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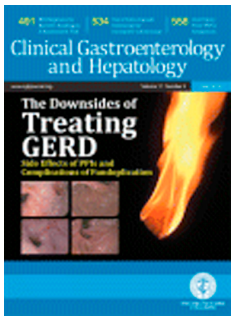

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Title: Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean—a Systematic Review

Short title: Latin IBD Characteristics

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Abbreviations: CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease; IBDU: unclassified inflammatory bowel disease; CI: confidence interval

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ABSTRACT

Background & Aims: The incidence of inflammatory bowel diseases (IBD) is increasing in Latin America. We performed a systematic review to identify clinical and epidemiologic features of IBD in Latin America (including Mexico, Central America, and South America) and the Caribbean.

Methods: We searched MEDLINE, EMBASE, and SciELO databases for clinical or epidemiologic studies of Crohn's disease (CD) or ulcerative colitis (UC) from Latin American and Caribbean countries and territories that reported incidence, prevalence, ratio of UC:CD, IBD phenotype, and treatment, through September 12, 2018. Data were extracted from 61 articles for analysis.

Results: The incidence and prevalence of IBD have been steadily increasing in Latin America and the Caribbean. The incidence of CD in Brazil increased from 0.08 per 100,000 person-years in 1988 to 0.68 per 100,000 person-years in 1991–1995 to 5.5 per 100,000 person-years in 2015. The highest reported prevalence of IBD was in Argentina, in 2007, at 15 and 82 per 100,000 person-years for CD and UC, respectively. The ratio of UC:CD exceeded 1 in all regions throughout Latin America and the Caribbean with the exception of Brazil. Treatment with tumor necrosis factor antagonists increased steadily for patients with CD (43.4% of all patients in Brazil were treated in 2014) but less so for patients with UC (4.5% of all patients were treated in 2014). Surgery for IBD decreased with time. In Chile, surgeries were performed on 57.0% of patients with CD and 18.0% of patients with UC during the period of 1990–2002; these values decreased to 38.0% and 5.0%, respectively, during the period of 2012–2015. In Peru, 6.9% of patients with UC received colectomies in the period of 2001–2003 and 6.2% in 2004–2014.

Conclusions: In a systematic review, we found the incidence of IBD to be increasing throughout Latin America and the Caribbean. Population-based epidemiology studies are needed to evaluate the increase in IBD in these regions, which differ from other global regions in climate, culture, demographics, diet, healthcare delivery and infrastructure, and socioeconomic status.

KEY WORDS: anti-TNF, ethnicity, race, risk factor, incidence, prevalence, inflammatory bowel disease.

INTRODUCTION

In the 21st century, the incidence of Crohn's disease (CD) and ulcerative colitis (UC) stabilized in the Western world.[1,2] The prevalence of the inflammatory bowel diseases (IBD) exceeded 0.3% of the population in North America, Europe, and Oceania.[2] In contrast, the prevalence of IBD in Asia, Africa, and South America was a fraction of the Western world. However, as newly industrialized countries experienced westernization, a wave of steadily rising incidence has followed.[2-5]

Population-based studies in Latin America and the Caribbean, regions including countries and territories in North America (i.e., Mexico), Central America, and South America, have demonstrated rising incidence of IBD.[6-11] However, data from the Southwest Hemisphere have been scarcer and less well organized due to less developed healthcare infrastructure available to capture clinical outcomes in registries and administrative healthcare databases.[2,6]

We conducted a systematic literature review of all CD and UC studies in Latin American and the Caribbean that reported phenotypic characteristics, hospitalization, surgery, drug penetration, incidence, or prevalence of IBD patients of any age or sex.

METHODS

Literature Search

Cohort and cross-sectional studies from all Latin American and Caribbean countries and territories that reported incidence, prevalence, hospitalization, surgery, medication, or phenotypic characteristics of IBD patients, were identified by searching MEDLINE and EMBASE, to September 12, 2018. SciELO, an Open Access database focused predominantly on research in Latin America,[12] was also searched to uncover articles that were not indexed in MEDLINE or EMBASE. Studies were limited to regional or national samples as well as population-based studies in the following regions: Latin America, Central America, the Caribbean, South America. Appendix A provides a list of countries and territories that were searched in each database. The systematic review was performed in accordance with the quality of reporting guidelines according to MOOSE[13] and PRISMA.[14] The search was not limited by language. The search was performed by an author with post-graduate training in systematic review (FEU).

Study Selection

Search results were reviewed by two independent reviewers (PGK, FEU), first as abstracts and then as full-texts. Abstracts were excluded if they did not report on IBD populations in Latin America or the Caribbean. Review articles were set aside for hand searching of their reference lists for any studies not found in the database search. Additional articles were found from expert knowledge of the IBD literature in Latin America. Articles in Portuguese or Spanish were reviewed and translated by PGK. Disagreements were resolved through discussion with a third reviewer (GGK). Abstracts were accepted if no follow-up, full-text study had yet been published.

Data Extraction

Data were extracted independently by PGK and FEU. Data extracted included first author, country or territory (including states within Brazil), local region, study period, age groups, incidence, prevalence, hospitalization (crude values), in addition to numbers and percentages of patients, medications prescribed, proportion of surgical treatment in the cohorts, and phenotypic characteristics (i.e., Montreal classification). When multiple studies used the same data source, we extracted relevant data from the most recent study population. Disagreements were resolved through discussion with a third reviewer (GGK). If necessary, authors were contacted in order to provide details of the data presented in their studies. Quality of the studies was assessed independently using a modified version of the Cochrane Collaboration-endorsed Newcastle-Ottawa Quality Assessment Scale.[15]

Data Summarization

Tables and figures were created to describe different aspects of IBD populations in Latin America and the Caribbean in our review as follows: incidence per 100,000 person-years, prevalence per 100,000 persons, ratio of patients diagnosed with UC versus CD at time of study entry, proportion of age at study entry point, proportion of the patients' disease location and behavior at study entry, proportion prescribed IBD medications (i.e., steroids, 5-ASA, immunomodulators, anti-TNF agents), and proportion of the IBD population with an intestinal resection.

The UC:CD ratio represents the average of UC (combined with IBDU if reported separately) to CD ratios, per country or per Brazilian state, limited to one ratio per study (the longest period of data per study). The UC:CD ratio was illustrated as six map classes using Jenks Natural Breaks.[16] The six selected classes were 0.48–0.68, 0.68–1.20, 1.20–1.94, 1.94–3.38, 3.38–4.87, 4.87–5.84 (a value greater than 1 denotes an area where UC is more common than

CD). The static maps were created using created using QGIS 2.18 (Open Source Geospatial Foundation, Chicago, Illinois, USA).

An interactive web-linked map was created to provide a narrative description of the key clinical and epidemiological finding for each region. The interactive map (http://people.ucalgary.ca/~ggkaplan/ibd-latinct.html) was created with ArcGIS Pro 2.3.0 and ArcGIS Online (Environmental Systems Research Institute, Redlands, California, USA).

