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Current global trends in the incidence of pediatric-onset inflammatory bowel disease

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Abstract

AIM

To perform a comprehensive review and provide an up-to-date synopsis of the incidence and trends of inflammatory bowel disease (IBD).

METHODS

We systematically searched the MEDLINE (source PubMed), EMBASE and Cochrane Library databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (period: 1985-2018) to identify studies reporting population-based data on the incidence of pediatric-onset (< 19 years at diagnosis) IBD in full manuscripts. Two authors carried out screening and data extraction. Choropleth interactive maps and temporal trends were used to illustrate the international differences and incidences of and changes in IBD and subtypes.

RESULTS

In total, one hundred forty studies reporting data from 38 countries were considered in this review. The highest annual pediatric incidences of IBD were 23/100000 person-years in Europe, 15.2/100000 in North America, and 11.4/100000 in Asia/the Middle East and Oceania. The highest annual incidences of Crohn's disease (CD) were 13.9/100000 in North America and 12.3/100000 in Europe. The highest annual incidences of ulcerative colitis (UC) were 15.0/100000 in Europe and 10.6/100000 in North America. The highest annual incidences of IBD-unclassified (IBD-U) were 3.6/100000 in Europe and 2.1/100000 in North America. In the time-trend analyses, 67% of CD, 46% of UC and 11% of IBD-U studies reported an increasing incidence ($P < 0.05$). The risk of IBD is increasing among first-generation of migrant populations.

CONCLUSION

Globally, the incidence of IBD varies greatly by geographical areas. The steadily increasing incidence of pediatric IBD over time indicates its emergence as a global disease, suggesting that studies should investigate the environmental risk factors among pediatric cohorts.

Key words: Children; Incidence; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Inflammatory bowel disease-unclassified

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Core tip: The incidence of inflammatory bowel disease (IBD) is unclear in the pediatric literature. We comprehensively reviewed and critically evaluated population-based and national cohort studies investigating the incidence of IBD and its global trends. One hundred forty studies met the inclusion criteria. The incidence of pediatric-onset IBD has been steadily increasing over time in different geographical areas in both developed and developing regions worldwide, whereas those in the West may have reached a plateau. This indicates the emergence of an IBD epidemic; however, incidence data from developing regions are limited. Exploring the changes and increasing incidence of pediatric IBD may provide new insights into the potential etiology of IBD.

Sýkora J, Pomahačová R, Kreslová M, Cvalínová D, Štych P, Schwarz J. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. *World J Gastroenterol* 2018; 24(25): 2741-2763 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i25/2741.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i25.2741>

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses the

following three forms of idiopathic inflammation of the gut: ulcerative colitis (UC), Crohn's disease (CD) and IBD-unclassified (IBD-U). The differentiation of IBD-U from CD and UC remains difficult; thus, the incidence of IBD-U must be explored. Approximately 25% of patients first present symptoms before the age of 18 years^[1], and the incidence in children over 10 years of age is clearly increasing^[2]. The incidence of IBD in industrialized countries is higher than that in developing countries; however, overwhelming data suggest that its prevalence is increasing worldwide in both adult^[3] and pediatric populations^[4] and that its distribution is uneven among regions^[5]. Many explanations have been proposed, but the hypothesis that exposure to environmental and genetic factors is a fundamental contributor to the development of IBD has been challenged by several new observations^[6-10]. Whether the etiology of pediatric-onset IBD differs from that of adult-onset IBD remains unknown^[11]. Thus, there is a great need to summarize global information regarding the pediatric IBD incidence and disease burden in different settings and perform subsequent analyses of the underlying factors.

The aim of this review is to delineate the incidence of pediatric IBD (defined as onset at an age < 19 years) and summarize the latest incidence trends based on a comprehensive review of credible studies.

MATERIALS AND METHODS

Search and study selection

We conducted a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^[12]. Articles were identified using computer-stored databases and manual search. A search of English and non-English language journals in the MEDLINE (source PubMed), EMBASE via OvidSP, and Cochrane Library databases was conducted to identify original studies investigating IBD incidence published between January 1, 1985 and March 2018. Suitable papers were subsequently catalogued. The Cochrane library was reviewed. We searched for the following strings according to the MeSH headings: "pediatric"[MeSH Terms] and "inflammatory bowel disease"[All Fields] or "Crohn's disease"[All Fields] or "ulcerative colitis"[All Fields] or "inflammatory bowel disease unclassified"[All Fields] or "indeterminate colitis"[All Fields] and "incidence"[All Fields] or "children"[MeSH terms] or "adolescents"[MeSH terms] and "population-based studies"[All Fields] or "national registries"[All Fields] or "health administrative database"[All Fields] and "individual country names"[MeSH terms]. The detailed search strategy is shown in Figure 1.

Data extraction

The data extraction was performed independently by two researchers (Schwarz J and Sýkora J) using set criteria to analyze the title and abstract and extract all relevant study-specific data required for the analysis.

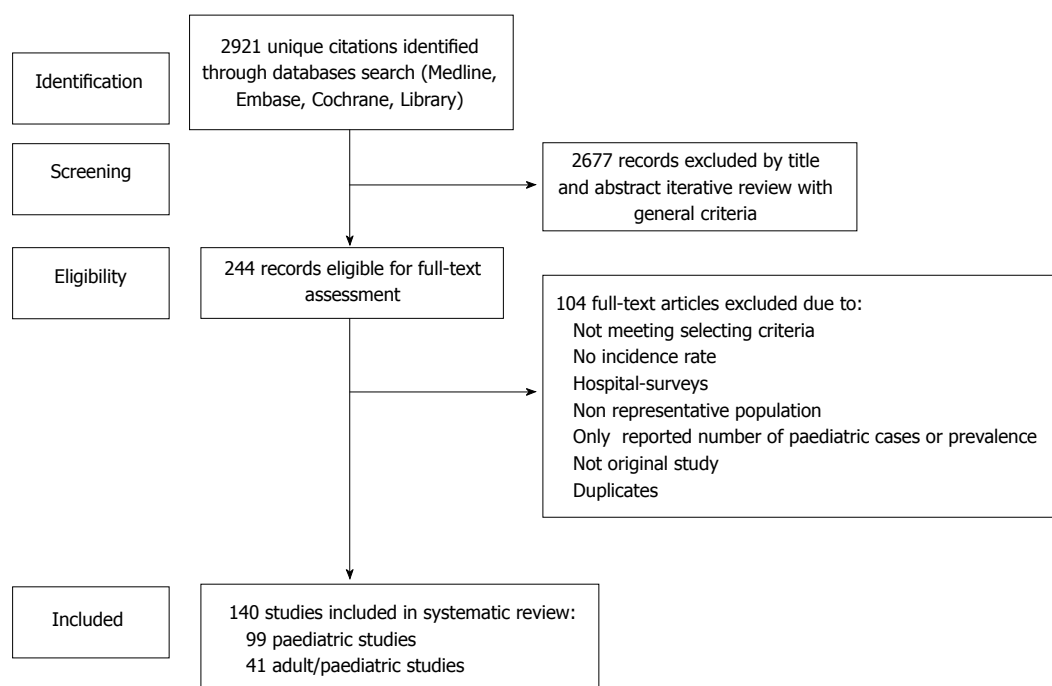


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart diagram for study selection.

This strategy was performed iteratively until no more relevant publications were found. During the full-text screening stage, we analyzed papers for inclusion suitability and adequate information regarding the incidence of IBD or calculation of incidence, and a final decision was made about inclusion/exclusion. In addition, the references in the relevant articles were checked by the first author. From each study, the data were extracted and sorted by the following variables: name of the study, leading author, journal, publication year, study period, type of study, age, study location, crude incidence rate and time trends. Double-extracted data were verified, when a disagreement occurred related to data extraction, this was resolved by consensus. Attempts were made to clarify missing data and any uncertainties or errors found in the studies by consulting with the corresponding authors. The rates were extrapolated from the figures if the articles reported data without specifying the numeric rates. The average incidence was calculated if the incidence rates were reported separately for females and males or by race/ethnicity. Reports focusing on immigrant/indigenous populations were analyzed separately based on the respective general population of the area. After the selection of appropriate articles extrapolating the incidence of IBD, a comprehensive review was performed. We only included original studies with a clear case ascertainment. A meta-analysis was not undertaken due to the variability in the included records; thus, a narrative review was conducted. The incidence was measured as the number of cases/100000 person-years, and the temporal evolution was examined to measure the effect of the calendar year on the incidence. All studies were organized by world and

regional distribution and subsequently analyzed based on the United Nations (UN) geoscheme devised by the UN Statistics Division^[13] regarding the assignment of countries or areas to specific groupings as follows: North America, Europe, Oceania, Asia, South America and Africa. We created interactive (choropleth) maps to visualize the resulting data worldwide and extrapolate the incidence at the country level. Choropleth maps depicting differences in the incidence rates by changes in color were employed. If data were reported for only a region within a country, the entire country was shown on the map.

