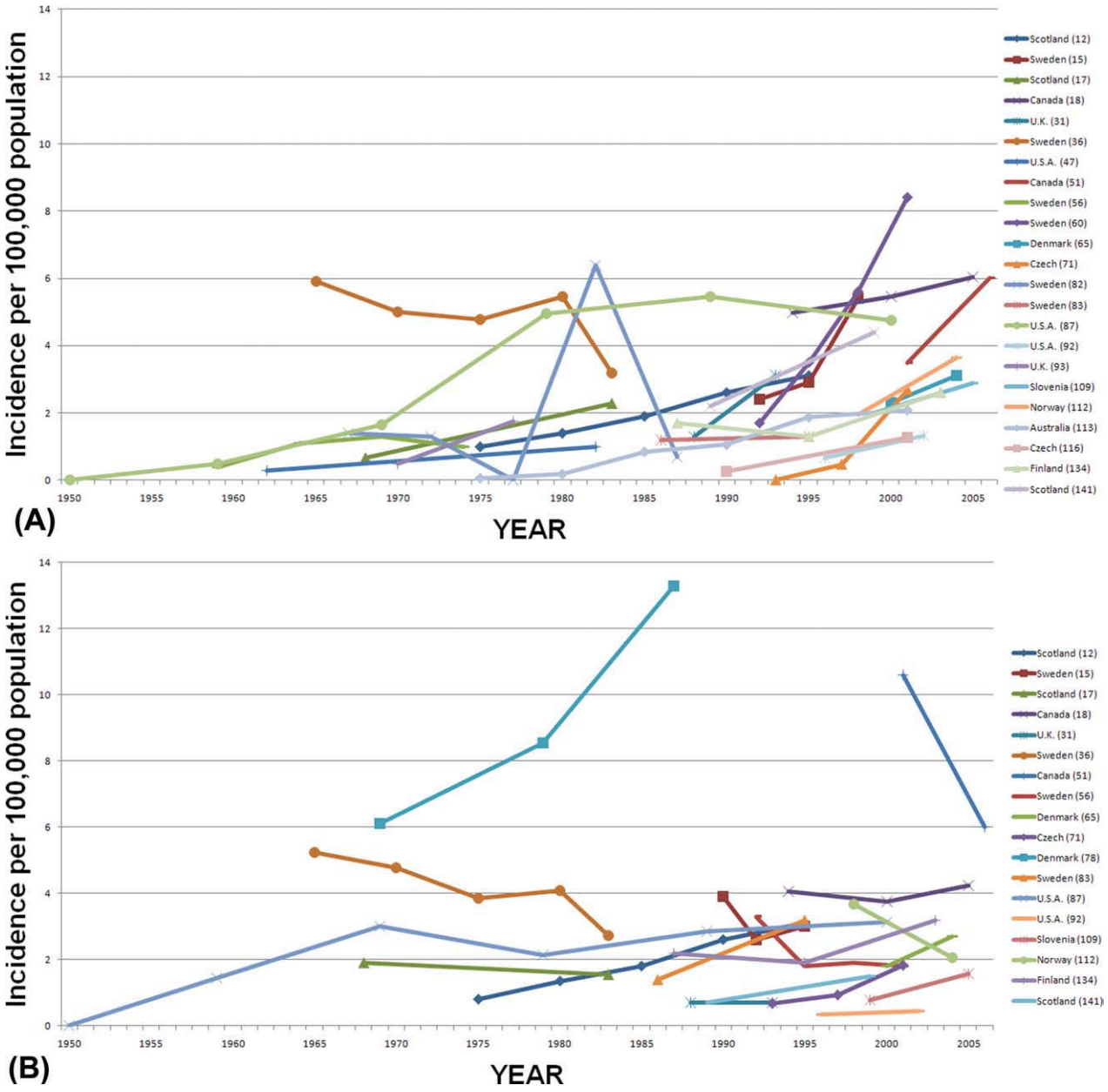


FIGURE 3. Temporal trends of incidence rates for (A) Crohn's disease and (B) ulcerative colitis in studies reporting incidence at multiple timepoints. Where a year range is reported, incidence rate is reported for the final year in the range (e.g., if incidence is reported for 1990–1999, rate is plotted as incidence for 1999).

increases, one (4.0%) reported decreased incidence, and nine (36.0%) reported no significant change. Of 20 studies calculating temporal trends in UC incidence, four (20.0%) reported significant increases, 13 (65.0%) reported no significant change, and three (15.0%) reported significantly decreased incidence. Figure 3 shows incidence rates over time for studies with incidence measurements in multiple time periods, whether or not authors calculated statistical trends over time.

Three studies reported statistically significant increases in incidence rates by age group. A study using health administrative data from Ontario, Canada reported significant increases in IBD incidence for 6-month to 4-year-old (5.0% per year, $P = 0.03$) and 5–9-year-old patients (7.6% per year, $P < 0.0001$), and CD incidence for patients aged 5–9 years old (8.7% per year, $P < 0.0001$).[18] By contrast, a recent report from Texas demonstrated significantly increased incidence of IBD in children

aged 10–14 and 15–17 with stable incidence in children under 10.[92] Another study reported significant increases in the UK from 1981–1995 of CD and UC patients aged 12–16 years (males with CD: from 4.7–7.4 per 100,000, males with UC: from 1.8–3.8 per 100,000, females with CD: from 3.4–6.0 per 100,000, females with UC: from 0.9–3.6 per 100,000) and females aged 7–11 years (for CD: from 1.2–2.8 per 100,000 population, for UC: from 1.2–2.4 per 100,000).[13] No regression estimates or *P*-values were reported in that study.