RESULTS

Studies Selected

We identified 1,434 articles that fulfilled our selection criteria: 255 from MEDLINE, 722 from EMBASE, and 457 from SciELO. 83 articles were selected for full-text review from MEDLINE and EMBASE, while 43 articles were selected from SciELO. Following full-text review, 41 articles were selected from MEDLINE and EMBASE, while 25 articles were selected from SciELO, and 4 articles were discovered outside of the database searches. In total, 61 articles were used for data extraction (Appendix B). An article matrix (Appendix C) denotes the IBD information provided in each study in the systematic review, with some studies providing information on more than one health measure: incidence (9), prevalence (8), UC:CD ratio (35), phenotype (46), medication (27), hospitalization (8), and surgery (38). Appendix D reports the quality assessment of the studies, while Appendix E lists the MOOSE[13] checklist and Appendix F lists the PRISMA[14] checklist.

Incidence

The incidence of both CD and UC steadily increased over the last decades (Figure 1, Table 1). For example, the incidence of IBD in Brazil was reported as 0.08 per 100,000 person-years in 1988,[17]

yet the incidence of CD rose sharply from 0.68 in 1991–1995[11] to 3.50 in 2001–2005,[11] reaching a peak incidence of CD of 5.48 in 2015,[18] while from 1991–1995 to 2001–2005 UC incidence rose from 3.86[11] to 5.3,[19] with a peak of 8.00 in 2015.[18] In Puerto Rico, incidence for CD and UC more than doubled from 1996–2000 (3.07–7.74).[20] Argentina, Uruguay, Guadeloupe and Martinique, and Panama all reported incidence values between 0.39 and 4.39.[7,21,22]

Prevalence

Prevalence of IBD steadily rose in Latin America and the Caribbean (Figure 2, Table 2). For example, the prevalence of CD in Brazil rose from 0.24 per 100,000 persons (1986–1990)[11] to 24.1 (2014),[19] while the prevalence of UC rose from 0.99[11] to 14.1[19] in the same period (Table 2). Prevalence of IBD was also high in Argentina (97.2),[23] Barbados (61),[8] Colombia (57.62 in 2012[25]), and Puerto Rico (38.22 in 2005).[26]

UC:CD Ratio

The ratio of UC to CD patients at study entry was greater than one in all regions with the exception of three Brazilian states (Figure 3). Within Brazil, which had an overall country UC:CD ratio of 1.081 and a range of 0.481 to 1.936, the Brazilian states of Alagoas, Rio de Janeiro, and Mato Grosso do Sul had UC:CD ratios of 0.481, 0.679, and 0.596, respectively. France's regions, Guadeloupe and Martinique, had a UC:CD ratio of 1.200. UC was more common than CD in Argentina (4.308), Cuba (4.867), Chile (2.914), Colombia (5.837), Mexico (4.798), Peru (3.375), Uruguay (4.160), and Venezuela (4.668) (Figure 3). The UC:CD ratios of the remaining countries were 2.429, 2.574, and 2.572 for Trinidad and Tobago, Barbados, and the U.S. territory Puerto Rico, respectively.

Phenotypes (Montreal Classification)

Phenotypic characteristics of CD and UC varied across Latin American and the Caribbean (Appendix G). The most common phenotypic characteristics for CD were age of diagnosis between 17 and 40 years (Montreal Classification A2), ileocolonic disease extent (L3), and inflammatory disease behavior (B1). Perianal CD varied from 12% in a Brazilian study[27] up to 53% in a study from Peru.[28] Disease extent of UC varied: distal proctitis (Montreal Classification E1) spanned from 0% in a Brazilian study[29] to 55.35% in a study from Puerto Rico,[30] left-sided colitis (Montreal Classification E2) varied from 11.1%[31] to 62.9%[32] in different studies from Peru, and extensive colitis (Montreal Classification E3) was 12% in a Brazilian study[33] and up to 77% in Argentina[34] (Appendix G).

Medications

The 5-ASA compounds were commonly used for CD, varying from 21.2% in Brazil[35] to 100% in Cuba.[36] High percentages of 5-ASA use were noted in UC patients, from 56.36%[19] to 100%.[37] Use of 5-ASA in Brazil had fallen for CD patients from 81.6% in 1970–1998[38] to 31.46% in 2013–2014,[19] while use for UC patients fell from 93.2% in 1980–1999[10] to 56.36% in 2013–2014[19] (Appendix H). Steroids were still widely used in the region, with percentages varying in CD and UC from 13.3%[39] to 87.5%.[40] Immunomodulators use for CD patients in Brazil rose from 8.3% in 1970–1998[38] to 71.7% in 2013–2014,[19] while use for UC patients rose from 5.4% in 1980–1999[10] to 19.4% in 2013–2014[19] (Appendix H).

Since approval of anti-TNF use in 2000, the proportion of patients with CD prescribed infliximab or adalimumab has risen steadily (Figure 4A, Appendix H). For example, in Brazil, 29.6% of CD patients received anti-TNF from 2005–2012,[41] rising to 43.4% in 2013–2014[19] (Figure 4A, Appendix H). In contrast, the proportion of UC patients prescribed anti-TNF after

2006 remained consistently low. For example, only 4.5% of UC patients were prescribed anti-TNF in Brazil in 2013–2014,[19] 7% and 1.4% in Uruguay in 2016–2017[42] (Figure 4B, Appendix H).

Hospitalization and Surgery

Hospitalizations were highest in Colombia[40] (CD: 75.0%, UC: 42.9%) and Peru[43] (CD: 75.0%, UC: 51.8%) and lowest in Brazil, where CD hospitalization had fallen from 83.3% in 1980–1999[10] to 29.2% in 2006,[44] and UC hospitalization had fallen from 63.0% in 1980–1999[10] to 43.8% in 2011–2012[45] (Appendix I).

Surgery for CD and UC steadily declined over time in several regions of Latin America: in Brazil from 1980–1999[10] (CD: 57.8%, UC: 21.9%) to 2016–2017[46] (CD: 31.7%, UC: 5.8%) and in Peru from 70.5% (CD) in 1990–2010[28] to 50.0% (CD) in 2004–2014[43] (Figure 4, Appendix J). In contrast, the proportion of colectomy for UC remained stable in many regions: in Peru from 6.9% in 2001–2003[32] to 6.2% in 2004–2014[43] and in Uruguay from 1951–2003[47] (UC: 8.3%) to 1985–2015[42] (UC: 10.5%) (Figure 4, Appendix J).

DISCUSSION

Our systematic review identified significant gaps in high quality population-based studies of IBD in Latin America and the Caribbean. Nonetheless, the available data indicate notable heterogeneity between the countries that may be driven by factors such as historical colonization, culture, socioeconomic status, genetic background, lifestyle, and diet. Future studies should focus on developing large population-based registries that describe the epidemiology, natural history, and outcomes of IBD.