Quality assessment of selected papers

The quality of the incidence studies was assessed by whether the diagnostic criteria were clearly defined or recognized criteria (Lennard-Jones, Copenhagen criteria) were implemented^[14]. The Critical Appraisal Skills Programme was used to appraise the principles of the studies based on the specific methodological designs of the included studies^[15]. We extrapolated the incidence at the country level and summarized the incidence rates by jurisdiction in each study. The quality characteristics of each paper are summarized in Table 1. The assessment of the studies yielded either an A or B quality ranking based on the representativeness of the cases. A representative study population was a prerequisite for a study to be included in this systematic review (A). Studies that included populations that were not sampled across the entire country or had a smaller population size were given a B quality ranking. Because all papers were considered to contribute to the determination of the incidence and differences in incidence estimates, we included all studies without a

Table 1 Summary of included pediatric-onset inflammatory bowel disease incidence studies stratified by continent and geographical areas

Country/Region/ Province	Age (yr)	Study period	IBD incidence	CD incidence	UC incidence	IBDU incidence	Setting	Year of publication	First author /reference	Representativeness of the case
Western and North Europe										
Austria/Styria	< 18	1997-2007		6.7 a	4.8a		R	2013	Petritsch W <i>et al</i> ^[122]	B
Denmark/ Eastern	< 15	1998-2000	4.3.	2.3.	1.8.	0.2	R	2002	Urne <i>et al</i> ^[108]	B
Denmark	< 17	1995-2013					P	2016	Larsen <i>et al</i> ^[109]	A
		2013		9.7a	6.7a					
Denmark/ Eastern	< 15	1998-2009	6.4a	3.2a,b	3.1a,b	0.2a	R	2011	Jakobsen <i>et al</i> ^[110]	B
Denmark	< 15	1995-2012		3.1a	2.7a		P	2014	Norgard <i>et al</i> ^[111]	A
Denmark/ Eastern	< 15	1998-2000	4.3a	2.3a	1.8a	0.2a	P	2008	Jakobsen <i>et al</i> ^[33]	B
		2002-2004	6.1	3.1	2.7	0.3				
Denmark	< 15	1980-2013		2.4a	3.3a		P	2017	Lophaven <i>et al</i> ^[103]	A
Denmark/ Copenhagen County	< 19	1962-1987			8.6-13.3a		P	1991	Langholz <i>et al</i> ^[106]	B
Denmark/ Copenhagen County	< 14	1962-1987	2.2a	0.2a	2.0a		P	1997	Langholz <i>et al</i> ^[105]	B
Denmark/ Copenhagen County	< 14	1962-1987			0.2		R	1992	Munkholm <i>et al</i> ^[62]	B
Denmark/ Copenhagen County	< 15	1962-1987		0.2-3.1a	2 - 1.6a		P	2009	Jakobsen <i>et al</i> ^[34]	B
Denmark	< 15	1981-1992		0.8a	2.5a		P	1997	Fonager <i>et al</i> ^[107]	A
Denmark/ Northern	< 14	1978-2002		1.5	2.7		P	2006	Jacobsen <i>et al</i> ^[104]	B
Denmark/ Copenhagen County	< 17	2003-2005		4.4	5.5		P	2006	Vind <i>et al</i> ^[102]	B
Finland	< 18	1987-2003	5a	2a	4a		P	2011	Lehtinen <i>et al</i> ^[65]	A
		2003	15	5	9.1					
Finland	< 17	1987-2003					P	2006	Turunen <i>et al</i> ^[64]	A
		1987	3.9a	1.7a	2.2a					
		2003	7	3.6	4.8	1				
Finland	< 17	1986-1992		1.0a			R	1998	Pebody <i>et al</i> ^[88]	A
Finland	< 18	1987-2003	6.5	2.1	4.1		P	2016	Lehtinen <i>et al</i> ^[89]	A
Finland	< 19	1987-2014	7-23a	6-8a	10-15a		R	2017	Virta <i>et al</i> ^[66]	A
	< 16	2011-2014	13		8					
France	< 17	1988-2011	3.1-6.3a				P	2016	Bequet <i>et al</i> ^[126]	A
France/Northern	< 17	1998-1999	3.1a	2.3a	0.8a	0.12a	P	2005	Auvin <i>et al</i> ^[43]	B
France/Northern	< 17	1988-2011	4.4a	3.2a	1.1a	0.1a	P	2017	Ghione <i>et al</i> ^[131]	B
France/Brittany	< 17	1994-1997	2.5	1.6	0.57		P	2000	Tourteliier <i>et al</i> ^[131]	B
France/Northern	< 19	1988-2007		3.4-5.9a			P	2011	Chouraki <i>et al</i> ^[32]	B
France/Northern	< 17	1988-2002		2.6			P	2008	Vernier-Massouille <i>et al</i> ^[127]	B
France/Northern	< 19	1988-2008		6.5-12.9a			P	2013	Gower-Rousseau <i>et al</i> ^[125]	B
France/Corsica	< 19	2002-2003		12.3	6.2		P	2007	Abakar-Mahamat <i>et al</i> ^[128]	B
France/Nord- Pas-de-Calais	< 17	1988-1989	3.1	2.1	0.5		P	1991	Gotttrand <i>et al</i> ^[130]	B
The Farose Islands	< 19	1960-2014	9.0 ² a	2.5 ² a	5 ² a	1.5 ² a	P,R	2016	Hammer <i>et al</i> ^[19]	A
Iceland	< 16	1950-2010					P,R	2013	Agnarsson <i>et al</i> ^[29]	A
		1951-1960	1.2	0.2	1.1					
		1961-1970	0.9	0.1	0.7					
		1971-1980	0.9	0.1	0.7					
		1981-1990	2.5a	1.2a	1.2a	0.1a				
		1991-2000/2001-2010	5.6/5.0	2.5/2.3	2.5/2.3	0.3/0.3				
Iceland	< 19	1990-1994		4.5	5		P	2000	Bjornsson <i>et al</i> ^[112]	A

Ireland	< 16	2000-2010	2.5-5.6a	2.3a	1.1a		R	2012	Hope <i>et al</i> ^[120]	A
Ireland	< 10	2000-2014	0.8-3.3a				P,R	2017	Coughlan <i>et al</i> ^[121]	A
The Netherlands	< 18	1999-2001	5.2	2.1	1.6	3.6	P	2004	van der Zaag-Loonen <i>et al</i> ^[124]	A
Germany/ Southern	< 15	2004-2006	4.0a	2.4a	1.1a		P	2008	Ott <i>et al</i> ^[123]	B
Norway/ Southeastern	< 16	1990-1994	4.2	2	2.1		P	2002	Bentsen <i>et al</i> ^[185]	B
Norway/ Southeastern	< 14	1990-1993			1.3		P	1996	Moum <i>et al</i> ^[95]	B
Norway/ Southeastern	< 16	1990-1993	4.7	2.7	2		P	2004	Stordal <i>et al</i> ^[93]	B
Norway/ Southeastern	< 18	2005-2007	10.9b	6.8b	3.6b	0.6	P	2009	Perminow <i>et al</i> ^[92]	B
Norway/ Southeastern	< 16	1993-2004	5.6-5.7a	2.0-3.6a	3.7-2.1a		P,R	2006	Perminow <i>et al</i> ^[60]	B
Norway/ Western	< 16	1984-1985	6.8	2.5	4.3	0	P	1989	Olafsdottir <i>et al</i> ^[97]	B
Norway/ Western	< 14	1984-1985		2.5			P	1988	Haug <i>et al</i> ^[163]	B
Norway/ Southeastern	< 14	1990	3	1.2	0.6		P	1995	Moum <i>et al</i> ^[94]	B
Norway/ Southeastern	< 14	1990-1993		0.94			P	1996	Moum <i>et al</i> ^[96]	B
Sweden/ Northern Stockholm	< 17	1990-1998	6.9a	3.8a	2.1a	1.1a	R	1999	Askling <i>et al</i> ^[99]	B
Sweden/ Northern Stockholm	< 15	1990-2001	7.4a	4.9a	2.2a	0.2a	P	2003	Hildebrand <i>et al</i> ^[59]	B
Sweden/ Southwestern	< 16	1983-1987	5.3	2.7	2.6	0.7	P	1994	Hildebrand <i>et al</i> ^[164]	B
Sweden/ Stockholm	< 15	2002-2007	12.8a,b	9.2a,b	2.8a,b		P	2013	Malmberg <i>et al</i> ^[38]	B
Sweden	< 15	1984-1995	4.6-7.0a	1.2-1.3a	1.4-3.2a	1.1a	P	2000	Lindberg <i>et al</i> ^[68]	A
Sweden	< 14	1963-1967 1983-1987		1.4 - 0.7a 0.7			R	1991	Lindberg <i>et al</i> ^[98]	A
Sweden/the Uppsala region	< 17	2005-2009	18.9		8.9		P	2013	Sjoberg <i>et al</i> ^[100]	B
Sweden/the Uppsala region	< 17	2005-2009		10			P	2014	Sjoberg <i>et al</i> ^[101]	B
Sweden/the Uppsala region	< 19	1965-1983 1965-1970 1975-1983		5.9-5.0a 4.8-3.2	5.2-4.8a 3.9-2.7		R	1991	Ekbom <i>et al</i> ^[56]	B
Sweden/Orebro	< 19	1963-1987			6		R	1992	Tysk <i>et al</i> ^[165]	B
Sweden/ Stockholm County	< 14	1955-1983		4.1			R	1997	Lapidus <i>et al</i> ^[35]	B
Sweden	< 15	1984-1985	4.8	1.7	1.7		P	1991	Hildebrand <i>et al</i> ^[166]	A
UK/ Scotland	< 16	2003-2008 1990-1995	7.8a 4.5	4.8a 2.9	2.1a 1.6	1.0a	P,R	2012	Henderson <i>et al</i> ^[2]	A
UK/Wessex Southern England	< 16	2002-2012/ 2013-2017						2014, 2018	Ashton <i>et al</i> Ashton <i>et al</i> ^[116,117]	B
		2002-2006	6.4a,b	3.8a,b	2.0a,b		P			
		2008-2012	9.4	5.9	2.6					
UK/Scotland	< 16	1981-1995	3.4	2.3a	1.2a		R	2004	Armitage <i>et al</i> ^[114]	A
UK/Wales	< 16	1996-2003	5.4	3.6	1.5		P	2006	Ahmed <i>et al</i> ^[30]	B
UK/Wales	< 16	1995-1997	2.6	1.4	0.8	0.5	P	2000	Hassan <i>et al</i> ^[118]	B
UK/Wales	< 16	1981-1995		2.5a	1.3a		R	2001	Armitage <i>et al</i> ^[53]	B
UK/ Northeastern Scotland	< 16	1980-1999								
		1980-1989		2.2	0.7		R	2002	Watson <i>et al</i> ^[115]	B
		1990-1999		4.4	1.5					
UK/Scotland	< 16	1968-1983		0.7-2.3a	1.9-1.6a		R	1989	Barton <i>et al</i> ^[61]	A
UK/Cardiff	< 16	1996-2005		2.7			R	2007	Gunesh <i>et al</i> ^[119]	B