DISCUSSION

This study examined the worldwide epidemiology of childhood-onset IBD. Comprehensive computer databases have made it possible to report trends in incidence of IBD, CD, and UC around the world using large disease registries, medical records, nationwide birth cohorts, or health administrative databases. Overall, the results of this systematic review suggest that the incidence of IBD is rising internationally. More specifically, the incidence of CD has risen significantly in several countries, while most studies have reported stable incidence of pediatric-onset UC. However, these trends are not described uniformly around the world and most countries lack accurate estimates of incidence and prevalence of pediatric IBD. In particular, there is a paucity of information on rates of pediatric IBD from developing nations in Asia, Africa, and South America. Description of epidemiologic trends from these regions may help investigators understand the effect of migration from underdeveloped to developed nations on the risk of IBD development. For example, the increased risk of IBD development in patients of South Asian origin upon their emigration to Canada and the UK has been reported,[146–148] raising the possibility that environmental factors interact with their genetic background to trigger this higher risk. The worldwide comparison of incidence risk in migrants may help elucidate these environmental triggers.

Twin studies have shown that inherited genetic risk factors alone play a small role in the pathogenesis of IBD (16%–36% concordance rates in monozygotic twins and 4% concordance rates in dizygotic twins), and thereby point to strong environmental influences.[149] Western lifestyle has been identified as a potential culprit in the evolution of IBD[150]; however, the environmental triggers of IBD have not been well delineated. The "cold chain hypothesis" suggests that refrigeration has altered the bacterial content of our diet, resulting in the increased growth of disease-triggering organisms.[151] As with atopic diseases, the "hygiene hypothesis" suggests that a cleaner environment, smaller families, and lower exposure to farm animals has resulted in increased risk of IBD in Westernized nations.[152,153] Nevertheless, individually identified triggers have been controversial and an explanation of differing trends in CD and UC remains elusive.[150] Recent research suggests that vitamin D is an inducer of NOD2 function, suggesting that vitamin D deficiency may play a role in disease development.[154] Vitamin D deficiency may explain the higher incidence of CD described in northern regions of some countries.[14,100] We were unable to confirm the north–south gradient in pediatric IBD based on our review. Despite higher rates of CD reported in Canada, Norway, and Sweden, research from southern European regions such as Corsica, Spain (Asturias), and Croatia has demonstrated a relatively higher incidence than countries of higher latitude in Europe such as Finland and northern France.

This discrepancy may be due to heterogeneity of data collection techniques, differences in disease classification, differences in the age limit used for pediatric patients, or referral bias, making it difficult to compare studies included in our systematic review. For example, some studies used hospital records while others used surveys and administrative data. However, several included studies reported rates across time and thus may more accurately represent the true trend in incidence of pediatric IBD. Of those calculating statistical trends, most examining CD demonstrated significantly increased incidence, while most examining UC demonstrated no statistically significant change. Similarly, when studies assessing incidence over time (but without statistical trend analysis) were plotted, a more consistent rise in CD incidence was demonstrated. UC incidence trends were not consistently rising (Fig. 3). These findings imply a worldwide increase in childhood-onset CD, but not UC. This is consistent with a systematic review of the epidemiology of CD in North America, which found increased incidence in adult-onset CD.[155]

This study not only functions to describe the incidence rates of pediatric IBD around the world, but also to highlight some of the key issues that limit the collection and analysis of IBD epidemiology data. As previously mentioned, it is difficult to compare across studies due to heterogeneity in data collection methods. This limitation is evident in studies from the same country that report vastly different estimates of incidence. Furthermore, the incidence rates reported for a specific country are often generalizations from regions within those countries. Some studies reported regional variation in rates of IBD using consistent methodologies, implying that different regions within a country may have different incidence rates. The relative rarity of pediatric IBD in most of the world prevents small area regional variation analysis of trends, and studies reporting incidence rarely describe health services factors that may have led to higher identification rates in some regions. Classification of CD and UC (particularly in nonprospectively collected data) may be subject to misclassification bias. Finally, the statistical tests used for analysis of trends varied across studies, with some reporting age- and sex-adjusted incidence while

others analyzed crude rates. This heterogeneity limits both the internal and external validity of studies as well as the applicability of findings to other regions.

This study was limited to published articles and some abstracts or government reports containing valuable information may have been excluded as a result. We felt that due to the unique difficulties in gathering accurate data it was important to include only peer-reviewed, published articles in an attempt to ensure quality. Additionally, the previously described weaknesses of the included studies may have resulted in incorrect conclusions in our assessment of incidence trends. We chose to include all studies describing the epidemiology of pediatric IBD, without quality assessment as an exclusion criterion, in order to provide the most comprehensive review of international incidence trends in the literature. Despite these limitations, we believe that this study addresses some of the key concerns in collecting and reporting of epidemiologic data and future researchers should strive for rigorous methods to improve the accuracy of their estimates.

