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Global prevalence and incidence of inflammatory bowel disease: a systematic review and meta-analysis of population-based studies

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ABSTRACT

Aim: The aim of this study was to systematically review the global epidemiology of Inflammatory Bowel Disease (IBD).

Background: IBD is a global concern, and its incidence is rising worldwide.

Methods: We searched PubMed, Scopus, and Web of Science from 1 January 2000 to 14 July 2022 using MeSH keywords. All population-based studies that reported the incidence or prevalence of IBD, Crohn's disease (CD), or ulcerative colitis (UC) were included. Random effect models were applied to combine the prevalence and incidence.

Results: Findings from 215 studies were analyzed. The global prevalence rates of IBD, CD, and UC were 229.7 per 100,000 (95% confidence interval: 212.4 to 247.0), 84.2 (78.5 to 89.9), and 120.4 (110.5 to 130.3), and the incidence was 9.7 per 100,000 person-years (9.2 to 10.2), 4.0 (3.8 to 4.2), and 5.0 (4.6 to 5.3), respectively. The highest IBD and CD incidence were seen in Oceania (21.3 [12.9 to 29.7] and 12.2 [8.5 to 15.9], respectively), while the highest incidence of UC was reported in North America (9.8 [6.7 to 12.8]). According to the pooled prevalence, Europe had the highest prevalence rates of IBD and UC (348.4 [315.2 to 381.5] and 198.6 [181.6 to 215.6], respectively), whereas Oceania was the continent with the highest CD prevalence (173.6 [151.8 to 195.4]).

Conclusion: Our findings showed that the incidence and prevalence of IBD in both developed and developing nations are mounting. Special focus should be placed on understanding and managing pediatric CD cases, necessitating targeted research and early interventions.

Keywords: Inflammatory bowel disease, IBD, Ulcerative colitis, Crohn's disease, Meta-analysis, Prevalence, Incidence.

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Introduction

Inflammatory bowel disease (IBD) encompasses a group of chronic gastrointestinal conditions, such as

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CD and UC. These diseases are characterized by recurrent intestinal inflammation believed to arise from a complex interplay between genetic predisposition, immune responses, environmental factors, and potentially dysregulated Intestinal microbiota (1, 2).

Recent epidemiological data suggest a notable shift in the incidence of IBD over the past decade, with a rising trend observed in developing regions of South America, Asia, and Africa. This pattern mirrors the progressive trajectory witnessed earlier in North America, Europe, and Oceania during the late twentieth century. Surprisingly, collective data from these developed, Westernized nations indicate either stable or declining incidence rates. Nevertheless, globally, the prevalence continues to escalate, contributing to a persistently high burden of the disease (3). According to a study published in 2019, the global count of patients diagnosed with IBD stood at approximately 4.9 million (4). China and the United States reported the highest numbers of IBD patients, respectively (5).

Unlike ulcerative colitis, CD has the potential to cause inflammation anywhere along the digestive tract, spanning from the mouth to the anus. This results in a wide spectrum of signs and symptoms, varying greatly based on the specific location affected. Conversely, in UC, inflammation is limited solely to the colonic mucosa. The severity of symptoms in UC is directly correlated with the extent of inflammation within the colon. Colonoscopy remains the gold standard for diagnosis of both UC and CD, and their pattern of involvement will usually assist the specialists to differentiate between all variants of inflammatory pathologies of the gut (6).

The global incidence and prevalence of IBD in both pediatric and adult patients are well reported (3, 7), but, the growing concern of this emerging epidemic has led to even more publications. This study set out to summarize all the studies published from 2000 to 2022 to clarify the latest trends and update the epidemiological map to depict a clearer picture of its global burden.

Methods

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for reporting (8). Databases, including PubMed, Scopus, and Web of Science, were used, and the search was performed in Title and Title/Abstract search fields from January 2000 to July 2022. The search strategy was designed utilizing the Medical Subject Headings (MeSH) database. A clinician expert in the field of Inflammatory Bowel Disease was asked for additional keywords.

Search Strategy in mentioned databases included ((“Crohn's Enteritis” OR “Regional Enteritis” OR “Crohn's Disease” OR “Crohn's Disease” OR “Inflammatory Bowel Disease 1” OR “Granulomatous Enteritis” OR “Enteritis, Regional” OR “Ileocolitis” OR “Granulomatous Colitis” OR “Terminal Ileitis” OR “Regional Ileitides” OR “Regional Ileitis” OR “Crohn Disease” OR “Idiopathic Proctocolitis” OR “Ulcerative Colitis” OR “Colitis Gravis” OR “Inflammatory Bowel Disease” OR IBD OR Colitis OR Ulcerative) AND (incidence OR prevalence OR Epidemiology OR Epidemiolog*) NOT (comment or editorial or letter)). The search strategy used for every database is presented in supplementary file 3 (Tables 1 to 3). Additionally, for manual searching, the Google Scholar search engine and the reference lists of related articles were reviewed.

Eligibility criteria

The inclusion criteria were as follows:

1. Original and peer-reviewed articles published in 2000 and later and available as full-text.
2. Population-based cohort studies.
3. Studies that reported the prevalence or incidence of IBD and/or CD and/or UC.
4. Studies that reported the prevalence and incidence as the number of patients in the sample size.
5. Studies that reported the prevalence and incidence in 100.000 individuals and the number of patients, and sample size were calculable.

The exclusion criteria were as follows:

1. Hospital-based and nursing home cohort studies
2. Any study design other than cohort, including case-control, case series, case report, interventional, and experimental studies.
3. Studies with non-explicit specified methodology.
4. Studies that did not report the prevalence and incidence of IBD based on the number of patients and

also these numbers were incalculable according to the data presented in the full text.
5. Studies with unavailable full texts.

Screening and selection process

The study selection process was undertaken in three phases. Firstly, duplicate articles were found using EndNote bibliography management software. Then, two independent researchers reviewed the titles and abstracts according to the eligibility criteria. In the last phase, all articles selected in the previous step were reviewed, and those that matched our eligibility criteria were selected for data extraction and quantitative synthesis.

Regarding the incidence meta-analysis, all studies with any date of publication were included, and the trend of incidence was evaluated. On the other hand, in order to avoid including duplicate populations through the calculation of the pooled prevalence, we included the most comprehensive or the most recent (selected by preference for most recent studies) studies in each country (9). In some countries, a nationwide study was not found; hence, more than one study that reported the prevalence in different regions was considered to estimate the prevalence of the country.

Data extraction

Data extraction was conducted using a standardized form by two independent researchers (Researcher A and Researcher B). Any disagreements were resolved by a third researcher (Researcher C). The following data were recorded: first author's name, publication year, study timeframe, country, sample size, number of IBD cases (CD and UC) and prevalence, and incidence rates (in age and sex groups).

Quality assessment

In the present meta-analysis, methodological quality assessment was done using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies (NOS). Methodological quality was assessed by two independent reviewers. In case of any disagreement, a third researcher was asked for the final resolution. This quality assessment tool is made of three main domains, including selection, comparability, and outcome. The maximum and minimum scores are nine and zero, respectively. Included papers were categorized into three groups according to NOS: score poor quality (0 to 2), fair quality (3 to 5), and good quality (6 to 9).