UK/ Leicestershire	< 10	1972-1989			0.3a,d		R	1992	Probert <i>et al</i> ^[27]	B
UK/Wales South Glamorgan	< 16	1983-1993		2.2a	0.7a		R	1996	Cosgrove <i>et al</i> ^[57]	B
		1983-1988		1.3	0.7					
		1989-1993		3.1	0.7					
UK/British Isles and Ireland	< 16	1998-1999	5.3a,d	3.1a,d	1.4a,d	0.6d	P	2001	Sawczenko <i>et al</i> ^[16]	A
UK/Scotland	< 19	1990-1992		2.9a			R	1999	Armitage <i>et al</i> ^[113]	A
UK/East London	< 20	1997-2001		2.3-7.3a,d	2.4-8.1a,d		R	2004	Tsironi <i>et al</i> ^[17]	
Northern America										
Canada/ Manitoba	< 17	1978-2007	6.9a	1.2-4.7a	0.5-1.6a		P	2014	El-Matary <i>et</i> ^[79]	B
Canada/ Metropolitan Toronto	< 17	1991-1996		3.7	2.7		R	2004	Griffiths ^[82]	B
Canada/ 5 Provinces	< 16	1999-2010	9.7a	6.5a	2.4a		R	2017	Benchimol <i>et al</i> ^[31]	A
Alberta			9.7	5.9	2.7					
Manitoba			7.2	4.2	2.8					
Nova Scotia			15.2	9.3	4.2					
Ontario			9.3	5.5	3.2					
Quebec			10.3	8.8	1					
Canada/ Suothwestern Ontario	< 17	1997-2006	13.3a	4.9a	8.1a	0.3a	R	2009	Grieci <i>et al</i> ^[81]	B
		1997-2001	14.3	3.5	10.6	0.2				
		2002-2006	12.4	6	6	0.4				
Canada/Ontario	< 18	1994-2005					P	2009	Benchimol <i>et al</i> ^[54]	B
		1994	9.5a	6.2a	4.4a					
		2005	11.4	7	4.8					
Canada/Ontario	< 19	1999-2008					P	2014	Benchimol <i>et al</i> ^[84]	B
	0-9		2.9a	1.3a	1.3a	0.3				
	10-19		21.5	12.8	7.6	1.1				
Canada/British Columbia	< 16	1985-2005	5.2d	3.7d	1.0d	0.5d	R	2007	Pinsk <i>et al</i> ^[18]	B
			15.2	6.4	6.7	2.1				
Canada/Ontario	< 18	1994-2009	9.4-13.2a	5.2-7.9a	3.9-4.1a		R	2014	Benchimol <i>et al</i> ^[84]	B
Canada/Eastern	< 20	1996-2009		14-11a ² c	4-6a ² c	0-1.5a ² c	P	2014	Leddin <i>et al</i> ^[83]	B
Canada/Quebec	< 19	2001-2008					R	2014	Bitton <i>et al</i> ^[78]	B
	0-9			2.0a	1.0a					
	10-19			20	4					
Canada/ 5 Provinces	< 19	1998-2000					P	2006	Bernstein <i>et al</i> ^[39]	A
Alberta				9.4a	4.1a					
British Columbia				5.4	3.2					
Manitoba				6.9	4.5					
Nova Scotia				12	5.7					
Saskatchewan				7.9	4.2					
Canada/Qubec	< 19	1993-2002		13.9			P	2009	Lowe <i>et al</i> ^[80]	B
U.S.A./Northern Carolina	< 17	1996-2006		2.2-4.3a,d	1.8-4.9a,d	0.5d	R	2010	Abramson <i>et al</i> ^[20]	B
U.S.A./Wisconsin	< 18	2000-2001	7.05d	4.6d	2.1d		P	2003	Kugathasan <i>et al</i> ^[21]	B
U.S.A./Wisconsin	< 18	2000-2007	9.5a,d	6.6a,d	2.4a,d	0.5a,d	P,R	2013	Adamiak <i>et al</i> ^[22]	B
U.S.A./Georgia	< 19	1986-1995		8.8a,d	5.3a,d		R	1998	Ogunbi <i>et al</i> ^[23]	B
U.S.A./Texas	< 17	1991-2002					R	2010	Malaty <i>et al</i> ^[52]	B
		1991-1996	1.1a	0.7a	0.3a	0.1a				
		1997-2002	2.4	1.3	0.5	0.7				
U.S.A/Olmstedt Minnesota	< 19	1940-2000		3.4a	2.4a		R	2007	Loftus <i>et al</i> ^[58]	B
		1990-2000		4.8	3.2					
U.S.A/Olmstedt Minnesota	< 14	1943-1982		0.75a			R	1988	Gollop <i>et al</i> ^[167]	B
U.S.A/Olmstedt Minnesota	< 19	1940-1993		2.5a			R	1998	Loftus <i>et al</i> ^[36]	B

U.S.A/Northern California	< 18	1996-2002		3	2.9		R	2008	Herrinton <i>et al</i> ^[76]	B
U.S.A/Olmstedt Minnesota	< 19	1940-1993			1.8		R	2000	Loftus <i>et al</i> ^[168]	B
U.S.A/Rhode Island	< 19	2008-2010					P	2016	Shapiro <i>et al</i> ^[77]	B
	0-9			4.5a	1.1a	0.0a				
	10-19			20.6	8.6	0.7				
Latin America										
Argentina/Provinces	< 18	2012-2013								
Argentina			0.4				P	2017	Vincentin <i>et al</i> ^[87]	A
Buenos Aires			0.3							
CABA			2.4							
Chaco			0.3							
Cordoba			0.3							
Corrientes			0.6							
Entre Rios			0.8							
Mendoza			0.2							
Misiones			0.9							
San Juan			1							
Tucana			0.2							
Africa										
Libya/Eastern/Benghazi	< 15	1997-2006					R	2009	Ahmaida <i>et al</i> ^[146]	B
		1997	0.0a							
		2000	0.2							
		2006	0.9							
Asia /Middle East										
Saudi Arabia	< 14	2003-2012	0.5	0.3	0.2		R	2014	El Mouzan <i>et al</i> ^[149]	A
Saudi Arabia/Riyadh	< 18	1993-2002	0.5				R	2006	El Mouzan <i>et al</i> ^[150]	B
Kuwait	< 15	1998-2008	2.2	1.5	0.6	0.03	R	2011	Al-Quabandi ^[151]	A
Israel/Tel Aviv	< 19	1970-1980			1		P	1989	Grossman <i>et al</i> ^[148]	B
Israel/Southeastern	< 19	1968-1992		3.6			R	1994	Odes <i>et al</i> ^[147]	B
the Kingdom of Bahrain	< 19	1990-2015		3.7a			P,R	2017	Zayyani <i>et al</i> ^[152]	A
		1990-1995		1.8						
		2010-2015		7.6						
Taiwan	< 18	1979-2000					R	2004	Tsai <i>et al</i> ^[154]	A
		1979-1995		0.9a	0.9a					
		1996-2000		2.6	1					
Singapore	< 18	1996-2009					R	2013	Chu <i>et al</i> ^[155]	A
		2000	2.2a							
		2008	11.4							
Taiwan	< 19	2000-2010					R	2015	Chia Jung Kuo <i>et al</i> ^[169]	A
	0-9			0.1a	0.1a					
	10-19			0.2	0.2					
Korea/South	< 19	2011-2014						2017	Jung <i>et al</i> ^[157]	B
	10-14			1.6 ²	2.0 ²		P			
	15-19			8.2 ²	4.8 ²					
China/Shanghai	< 18	2000-2010	5.5a	2.9a	2.5a		R	2013	Wang <i>et al</i> ^[153]	B
Korea/Seoul	< 19	1986-1997					R	2000	Yang <i>et al</i> ^[156]	B
	0-9	1986-1995/1995-1997			0-0.2					
Australasia	10-19	1986-1995/1995-1997			0.2-0.9					
Australia/Randwick	< 16	1987-2011	33.1-4.3d				R	2014	Naidoo <i>et al</i> ^[24]	B
Australia/Victoria	< 16	1971-2001		0.1-2.0a			R	2003	Phavichitr <i>et al</i> ^[158]	B
Australia/Victoria	< 16	1983-1998		2.0a			R	2009	Ponsonby <i>et al</i> ^[37]	B
Australia/Victoria	< 16	1950-2009			0.4-1.6a		R	2013	Schildkraut <i>et al</i> ^[159]	B