The incidence of pediatric-onset IBD (and CD in particular) seems to be increasing for uncertain reasons. This increase has been demonstrated both in Western regions such as Canada, France, and northern Europe and in former eastern European bloc countries such as the Czech Republic, Croatia, and Hungary. Understanding the changes in trends of pediatric IBD is crucial to unraveling its etiology. Further research is required to investigate and compare trends between developing and developed countries to gain more insight regarding possible environmental factors associated with IBD. As well, key information about interactions between genetics and environment can be studied by examining the effect of migration. By describing the international rates of childhood-onset IBD, we hope to stimulate research that may eventually lead to a more comprehensive theory about the etiology and risk factors for the development of pediatric IBD.

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REFERENCES

1. Economou M, Pappas G. New global map of Crohn's disease: genetic, environmental, and socioeconomic correlations. *Inflamm Bowel Dis*. 2008;14:709–720.
2. Kelsen J, Baldassano RN. Inflammatory bowel disease: the difference between children and adults. *Inflamm Bowel Dis*. 2008;14(suppl 2): S9–11.
3. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology*. 2008;135:1114–1122.
4. Imielinski M, Baldassano RN, Griffiths A, et al. Common variants at five new loci associated with early-onset inflammatory bowel disease. *Nat Genet*. 2009;41:1335–1340.
5. Kugathasan S, Baldassano RN, Bradfield JP, et al. Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. *Nat Genet*. 2008;40:1211–1215.
6. Jenks GF, Caspall FC. Error on choroplethic maps: definition, measurement, reduction. *Ann Assoc Am Geographers*. 1971;61:217–244.
7. Abakar-Mahamat A, Filippi J, Pradier C, et al. Incidence of inflammatory bowel disease in Corsica from 2002 to 2003. *Gastroenterol Clin Biol*. 2007;31:1098–1103.
8. Ahmaida AI, Al-Shaikhi SA. Childhood inflammatory bowel disease in Libya: epidemiological and clinical features. *Libyan J Med*. 2009;4: 70–74.
9. Ahmed M, Davies IH, Hood K, et al. Incidence of paediatric inflammatory bowel disease in South Wales. *Arch Dis Child*. 2006;91: 344–345.
10. Appleyard CB, Hernandez G, Rios-Bedoya CF. Basic epidemiology of inflammatory bowel disease in Puerto Rico. *Inflamm Bowel Dis*. 2004;10:106–111.
11. Arin Letamendia A, Borda Celaya F, Burusco Paternain MJ, et al. [High incidence rates of inflammatory bowel disease in Navarra (Spain). Results of a prospective, population-based study]. *Gastroenterol Hepatol*. 2008;31:111–116.
12. Armitage E, Drummond H, Ghosh S, et al. Incidence of juvenile-onset Crohn's disease in Scotland. *Lancet*. 1999;353:1496–1497.
13. Armitage E, Drummond HE, Wilson DC, et al. Increasing incidence of both juvenile-onset Crohn's disease and ulcerative colitis in Scotland. *Eur J Gastroenterol Hepatol*. 2001;13:1439–1447.
14. Armitage EL, Aldhous MC, Anderson N, et al. Incidence of juvenile-onset Crohn's disease in Scotland: association with northern latitude and affluence. *Gastroenterology*. 2004;127:1051–1057.
15. Askling J, Grahnquist L, Ekbom A, et al. Incidence of paediatric Crohn's disease in Stockholm, Sweden. *Lancet*. 1999;354:1179.
16. Auvin S, Molinie F, Gower-Rousseau C, et al. Incidence, clinical presentation and location at diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in northern France (1988–1999). *J Pediatr Gastroenterol Nutr*. 2005;41:49–55.
17. Barton JR, Gillon S, Ferguson A. Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983; marginal fall in ulcerative colitis, three-fold rise in Crohn's disease. *Gut*. 1989;30: 618–622.
18. Benchimol EI, Guttmann A, Griffiths AM, et al. Increasing incidence of paediatric inflammatory bowel disease in Ontario, Canada: evidence from health administrative data. *Gut*. 2009;58:1490–1497.
19. Bentsen BS, Moum B, Ekbom A. Incidence of inflammatory bowel disease in children in southeastern Norway: a prospective population-based study 1990–94. *Scand J Gastroenterol*. 2002;37:540–545.
20. Bernstein CN, Blanchard JF, Rawsthorne P, et al. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am J Epidemiol*. 1999;149:916–924.
21. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study [see Comment]. *Am J Gastroenterol*. 2006;101:1559–1568 [Erratum, *Am J Gastroenterol*. 2006;101:1945].
22. Bjornsson S, Johannsson JH. Inflammatory bowel disease in Iceland, 1990–1994: a prospective, nationwide, epidemiological study. *Eur J Gastroenterol Hepatol*. 2000;12:31–38.
23. Bjornsson S, Johannsson JH, Oddsson E. Inflammatory bowel disease in Iceland, 1980–89. A retrospective nationwide epidemiologic study. *Scand J Gastroenterol*. 1998;33:71–77.
24. Bonnevie O, Riis P, Anthonisen P. An epidemiological study of ulcerative colitis in Copenhagen County. *Scand J Gastroenterol*. 1968; 3:432–438.