Despite important variation in the incidence of both UC and CD in Latin America and the Caribbean, our review suggests that incidence has steadily increased over the past decades. Farrukh and Mayberry, in a descriptive review of the incidence and prevalence of IBD in Latin America, speculated that epidemiological patterns have mirrored the evolution of IBD in Spain during the 20th century.[9] Historically, UC was diagnosed more commonly than CD in the Western world. During the 20th century, numerous studies confirmed a transition in the UC:CD ratio such that CD approximated the diagnosis of UC, and in many Western countries became more common. Similar to the Western world, regions within Latin America that are associated with higher economic development, industrialization, and westernization of environmental exposures (e.g., diet) reported higher proportions of CD. Improved healthcare access and delivery may also influence the diagnosis of CD.

After decades of rising incidence, the prevalence of IBD has been expanding. Consequently, the prevalence of IBD in Latin America is equivalent to many countries in Asia and is approximating countries in Southern and Eastern Europe. As more individuals live with IBD, caring for these patients will exact a tremendous stress on the healthcare systems within Latin

America and the Caribbean. Expansion of national registries of IBD are necessary for surveillance of the burden of IBD across these countries.

Important variation in the prescription of medications was observed throughout the continent. The use of corticosteroids was high for both diseases. Moreover, the use of 5-ASA compounds for CD is common, probably due to difficult access to biologics in some areas. The proportion of patients treated with anti-TNF therapy were also variable between the countries. Some studies demonstrated approximately 40% of biologic penetration for CD in more developed areas. Case series from other countries did not have such a high penetration, possibly due to difficulties in patient care, access to these agents, and the lack of specific local IBD study groups or associations that could increase the level of patient care.

With the rising prevalence of IBD, countries in Latin America and the Caribbean can expect higher rates of hospitalization and surgeries and, in turn, greater utilization of expensive biologics to treat flares and prevent complications of IBD. Our review demonstrated an increase in the use of anti-TNF therapy in the management of CD, mostly after the approval of infliximab around the year 2000. In juxtaposition, surgery for CD decreased in the same period. Increased use of anti-TNF therapy for CD was likely related to greater disease awareness, better diagnostic techniques, and management strategies. In contrast, surgery rates for UC in the 21st century were relatively stable throughout Latin America. Similarly, the use of anti-TNF therapy for UC did not increase significantly in Latin American and Caribbean countries after 2006 when the ACT randomized controlled studies demonstrated the efficacy of infliximab in UC.[48] These findings may be explained by difficulties in accessing anti-TNF therapies for UC, mostly based in limited reimbursement from both public and private payors in many countries. As access to biologics

298 expands and increased awareness of therapeutic strategies for managing IBD (e.g., less reliance
299 on mesalamine for treatment of CD) rises, we can anticipate that rates of hospitalization and
300 surgery will continue to fluctuate in this region of the globe.

301 The major strength of our review was the inclusion of a local database (SciELO) in
302 addition to MEDLINE and EMBASE. By including papers written in local languages, more data
303 could be captured, and we believe this could be used as an example in methodology for future
304 reviews in different parts of the world. This systematic review has some limitations that may
305 influence the interpretation of our results. The information collected varied between studies,
306 and data were based predominantly on cross-sectional studies. Most of the data were derived
307 from tertiary centres from larger cities. Variables such as frequency of medication use,
308 hospitalization, and surgery are described in crude values, with no defined follow-up. As the
309 healthcare infrastructure in Latin American and Caribbean regions advances to include greater
310 use of electronic administrative databases, a more complete picture of the health services and
311 outcomes of IBD will become available. Further, temporal trend analyses on incidence and
312 prevalence of IBD were derived from a few population-based studies with sufficient longitudinal
313 data and thus extrapolation of the rising incidence and prevalence of IBD throughout Latin
314 America and the Caribbean is an assumption that needs to be confirmed in future population-
315 based studies.

316 Finally, the quality assessment demonstrated that the majority of included studies were
317 of low quality. For example, only 16 of the 61 studies were population-based. Outcomes such as
318 medication usage and surgery need to be interpreted cautiously and in the context of the
319 limitation of including lower quality studies. Moreover, the paucity of high quality studies

highlights an important gap in the literature and serves as a clarion call to invest in the infrastructure, resources, and personnel necessary to conduct non-biased observational research in Latin America and the Caribbean.

In summary, this systematic review on the clinical and epidemiological characteristics of IBD in Latin America and the Caribbean demonstrated that the incidence and prevalence of IBD may be increasing and that the UC:CD ratios are evolving throughout the continent. The phenotypes of IBD observed varied slightly between the countries but are consistent to what is seen in other parts of the world. The increase in the use of anti-TNF agents for CD may be correlated to a decrease in surgery; the same pattern was not observed in UC. This comprehensive systematic review outlines the important burden of IBD in Latin America and the Caribbean and emphasizes the need for better registries and population-based studies in this region of the world.

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Figure Legend:

Figure 1. Incidence.

Figure 2. Prevalence.

Figure 3. UC:CD ratio.

Figure 4. Proportion of patients with Crohn's disease (Figure 4A) and ulcerative colitis (Figure 4B) prescribed anti-TNF therapy and undergoing an intestinal resection.

Supplementary Figure. Interactive map: https://people.ucalgary.ca/~ggkaplan/ibd-latinct.html.

Table 1. Incidence per 100,000 person-years.

First Author and Publication Year	Country	Study Period	IBD Incidence	CD Incidence	UC Incidence
de la Cal 1999[21]	Argentina	1987-1993			2.17
Edwards 2008[8]	Barbados	1980-1984	1.58	0.28	1.30
Edwards 2008[8]	Barbados	1985-1989	2.56	0.64	1.92
Edwards 2008[8]	Barbados	1990-1994	3.60	1.30	2.30
Edwards 2008[8]	Barbados	1995-1999	3.05	0.71	2.34
Edwards 2008[8]	Barbados	2000-2004	2.19	0.61	1.58
Victoria 2009[11]	Brazil	1986-1990	0.98	0.24	0.74
Parente 2015[17]	Brazil	1988	0.08	0.08	0.00
Victoria 2009[11]	Brazil	1991-1995	4.54	0.68	3.86
Parente 2015[17]	Brazil	1998	0.34	0.20	0.14
Victoria 2009[11]	Brazil	1996-2000	8.24	1.48	6.76
Victoria 2009[11]	Brazil	2001-2005	7.98	3.50	4.48
Parente 2015[17]	Brazil	2008	1.39	0.54	0.85
Parente 2015[17]	Brazil	2012	1.26	0.61	0.65
Gasparini 2018[18]	Brazil	2012	13.57	6.83	6.73
Gasparini 2018[18]	Brazil	2013	13.55	6.62	6.92
Lima-Martins 2018[19]	Brazil	2014	7.7	2.4	5.3
Gasparini 2018[18]	Brazil	2014	12.65	5.66	6.99
Gasparini 2018[18]	Brazil	2015	13.49	5.48	8.00
Edouard 2005[7]	Guadeloupe and Martinique	1997-1999	4.39	1.95	2.44
de la Cal 1999[21]	Panama	1987-1993			1.20
Appleyard 2004[20]	Puerto Rico	1996	3.07	0.49	2.57
Appleyard 2004[20]	Puerto Rico	1997	4.1	1.2	2.8
Appleyard 2004[20]	Puerto Rico	1998	5.0	0.9	4.0
Appleyard 2004[20]	Puerto Rico	1999	4.7	1.2	3.4
Appleyard 2004[20]	Puerto Rico	2000	7.74	1.96	5.78
Buenavida 2011[22]	Uruguay	2007-2008	2.63	0.39	2.25