New Zealand	< 16	2015	5.2	3.5	1	0.7	P	2017	Lopez <i>et al</i> ^[160]	A
New Zealand/ Canterbury	< 16	1996-2015	7.2a				P	2018	Lopez <i>et al</i> ^[161]	B
New Zealand	< 15	2002-2003	2.9d	1.9d	0.5d		P	2008	Yap <i>et al</i> ^[126]	A
Southern Europe										
Italy/Florence	< 15	1978-1992		1.9-3.4a	3.8-9.6a		R	1996	Trallori <i>et al</i> ^[136]	B
Italy/Lazio	< 19	2008-2009					R	2014	Domenicantonio <i>et al</i> ^[135]	B
	0-9			2.5	2					
	10-19			8.72	7.52					
Italy	< 18	1996-2003	0.9-1.4a				P	2008	Castro <i>et al</i> ^[163]	A
Italy/Lombardia	< 14	1990-1993		1.2	1.2			1996	Ranzi <i>et al</i> ^[134]	B
Spain	< 18	1996-2009	1.0-2.8a,b	0.5-1.7a,b	0.4-0.9a,b		R	2013	Martin de Carpi <i>et al</i> ^[42]	A
Spain/the Vigo area	< 15	2010	18.3	10.3	8.7	1.2	P	2015	Fernandéz <i>et al</i> ^[50]	B
Spain/Navarra	< 14	2001-2003	2.6	1.7	0.9	0.6	P	2008	Letamendia <i>et al</i> ^[137]	B
Spain	< 18	1985-1995	0.2a ¹				R	2014	Martin de Carpi <i>et al</i> ^[51]	A
Spain/Asturias	< 14	1993-2000	0.3	0.2	0.1		P,R	2004	Fernandez Gonzalez ^[170]	B
Spain/Northern	< 14	2000-2002		5.8	1.6		P	2004	Rodrigo <i>et al</i> ^[44]	B
Spain/Aragon	< 14	1992-1995		0.4a	0.3a		P	1999	Lopez Miguel <i>et al</i> ^[171]	B
Malta	< 15	1993-2005		1.3a	7.9a		R	2008	Cachia <i>et al</i> ^[138]	A
Central and Eastern Europe										
Croatia/ Primorsko- Goranska	< 18	2000-2004		8.7	0.9		P	2006	Sincic <i>et al</i> ^[47]	B
Czech Republic/ Moravia	< 16	1998-2001	2.2a	2.7a	1.8a	0.3a	R	2004	Kolek <i>et al</i> ^[140]	B
Czech Republic	< 15	1990-2001		0.3-1.3a			P,R	2006	Pozler <i>et al</i> ^[139]	A
Czech Republic/ West Bohemia	< 19	2000-2015	10.0a	6.2a	2.8a	1.0a	P	2017	Schwarz <i>et al</i> ^[45]	B
	< 15		7.3	4.6	2	0.7	P			
Hungary	< 16	2007-2009	7.5	4.7	2.3	0.5	P	2013	Muller <i>et al</i> ^[141]	A
Hungary/ Veszprem	< 19	1977-2011		0.0-7.2a	0.7-5.2a		P,R	2014	Lovasz <i>et al</i> ^[46]	B
Slovenia/ Northestern	< 18	2002-2010	7.6	4.6	2.8		R	2014	Urlep <i>et al</i> ^[49]	B
		2002-2004	5.7	3.9	1.8					
		2008-2010	8.9	5	3.4					
Slovenia	< 18	2002-2010	7.6a,b	4.5a,b	2.9a,b	0.2a,b	R	2015	Urlep <i>et al</i> ^[48]	A
		2002-2004	5.8	3.6	2.2					
		2005-2007	8.6	5.1	3.2					
		2008-2010	8.4	4.9	3.2					
Slovenia/ Western	< 17	1994-2005	4.0a	2.4a	1.1a	0.5a	R	2009	Orel <i>et al</i> ^[143]	B
		1994-1999	3	2	0.8	0.3				
		2000-2005	5.1	2.9	1.6	0.69				
Yugoslavia/ Zagreb Croatia	< 14	1980-1989		1.76			P,R	1991	Vucelic <i>et al</i> ^[145]	B
Yugoslavia/ Zagreb Croatia	< 14	1980-1989			3.1		P,R	1991	Vucelic <i>et al</i> ^[144]	B
Poland	< 18	2002-2004	2.7	0.6	1.3	0.8	P	2009	Karolewska- Bochenek <i>et al</i> ^[67]	A
Hungary/ Western	< 18	1977-2008		7.5a	5.5a		P	2011	Lakatos <i>et al</i> ^[142]	B

¹An approximate incidence rate at the beginning of the 25-year period based on the estimative population between the demographic census of 1981 and 1991; ²The incidence rates were extrapolated from Figures. Incidence: Incidence rates per 100000 person-years; P: Prospective; R: Retrospective; P,R: Prospective/retrospective; a: Statistical significant for time trend analysis ($P < 0.05$); b: Study incorporated previously published cohort for comparison from the same geographical area the rest of pediatric population; c: The only one study under the age of 20 years d: Studies on race, ethnicity and migration compared to the rest of pediatric population. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IBD-U: Inflammatory bowel disease-unclassified.

Table 2 Summary of range in pediatric-onset inflammatory bowel disease incidence stratified by continent and geographical regions

Regions	IBD incidence	UC incidence	CD incidence	IBD-U incidence	Time period
Europe					
North/West	0.5-23	0.3-15	0.2-12.3	0.2-3.6	1951-2017
East	2.7-10.0	0.9-5.2	0.25-8.6	0.3-1	1997-2015
South	0.1-18.3	0.1-9.6	0.5-10.3	0.6-1.2	1978-2005
North America	1.1-15.2	0.5-10.6	0.7-13.9	0.2-2.1	1940-2010
Latin America	0.2-2.4	NR	NR	NR	2012-2013
Africa	0.0-0.9	NR	NR	NR	1997-2006
Asia/Middle East	0.5-11.4	0.2-3.9	0.3-3.7	0.1	1968-2012
Australasia	2.9-7.3	0.4-1	0.1-3.5	0.7	1971-2015

NR: Not reported; Incidence: Incidence rates per 100000 person-years; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IBD-U: Inflammatory bowel disease-unclassified.

quality assessment of each manuscript.

Summarization of data

Population-based or national/subnational cohort studies reporting incidence were included in the analysis of the temporal evolution of IBD. The inclusion criteria were as follows: (1) Population-based or national cohort/health care administrative database studies (a study was considered population-based if all residents within specific areas were included, and the study population was representative of the catchment area; studies were considered at the national level as stated in the report or if the study was multicenter involving multiple regions in a country, sub-national level if only a particular region was evaluated, or city level); (2) published full-text manuscripts; (3) studies defining pediatric patients as patients younger than 19 years of age; (4) studies describing patients in the entire age range; and (5) studies performed within the geographical regions outlined by the UN. The exclusion criteria were as follows: (1) Studies with a sample size < 5 patients; (2) studies that did not report original data (*e.g.*, review articles, meta-analyses, conference presentations, and guidelines); (3) studies that only demonstrated the incidence of adult-onset IBD (IBD onset after the age of 19 years); (4) studies reporting hospital surveys; (5) studies reporting only the number of pediatric cases (no incidence per population) and prevalence studies because our interest was disease incidence; (6) studies without defined study periods; and (7) duplicate studies reporting the same outcome in an identical cohort. To avoid selection bias due to cohort overlap, only the most recent study was included.

RESULTS

Study characteristics

In total, 140 papers were retrieved, and a significant proportion of the studies was conducted in European countries (96 in Europe, 23 in North America, and the remaining 21 in Latin America, Africa, Asia/Middle East and Oceania); overall, the studies reported the IBD incidence in 38 countries. Moreover, wide variability

in study design was observed. The upper age limit defining the pediatric population differed across the studies and ranged mostly between 15 and 19 years. The characteristics, distribution and detailed results of the 140 incidence studies, including references, are summarized in Table 1. As shown in Table 1, the ratio of CD to UC and IBD-U varied geographically. Of the included papers, 99 (71%) reported the IBD incidence in children, while the remaining 41 (29%) reported the rates of IBD in non-pediatric studies, but distinctions were made between adults and children in reporting the data. Of the 140 studies, the sample frame was prospective in 72 (51%) studies and retrospective in 57 (41%) studies. The data of the 11 (8%) studies were combined for this analysis.

Incidence of IBD

Broad variation was observed in the incidence rates, which ranged from 0.5 to 23/100000 for IBD, 0.1 to 13.9/100000 for CD, 0.3 to 15.0/100000 for UC, and 0.0 to 3.6/100000 for IBD-U. As shown in Table 2, the incidence of IBD greatly varied based on the geographical region. The regions with the highest IBD burden were Europe (0.2-23/100000) and North America (1.1-15.2/100000). The regions with the lowest reported IBD incidence were Oceania (2.9-7.2/100000), Asia (0.5-11.4/100000), Latin America (0.2-2.4/100000) and Africa (0.0-0.9/100000). The regions with the highest reported incidence of CD were North America (13.9/100000) and Europe (12.9/100000), while the highest rates of UC were 15.0/100000 in Europe and 10.6/100000 in North America. The highest incidence of IBD-U was 3.6/100000 in Europe and 2.1/100000 in North America. The current global status of the IBD incidence is shown in Figures 2-5.