Risk of bias assessment and sensitivity analysis

Considering the number of included studies, a visual method (funnel plot) and a statistical method (Egger's linear regression test) were used to identify the risk of bias in the included studies. Additionally, a sensitivity analysis was conducted to evaluate the impact of each study on the pooled estimates by systematically excluding each study one by one (10).

Statistical analysis and synthesis

Our synthesis included studies that examined the incidence and prevalence rates of IBD, CD, and UC using patient counts, even if these values were extractable based on the information provided in full-text of the study. Pooled estimates of IBD, CD, and UC incidence and prevalence were calculated using the number of patients and the total population studied. A meta-analysis was conducted using STATA software version 11. Statistical heterogeneity was evaluated using I-square statistic. Heterogeneity was classified into three levels: low (less than 25%), moderate (25 to 50%), and high (more than 50%) (11). The random-effects models were used based on the heterogeneity status. In the case of high methodological heterogeneity, random effects models were applied. Meta-regression was carried out for the years of follow-up, the last year of follow-up, and the sample size.

An illustration of a heat map for the global prevalence and incidence of IBD, CD, and UC was conducted using Excel software.

Ethical approval

Study protocol has been registered in Shiraz University of medical sciences due to code 27809.

Results

Study selection process

A systematic database search yielded 30,501 results. Duplicate records were removed, and 19 913 articles entered the screening process. After title and abstract screening, 1078 articles were selected for full-text assessment. Finally, 215 articles were chosen for

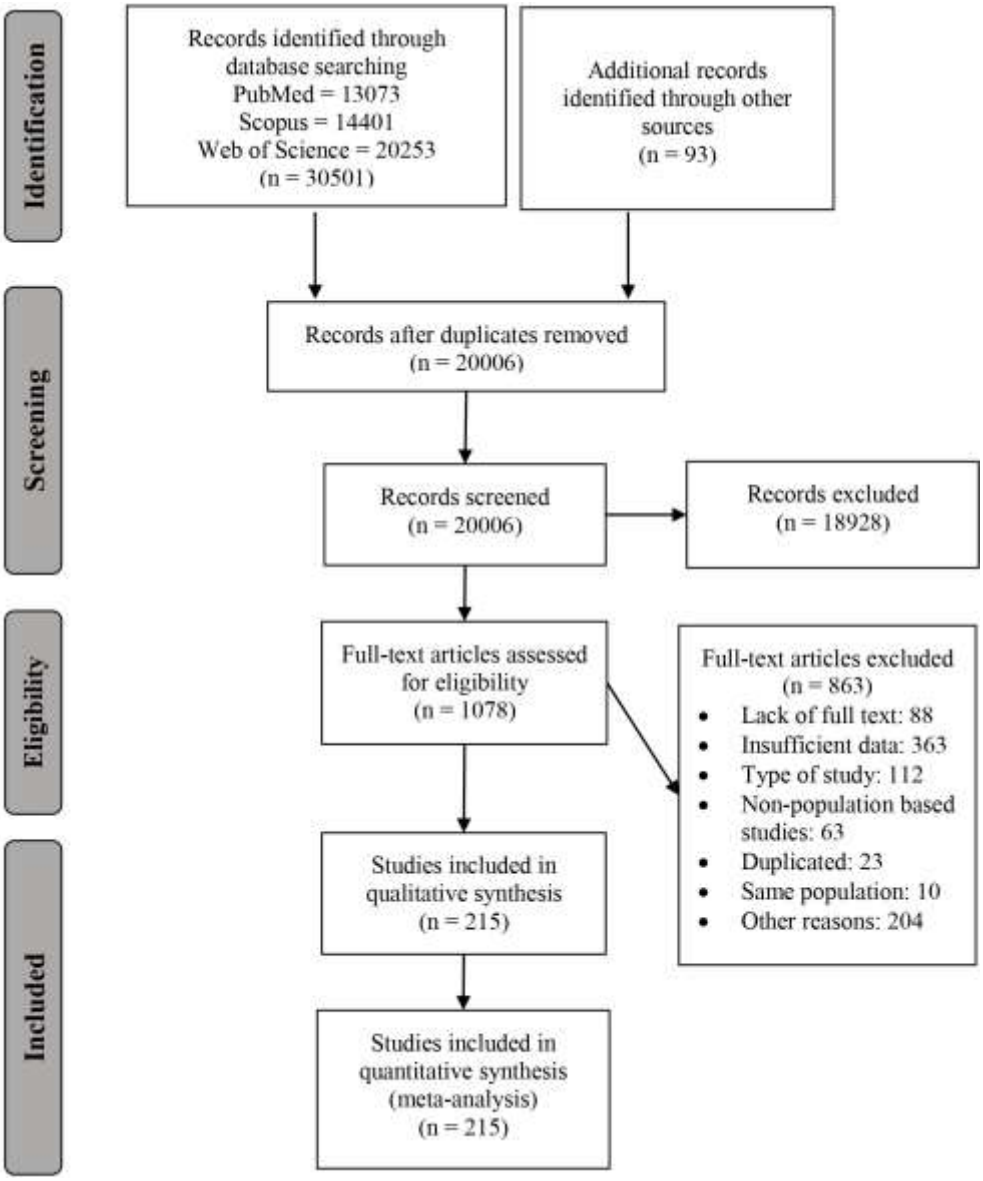


Figure 1. PRISMA flowchart for the study selection process

quantitative synthesis, and all were included in the meta-analysis (Figure 1).

Study characteristics

This meta-analysis included 215 studies that were mainly conducted in Europe (n=115). There were also 48 studies in Asia, 30 in North America, 12 in South America, 9 in Oceania, and one study in Africa. Prevalence and incidence of IBD were reported in 47 and 187 studies, respectively. Prevalence and incidence of CD were reported in 46 and 184 studies, and for UC in 47 and 187 studies, respectively (Supplementary Table 1).

Quality assessment

Based on the quality assessment process, 166 studies had good quality and 49 had fair quality. There was no study of poor quality.

Risk of bias assessment

Funnel plots for the assessment of publication bias based on IBD, CD, and UC incidence showed a heterogeneous distribution, indicating the presence of considerable publication bias (Supplementary Figures 1, 3, and 5). The results of Egger's test for the evaluation of publication bias based on IBD (t: 6.94, P value <0.001), CD (t: 6.27, P value <0.001), and UC (t:

6.52, P value <0.001) showed a significant publication bias (Supplementary Figures 2, 4, and 6).

The results of the sensitivity analysis revealed a considerable impact on the pooled prevalence of IBD after excluding the study by Mendall et al. (12) (208.5 per 100,000 [95% CI: 191.2 to 225.9]). Moreover, additional sensitivity analyses for IBD incidence were conducted by excluding Yamamoto-Furusho et al. (13) (10.3 per 100,000 person-years [95% CI: 9.6 to 11.0]) and Limketkai et al. (14) (8.2 per 100,000 person-years [95% CI: 7.8 to 8.5]).