472 **Table 2. Prevalence per 100,000 persons.**
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First Author and Publication Year	Country	Study Period	IBD Prevalence	CD Prevalence	UC Prevalence
Sobrero 2009[23]	Argentina	2007	97.2	15.0	82.2
Edwards 2008[8]	Barbados	2004	61.0	16.7	44.3
Victoria 2009[11]	Brazil	1988	1.23	0.24	0.99
Victoria 2009[11]	Brazil	1993	5.67	0.90	4.77
Victoria 2009[11]	Brazil	1998	13.52	2.32	11.2
Victoria 2009[11]	Brazil	2003	20.46	5.65	14.81
Parente 2015[17]	Brazil	2012	12.8		
Lima-Martins 2018[19]	Brazil	2014	38.2	24.1	14.1
Yepes-Barreto 2010[24]	Colombia	2006	29	7	22
Juliao 2018[25]	Colombia	2012	57.62	5.85	51.77
Vendrell 2013[26]	Puerto Rico	2002	33.23	11.43	21.72
Vendrell 2013[26]	Puerto Rico	2003	32.42	11.96	20.46
Vendrell 2013[26]	Puerto Rico	2004	37.26	12.93	24.33
Vendrell 2013[26]	Puerto Rico	2005	38.22	14.9	23.32

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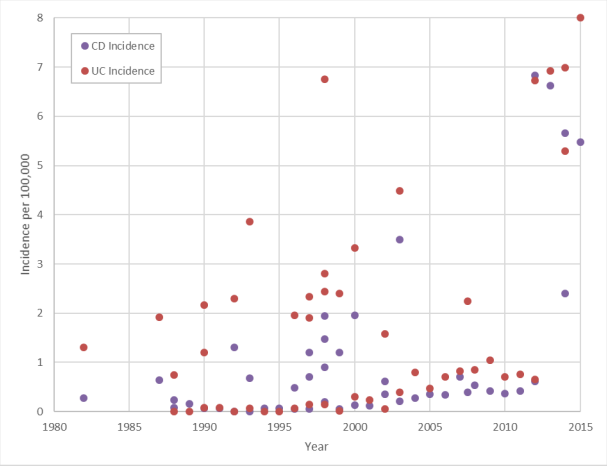
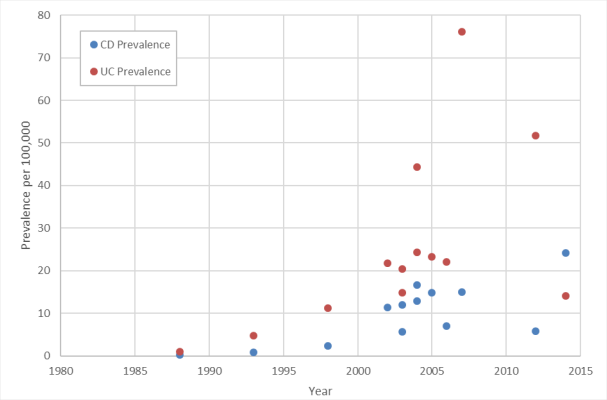
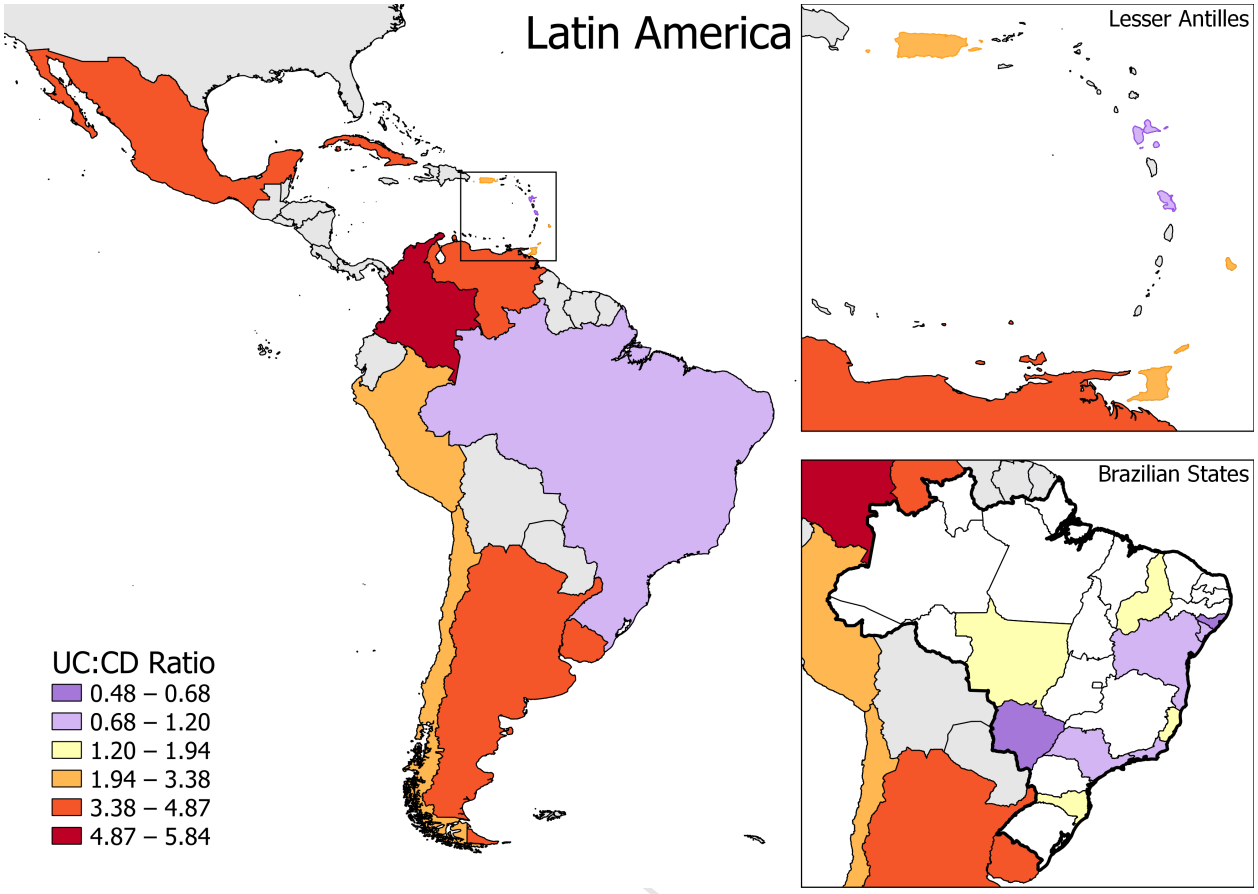
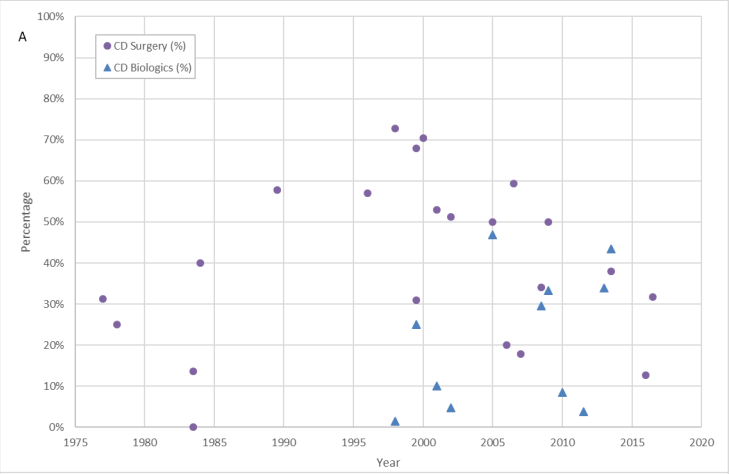
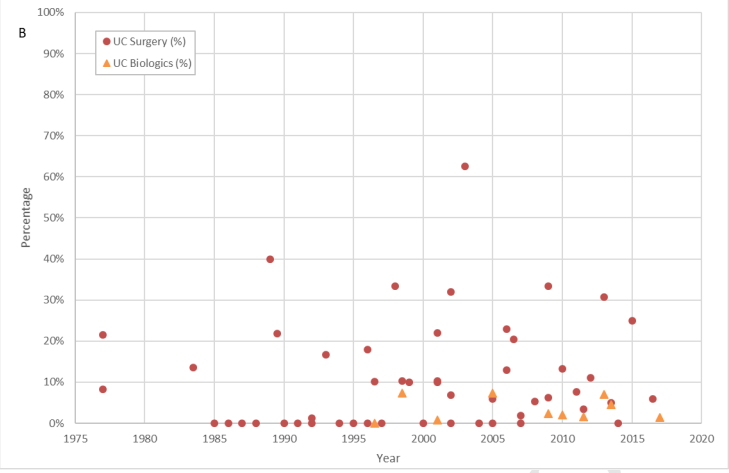
475