Time trends in pediatric IBD

The incidence of IBD has been increasing worldwide. The time-trend analysis illustrated an increasing or stable incidence in North America, Europe and Oceania and an increasing incidence in newly industrialized countries in Asia, the Middle East and Africa. Of the 41 articles reporting the statistical significance ($P < 0.05$)

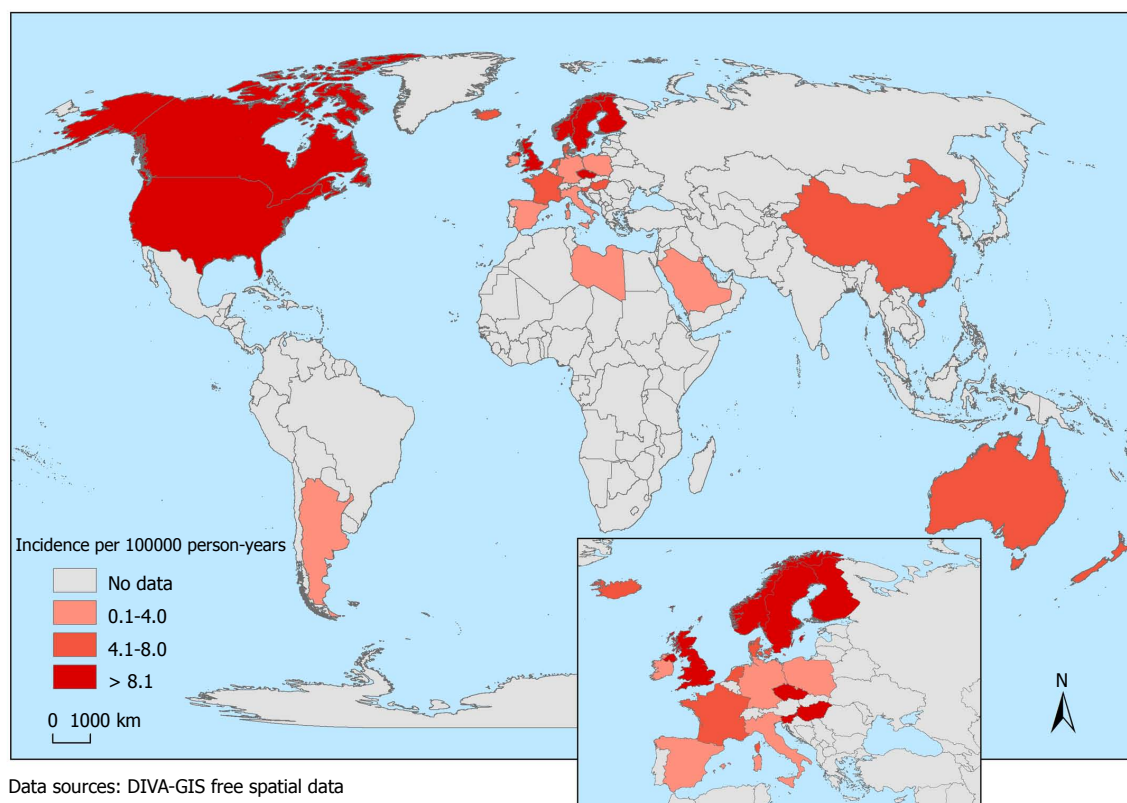


Figure 2 Worldwide pediatric inflammatory bowel disease incidence rates. Inflammatory bowel disease (IBD) choropleth map of global incidence of pediatric IBD divided into four colors representing unknown, low, indeterminate and high occurrence of disease. Grey reflects absence of data.

of a time-trend analysis of the overall IBD incidence, 30 (73%) studies reported an increasing incidence, 11 (27 %) studies reported no significant changes, and no studies reported a decreasing incidence. Of the 71 studies that calculated the CD incidence, 48 (67%) studies reported a significant increase, 2 (3%) studies reported a significant decrease, and 21 (30%) studies observed no significant changes. Of the 63 UC studies, 29 (46%) studies reported a significant increase, 29 (46 %) studies reported no significant changes, and 5 (8%) studies reported a significant decreasing trend. Of the 19 studies calculating the IBD-U incidence, 2 (11%) studies reported a significant increase, and 17 (89%) studies reported no significant change.

Description of incidence studies involving migrant and racial groups

Ten studies stratified according to migrant and race/ethnicity in South Asian (SA), Asian, African-American, Hispanic, Caucasian and Polynesian populations^[16-26]. The two studies performed in Canada described the SA pediatric population, and one study compared non-immigrants to SA immigrants^[18,25]. The three UK studies described the incidence in children with an Asian background^[16,17,27]. The four studies performed in the US investigated Hispanic, Asian, African-American and Caucasian populations^[20-22,28]. One study performed in New Zealand (NZ) described Polynesian children^[26], one study performed in Australia compared Middle

Eastern ethnicities^[24], one study described the Faroese Islands^[19], and the same authors described the risk of IBD in first-generation Faroese immigrants.

DISCUSSION

This rigorous and timely review has several important contributions. First, wide geographical and temporal variations were observed globally. Second, North America, Northern Europe and the UK have the highest incidence worldwide. The incidences of IBD in Southern and Eastern Europe and the Southern Hemisphere also appeared to be high, whereas the incidence was lower, but climbing, in Africa, South America, and Asia. Third, the incidence of IBD is substantially increasing in worldwide regions; however, data published during the previous two decades demonstrate the plateauing incidence of IBD in the Western world after a previously documented increase^[22,29-38], but incidence remains high. Currently, the incidence might be sharply increasing in Southern and Eastern Europe and in Oceania. IBD is emerging in other parts of the world (*i.e.*, certain parts of Asia/the Middle East, Africa) approaching the rates reported in westernized nations, but given the accelerating incidence found in many of these areas, the incidence is expected to increase. These trends clearly parallel those of the West that occurred along with the increasing development more than four decades ago indicating an emerging epidemic of IBD

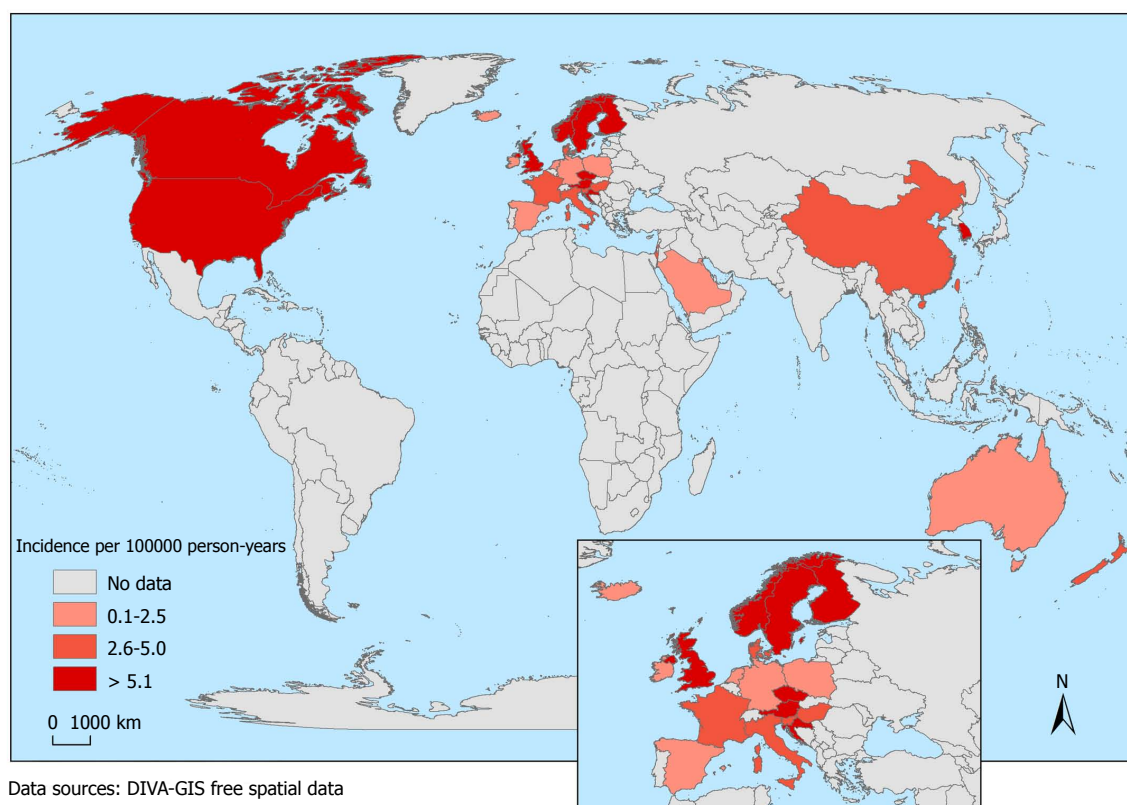


Figure 3 Worldwide pediatric Crohn's disease incidence rate. Crohn's disease choropleth map of global incidence of pediatric inflammatory bowel disease divided into four colors representing unknown, low, indeterminate and high occurrence of disease. Grey reflects absence of data.

worldwide. This gap is considerably less pronounced in 2018, and the narrowing differential gap may have important implications for the worldwide IBD sequelae. The incidence has increased in recent decades up to 23 for IBD in Finland, 13.9 for CD in Canada, 15 for UC in Finland, and 3.6/100000 for IBD-U in the Netherlands. Few studies using north-south/west-east gradients have demonstrated particularly high rates in the north^[39-42], except for northern France^[43] and Spain^[44]. Although our review did not specifically investigate disease incidence gradients, this phenomenon has been less prominent over the last three decades^[45-51].

The global incidence rates of IBD have risen during the 20th century but data obtained during the previous two decades are conflicting. The incidence of IBD has increased mainly due to pediatric CD^[42,51,52], whereas the incidence of UC has remained stable, although an inverse distribution of CD and UC has been reported^[2,4,20,31,32,38,53-57]. Since 1950, 60% of CD and 20% of UC pediatric studies have shown a significant increase in incidence^[4]. 75% of CD and 60% of UC studies show increasing incidence in adults^[55]. In our systematic review, since 1985, 67% of studies investigating CD, 46% of studies investigating UC, and 11 % of studies investigating IBD-U have reported significant increasing in incidence worldwide. Thus, the incidence rates might be increasing in virtually all regions worldwide. However, the increase in UC was more modest. We intriguingly suggest that the rising

incidence of UC may be attributable to the fact that in the emerging areas with a low incidence of IBD, UC has emerged first, followed by CD after a variable period^[58], similar to trends in earlier studies from the West^[4,56,59-63].

CD predominates over UC and IBD-U in areas with a high IBD incidence. Recent data indicate higher rates of pediatric CD than UC in Europe and North America, except in Scandinavia^[64-66], Northern California^[20], Southern^[63] and Eastern Europe^[67], where the incidence of UC exceeds that of CD. The reasons for these striking differences in the rates among the three subtypes of IBD remain uncertain^[28,68,69]. IBD-U is more frequently found in children than adults (children 12.7% vs adults 6.0%, $P < 0.0001$)^[70].