25. Brahme F, Lindstrom C, Wenckert A. Crohn's disease in a defined population. An epidemiological study of incidence, prevalence, mortality, and secular trends in the city of Malmo, Sweden. *Gastroenterology*. 1975;69:342–351.
26. Brullet E, Bonfill X, Urrutia G, et al. [Epidemiological study on the incidence of inflammatory bowel disease in 4 Spanish areas. Spanish Group on the Epidemiological Study of Inflammatory Bowel Disease]. *Med Clin (Barc)*. 1998;110:651–656.
27. Cachia E, Calleja N, Aakeroy R, et al. Incidence of inflammatory bowel disease in Malta between 1993 and 2005: a retrospective study. *Inflamm Bowel Dis*. 2008;14:550–553.
28. Calkins BM, Lilienfeld AM, Garland CF, et al. Trends in incidence rates of ulcerative colitis and Crohn's disease. *Dig Dis Sci*. 1984;29: 913–920.
29. Castro M, Papadatou B, Baldassare M, et al. Inflammatory bowel disease in children and adolescents in Italy: data from the pediatric national IBD register (1996–2003). *Inflamm Bowel Dis*. 2008;14: 1246–1252.
30. Colombel JF, Dupas JL, Cortot A, et al. [Incidence of inflammatory bowel disease in the Nord-Pas-de-Calais region and the Somme area of France in 1988]. *Gastroenterol Clin Biol*. 1990;14:614–618.
31. Cosgrove M, Al-Atia RF, Jenkins HR. The epidemiology of paediatric inflammatory bowel disease. *Arch Dis Child*. 1996;74:460–461.
32. Cottone M, Cipolla C, Orlando A, et al. Epidemiology of Crohn's disease in Sicily: a hospital incidence study from 1987 to 1989. "The Sicilian Study Group of Inflammatory Bowel Disease." *Eur J Epidemiol*. 1991;7:636–640.
33. Devlin HB, Datta D, Dellipiani AW. The incidence and prevalence of inflammatory bowel disease in North Tees Health District. *World J Surg*. 1980;4:183–193.
34. Dirks E, Forster S, Thom M, et al. [Prospective study of the incidence and prevalence of ulcerative colitis in a large urban population in Germany (western Ruhr area)]. *Z Gastroenterol*. 1994;32: 332–337.
35. Edouard A, Paillaud M, Merle S, et al. Incidence of inflammatory bowel disease in the French West Indies (1997–1999). *Gastroenterol Clin Biol*. 2005;29:779–783.
36. Ekbom A, Helmick C, Zack M, et al. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterology*. 1991;100:350–358.
37. El Mouzan MI, Abdullah AM, Al Habbal MT. Epidemiology of juvenile-onset inflammatory bowel disease in central Saudi Arabia. *J Trop Pediatr*. 2006;52:69–71.
38. Evans JG, Acheson ED. An epidemiological study of ulcerative colitis and regional enteritis in the Oxford area. *Gut*. 1965;6:311–324.
39. Fellows IW, Freeman JG, Holmes GK. Crohn's disease in the city of Derby, 1951–85. *Gut*. 1990;31:1262–1265.
40. Fernandez Gonzalez N, Bousono Garcia C, Ramos Polo E, et al. Inflammatory bowel disease in pediatric patients in Asturias, Spain, (1993–2000): epidemiology and clinical features [Spanish]. *Acta Pediatr Esp*. 2004;62:466–472.
41. Fernandez P, Lozano MJ, Vitoria JC, et al. Multicenter study of 60 cases of chronic inflammatory bowel disease during childhood in northern Spain [Spanish]. *An Esp Pediatr*. 1994;40:435–442.
42. Fonager K, Sorenson HT, Olsen J. Change in incidence of Crohn's disease and ulcerative colitis in Denmark. A study based on the National Registry of Patients, 1981–1992. *Int J Epidemiol*. 1997;26: 1003–1008.
43. Garland CF, Lilienfeld AM, Mendeloff AI, et al. Incidence rates of ulcerative colitis and Crohn's disease in fifteen areas of the United States. *Gastroenterology*. 1981;81:1115–1124.
44. Gearry RB, Richardson A, Frampton CMA, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. *Inflamm Bowel Dis*. 2006;12:936–943.
45. Gjone E, Orning OM, Myren J. Crohn's disease in Norway 1956–63. *Gut*. 1966;7:372–374.