Need to Know

Background: We performed a systematic review to identify clinical and epidemiologic features of inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, in Latin America (including Mexico, Central America, and South America) and the Caribbean.

Findings: The incidence and prevalence of IBD are increasing throughout Latin America and the Caribbean. Population-based epidemiology studies are needed to evaluate the increase in IBD in these regions, which differ from other global regions in climate, culture, demographics, diet, healthcare delivery and infrastructure, and socioeconomic status

Implications for Patient Care: Physicians in Latin America and the Caribbean should be aware that more patients will be presenting with IBD.

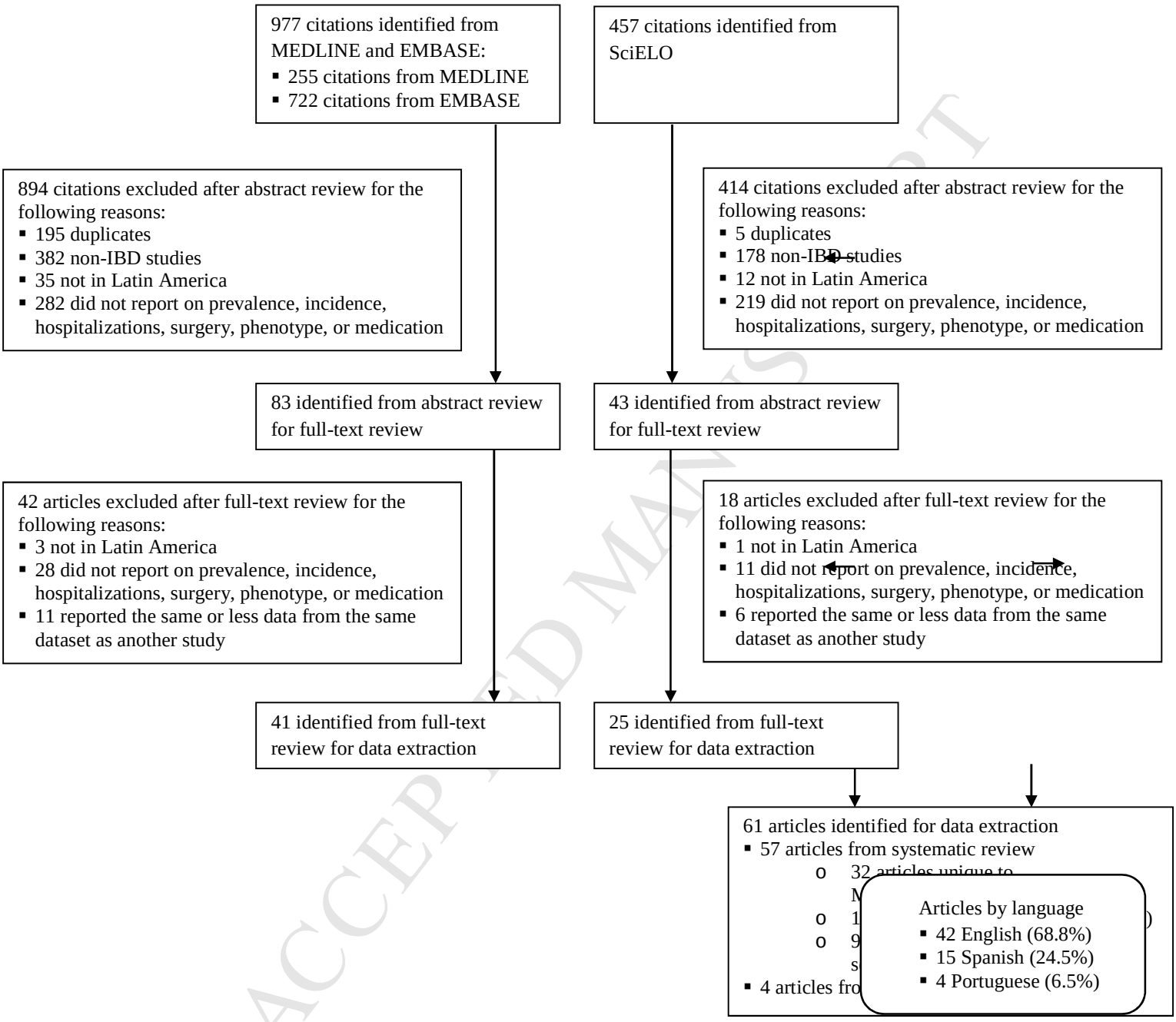
Appendix A: Search Strategy.