Notably, the sensitivity analysis for CD prevalence did not reveal any study significantly influencing the pooled estimate. However, for CD incidence, excluding the study by Hou et al. (15) led to a pooled incidence of 3.8 per 100,000 person-years (95% CI: 3.6 to 4.0).

Furthermore, the sensitivity analysis for UC prevalence demonstrated notable changes in the pooled prevalence of UC after omitting the studies by Agrawal et al. (16) (107.2 per 100,000 [95% CI: 98.7 to 116.2]) and Mendall et al. (12) (106.4 per 100,000 [95% CI: 96.5 to 116.3]). Additionally, sensitivity analysis for UC incidence exhibited considerable changes after excluding studies by Jussila et al. (17) (4.8 per 100,000 person-years [95% CI: 4.4 to 5.1]) and Hou et al. (15) (4.7 per 100,000 person-years [95% CI: 4.3 to 5.0]).

Meta-analysis results

Epidemiology of IBD

Worldwide prevalence and incidence of IBD were 229.7 per 100,000 (95% confidence interval: 212.4 to 247.0) and 9.7 per 100,000 person-years (95% CI: 9.2 to 10.2), respectively. The prevalence and incidence in males were 287.8 per 100,000 (95% CI: 265.9 to 309.6) and 6.8 per 100,000 person-years (95% CI: 4.6 to 9.1), respectively, and slightly lower in females (253.2 per 100,000 [95% CI: 235.7 to 270.7] and 6.2 per 100,000 person-years [95% CI: 4.4 to 8.0], respectively) (Table 1, Table 2, and Figure 3).

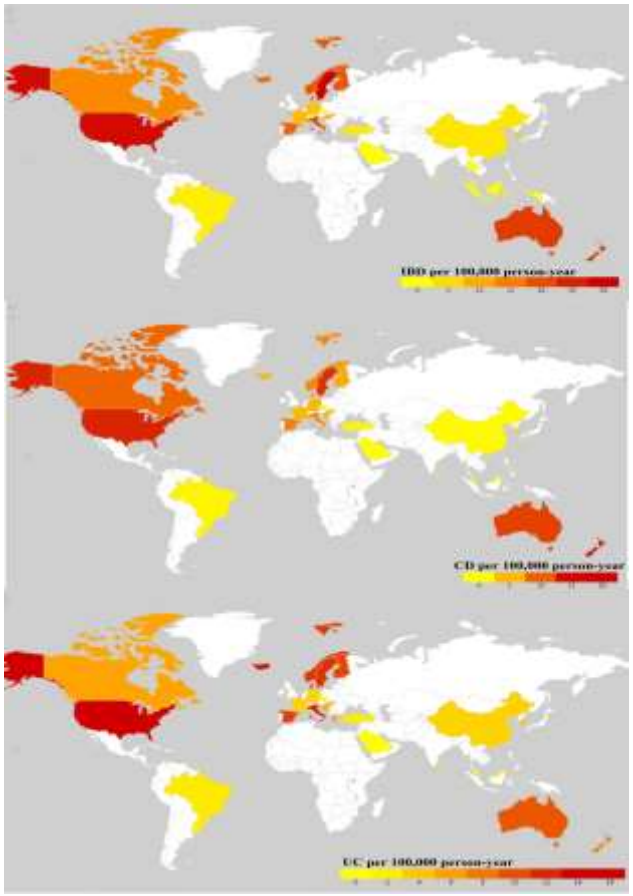


Figure 2. Illustration of the global incidence of Inflammatory Bowel Disease, CD, and UC

Table 1. Prevalence of inflammatory bowel disease

	Inflammatory Bowel Disease			Crohn's Disease			Ulcerative Colitis		
	Number of study	I square	Prevalence (95% CI)	Number of study	I square	Prevalence (95% CI)	Number of study	I square	Prevalence (95% CI)
Overall	47	99.99	229.7 (212.4 to 247.0)	46	99.98	84.2 (78.5 to 89.9)	47	99.98	120.4 (110.5 to 130.3)
Gender									
Male	12	99.96	287.8 (265.9 to 309.6)	10	99.90	89.3 (80.8 to 97.9)	10	99.95	151.4 (136.7 to 166.1)
Female	11	99.93	253.2 (235.7 to 270.7)	9	99.82	75.8 (69.3 to 82.3)	9	99.89	120.5 (108.8 to 132.3)
Age group									
Adult	9	99.98	245.4 (198.7 to 292.0)	9	99.95	84.1 (73.7 to 94.6)	9	99.98	132.7 (101.8 to 163.5)
Children	19	99.88	46.6 (42.6 to 50.6)	17	99.79	20.9 (19.3 to 22.6)	17	99.71	19.6 (18.0 to 21.3)
Continent									
Asia	11	99.97	51.0 (32.9 to 69.0)	10	99.91	17.9 (13.1 to 22.6)	12	99.96	22.4 (9.5 to 35.2)
Europe	23	99.99	348.4 (315.2 to 381.5)	23	99.98	116.5 (104.9 to 128.0)	22	99.98	198.6 (181.6 to 215.6)
North America	4	99.99	252.3 (-24.3 to 528.8)	4	99.99	113.3 (-20.7 to 247.2)	4	99.98	116.3 (12.3 to 220.3)
South America	6	99.91	50.9 (37.7 to 64.1)	6	99.88	19.8 (14.0 to 25.6)	6	99.90	30.0 (19.6 to 40.4)
Oceania	3	.	328.6 (307.3 to 349.9)	3	.	173.6 (151.8 to 195.4)	3	.	146.3 (134.9 to 157.7)
Period of time*									
5-year categorization									
To 2002	7	99.99	161.3 (95.6 to 226.9)	6	99.99	69.9 (38.5 to 101.4)	8	99.99	78.6 (44.7 to 112.5)
2002 to 2007	11	99.98	71.4 (64.4 to 78.5)	13	99.47	23.4 (20.6 to 26.1)	12	99.55	35.2 (31.5 to 38.8)
2007 to 2012	9	99.99	321.0 (170.0 to 471.9)	9	99.97	119.8 (65.8 to 173.9)	9	99.98	167.6 (85.9 to 249.3)
2012 to 2017	12	99.76	290.5 (260.6 to 320.4)	11	99.97	97.3 (87.8 to 106.9)	11	99.98	168.8 (148.3 to 189.2)
2017 to 2022	8	99.99	305.1 (119.9 to 490.4)	7	99.98	124.0 (51.9 to 196.1)	7	99.99	168.5 (80.3 to 256.7)

CI: confidence interval. Prevalence values were calculated as patient(s) in 100,000. *Categorization was performed based on the last year of follow-up.