46. Goebell H, Dirks E, Forster S, et al. A prospective analysis of the incidence and prevalence of Crohn's disease in an urban population in Germany. *Eur J Gastroenterol Hepatol*. 1994;6: 1039–1045.
47. Gollop JH, Phillips SF, Melton LJ, 3rd et al. Epidemiologic aspects of Crohn's disease: a population based study in Olmsted County, Minnesota, 1943–1982. *Gut*. 1988;29:49–56.
48. Gottrand F, Colombel JF, Moreno L, et al. [Incidence of inflammatory bowel diseases in children in the Nord-Pas-de-Calais region]. *Arch Fr Pediatr*. 1991;48:25–28.
49. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol*. 2009;104:2080–2088.
50. Gower-Rousseau C, Salomez JL, Dupas JL, et al. Incidence of inflammatory bowel disease in northern France (1988–1990). *Gut*. 1994;35:1433–1438.
51. Grieci T, Butter A. The incidence of inflammatory bowel disease in the pediatric population of southwestern Ontario. *J Pediatr Surg*. 2009;44:977–980.
52. Grossman A, Fireman Z, Lilos P, et al. Epidemiology of ulcerative colitis in the Jewish population of central Israel 1970–1980. *Hepatogastroenterology*. 1989;36:193–197.
53. Hassan K, Cowan FJ, Jenkins HR. The incidence of childhood inflammatory bowel disease in Wales. *Eur J Pediatr*. 2000;159: 261–263.
54. Haug K, Schrumpf E, Barstad S, et al. Epidemiology of ulcerative colitis in western Norway. *Scand J Gastroenterol*. 1988;23:517–522.
55. Haug K, Schrumpf E, Halvorsen JF, et al. Epidemiology of Crohn's disease in western Norway. Study Group of Inflammatory Bowel Disease in Western Norway. *Scand J Gastroenterol*. 1989;24: 1271–1275.
56. Hellers G. Crohn's disease in Stockholm county 1955–1974. A study of epidemiology, results of surgical treatment and long-term prognosis. *Acta Chir Scand Suppl*. 1979;490:1–84.
57. Herrinton LJ, Liu L, Lewis JD, et al. Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996–2002. *Am J Gastroenterol*. 2008;103:1998–2006.
58. Higashi A, Watanabe Y, Ozasa K, et al. Prevalence and mortality of ulcerative colitis and Crohn's disease in Japan. *Gastroenterol Jpn*. 1988;23:521–526.
59. Hildebrand H, Brydolf M, Holmquist L, et al. Incidence and prevalence of inflammatory bowel disease in children in south-western Sweden. *Acta Paediatr*. 1994;83:640–645.
60. Hildebrand H, Finkel Y, Grahnquist L, et al. Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990–2001. *Gut*. 2003;52:1432–1434.
61. Hildebrand H, Fredrikzon B, Holmquist L, et al. Chronic inflammatory bowel disease in children and adolescents in Sweden. *J Pediatr Gastroenterol Nutr*. 1991;13:293–297.
62. Hoj L, Jensen PB, Bonnevie O, et al. An epidemiological study of regional enteritis and acute ileitis in Copenhagen County. *Scand J Gastroenterol*. 1973;8:381–384.
63. Humphreys WG, Parks TG. Crohn's disease in Northern Ireland—a retrospective survey of 159 cases. *Ir J Med Sci*. 1975;144:437–446.
64. Jacobsen BA, Fallingborg J, Rasmussen HH, et al. Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978–2002. *Eur J Gastroenterol Hepatol*. 2006;18:601–606.
65. Jakobsen C, Wewer V, Urne F, et al. Incidence of ulcerative colitis and Crohn's disease in Danish children: still rising or levelling out? *J Crohn's Colitis*. 2008;2:152–157.
66. Jayanthi V, Probert CS, Pinder D, et al. Epidemiology of Crohn's disease in Indian migrants and the indigenous population in Leicestershire. *Q J Med*. 1992;82:125–138.
67. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol*. 2007;5:1424–1429.
68. Karolewska-Bochenek K, Lazowska-Przeorek I, Albrecht P, et al. Epidemiology of inflammatory bowel disease among children in Poland. *Digestion*. 2009;79:121–129.
69. Kildebo S, Breckan R, Nordgaard K, et al. The incidence of Crohn's disease in northern Norway from 1983 to 1986. Northern Norway Gastroenterology Society. *Scand J Gastroenterol*. 1989;24:1265–1270.