Database	Time Period	Search Terms
(OVID) MEDLINE	1946 – 12 September 2018*	(latin america/ or exp central america/ or exp south america/ or exp caribbean region/ or mexico/ or (antigua or barbuda or argentina or bahamas or barbados or belize or bolivia or brazil or chile or colombia or costa rica or cuba or dominica or dominican republic or ecuador or el salvador or grenada or guatemala or guyana or haiti or honduras or jamaica or mexico or new providence or nicaragua or panama or paraguay or peru or saint kitt or nevis or saint lucia or grenadines or suriname or trinidad or tobago or uruguay or venezuela).mp. or (anguilla or west indies or antilles or aruba or bonaire or british virgin or caicos or caribbean or cayman or curacao or falkland or french guiana or guadeloupe or guyane or martinique or montserrat or puerto rico or saint barthelemy or saint croix or saint martin or sint maarten or south georgia or south sandwich or tortola or turks or virgin gorda or virgin islands).mp.) and (*enteritis/ or exp inflammatory bowel diseases/ or inflammatory bowel*.mp. or ibd.mp. or (ulcerative adj5 colitis).mp. or crohn*.mp.) and (epidemiology/ or epidemiolog*.mp. or incidence/ or incidence*.mp. or prevalence/ or prevalence*.mp. or frequenc*.mp. or phenotype/ or phenotype*.mp. or drug therapy/ or drug*.mp. or medication*.mp. or hospitalization/ or hospitalization*.mp. or hospitalisation*.mp. or colorectal surgery/ or surger*.mp.)
(OVID) EMBASE	1972 – 12 September 2018*	((exp "south and central america"/ or exp mexico/ or (antigua or barbuda or argentina or bahamas or barbados or belize or bolivia or brazil or chile or colombia or costa rica or cuba or dominica or dominican republic or ecuador or el salvador or grenada or guatemala or guyana or haiti or honduras or jamaica or mexico or new providence or nicaragua or panama or paraguay or peru or saint kitt or nevis or saint lucia or grenadines or suriname or trinidad or tobago or uruguay or venezuela).mp. or (anguilla or west indies or antilles or aruba or bonaire or british virgin or caicos or caribbean or cayman or curacao or falkland or french guiana or guadeloupe or guyane or martinique or montserrat or puerto rico or saint barthelemy or saint croix or saint martin or sint maarten or south georgia or south sandwich or tortola or turks or virgin gorda or virgin islands).mp.) and (*enteritis/ or inflammatory bowel disease/ or inflammatory bowel*.mp. or ibd.mp. or ulcerative colitis/ or (ulcerative adj5 colitis).mp. or exp crohn disease/ or crohn*.mp.) and (epidemiology/ or epidemiolog*.mp. or incidence/ or incidence*.mp.

		or prevalence/ or prevalence*.mp. or frequency/ or frequenc*.mp. or phenotype/ or phenotype*.mp. or drug therapy/ or drug*.mp. or medication*.mp. or hospitalization/ or hospitalization*.mp. or hospitalisation*.mp. or surger*.mp.)
SciELO	1909 – 12 September 2018*	((inflammatory bowel disease) or (inflammatory bowel*) or (ibd) or (ulcerative colitis) or (crohn's disease) or (crohn*)) and ((epidemiolog*) or (incidence*) or (prevalence*) or (frequenc*) or (phenotype*) or (drug*) or (medication*) or (hospitalization*) or (hospitalisation*) or (surger*))

*Original search to 24 January 2018; updated to 12 September 2018 before submission.

Appendix B: Study Selection.



Appendix C: Article matrix describing the countries in Latin America and the Caribbean that provided data on any of IBD incidence, prevalence, UC:CD ratio, phenotype, medication, hospitalization, or surgery.

First Author and Publication Year	Country (Region)	Incidence	Prevalence	UC:CD Ratio	Phenotype	Medication	Hospitalization	Surgery
Appleyard 2004[1]	Puerto Rico (Guayama, Ponce, San German, Yauco, and Mayagüez)	yes		yes				
Arantes 2017[2]	Brazil (Campo Grande, Mato Grosso do Sul)			yes	yes	yes		
Arbelo 2002[3]	Cuba (not reported)			yes	yes			yes
Barros 2014[4]	Brazil (Maceió, Alagoas)			yes				yes
Bartholomew 1979[5]	Trinidad and Tobago (nationwide)			yes				yes
Bechara 2015[6]	Brazil (Belo Horizonte, Minas Gerais)				yes	yes		yes
Bendano 2010[7]	Peru (Lima)				yes	yes		
Bosques-Padilla 2011[8]	Mexico				yes	yes		yes

First Author and Publication Year	Country (Region)	Incidence	Prevalence	UC:CD Ratio	Phenotype	Medication	Hospitalization	Surgery
	(Monterrey)							
Buenavida 2011[9]	Uruguay (Artigas, Salto, Lavalleja, San José, and Montevideo)	yes		yes				
Calderon 2004[10]	Peru (Lima)				yes			yes
Campos 2013[11]	Brazil (São Paulo)			yes	yes			
Choquet 2004[12]	Mexico (Mexico D.F.)				yes			yes
da Silva 2015[13]	Brazil (Salvador, Bahia)				yes	yes	yes	yes
de Barros 2017[14]	Brazil (Porto Alegre, Rio Grande do Sul)				yes	yes	yes	yes
de la Cal 1999[15]	Argentina (Pueyrredon) and Panama (Colon)	yes			yes			
de la Cruz-Guillen 2011[16]	Mexico (Mexico City)				yes	yes		yes

First Author and Publication Year	Country (Region)	Incidence	Prevalence	UC:CD Ratio	Phenotype	Medication	Hospitalization	Surgery
Delmondes 2015[17]	Brazil (Aracaju, Sergipe)			yes	yes			
Dolcini 1967[18]	Argentina (Buenos Aires)				yes			yes
dos Santos 2017[19]	Brazil (Rio de Janeiro)			yes	yes			yes
Edouard 2005[20]	Guadeloupe and Martinique (nationwide)	yes		yes	yes			
Edwards 2008[21]	Barbados (nationwide)	yes	yes	yes	yes			
Figueroa 2005[22]	Chile (Santiago)			yes	yes	yes		yes
Gaburri 1998[23]	Brazil (Juiz de Fora, Minas Gerais)				yes	yes		yes
García 2014[24]	Cuba (Havana)				yes	yes		
Gasparini 2018[25]	Brazil (São Paulo State)	yes		yes				
Hardt 2012[26]	Brazil (Paraná, Santa Catarina and São Paulo states)				yes			