Table 2. Incidence of inflammatory bowel disease

	Inflammatory Bowel Disease			Crohn's Disease			Ulcerative Colitis		
	Number of study	I-square	Incidence (95% CI)	Number of study	I-square	Incidence (95% CI)	Number of study	I-square	Incidence (95% CI)
Overall	187	99.88	9.7 (9.2 to 10.2)	184	99.77	4.0 (3.8 to 4.2)	187	99.76	5.0 (4.6 to 5.3)
Gender									
Male	11	94.69	6.8 (4.6 to 9.1)	11	76.71	1.0 (0.5 to 1.5)	13	88.00	3.2 (2.0 to 4.4)
Female	13	92.20	6.2 (4.4 to 8.0)	13	75.74	1.0 (0.5 to 1.5)	15	86.72	3.6 (2.4 to 4.8)
Age group									
Adult	13	99.69	9.1 (7.8 to 10.5)	13	98.23	0.8 (0.6 to 1.0)	12	98.83	2.6 (1.9 to 3.3)
Children	56	98.42	3.3 (3.0 to 3.6)	55	97.21	1.7 (1.5 to 1.9)	54	95.20	0.9 (0.8 to 1.0)
Continent									
Asia	47	99.51	2.2 (1.8 to 2.6)	42	99.02	0.9 (0.7 to 1.0)	42	99.24	1.6 (1.3 to 2.0)
Europe	94	99.51	12.8 (11.5 to 14.2)	95	98.55	5.1 (4.5 to 5.7)	98	99.12	6.4 (5.8 to 7.0)
North America	23	99.97	20.8 (13.6 to 27.9)	24	99.95	10.7 (6.8 to 14.6)	25	99.95	9.8 (6.7 to 12.8)
South America	11	98.72	1.4 (1.0 to 1.9)	11	94.32	0.2 (0.1 to 0.3)	11	98.24	0.9 (0.6 to 1.2)
Oceania	11	98.34	21.3 (12.9 to 29.7)	11	99.77	12.2 (8.5 to 15.9)	10	96.04	7.8 (4.4 to 11.3)
Country									
Australia	7	98.37	21.0 (11.0 to 31.0)	7	96.84	10.7 (7.1 to 14.4)	6	96.52	8.6 (3.0 to 14.2)
Bahrain	.	.	.	2	.	0.8 (0.4 to 1.3			
Bosnia and Herzegovina	.	.	.	2	.	3.0 (1.9 to 4.2)	2	.	4.4 (3.1 to 5.8)
Brazil	5	98.59	2.2 (0.3 to 4.1)	5	95.76	0.8 (0.1 to 1.6)	5	97.90	1.3 (0.2 to 2.5)
Canada	10	99.77	12.7 (10.0 to 15.5)	11	99.74	8.7 (6.8 to 10.7)	10	99.57	4.7 (3.5 to 5.8)
Czech Republic	2	.	0.7 (0.5 to 1.0)	3	.	0.4 (0.2 to 0.6)	3	.	0.2 (0.1 to 0.4)
China	8	96.79	3.0 (2.2 to 3.7)	9	94.36	0.5 (0.3 to 0.8)	8	94.40	2.4 (1.6 to 3.2)
Croatia	4	69.69	11.4 (7.9 to 14.9)	4	66.93	4.7 (2.5 to 6.8)	4	48.52	5.9 (3.9 to 7.8)
Denmark	9	99.41	16.3 (7.6 to 25.1)	9	98.02	6.2 (3.2 to 9.2)	9	99.15	9.2 (3.7 to 14.7)
Finland	4	99.61	18.2 (3.0 to 33.4)	3	.	4.9 (-0.7 to 10.5)	4	99.63	9.5 (-3.1 to 22.1)
France	9	98.51	7.4 (4.4 to 10.4)	9	95.57	4.1 (2.8 to 5.5)	9	97.15	2.4 (1.2 to 3.5)
Germany	2	.	6.7 (5.4 to 7.9)	2	.	4.1 (3.1 to 5.1)	2	.	2.3 (1.6 to 3.0)
Greece	.	.	.	.	.	.	2	.	5.4 (3.5 to 7.3)
Hungary	4	98.93	8.5 (4.2 to 12.9)	4	98.08	4.0 (1.6 to 6.4)	4	97.23	3.5 (1.2 to 5.7)
Iceland	3	0.0	16.1 (1.2 to 30.9)	3	.	4.1 (1.3 to 6.8)	3	.	11.9 (-0.2 to 23.9)
Indonesia	2	0.0	0.5 (0.2 to 0.7)	.	.	.	.	.	.
Israel	.	.	.	.	.	.	.	.	.
Italy	6	91.63	20.8 (10.8 to 30.8)	6	87.15	7.1 (2.5 to 11.7)	6	91.06	11.9 (4.7 to 19.1)
Kuwait	.	.	.	2	.	4.2 (3.5 to 4.8)	3	.	1.6 (0.5 to 2.8)
Malaysia	4	33.44	0.4 (0.2 to 0.7)	3	.	0.1 (0.0 to 0.3)	3	.	0.3 (0.0 to 0.6)
Netherlands	2	.	5.1 (4.4 to 5.8)	.	.	.	.	.	.
New Zealand	4	96.05	21.8 (8.8 to 34.8)	4	93.81	14.4 (5.9 to 22.8)	4	94.40	6.7 (1.3 to 12.2)
Norway	9	97.49	17.8 (11.4 to 24.3)	9	91.27	6.7 (4.6 to 8.8)	9	97.74	10.1 (5.1 to 15.0)
Singapore	2	.	0.7 (0.5 to 0.8)	.	.	.	.	.	.
Slovenia	3	.	6.6 (1.8 to 11.4)	3	.	3.8 (0.9 to 6.7)	3	.	2.3 (0.1 to 4.4)
South Korea	7	98.90	6.4 (4.2 to 8.5)	8	98.91	2.7 (1.6 to 3.7)	8	99.30	3.0 (1.2 to 4.8)
Spain	11	98.76	16.8 (10.6 to 23.1)	11	96.57	7.2 (4.7 to 9.7)	13	97.61	9.8 (6.6 to 13.1)
Sri Lanka	3	.	1.3 (0.7 to 1.9)	2	.	0.6 (0.4 to 0.8)	2	.	1.0 (0.7 to 1.3)
Sweden	4	98.12	27.6 (12.3 to 42.9)	6	96.90	11.6 (5.8 to 17.5)	6	97.49	10.5 (5.6 to 15.4)
Taiwan	7	96.82	0.9 (0.7 to 1.2)	6	81.02	0.2 (0.2 to 0.3)	7	90.15	0.8 (0.6 to 0.9)