70. Kildebo S, Nordgaard K, Aronsen O, et al. The incidence of ulcerative colitis in Northern Norway from 1983 to 1986. *Scand J Gastroenterol*. 1990;25:890–896.
71. Kolek A, Janout V, Tichy M, et al. The incidence of inflammatory bowel disease is increasing among children 15 years old and younger in the Czech Republic. *J Pediatr Gastroenterol Nutr*. 2004;38:362–363.
72. Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr*. 2003;143:525–531.
73. Kyle J. An epidemiological study of Crohn's disease in northeast Scotland. *Gastroenterology*. 1971;61:826–833.
74. Kyle J. Crohn's disease in the northeastern and northern Isles of Scotland: an epidemiological review. *Gastroenterology*. 1992;103: 392–399.
75. Ladas S-D, Mallas E, Giorgiotis K, et al. Incidence of ulcerative colitis in Central Greece: a prospective study. *World J Gastroenterol*. 2005;11:1785–1787.
76. Lakatos L, Mester G, Erdelyi Z, et al. [Epidemiology of inflammatory bowel diseases in Veszprem county of Western Hungary between 1977 and 2001]. *Orv Hetil*. 2003;144:1819–1827.
77. Landau D-A, Goldberg A, Levi Z, et al. The prevalence of gastrointestinal diseases in Israeli adolescents and its association with body mass index, gender, and Jewish ethnicity. *J Clin Gastroenterol*. 2008;42:903–909.
78. Langholz E, Munkholm P, Haagen Nielsen O, et al. Incidence and prevalence of ulcerative colitis in Copenhagen County from 1962 to 1987. *Scand J Gastroenterol*. 1991;26:1247–1256.
79. Langholz E, Munkholm P, Krasilnikoff PA, et al. Inflammatory bowel diseases with onset in childhood. Clinical features, morbidity, and mortality in a regional cohort. *Scand J Gastroenterol*. 1997;32: 139–147.
80. Lapidus A, Bernell O, Hellers G, et al. Incidence of Crohn's disease in Stockholm County 1955–1989. *Gut*. 1997;41:480–486.
81. Lee FI, Costello FT. Crohn's disease in Blackpool—incidence and prevalence 1968–80. *Gut*. 1985;26:274–278.
82. Lindberg E, Jornerot G. The incidence of Crohn's disease is not decreasing in Sweden. *Scand J Gastroenterol*. 1991;26:495–500.
83. Lindberg E, Lindquist B, Holmquist L, et al. Inflammatory bowel disease in children and adolescents in Sweden, 1984–1995. *J Pediatr Gastroenterol Nutr*. 2000;30:259–264.
84. Lindberg J, Stenling R, Palmqvist R, et al. Early onset of ulcerative colitis: long-term follow-up with special reference to colorectal cancer and primary sclerosing cholangitis. *J Pediatr Gastroenterol Nutr*. 2008;46:534–538.
85. Linden G, Moller C. Ulcerative colitis in Finland. II. One-year incidence in all hospitals. *Dis Colon Rectum*. 1971;14:264–266.
86. Lindquist BL, Jarnerot G, Wickbom G. Clinical and epidemiological aspects of Crohn's disease in children and adolescents. *Scand J Gastroenterol*. 1984;19:502–506.
87. Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm Bowel Dis*. 2007; 13:254–261.
88. Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Crohn's disease in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gastroenterology*. 1998;114:1161–1168 [Erratum, *Gastroenterology* 1999;116:1507].
89. Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gut*. 2000;46:336–343.
90. Lopez Miguel C, Sicilia B, Sierra E, et al. [Incidence of inflammatory bowel disease in Aragon: outcome of a prospective population-based study]. *Gastroenterol Hepatol*. 1999;22:323–328.
91. Lowe A-M, Roy P-O, B-Poulin M, et al. Epidemiology of Crohn's disease in Quebec, Canada. *Inflamm Bowel Dis*. 2009;15: 429–435.
92. Malaty HM, Fan X, Opekun AR, et al. Rising incidence of inflammatory bowel disease among children: a 12-year study. *J Pediatr Gastroenterol Nutr*. 2010;50:27–31.
93. Mayberry J, Rhodes J, Hughes LE. Incidence of Crohn's disease in Cardiff between 1934–1977. *Gut*. 1979;20:602–608.