First Author and Publication Year	Country (Region)	Incidence	Prevalence	UC:CD Ratio	Phenotype	Medication	Hospitalization	Surgery
Iade 2005a[27]	Uruguay (Montevideo)			yes	yes			yes
Iade 2005b[28]	Uruguay (Montevideo)			yes	yes			yes
Illescas 1999[29]	Peru (Lima)				yes	yes		
Juliao 2018[30]	Colombia (Medellin)		yes	yes				
Juliao-Baños 2010[31]	Colombia (Medellin)			yes	yes	yes	yes	yes
Kleinubing-Junior 2011[32]	Brazil (Joinville, Santa Catarina)			yes	yes	yes		
Lee 1988[33]	Jamaica (not reported)							yes
Lima 2017[34]	Brazil (Salvador, Bahia)			yes	yes	yes		yes
Lima-Martins 2018[35]	Brazil (Espirito Santo state)	yes	yes	yes	yes	yes		
Luciano 2018[36]	Uruguay (Montevideo)				yes	yes		yes
Melendez 2011[37]	Puerto Rico			yes		yes		yes

First Author and Publication Year	Country (Region)	Incidence	Prevalence	UC:CD Ratio	Phenotype	Medication	Hospitalization	Surgery
	(not reported)							
Micames 1983[38]	Puerto Rico (San Juan)						yes	yes
Moreno 1989[39]	Puerto Rico (not reported)			yes	yes			yes
Paredes-Méndez 2016[40]	Peru (Lima)			yes	yes	yes	yes	yes
Parente 2015[41]	Brazil (Piauí state)	yes	yes	yes	yes			
Quintana 2012[42]	Chile (Santiago)				yes			yes
Rodríguez-Castro 2013[43]	Costa Rica (not reported)				yes	yes		yes
Ruiz 2009[44]	Argentina (not reported)			yes	yes			
Santana 2007[45]	Brazil (Salvador, Bahia)				yes	yes	yes	yes
Sarmiento 2018[46]	Mexico (nationwide)			yes	yes	yes		yes
Sihues 2008[47]	Venezuela (Maracaibo)			yes	yes			

First Author and Publication Year	Country (Region)	Incidence	Prevalence	UC:CD Ratio	Phenotype	Medication	Hospitalization	Surgery
Silva 2008[48]	Brazil (Rio de Janeiro)				yes			yes
Simian 2016[49]	Chile (Santiago)			yes	yes	yes	yes	yes
Sobrero 2009[50]	Argentina (not reported)		yes	yes				yes
Souza 2002[51]	Brazil (Ribeirão Preto, São Paulo state)			yes	yes	yes	yes	yes
Souza 2008[52]	Brazil (Mato Grosso state)			yes	yes			yes
Torres 2010[53]	Brazil (São José do Rio Preto, São Paulo state)				yes	yes		yes
Torres 2012[54]	Puerto Rico (San Juan)				yes			yes
Vendrell 2013[55]	Puerto Rico (nationwide)		yes	yes				
Victoria 2009[56]	Brazil (Botucatu, São Paulo state)	yes	yes					
Vivan 2017[57]	Brazil (Campo Grande, Mato Grosso do sul			yes		yes		yes

First Author and Publication Year	Country (Region)	Incidence	Prevalence	UC:CD Ratio	Phenotype	Medication	Hospitalization	Surgery
	state)							
Yamamoto-Furusho 2009[58]	Mexico (Mexico D.F.)				yes	yes		yes
Yamamoto-Furusho 2015[59]	Mexico (Mexico D.F.)				yes	yes		yes
Yamamoto-Furusho 2018[60]	Mexico (nationwide)			yes				
Yepes-Barreto 2010[61]	Colombia (Cartagena)		yes					

Appendix D: Quality Assessment.

First Author and Publication Year	Country	Was the study population-based?	How were patients identified?	Were any groups excluded from the study for demographic reasons? (age, sex, ethnicity)	Was a control group included?	Was there a new outcome at the end of the study?
Appleyard 2004[1]	Puerto Rico	yes, 16 of 19 clinics in the area reported information	hospital database	patients younger than 15 were excluded	no / not applicable	yes
Arantes 2017[2]	Brazil	uncertain, only 1 health center reported information while the total number of centers serving the area is unknown	hospital database	no excluded groups were specified	no / not applicable	yes
Arbelo 2002[3]	Cuba	uncertain, the number of departments that responded is unknown	medical records	patients older than 19 were excluded	no / not applicable	yes
Barros 2014[4]	Brazil	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	hospital database	no excluded groups were specified	no / not applicable	yes
Bartholomew 1979[5]	Trinidad and Tobago	no, the authors stated that no attempt was made to determine the total number of admissions in the area	hospital database	no excluded groups were specified	no / not applicable	yes
Bechara 2015[6]	Brazil	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	hospital database	no excluded groups were specified	no / not applicable	yes
Bendano 2010[7]	Peru	no, only 1 of 2 hospitals reported information	medical records	no excluded groups were specified	no / not applicable	yes
Bosques-Padilla 2011[8]	Mexico	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	hospital database	no excluded groups were specified	no / not applicable	yes

First Author and Publication Year	Country	Was the study population-based?	How were patients identified?	Were any groups excluded from the study for demographic reasons? (age, sex, ethnicity)	Was a control group included?	Was there a new outcome at the end of the study?
Buenavida 2011[9]	Uruguay	yes, the registry used was nationwide	IBD registry	patients younger than 14 were excluded	no / not applicable	yes
Calderon 2004[10]	Peru	no, only 1 of 2 hospitals reported information	medical records	patients younger than 14 were excluded	no / not applicable	yes
Campos 2013[11]	Brazil	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	hospital database	no excluded groups were specified	no / not applicable	yes
Choquet 2004[12]	Mexico	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	medical records	patients younger than 15 were excluded	no / not applicable	yes
da Silva 2015[13]	Brazil	yes, 2 of 2 IBD treatment referral centers reported information	IBD registry	no excluded groups were specified	no / not applicable	yes
de Barros 2017[14]	Brazil	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	IBD registry	no excluded groups were specified	no / not applicable	yes
de la Cal 1999[15]	Argentina and Panama	yes, in Panama the only hospital in the area reported information; yes, in Argentina all hospitals in the area reported information	medical records	no excluded groups were specified	no / not applicable	yes
de la Cruz-Guillen 2011[16]	Mexico	no, only 1 of several hospitals reported information	medical records	no excluded groups were specified	no / not applicable	yes
Delmondes 2015[17]	Brazil	uncertain, only 1 hospital reported information while the total number of	hospital database	no excluded groups were specified	no / not applicable	yes