	Inflammatory Bowel Disease			Crohn's Disease			Ulcerative Colitis		
	Number of study	I-square	Incidence (95% CI)	Number of study	I-square	Incidence (95% CI)	Number of study	I-square	Incidence (95% CI)
Thailand	2	.	0.4 (0.3 to 0.5)	.	.	.	.	.	.
Turkey	2	.	2.7 (2.4 to 2.9)	2	.	0.7 (0.5 to 0.8)	3	.	1.2 (0.0 to 2.4)
United Kingdom	15	99.61	9.1 (6.2 to 12.0)	15	97.19	3.2 (2.3 to 4.1)	14	98.60	2.5 (1.7 to 3.4)
United States	13	99.98	26.5 (8.3 to 44.7)	13	99.96	12.3 (3.1 to 21.4)	15	99.95	13.1 (5.2 to 20.9)
Uruguay	2	.	0.6 (0.3 to 0.8)	2	.	0.1 (0.0 to 0.2)	2	.	0.5 (0.3 to 0.7)
Saudi Arabia	2	.	0.2 (0.1 to 0.3)	2	.	0.1 (0.0 to 0.2)	2	.	0.1 (0.1 to 0.2)
Period of time*									
2-year categorization									
2000 and 2001	11	98.51	8.8 (6.2 to 11.4)	10	97.52	4.9 (3.1 to 6.7)	12	95.39	4.1 (2.8 to 5.4)
2002 and 2003	14	98.58	6.1 (5.0 to 7.3)	16	99.42	4.5 (3.6 to 5.5)	16	97.66	3.1 (2.3 to 3.8)
2004 and 2005	12	97.90	7.7 (5.9 to 9.5)	12	95.69	3.0 (2.1 to 3.8)	13	95.27	3.2 (2.3 to 4.1)
2006 and 2007	11	99.50	13.4 (6.5 to 20.2)	15	98.96	4.9 (3.5 to 6.2)	13	99.16	5.8 (2.5 to 9.1)
2008 and 2009	21	99.69	17.6 (15.2 to 19.9)	23	99.27	7.4 (6.2 to 8.5)	24	99.31	7.2 (6.4 to 8.1)
2010 and 2011	25	99.37	7.3 (6.4 to 8.3)	25	98.76	2.5 (2.1 to 2.9)	25	98.94	3.0 (2.5 to 3.5)
2012 and 2013	37	99.51	3.9 (3.3 to 4.5)	26	98.98	1.9 (1.5 to 2.4)	26	99.40	3.2 (2.5 to 4.0)
2014 and 2015	16	99.89	11.1 (8.6 to 13.6)	16	99.81	4.6 (3.4 to 5.7)	15	99.88	5.5 (3.6 to 7.4)
2016 and 2017	11	99.99	17.3 (3.7 to 30.9)	11	99.98	6.7 (1.2 to 12.2)	9	99.98	8.4 (1.5 to 15.2)
2018 and 2019	7	99.70	11.6 (7.0 to 16.3)	7	99.19	4.3 (2.5 to 6.2)	7	99.49	6.6 (3.8 to 9.3)
2020 and 2021	2	.	8.6 (7.4 to 9.8)	2	.	0.7 (0.3 to 1.0)	2	.	4.7 (3.8 to 5.6)
3-year categorization									
To 2002	36	98.79	8.7 (7.9 to 9.5)	38	99.00	4.6 (4.0 to 5.1)	43	97.23	3.4 (3.0 to 3.9)
2003 to 2006	23	97.85	6.4 (5.5 to 7.3)	28	96.64	1.5 (1.2 to 1.7)	28	95.47	3.0 (2.5 to 3.6)
2007 to 2010	46	99.64	13.7 (12.6 to 14.7)	48	99.18	5.3 (4.9 to 5.7)	49	99.29	6.1 (5.6 to 6.7.)
2011 to 2014	53	99.59	5.5 (4.8 to 6.1)	41	99.09	2.6 (2.1 to 3.0)	41	99.48	3.6 (3.0 to 4.2)
2015 to 2018	24	99.98	12.8 (9.3 to 16.3)	25	99.96	5.0 (4.0 to 6.1)	22	99.96	6.4 (4.3 to 8.6)
2019 to 2022	4	95.49	14.7 (8.7 to 20.8)	4	97.27	6.8 (1.8 to 11.8)	4	94.67	7.7 (3.8 to 11.6)

CI: confidence interval. Incidence values were calculated as patient(s) in 100,000 person-year. *Categorization was performed based on the last year of follow-up.

Table 3. Incidence trend of the inflammatory bowel disease in children

	Inflammatory Bowel Disease			Crohn's Disease			Ulcerative Colitis		
	Number of study	I-square	Incidence (95% CI)	Number of study	I-square	Incidence (95% CI)	Number of study	I-square	Incidence (95% CI)
Period of time*									
3-year categorization									
To 200	11	97.33	4.7 (3.3 to 6.1)	13	96.07	3.0 (2.1 to 3.9)	12	90.30	1.5 (1.0 to 1.9)
2002 to 2004	7	93.87	4.6 (2.6 to 6.5)	8	68.96	1.7 (1.1 to 2.2)	7	90.58	1.7 (0.8 to 2.5)
2005 to 2007	6	96.94	7.2 (3.3 to 11.1)	4	92.50	4.3 (1.4 to 7.3)	5	73.68	1.6 (0.3 to 2.8)
2008 to 2010	12	97.78	4.9 (3.8 to 5.9)	11	98.01	3.1 (2.3 to 4.0)	11	96.75	1.7 (1.2 to 2.2)
2011 to 2013	8	96.77	2.0 (1.4 to 2.6)	7	93.87	0.7 (0.4 to 1.1)	7	92.91	0.6 (0.3 to 0.8)
2014 to 2016	7	93.23	0.9 (0.5 to 1.3)	7	88.82	0.5 (0.2 to 0.8)	7	81.05	0.3 (0.1 to 0.6)
2017 to 2019	3	.	5.3 (-0.4 to 11.0)	3	.	2.2 (-0.1 to 4.6)	3	.	2.7 (-0.4 to 5.9)
2020 to 2022	2	.	3.1 (2.5 to 3.7)	2	.	2.2 (1.7 to 2.7)	2	.	0.9 (0.6 to 1.2)

CI: confidence interval. Incidence values were calculated as patient(s) in 100,000 person-year. *Categorization was performed based on the last year of follow-up.

Continent-based subgroup analysis of IBD prevalence ranged from 348.4 per 100,000 (95% CI: 315.2 to 381.5) in Europe to 50.9 per 100,000 (95% CI: 37.7 to 64.1) in South America. The global incidence of IBD through the continents' pooled estimates showed a range from 21.3 per 100,000 person-years (95% CI: 12.9 to 29.7) in Oceania to 1.4 per 100,000 person-years (95% CI: 1.0 to 1.9) in South America (Table 1 and Table 2).

Subgroup analysis by country showed a varying range of IBD incidence from 27.6 per 100,000 person-years (95% CI: 12.3 to 42.9) in Sweden to 0.2 per 100,000 person-years (95% CI: 0.1 to 0.3) in Saudi Arabia (Table 2 and Figure 2).

Evaluation of the pooled prevalence of IBD during the last two decades showed a decrease from 161.3 per 100,000 ([95% CI: 95.6 to 226.9] in 2000) to 71.4 per 100,000 ([95% CI: 64.4 to 78.5] in 2002 to 2007). Following that, it increased to 321.0 per 100,000 (95% CI: 170.0 to 471.9) during the period 2007 to 2012. Subsequently, the pooled prevalence was 290.5 per 100,000 (95% CI: 260.6 to 320.4) between 2012 and 2017. Finally, from 2017 to 2022, the rate increased to 305.1 per 100,000 (95% CI: 119.9 to 490.4) at the end of the time period (Table 1).