Considerable geographical diversity in IBD is observed. Moreover, several studies have reported different incidence rates within a country^[31,65], highlighting the role of the environment^[25]. Global data exploring the similarities and differences might call for future studies to extensively study genetic-environment interactions^[71] providing an opportunity to further identify the contributing factors in locations where IBD is emerging rapidly^[72]. Rates among ethnical/racial groups raise further questions^[7] regarding why the children of immigrants from the developing world have increased rates of IBD. For example, the incidences of IBD among immigrants of SA origin in Canada^[18,25], the UK^[16,27], and in immigrants of Middle-Eastern descent in Australia have been reported^[24]. In the state of

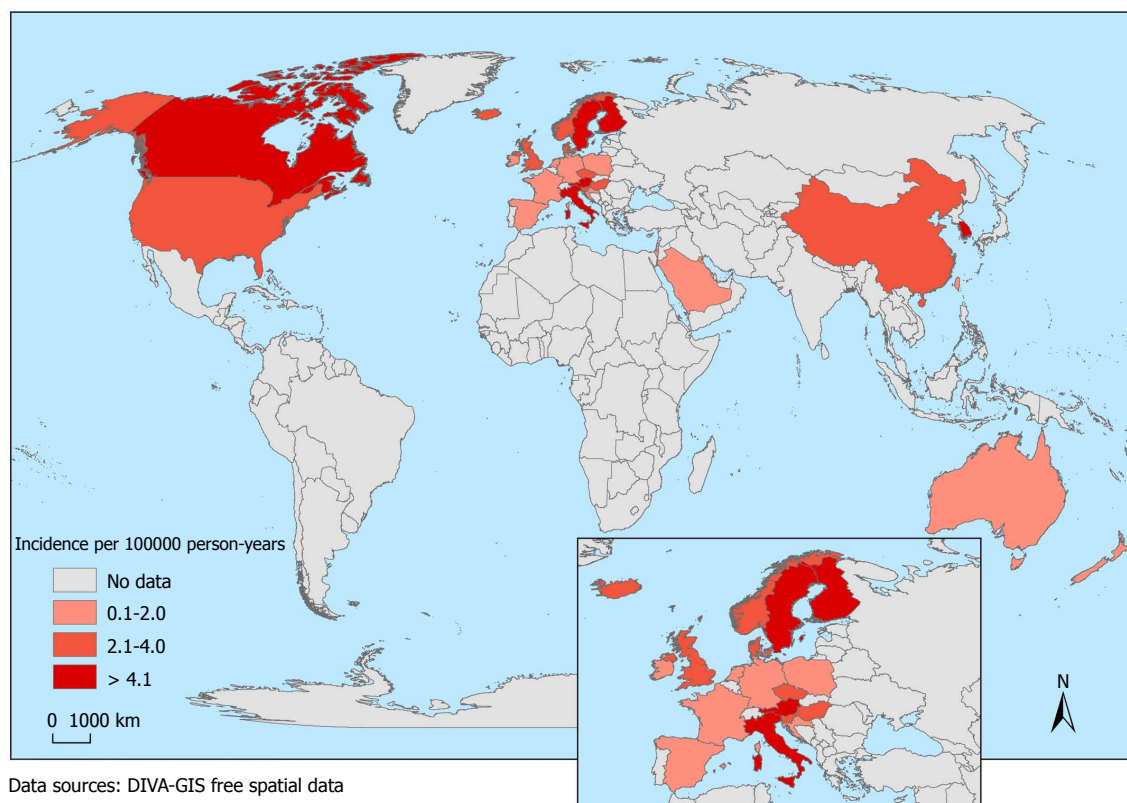


Figure 4 Worldwide pediatric ulcerative colitis incidence rate. Ulcerative colitis choropleth map of global incidence of pediatric inflammatory bowel disease divided into four colors representing unknown, low, indeterminate and high occurrence of disease. Grey reflects absence of data.

Georgia, the highest incidence of CD in African American children was reported^[23]. The key factor of migration influencing disease onset is likely exposure to a different environment than that in the country of origin^[7,73]. Additionally, indigenous populations in developed countries have a much lower IBD incidence^[74].

North America

The incidence of IBD in North America is among the highest in the world and is increasing^[4,20,22]. There are no national cohorts of pediatric IBD in the USA because the health system is not ideal for conducting population studies^[75]. In general, data have been obtained from single regions and must be extrapolated to other geographical regions of the United States. The incidence of IBD in the entire state of Wisconsin (2000-2007) was 9.5/100000^[22], which is similar to the incidence reported in Ontario, Canada^[54], but the incidence of both CD and UC has remained stable. Regarding the members of the Kaiser Permanente Northern California health plan (KPNC) (1996-2006), the data somewhat differed likely due to the different mix of races/ethnicities than that observed in other parts of the United States. The incidence of UC demonstrated a significant 2.7-fold increase, and CD remained stable^[20]. Hispanic and SA children had predominantly UC, suggesting the presence of possible etiological differences among ethnicities. Another study conducted in KPNC reported similar levels of IBD^[76], while the incidence in children

of African-American origin in Georgia was much higher (7.1/100000)^[23]. In a Texas cohort, an increasing incidence of IBD among children with evidence of more CD than UC and IBD-U from 1991 to 2002 has been reported. Caucasians had a higher IBD incidence rate than African-Americans or Hispanics, and African Americans had predominantly CD^[52]. Comparable values have been reported in Wisconsin. The mean incidence of CD was double that of UC. An equal IBD incidence was observed among all ethnic groups^[21]. In the Olmsted County population, the incidence was 4.8 for CD and 3.2/100000 for UC, and remained stable between 1990 and 2000^[36,58]. Data from Texas, Georgia, Wisconsin and from comparable studies in KPNC found rates similar to those in Olmsted County^[20,76]. However, the ratio of CD/UC cases was greater in Olmsted County, Atlanta and Wisconsin, compared to the greater incidence of UC in KPNC. These results may be attributable to the ethnic demographics of the respective populations. In contrast, a much higher rate was found in the state of Rhode Island^[77] compared with older cohorts from other parts of the U.S.^[21,23,36,52].

The incidence of IBD in Canada is among the highest reported to date as documented in previous single-province studies^[18,78-82] and large multi-province trials^[31,39,83]. The incidence in Ontario has steadily increased from 9.5 (in 1994) to 11.4/100000 (in 2005). However, the incidence of UC was stable^[54], and the incidence significantly increased from 9.4 to 13.2/100000

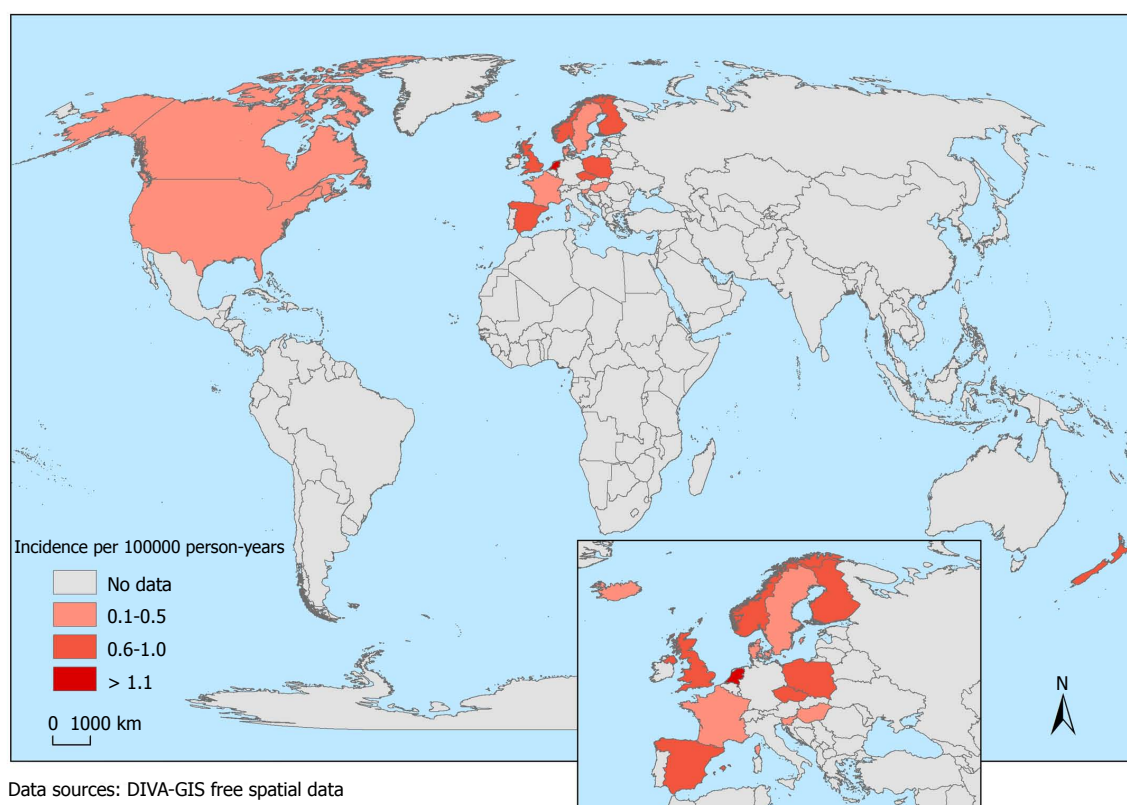


Figure 5 Worldwide pediatric inflammatory bowel disease-unclassified incidence rate. Inflammatory bowel disease-unclassified choropleth map of global incidence of pediatric inflammatory bowel disease divided into four colors representing unknown, low, indeterminate and high occurrence of disease. Grey reflects absence of data.