94. Morris T, Rhodes J. Incidence of ulcerative colitis in the Cardiff region 1968–1977. *Gut*. 1984;25:846–848.
95. Moum B, Vatn MH, Ekbom A, et al. Incidence of ulcerative colitis and indeterminate colitis in four counties of southeastern Norway, 1990–93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. *Scand J Gastroenterol*. 1996;31:362–366.
96. Moum B, Vatn MH, Ekbom A, et al. Incidence of Crohn's disease in four counties in southeastern Norway, 1990–93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. *Scand J Gastroenterol*. 1996;31:355–361.
97. Moum B, Vatn MH, Ekbom A, et al. Incidence of inflammatory bowel disease in southeastern Norway: evaluation of methods after 1 year of registration. Southeastern Norway IBD Study Group of Gastroenterologists. *Digestion*. 1995;56:377–381 [Erratum, *Digestion* 1996;57:104].
98. Munkholm P, Langholz E, Nielsen OH, et al. Incidence and prevalence of Crohn's disease in the county of Copenhagen, 1962–87: a sixfold increase in incidence. *Scand J Gastroenterol*. 1992;27:609–614.
99. Myren J, Gjone E, Hertzberg JN, et al. Epidemiology of ulcerative colitis and regional enterocolitis (Crohn's disease) in Norway. *Scand J Gastroenterol*. 1971;6:511–514.
100. Nerich V, Monnet E, Etienne A, et al. Geographical variations of inflammatory bowel disease in France: a study based on national health insurance data. *Inflamm Bowel Dis*. 2006;12:218–226.
101. Niv Y, Abuksis G, Fraser GM. Epidemiology of Crohn's disease in Israel: a survey of Israeli kibbutz settlements. *Am J Gastroenterol*. 1999;94:2961–2965.
102. Niv Y, Abuksis G, Fraser GM. Epidemiology of ulcerative colitis in Israel: a survey of Israeli kibbutz settlements. *Am J Gastroenterol*. 2000;95:693–698.
103. Nordenvall B, Brostrom O, Berglund M, et al. Incidence of ulcerative colitis in Stockholm County 1955–1979. *Scand J Gastroenterol*. 1985;20:783–790.
104. Norlen BJ, Krause U, Bergman L. An epidemiological study of Crohn's disease. *Scand J Gastroenterol*. 1970;5:385–390.
105. Nyhlin H, Danielsson A. Incidence of Crohn's disease in a defined population in northern Sweden, 1974–1981. *Scand J Gastroenterol*. 1986;21:1185–1192.
106. Odes HS, Locker C, Neumann L, et al. Epidemiology of Crohn's disease in southern Israel. *Am J Gastroenterol*. 1994;89:1859–1862.
107. Ogunbi SO, Ransom JA, Sullivan K, et al. Inflammatory bowel disease in African-American children living in Georgia. *J Pediatr*. 1998;133:103–107.
108. Olafsdottir EJ, Fluge G, Haug K. Chronic inflammatory bowel disease in children in western Norway. *J Pediatr Gastroenterol Nutr*. 1989;8:454–458.
109. Orel R, Kamhi T, Vidmar G, et al. Epidemiology of pediatric chronic inflammatory bowel disease in central and western Slovenia, 1994–2005. *J Pediatr Gastroenterol Nutr*. 2009;48:579–586.
110. Ott C, Obermeier F, Thieler S, et al. The incidence of inflammatory bowel disease in a rural region of Southern Germany: a prospective population-based study. *Eur J Gastroenterol Hepatol*. 2008;20:917–923.
111. Perminow G, Brackmann S, Lyckander LG, et al. A characterization in childhood inflammatory bowel disease, a new population-based inception cohort from south-eastern Norway, 2005–07, showing increased incidence in Crohn's disease. *Scand J Gastroenterol*. 2009;44:446–456.
112. Perminow G, Frigessi A, Rydning A, et al. Incidence and clinical presentation of IBD in children: comparison between prospective and retrospective data in a selected Norwegian population. *Scand J Gastroenterol*. 2006;41:1433–1439.
113. Phavichitr N, Cameron DJS, Catto-Smith AG. Increasing incidence of Crohn's disease in Victorian children. *J Gastroenterol Hepatol*. 2003;18:329–332.
114. Pinchbeck BR, Kirdeikis J, Thomson AB. Inflammatory bowel disease in northern Alberta. An epidemiologic study. *J Clin Gastroenterol*. 1988;10:505–515.