There was a fluctuation in the pooled estimated incidence within the last two decades. The analysis showed two peaks in 2008 and 2009 (17.6 per 100,000

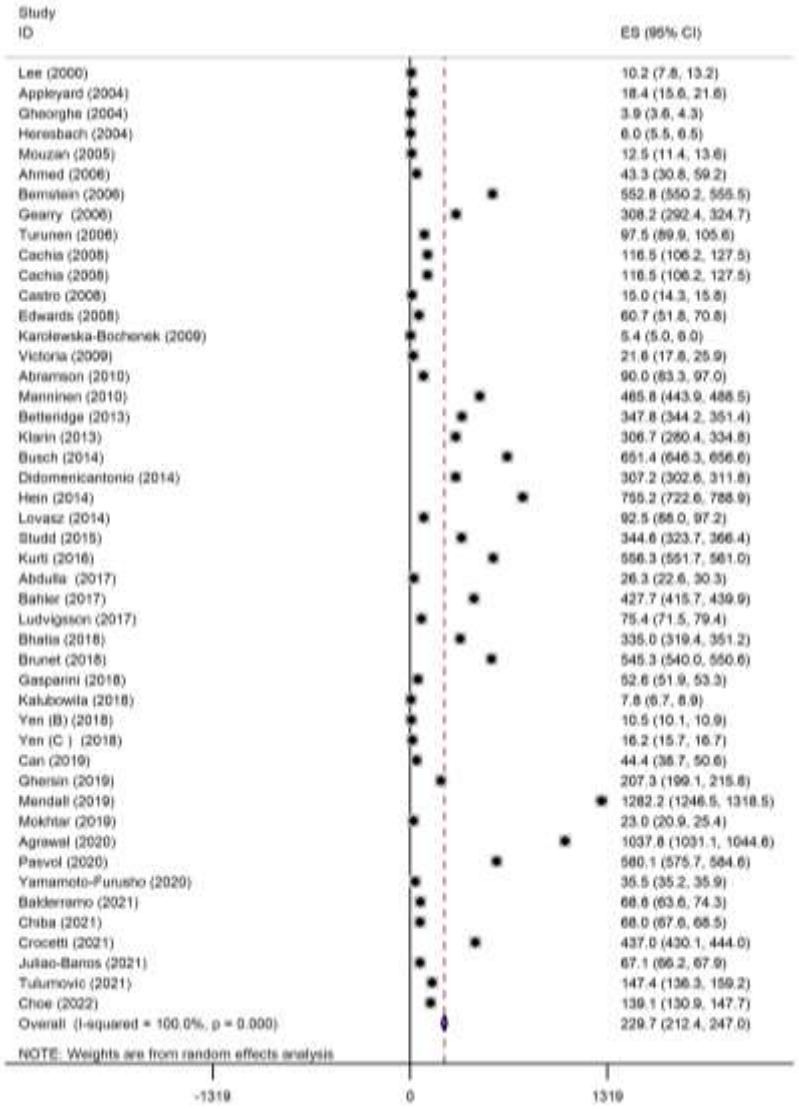


Figure 3. Forest plot for pooled prevalence of IBD

person-years [95% CI: 15.2 to 19.9]) and 2016 and 2017 (17.3 per 100,000 person-years [95% CI: 3.7 to 30.9]), and finally, the incidence decreased during last years to 8.6 per 100,000 person-years (95% CI: 7.4 to 9.8) (Table 2).

Evaluation of the IBD incidence trend in children over the study period showed that the incidence ranged from 7.2 per 100,000 person-years (95% CI: 3.3 to 11.1) from 2005 to 2007 to 0.9 per 100,000 person-years (95% CI: 0.5 to 1.3) in 2014 to 2016 (Table 3).

Epidemiology of Crohn's Disease

Pooled prevalence and incidence of CD were 84.2 per 100,000 (95% CI: 78.5 to 89.9) and 4.0 per 100,000 person-years (95% CI: 3.8 to 4.2), respectively. Based on gender, the prevalence of CD was higher in males than that in females (89.3 per 100,000 persons [95% CI: 80.8 to 97.9] and 75.8 per 100,000 persons [95% CI: 69.3 to 89.3], respectively), but a similar value was observed for the incidence in both genders (1.0 per 100,000 people [95% CI: 0.5 to 1.5]) (Table 1, Table 2, and Figure 4).

Subgroup analysis based on continent showed a broad range of prevalence from 173.6 per 100,000 (95% CI: 151.8 to 195.4) in Oceania to 19.8 per 100,000 (95% CI: 14.0 to 25.6) in South America and incidence from 12.2 per 100,000 person-years (95% CI: 8.5 to 15.9) in Oceania to 0.2 per 100,000 person-years (95% CI: 0.1 to 0.3) in South America (Table 1 and Table 2).

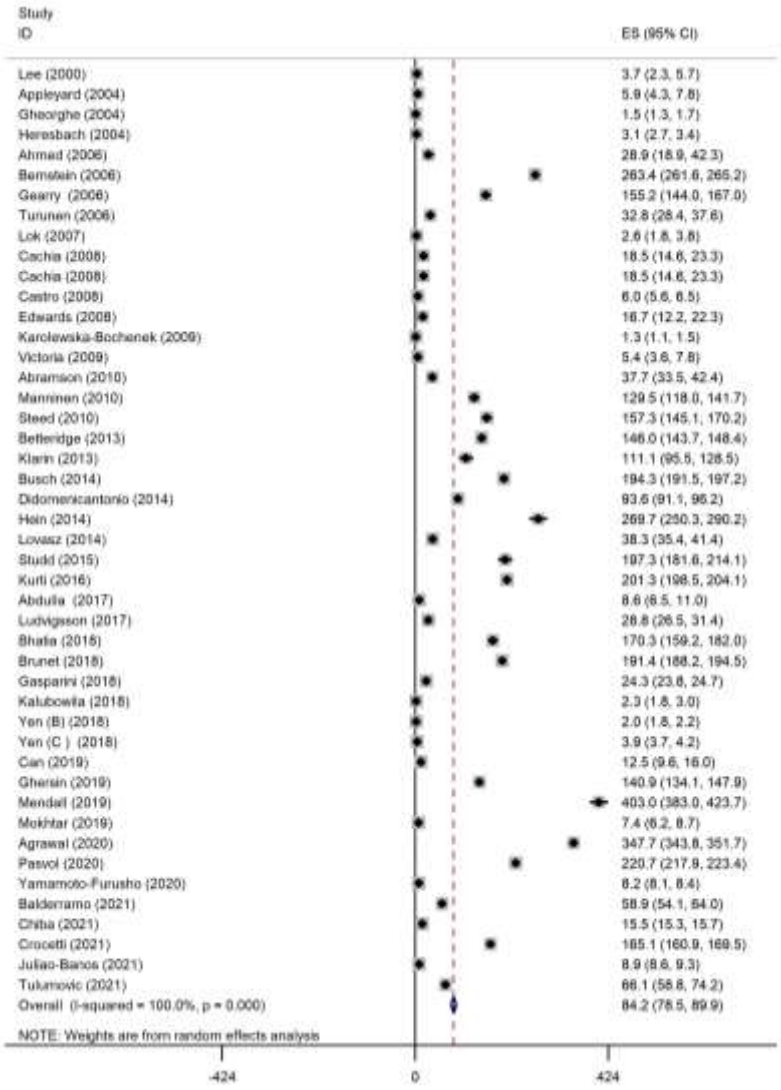


Figure 4. Forest plot for pooled prevalence of CD

The pooled incidence of CD within the countries showed a range from 14.4 per 100,000 person-years (5.9 to 22.8) in New Zealand to 0.1 per 100,000 person-years in Uruguay, Saudi Arabia, and Malaysia (95% CI: 0.0 to 0.2 for Uruguay and Saudi Arabia and 0.0 to 0.2 for Malaysia) (Table 2).