(1994-2009)^[84]. Although the incidence of IBD in Ontario decreased from 14.3 to 12.4/100000 in 1997-2006, the incidence of CD nearly doubled^[81], which is similar to another Canadian study^[39]. Among the best studies in the region, 3 studies determined the incidence of IBD in five provinces of Canada^[31,83,84]. The overall incidence was 9.7/100000, and CD was the predominant form of IBD similar to data from Nordic countries^[85]. The incidence of IBD was the lowest in Manitoba and the highest in Nova Scotia. The incidence of IBD remained stable after stratifying into CD and UC during the first decade of the twenty-first century, except for an increase in incidence among the youngest group. By extrapolating the results to the entire country, approximately 650 children are diagnosed with IBD yearly, affecting up to 2695 children (< 16 years) in 2008^[31]. Similarly, a study from Ontario observed the most rapid increase in children (< 10 years) between 1994 and 2008^[86]. Recent data from Canada suggest that the rate of incidence of pediatric IBD is plateauing, indicating a reversal after a long period of ongoing increase^[18,31,78,83].

Latin America

In Argentina, IBD remains uncommon according to a study conducted from 2012 to 2013^[87]. The total incidence was 0.4/100000 ranging from 0.2 to 2.4/100000. We could not find other data related to Argentinian children or children in other countries in Latin America for comparison.

Northern and Western Europe

The incidence rates reported in Scandinavia are among the highest rates published to date indicating higher rates of CD than UC and IBD-U but Finland is among the few countries that reportedly show a predominance of UC, whereas the incidence of CD has become relatively greater than that of UC in North America and the UK^[20,64,66]. The incidence of IBD has almost doubled between 1987 and 2003^[64] and tripled between 1987 and 2014, with a steeper increase in the incidence of UC compared to that of CD^[66]. The incidence of UC increased from 4 to 9/100000 and that of CD increased from 2 to 5/100000^[65,88-90] confirming a strongly increasing trend in Finland since the late 1980s. A Norwegian study covered the period of 1993-2004^[60]. The incidence of IBD did not change and a trend towards an increase in CD and reduction in UC was recorded, which is similar to the finding of the IBSEN study of 1990-1994^[91]. A subsequent study (2005-2007) performed in the same catchment area^[92] showed that the incidence of IBD was 10.6/100000 indicating a marked increase in the incidence of CD although incidence of UC has been stabilized in Southeastern Norway compared with the rates over the previous 15 years^[60,93-96]. Similarly, Canada had high a incidence of 9.7/100000^[31]. The incidence of CD between 1984 and 1985 was 2.5/100000, whereas the incidence of UC was 4.3/100000 with a lower incidence of UC in Western

Norway compared to that in Southeastern Norway^[97], which is similar to the results reported in a subsequent study in Southeastern Norway (1990-1994)^[85]. An increase in the incidence of CD was observed in Northern Stockholm (1990-2001), while the incidence of UC was stable, and a significant increase was observed in the overall incidence of IBD^[59]. In a follow-up paper (2002-2007), the incidence of IBD had plateaued. The incidence rate was 9.2 for CD and 2.8/100000 for UC^[38] and the incidence of UC significantly increased but not of CD. The incidence of IBD significantly increased between 2000 and 2007 compared to that reported in an earlier study conducted in the same region (1990-2001)^[38]. These rates are relatively higher than those reported in other studies on pediatric IBD, although the rates are similar to those reported in studies conducted in Canada^[54,81], Norway^[92], and Finland^[65]. Lindberg *et al.*^[68] suggested that the incidence of UC increased (from 1.4 to 3.2/100000), whereas that of CD and IBD-U remained stable (1984-1995), which is similar to the results of a study conducted from 1963-1987^[98]. The incidence of IBD, CD, UC and IBD-U was 6.9, 3.8, 2.1, and 1.1/100000, respectively, in Northern Stockholm (1990-1998). After more than a decade of a stable incidence of IBD in Scandinavia^[35], the incidence of CD significantly increased from 1990 to 1998, while the corresponding incidence of UC and IBD-U remained unchanged^[99]. As a part of the Swedish ICURE study (2005-2009), the incidence of pediatric IBD in Uppsala County, just north of Stockholm, was among the highest reported in Europe^[100,101]. In Denmark, the incidence of IBD has steadily increased from the 1960s until 2013^[102-104], except for in one study^[105]. An increase in IBD from the 1980s to 2013 was observed, but the incidence rates increased the most in patients (< 15 years) with CD^[103]. The incidence rate of UC increased from 1962 to 1987 in the county of Copenhagen^[106], and Fonager *et al.*^[107] discovered an increasing incidence of CD but a rather stable incidence of UC with a tendency towards decreasing from 1987 to 1992. Compared to earlier Danish investigations, the incidence of CD had increased nearly 15-fold, whereas the incidence of UC remained stable between 1962 and 2006^[34,102,108]. Another study observed an insignificant increase in the incidence of IBD between 1998 and 2004^[33], indicating that the previously observed increasing incidence might be levelling. A significant increase in the incidence of IBD was also reported in recent Danish nationwide comparisons from 1995 to 2013^[109-111]. The IBD incidence (< 19 years) has increased in isolated regions as the Faroe Islands (part of the Danish realm) (1960-2014)^[19] with the predominance of UC comparable to findings obtained in the Nordic countries^[64,66,105]. The incidence among Icelandic children is closest to that observed in Denmark^[34] and Sweden^[59] but lower than that observed in Norway^[54,92]. Between 1980 and 2010, a sharp increase in IBD incidence was observed, however, the incidence levelled from 2000 to 2010^[29,112] similar to

the findings in Denmark and Wisconsin^[22,34] but lower compared to other Northern countries.

Sawczenko *et al.*^[16] discovered an incidence of 5.3/100000 in the British Isles; CD was twice as common as UC, accounting for approximately 700 new cases/year in the UK and the Republic of Ireland. A greater proportion of SA children had UC than non-immigrants^[16]. In Scotland, incidence data spanning over 40 years showed a dramatic increase in IBD with a marginal decrease in the incidence of UC but an increasing incidence of CD from 1968 to 1983. In follow-up studies, the increase in CD continued between 1990 and 1992^[61,113]. In contrast, the incidence of CD continues to increase, and the incidence of UC is also apparently increasing from 1981 to 1995^[53]. Other Scottish studies showed an increase in the incidence of CD from 1981 to 1995 but no difference was observed in the incidence of UC^[16,114,115]. By comparing the periods 1990-1995 to 2003-2008, significant increases were observed in the incidence of IBD, CD and UC^[2]. Data obtained in Wessex, England reported an incidence of 9.37/100000 which significantly increased from 2002 to 2012^[116]. The most recent figures (2013-2017) were reported and compared to previously published Wessex data, demonstrating the most contemporary incidence and trend over 16 years^[117]. Similar findings have been observed among Welsh children^[57] and appears to have plateaued between 1995 and 1997^[118]. In 1995-2003, the overall incidence of IBD was 5.4/100000 and had reached a plateau^[30,118], but data obtained during 1996-2005 show that the incidence of CD is continuing to slowly increase in Cardiff^[119]. An increasing incidence of IBD in Irish children was observed between 1998 and 2014^[16,120,121], which is consistent with the global trends^[2,4]. Another study also confirms the continuous increase in the incidence of IBD, particularly UC^[121].

In Austria, the overall incidence of CD and UC have increased from 1997 to 2007^[122]. This finding is in contrast to Germany^[123] and the Netherlands^[124]. For example, a German study did not show any significant change in the IBD incidence^[123]. Worldwide, strikingly, the high proportion of IBD-U was observed in the Netherlands^[124] and the incidence of IBD cases is comparable with that reported in other European countries. In France, the incidence of CD significantly increased, while the incidence of UC remains unchanged from 1988 to 2011^[32,43,125-128]. The most remarkable observation (the EPIMAD Registry) has been a striking increase from 1988 to 2008 in the incidence of CD (< 19 years)^[125], and the rates also significantly rose from 1988 to 2011^[32,126,127]. Surprisingly, in Corsica, using the same registry (EPIMAD), the incidence of CD was close to that observed in other metropolitan French regions; however, the incidence of IBD for UC in Corsica is two-fold higher than that reported in other French regions^[128]. In Brittany, the incidence of IBD in childhood was similar to data obtained in Northern France and Nord-Pas-de-Calais^[129,130]. Between 1988 and 2011, a dramatic increase was observed in the incidence of both

UC and CD in French adolescents^[131]. Other than the Swiss IBD Cohort Study (SIBDCS)^[132] and the Belgian registry for pediatric CD (BELCRO)^[133], up-to-date data regarding the incidence and trends are lacking.

Southern Europe

A registry in Italy (1996-2003) showed a significant increase in the incidence of IBD from 0.89 to 1.39/100000 in all 3 pathologies^[63], which is comparable to the incidence in Lombardia (1990-1993)^[134]. Of note, Italy had a low incidence of IBD earlier, with an initial increase in UC exceeding CD and IBD-U, followed by an increase in the CD incidence, while the UC incidence was stable from 1998-2003^[63]. In contrast, the incidence of IBD in central Italy (1978-1992) was comparable to that in the Nordic countries^[135,136]. The incidence of IBD was shown to have significantly increased in Spain^[44,137]. The SPIRIT (1996-2009) and EXPERIENCE registries (1985-1995) contribute to the complete description of the changes in pediatric IBD in Spain. A three-fold collective increase in IBD (1996-2009) was observed, with another three-fold increase in CD and a two-fold increase in UC, while a lower proportion of IBD-U was described^[42]. According to the two latter studies extending the trends to a full 25-year period, these registries showed a sixteen-fold increase in Spain^[42,51]. Notably, the incidence of IBD (mainly CD) (18.3/100000) in the Vigo area was the highest compared to that in former Spanish pediatric cohorts^[50]. In Malta, UC showed an almost significant increasing trend, but no significant trend in CD was observed^[138].