115. Pinsk V, Lemberg DA, Grewal K, et al. Inflammatory bowel disease in the South Asian pediatric population of British Columbia [see Comment]. *Am J Gastroenterol*. 2007;102:1077–1083.
116. Ponsonby AL, Catto-Smith AG, Pezic A, et al. Association between early-life factors and risk of child-onset Crohn's disease among Victorian children born 1983–1998: a birth cohort study. *Inflamm Bowel Dis*. 2009;15:858–866.
117. Pozler O, Maly J, Bonova O, et al. Incidence of Crohn disease in the Czech Republic in the years 1990 to 2001 and assessment of pediatric population with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2006;42:186–189.
118. Probert CS, Jayanthi V, Pinder D, et al. Epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire.. *Gut*. 1992;33:687–693.
119. Ranzi T, Bodini P, Zambelli A, et al. Epidemiological aspects of inflammatory bowel disease in a north Italian population: a 4-year prospective study. *Eur J Gastroenterol Hepatol*. 1996;8:657–661.
120. Rodrigo L, Riestra S, Nino P, et al. A population-based study on the incidence of inflammatory bowel disease in Oviedo (Northern Spain). *Rev Esp Enferm Dig*. 2004;96:296–305.
121. Romberg-Camps MJL, Hesselink-van de Kruijs MAM, Schouten LJ, et al. Inflammatory bowel disease in South Limburg (the Netherlands) 1991–2002: incidence, diagnostic delay, and seasonal variations in onset of symptoms. *J Crohn's Colitis*. 2009;3:115–124.
122. Ruiz Ochoa V. [Epidemiologic study of Crohn's disease in Galicia from 1976 to 1983]. *Rev Esp Enferm Apar Dig*. 1984;66: 273–279.
123. Russel MG, Dorant E, Volovics A, et al. High incidence of inflammatory bowel disease in The Netherlands: results of a prospective study. The South Limburg IBD Study Group. *Dis Colon Rectum*. 1998;41:33–40.
124. Sawczenko A, Sandhu BK, Logan RF, et al. Prospective survey of childhood inflammatory bowel disease in the British Isles. *Lancet*. 2001;357:1093–1094.
125. Sincic BM, Vucelic B, Persic M, et al. Incidence of inflammatory bowel disease in Primorsko-goranska County, Croatia, 2000–2004: A prospective population-based study. *Scand J Gastroenterol*. 2006;41: 437–444.
126. Smith IS, Young S, Gillespie G, et al. Epidemiological aspects of Crohn's disease in Clydesdale 1961–1970. *Gut*. 1975;16:62–67.
127. Srivastava ED, Mayberry JF, Morris TJ, et al. Incidence of ulcerative colitis in Cardiff over 20 years: 1968–87. *Gut*. 1992;33: 256–258.
128. Stewenius J, Adnerhill I, Ekelund G, et al. Ulcerative colitis and indeterminate colitis in the city of Malmo, Sweden. A 25-year incidence study. *Scand J Gastroenterol*. 1995;30:38–43.
129. Stordal K, Jahnsen J, Bentsen BS, et al. Pediatric inflammatory bowel disease in southeastern Norway: a five-year follow-up study. *Digestion*. 2004;70:226–230.
130. Stowe SP, Redmond SR, Stormont JM, et al. An epidemiologic study of inflammatory bowel disease in Rochester, New York. Hospital incidence. *Gastroenterology*. 1990;98:104–110.
131. Torres EA, De Jesus R, Perez CM, et al. Prevalence of inflammatory bowel disease in an insured population in Puerto Rico during 1996. *P R Health Sci J*. 2003;22:253–258.
132. Tourtelier Y, Dabadie A, Tron I, et al. [Incidence of inflammatory bowel disease in children in Brittany (1994–1997). Breton association of study and research on digestive system diseases (Abermad)]. *Arch Pediatr*. 2000;7:377–384.
133. Tragnone A, Corrao G, Miglio F, et al. Incidence of inflammatory bowel disease in Italy: a nationwide population-based study. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). *Int J Epidemiol*. 1996;25:1044–1052.
134. Turunen P, Kolho K-L, Auvinen A, et al. Incidence of inflammatory bowel disease in Finnish children, 1987–2003. *Inflamm Bowel Dis*. 2006;12:677–683.
135. Tysk C, Jarnerot G. Ulcerative proctocolitis in Orebro, Sweden. A retrospective epidemiologic study, 1963–1987. *Scand J Gastroenterol*. 1992;27:945–950.
136. Urne FU, Paerregaard A. [Chronic inflammatory bowel disease in children. An epidemiological study from eastern Denmark 1998–2000]. *Ugeskr Laeger*. 2002;164:5810–5814.
137. van der Zaag-Loonen HJ, Casparie M, Taminiau JAJM, et al. The incidence of pediatric inflammatory bowel disease in the Netherlands: 1999–2001. *J Pediatr Gastroenterol Nutr*. 2004;38:302–307.
138. Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol*. 2006;101:1274–1282.
139. Vucelic B, Korac B, Sentic M, et al. Ulcerative colitis in Zagreb, Yugoslavia: Incidence and prevalence 1980–1989. *Int J Epidemiol*. 1991;20:1043–1047.
140. Vucelic B, Korac B, Sentic M, et al. Epidemiology of Crohn's disease in Zagreb, Yugoslavia: a ten-year prospective study. *Int J Epidemiol*. 1991;20:216–220.
141. Watson AJ, Johnston AT, Barker PM, et al. The presentation and management of juvenile-onset chronic inflammatory bowel disease in Northeastern Scotland. *J Pediatr Surg*. 2002;37:83–86.
142. Yang SK, Hong WS, Min YI, et al. Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong District, Seoul, Korea, 1986–1997. *J Gastroenterol Hepatol*. 2000;15:1037–1042.
143. Yang S-K, Yun S, Kim J-H, et al. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986–2005: a KASID study. *Inflamm Bowel Dis*. 2008;14:542–549.
144. Yao T, Matsui T, Hiwatashi N. Crohn's disease in Japan: diagnostic criteria and epidemiology. *Dis Colon Rectum*. 2000;43:S85–93.
145. Yap J, Wesley A, Mouat S, et al. Paediatric inflammatory bowel disease in New Zealand. *NZ Med J*. 2008;121:19–34.
146. Carr I, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second-generation South Asians in Leicester (1991–1994). *Am J Gastroenterol*. 1999;94:2918–2922.
147. Pinsk V, Lemberg DA, Grewal K, et al. Inflammatory bowel disease in the South Asian pediatric population of British Columbia. *Am J Gastroenterol*. 2007;102:1077–1083.
148. Tsironi E, Feakins RM, Probert CS, et al. Incidence of inflammatory bowel disease is rising and abdominal tuberculosis is falling in Bangladeshis in East London, United Kingdom. *Am J Gastroenterol*. 2004;99:1749–1755.
149. Binder V. Genetic epidemiology in inflammatory bowel disease. *Dig Dis*. 1998;16:351–355.
150. Lakatos PL. Environmental factors affecting inflammatory bowel disease: have we made progress? *Dig Dis*. 2009;27:215–225.
151. Hugot JP, Alberti C, Berrebi D, et al. Crohn's disease: the cold chain hypothesis. *Lancet*. 2003;362:2012–2015.
152. Bernstein CN, Rawsthorne P, Cheang M, et al. A population-based case control study of potential risk factors for IBD. *Am J Gastroenterol*. 2006;101:993–1002.
153. Radon K, Windstetter D, Poluda AL, et al. Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study. *Pediatrics*. 2007;120:354–361.
154. Wang TT, Dabbas B, Laperriere D, et al. Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NOD2/CARD15-defensin beta2 innate immune pathway defective in Crohn disease. *J Biol Chem*. 2010;285:2227–2231.
155. Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. *Aliment Pharmacol Ther*. 2002;16:51–60.
156. Dabadie A, Tourtelier Y, Alexandre JL, et al. [Outcome of unclassified colitis in the ABERMAD register (inflammatory bowel disease). Effect of follow-up on incidence. Breton Association for Study and Research on Digestive System Diseases]. *Arch Pediatr*. 2000;7:1011.