Similar to IBD epidemiology, the prevalence of CD showed fluctuations over the last decades. Pooled estimated prevalence varied from 23.4 per 100,000 (95% CI: 20.6 to 26.1) during 2002 to 2007 to 124.0 per 100,000 (95% CI: 51.9 to 196.1) in 2017 to 2022 (Table 1).

The combined incidence of CD varied from 0.7 per 100,000 person-years (95% CI: 0.3 to 1.0) during 2020 and 2021 to 7.4 per 100,000 person-years (95% CI: 6.2 to 8.5) between 2008 and 2009 (Table 2).

Evaluation of CD incidence trend in children over the study period showed that its incidence was 4.3 per 100,000 person-years (95% CI: 1.4 to 7.3) from 2005 to 2007 and 0.5 per 100,000 person-years (95% CI: 0.2 to 0.8) in 2014 to 2016 (Table 3).

Epidemiology of Ulcerative Colitis

Meta-analysis of worldwide prevalence and incidence of UC showed values equal to 120.4 per 100,000 (95% CI: 110.5 to 130.3) and 5.0 per 100,000 person-years (95% CI: 4.6 to 5.3), respectively (Table 1, Table 2, and Figure 5). Prevalence and incidence of UC in males were 151.4 per 100,000 persons (136.7 to

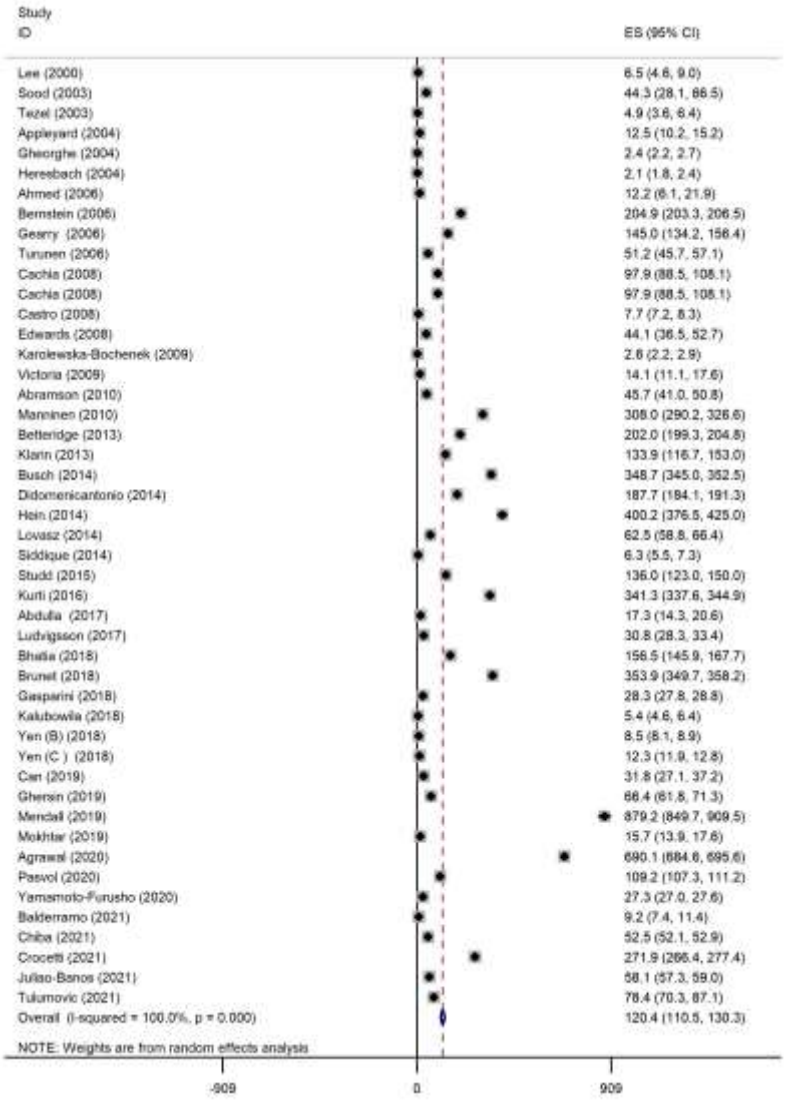


Figure 5. Forest plot for pooled prevalence of UC

166.1) and 3.2 per 100,000 person-years (2.0 to 4.4), and in females were 120.5 per 100,000 persons (108.8 to 132.3) and 3.6 per 100,000 person-years (2.4 to 4.8) (Tables 1 and 2).

The subgroup analysis by continents showed that prevalence was highest in Europe (198.6 per 100,000 [95% CI: 181.6 to 215.6]) and lowest in Asia (22.4 per 100,000 [95% CI: 9.5 to 32.2]). The highest incidence of UC was seen in North America (9.8 per 100,000 person-years [95% CI: 6.7 to 12.8]) and the lowest incidence was reported in South America (0.9 per 100,000 person-years [95% CI: 0.6 to 1.2]) (Tables 1 and 2).

The combined incidence of UC within countries ranged from 13.1 per 100,000 person-years (95% CI: 5.2 to 20.9) in the United States to 0.1 per 100,000 person-years (95% CI: 0.1 to 0.2) in Saudi Arabia (Table 2).

According to the changes in UC epidemiology in the last two decades, subgroup analysis based on the time of follow-up was conducted. Our findings showed an increase in prevalence from 2002 to 2007 (35.2 per 100,000 [95% CI: 31.5 to 38.8]) to a steady level of 168 per 100,000 during 2007 to 2022 (Table 2). The pooled estimated incidence of UC was in a range from 8.4 per 100,000 person-years (95% CI: 1.5 to 15.2) in 2016 and 2017 to 3.0 per 100,000 person-years (95% CI: 2.5 to 3.5) in 2010 and 2011 (Table 2).

UC incidence trend in children over the study period ranged from 2.7 per 100,000 person-years (95% CI: -0.4 to 5.9) from 2017 to 2019 to 0.3 per 100,000 person-years (95% CI: 0.1 to 0.6) from 2014 to 2016 (Table 3).

Epidemiology of IBD, CD, and UC in children and adults

Meta-analysis results showed a considerable difference in the prevalence and incidence of IBD between children and adult groups. The prevalence rates of IBD in children and adult subgroups were 46.6 per 100,000 (95% CI: 42.6 to 50.6) and 245.4 per 100,000 (95% CI: 198.7 to 292.0), respectively. The incidence of IBD was 3.3 per 100,000 person-years (95% CI: 3.0 to 3.6) and 9.1 per 100,000 person-years (95% CI: 7.8 to 10.5), respectively (Table 1 and Table 2).