Central and Eastern Europe

A sharp increase in the incidence of IBD is particularly noticeable in the Czech Republic, Hungary, Slovenia and Croatia, but not in Poland. The results of the 3 studies conducted in the Czech Republic are comparable to the West. Pozler *et al.*^[139] showed a five-fold increase in the incidence of CD. Kolek *et al.*^[140] published results from Moravia (the eastern part of the Czech Republic) showing increasing incidence of CD and UC between 1999 and 2001. The Czech Republic has among the highest rates of IBD worldwide as recently observed by our group (2000-2015)^[45] (10.0, 6.2, 2.8 and 1.0/100000 for IBD, CD, UC and IBD-U, respectively) and have been shown to be increasing in future projections^[45]. In neighboring Poland, UC incidence was higher than that of CD with significant regional differences, but the incidence was markedly lower than that observed in the West. Of note the incidence of IBD-U was surprisingly high^[67]. An increasing incidence of IBD has been reported in Hungary^[46,141,142] comparable to the rate of Slovenia from 1994 to 2010^[48,49,143]. One other publication^[47] reported much higher rates in Croatia (2000-2004) compared to previous reports^[144,145].

Africa

Expectedly, knowledge regarding the incidence of IBD

in the entire African pediatric population is limited, but the incidence of IBD increased from 0.0/100000 in 1997 to 0.2/100000 in 2002 and 0.9/100000 in 2006 in Libya^[146].

Asia/the Middle East

In Israel, the estimated incidence of CD and UC was 3.7 and 0.9/100000, respectively^[147,148], which are comparable, but at the lower end, with those in the West^[16,21]. 2 studies reported that the IBD incidence (0.5/100000) is lower than that in Western countries among children in Saudi Arabia from 1993 to 2012^[149,150]. A higher incidence was reported in Kuwait and Bahrain (states neighboring Saudi Arabia). In Kuwait, the incidence was more than triple that reported in neighboring Saudi Arabia^[151]. This finding provides an annual incidence of 2.16/100000 for IBD, whereas the incidence of CD is 1.53, UC is 0.6 and IBD-U is 0.03/100000. A remarkable finding reported in the Arabian Gulf region is the high incidence of CD in Bahrain^[152], which is comparable to Western areas. The lower incidence of IBD in Asia compared with that in Western countries is not universal, and the incidence in China is higher than that in other regions in Asia. This incidence is considered low compared to that in North America and the Nordic countries but not that low compared to the incidence in Scotland^[53,113,114] and France^[43] and is higher than that in Italy^[63]. In China, a multicenter audit of over a decade of experience with childhood IBD between 2000 and 2010 in Shanghai has shown a steadily increasing trend (< 14 years). The incidence of IBD in 2010 was 6.1/100000, which is 12-fold higher than the incidence in 2001^[153]. Recent data on Taiwan also demonstrated a substantial increase in the incidence of IBD, which is mainly attributable to CD, while the incidence of UC did not change significantly^[154]. Singapore also witnessed a remarkable increase from 2000-2008; the incidence rates were 5.2-fold greater than those assessed 9 years earlier (from 2.2 to 11.4/100000)^[155], which is similar to a report from Scandinavia^[66]. The incidence of IBD has been increasing in Korea recently^[156,157].

Australasia

Early studies conducted in Australia and NZ (collectively termed Australasia) mirror the incidence observed in the Northern Hemisphere^[54,65]. Two Victorian studies from the same area of Australia clearly show increasing rates of both CD and UC. The incidence of CD increased 10-fold over 30 years until 2001^[158]. Additionally, an eleven-fold increase was seen in UC with particular increases in the early 1990s, and the incidence has yet to plateau^[159]. Using the 1983-1998 population data, the incidence was estimated to be 2.01/100000 for CD among Victorian children with a documented increase^[37]. A study conducted in the Sydney area showed much higher rates of IBD in children of Middle-Eastern descent^[24]. In contrast, low rates of IBD were

observed in the following indigenous populations: Aborigines and Maori^[74]. Yap *et al.*^[26] calculated the incidence of IBD, CD and UC to be 2.9, 1.9 and 0.5/100000, respectively in NZ, which is at the lower end compared with the incidence in Europe. Recently, Lopez *et al.*^[160] provided important data pertaining to the incidence of pediatric IBD in NZ. The incidence of IBD, CD, UC and IBD-U in NZ in 2015 were 5.2, 3.5, 1.0 and 0.7/100000, respectively. A 4-fold increase was observed in the incidence of childhood IBD in the Canterbury Province of NZ between 1996 and 2015. The annual incidence rate was 7.18/100000 with the preponderance of CD over UC (8.4:1)^[160,161].

Limitations of the study

Limitations include heterogeneity in population characteristics among the different studies which were also conducted at different times. Most countries lack accurate estimates of the incidence of pediatric IBD. A direct inter-region comparison may be limited due to the use of different diagnostic criteria and geographic distribution^[25]. Also, study quality, case ascertainment, different database capture systems, and methodological problems demonstrated heterogeneity, emphasizing the importance of nationwide registries for retrieval of specific health data^[62] including a well-established referral system with uniform criteria^[40]. This recommendation underlines the need for uniform diagnostic guidelines for the accuracy of comparison among populations^[38,162]. Some studies observed crude incidence rates, while other studies reported age- and/or sex-adjusted rates. Some studies did not reflect the countries' true incidence, because selected areas of the country were sampled instead of the entire country. We should target large databases at the national/international levels providing a more comprehensive analysis^[41]. The other limitation rests with the retrospective design of a number of studies and a better categorisation of migrants. The differences in the various age brackets with great impact on incidence rate should be considered as studies involving a higher defined age limit had higher incidence figures^[92]. Despite these limitations, these considerations are unlikely to have had major effects on the reporting the changes in the incidence of IBD across time and geography.

Conclusion

The incidence of pediatric IBD (mainly CD) has recently dramatically increased emerging as a globally important changing pediatric disease. In a rapidly changing world, the dramatically increasing incidence of IBD has been observed in the Western world, Oceania and Eastern and Southern Europe, despite a stabilization of incidence rates in the West. The incidence appears to be rising both in newly industrialized and developing countries, and among first-generation of immigrants. Regarding IBD, knowledge of its etiology is limited, and awareness of the patterns of its global incidence could offer

new clues, but the complex interplay of genetic and environmental factors remains unclear. Investigations of IBD performed where it is rapidly emerging provide an opportunity to identify the contributing factors. Efforts at global co-ordination for more prospective, population-based studies in children should be encouraged.

ARTICLE HIGHLIGHTS

Research background

The incidence of inflammatory bowel disease (IBD) is increasing globally. Multiple studies have reported the pediatric IBD incidence in individuals over the past few years. However, the global and regional IBD incidences in childhood and their trends over time are not well reported. The highest pediatric incidence is traditionally observed in industrialized countries in North America and Western Europe. The incidence of IBD is increasing in both developed and developing countries. The variations in the disease incidence may reflect differences in the distribution of various environmental triggers for the disease within specific areas. The changing incidence of pediatric IBD worldwide provides an opportunity to study disease etiology.

Research motivation

The incidence of IBD is increasing worldwide in both adults and children. Thus, epidemiological knowledge is essential for defining new etiological hypotheses and predictors of the development of IBD to better define how environmental factors might influence disease onset and to guide future studies. Furthermore, additional evidence has recently become available due to the publication of previous reviews, but many incidence rates have since changed. Consequently, currently, a window of opportunity exists for the completion of a new, rigorous pediatric systematic review.

Research objectives

The authors aimed to summarize up-to-date studies investigating the incidence of pediatric-onset IBD and track the changes over time based on a comprehensive search of credible published pediatric studies and current knowledge regarding pediatric IBD incidence.

Research methods

A systematic review was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched electronic databases (MEDLINE, EMBASE, and Cochrane Library). Studies investigating the incidence and trends of pediatric IBD over time were eligible for inclusion. Interactive maps and temporal trends were used to illustrate the incidences of and changes in IBD.

Research results

One hundred forty studies met the inclusion criteria, demonstrating a substantial increase in the incidence of pediatric IBD and great geographic variations. The incidence of IBD remains the highest in the northern populations of Europe and America and has remained stable or even decreased. Rising rates of pediatric IBD were observed in previously low-incidence areas and much of the developing world, and among children of immigrants. The incidence rates of Crohn's disease (CD) and ulcerative colitis (UC) vary worldwide between 0.2/100000 and 13.9/100000 and between 0.1/100000 and 15/100000, respectively. In the time-trend analyses, 67% of CD and 46% of UC studies reported a significant increase.

Research conclusions

This study is among the most comprehensive studies to summarize the global IBD incidence. The IBD incidence is increasing or stable over time in both developed and developing regions of the world, indicating an emerging epidemic of the disease outside the Western world, whereas those in Northern Europe may have reached a plateau. The reasons contributing to these continued increases remain unclear. Whether genetic or environmental factors are the cause of these differences remains to be determined. Investigations of

IBD performed in locations where it is emerging rapidly provide an opportunity to further identify the causative factors within specific populations. Whether the incidence of IBD in children will continue to increase or remain static is unclear.

Research perspectives

Our data may serve as an essential resource for future studies and can be used to prioritize public health efforts in areas with the highest incidence. Knowing the increasing incidence of IBD and different geographic distribution may provide new insight into the etiology of pediatric IBD and direct future investigative studies. We must find ways to match genetic and environmental factors to pediatric IBD. An understanding of the early evolution of IBD is important and must be further investigated to unravel its etiology. This understanding is particularly important for preventing or curing the disease during the early stages. Attempts to perform studies with global coordination and additional prospective, population-based studies should be encouraged.

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