Subgroup combination analysis of prevalence and incidence based on age groups showed a considerably greater prevalence of CD in adults (84.1 per 100,000 [95% CI: 73.7 to 94.6] in adults versus 20.9 per 100,000 [95% CI: 19.3 to 22.6] in children). In contrast, the incidence of CD was two times greater in children (1.7 per 100,000 person-years [95% CI: 1.5 to 1.9] in children versus 0.8 per 100,000 person-years [95% CI: 0.6 to 1.0] in adults) (Tables 1 and 2).

According to findings, pooled prevalence and incidence of UC in adults were 132.7 per 100,000 (95% CI: 101.8 to 163.5) and 2.6 per 100,000 person-years (95% CI: 1.9 to 3.3), respectively, and in children were 19.6 per 100,000 (95% CI: 18.0 to 21.3) and 0.9 per 100,000 person-years (95% CI: 0.8 to 1.0), respectively (Tables 1 and 2).

Meta-regression analysis

Meta-regression analysis was performed to evaluate the effect duration of follow-up (Adjusted-R2=0.51%, I2 residual= 99.88%, P value= 0.183), last year of follow-up (Adjusted-R2= -0.59%, I2 residual= 99.88%, P value= 0.877), and sample size (Adjusted-R2= -0.26%, I2 residual= 99.88%, P value= 0.518) on IBD incidence (Supplementary Figures 7, 8, and 9). Additionally, the same avaliotion was performed to assess the effect of follow-up (Adjusted-R2= 3.0%, I2 residual= 99.77%, P value= 0.013), last year of follow-up (Adjusted-R2= -0.56%, I2 residual= 99.77%, P value= 0.664), and sample size (Adjusted-R2= 0.91%, I2 residual= 99.77%, P value= 0.170) on CD incidence (Supplementary Figures 10, 11, and 12). Lastly, the effect of follow-up (Adjusted-R2=1.45%, I2 residual= 99.75%, P value= 0.077), last year of follow-up (Adjusted-R2= -0.54%, I2 residual= 99.76%, P value= 0.710), and sample size (Adjusted-R2= 0.05%, I2 residual= 99.76%, P value= 0.376) on UC incidence were also evaluated (Supplementary Figures 13, 14, and 15).

According to the presented findings, duration of follow-up was the only variable that showed a significant effect on CD incidence (Supplementary Figure 10).

Discussion

This study aimed to provide a global prevalence and incidence of IBD from 2000 to 2022. The global prevalence of IBD, CD, and UC was 229.7, 84.2, and 120.4 per 100,000, and the incidence rates were 9.7, 4, and 5 per 100,000 person-years, respectively. It seems that the global pooled incidence of UC and CD is getting closer to the prevalence, in which UC is still more prevalent than CD. A similar trend was reported in a global study in 2017, in almost all regions of the

world, and the prevalence of UC was found to be higher than CD (3). Increased incidence of CD and UC, requires further investigations for prevention, and treatment. Healthcare planning and education are also needed to avoid the upcoming burden of IBD.

The prevalence of IBD, CD, and UC appeared to be higher among adults compared to children. Similarly, this trend was observed in the incidence rates of IBD and UC. However, this meta-analysis, which included a sufficient number of studies (n=56), confirmed that from 2000 to 2022, the incidence of CD in children was twice that of adults. Studies have shown a continuous increase in the incidence of IBD in children across Europe since 1970, observed in both UC and CD cases, with a particularly significant rise in CD cases (18). This global rising rate of IBD in children (primarily due to the increasing incidence of CD) is demonstrated in both developed and developing nations (19). Consequently, there is a need for further investigations to pinpoint specific environmental and genetic risk factors associated with IBD in children.

This meta-analysis revealed that since 2000, Europe exhibited the highest prevalence of IBD and UC, whereas Oceania demonstrated the highest prevalence of CD. Conversely, South America had the lowest prevalence of IBD and CD, with Asia recording the lowest prevalence of UC. Compared to the results of a systematic review conducted in 2017, the highest age-standardized prevalence rates were observed in North America, while the lowest rates were found in the Caribbean (20). However, that study acknowledged a shift in incidence rates, noting that both UC and CD exhibited either stable or decreasing incidence trends in industrialized countries (3). We found that the incidence remains high in these countries. The current study showed that since 2000, Sweden, New Zealand, and the United States have had the highest incidence of IBD, CD, and UC, respectively. Also, Oceania had the highest incidence rates of IBD and CD, and North America was the continent with the highest incidence rate of UC. On the other hand, the lowest incidence was found in South America. Therefore, we strongly recommend that researchers, clinicians, and health policymakers in both industrialized and non-industrialized nations proactively enhance their clinical infrastructure and educate specialized personnel. Such preparation is essential for effectively managing the present and future burdens of this complex, socially and economically impactful disease (21, 22). Moreover, with rapid urbanization and westernization, developing nations are likely to mirror the progression of IBD observed in the Western world.

Between 2000 and 2022, the pooled prevalence rates of IBD, UC, and CD exhibited an upward trend, mirroring findings from a recent global burden of disease study that indicated an increased age-standardized prevalence of IBD from 1990 to 2017 (20). Despite this overall rising trend in prevalence, some year to year inconsistencies exist in the results that need more rigorous studies for confirmation.

Although without the meta-analysis, the relatively stable or decreasing incidence trend of IBD in industrialized countries and increased incidence of IBD in newly industrialized ones from 1990 to 2016 have been documented, our meta-analysis shows that the global incidence of IBD seems to be increasing from 2002 to 2019.

Based on the literature (23, 24), the type of outcome analysis (continuous or binary) should be considered when interpreting the I2 index in meta-analysis. In the case of continuous outcomes, a high number of included studies leads to a large I2 value, but in meta-analyses of binary outcomes, this situation does not exist (25). We encountered high statistical heterogeneity in our meta-analysis of incidence and prevalence. To identify potential sources of this heterogeneity, we conducted a subgroup analysis. However, according to the literature (24), high heterogeneity in prevalence and incidence meta-analyses is common, and the I2 index may not be an adequate measure for evaluating this issue in these types of studies.

This systematic review was conducted based on a large number of high-quality studies. As is typical in meta-analyses of epidemiological studies, there was considerable heterogeneity in most estimates; however, meta-regression analysis revealed that variables such as sample size, duration of follow-up, and the last year of follow-up did not significantly impact the estimated incidences.

Nevertheless, the results are constrained by limitations, notably inadequate data availability for analyzing the incidence trend in adults and for distinguishing between males and females separately.

Furthermore, due to a scarcity of studies in many countries, the ability to conduct comprehensive meta-analyses was restricted, often leading to inconclusive results, especially when fewer than five studies were included.

Conclusion

Our findings showed that the incidence and prevalence of IBD in both developed and developing nations are mounting. Special focus should be given to the understanding and managing pediatric CD cases, necessitating targeted research and early interventions. Investment in further research, particularly population-based cohort studies, is crucial to identify evolving trends and risk factors associated with IBD.

Conflict of interests

The authors declare no conflict of interest.

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