First Author and Publication Year	Country	Was the study population-based?	How were patients identified?	Were any groups excluded from the study for demographic reasons? (age, sex, ethnicity)	Was a control group included?	Was there a new outcome at the end of the study?
		hospitals serving the area is unknown				
Dolcini 1967[18]	Argentina	uncertain, only 1 clinic reported information while the total number of clinics serving the area is unknown	not explicitly reported	no excluded groups were specified	no / not applicable	yes
dos Santos 2017[19]	Brazil	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	IBD registry	no excluded groups were specified	no / not applicable	yes
Edouard 2005[20]	Guadeloupe and Martinique	yes, all gastroenterologists practicing in the area	physician survey	no excluded groups were specified	no / not applicable	yes
Edwards 2008[21]	Barbados	yes, the only hospital in the area reported information	hospital database	patients without African ancestry were excluded	no / not applicable	yes
Figueroa 2005[22]	Chile	no, only 3 of several hospitals reported information	medical records	patients younger than 13 were excluded	no / not applicable	yes
Gaburri 1998[23]	Brazil	no, only 1 of several hospitals reported information	medical records	no excluded groups were specified	no / not applicable	yes
García 2014[24]	Cuba	no, only 1 of several hospitals reported information	medical records	no excluded groups were specified	no / not applicable	yes
Gasparini 2018[25]	Brazil	yes, a medication claims database representing 70% of the population	medication claims database	no excluded groups were specified	no / not applicable	yes
Hardt 2012[26]	Brazil	uncertain, only 5 reference centers reported information while the total	hospital	no excluded groups were	no / not	yes

First Author and Publication Year	Country	Was the study population-based?	How were patients identified?	Were any groups excluded from the study for demographic reasons? (age, sex, ethnicity)	Was a control group included?	Was there a new outcome at the end of the study?
		number of reference centers serving the area is unknown	database	specified	applicable	
Iade 2005a[27]	Uruguay	yes, the database represents most of the population (although not for privately insured)	hospital database	no excluded groups were specified	no / not applicable	yes
Iade 2005b[28]	Uruguay	yes, the database represents most of the population (although not for privately insured)	hospital database	no excluded groups were specified	no / not applicable	yes
Illescas 1999[29]	Peru	no, only 1 of 2 hospitals reported information	hospital database	no excluded groups were specified	no / not applicable	yes
Juliao 2018[30]	Colombia	yes, the claims database is national	health insurance claims database	children were excluded	no / not applicable	yes
Juliao-Baños 2010[31]	Colombia	uncertain, the hospital that reported information was stated to represent a "large percentage of the city's population" but it is unknown whether this is a majority percentage of the area	hospital database	no excluded groups were specified	no / not applicable	yes
Kleinubing-Junior 2011[32]	Brazil	uncertain, only 2 hospitals reported information while the total number of hospitals serving the area is unknown	hospital database	no excluded groups were specified	no / not applicable	yes
Lee 1988[33]	Jamaica	uncertain, only 1 hospital reported information while the total number of	medical records	no excluded groups were specified	no / not applicable	yes

First Author and Publication Year	Country	Was the study population-based?	How were patients identified?	Were any groups excluded from the study for demographic reasons? (age, sex, ethnicity)	Was a control group included?	Was there a new outcome at the end of the study?
		hospitals serving the area is unknown				
Lima 2017[34]	Brazil	yes, 2 of 2 IBD treatment referral centers reported information	not explicitly reported	patients younger than 18 and patients older than 60 were excluded	yes	yes
Lima-Martins 2018[35]	Brazil	uncertain, only 1 pharmaceutical registry reported information while the total number of registries serving the area is unknown	medication claims database	no excluded groups were specified	no / not applicable	yes
Luciano 2018[36]	Uruguay	uncertain, only 2 hospitals reported information while the total number of hospitals serving the area is unknown	not explicitly reported	children were excluded	no / not applicable	yes
Melendez 2011[37]	Puerto Rico	uncertain, only 1 IBD registry reported information while the total number of registries in the area is unknown	IBD registry	no excluded groups were specified	no / not applicable	yes
Micames 1983[38]	Puerto Rico	yes, 2 of 2 hospitals reported information	not explicitly reported	no excluded groups were specified	no / not applicable	yes
Moreno 1989[39]	Puerto Rico	no, only 1 of 2 hospitals reported information	medical records	no excluded groups were specified	no / not applicable	yes
Paredes-Méndez 2016[40]	Peru	no, only 1 of 2 hospitals reported information	medical records	no excluded groups were specified	no / not applicable	yes
Parente 2015[41]	Brazil	yes, the hospital serves 85% of the population	not explicitly reported	patients younger than 18 were excluded	no / not applicable	yes

First Author and Publication Year	Country	Was the study population-based?	How were patients identified?	Were any groups excluded from the study for demographic reasons? (age, sex, ethnicity)	Was a control group included?	Was there a new outcome at the end of the study?
Quintana 2012[42]	Chile	no, only 1 of several hospitals reported information	not explicitly reported	no excluded groups were specified	no / not applicable	yes
Rodríguez-Castro 2013[43]	Costa Rica	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	medical records	no excluded groups were specified	no / not applicable	yes
Ruiz 2009[44]	Argentina	uncertain, only 3 clinics reported information while the total number of clinics serving the area is unknown	not explicitly reported	adults were excluded	no / not applicable	yes
Santana 2007[45]	Brazil	no, only 1 of 2 hospitals reported information	not explicitly reported	patients younger than 19 were excluded	no / not applicable	yes
Sarmiento 2018[46]	Mexico	yes, the registry is national	hospital database	no excluded groups were specified	no / not applicable	yes
Sihues 2008[47]	Venezuela	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	medical records	no excluded groups were specified	no / not applicable	yes
Silva 2008[48]	Brazil	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	medical records	no excluded groups were specified	no / not applicable	yes
Simian 2016[49]	Chile	no, only 1 of several hospitals reported information	IBD registry	patients younger than 15 were excluded	no / not applicable	yes
Sobrero 2009[50]	Argentina	uncertain, only 1 health maintenance organization reported information while the total number of health maintenance organizations serving the area is	hospital database	no excluded groups were specified	no / not applicable	yes

First Author and Publication Year	Country	Was the study population-based?	How were patients identified?	Were any groups excluded from the study for demographic reasons? (age, sex, ethnicity)	Was a control group included?	Was there a new outcome at the end of the study?
		unknown				
Souza 2002[51]	Brazil	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	medical records	no excluded groups were specified	no / not applicable	yes
Souza 2008[52]	Brazil	uncertain, only 1 registry reported information while the total number of registries serving the area is unknown	hospital database	no excluded groups were specified	no / not applicable	yes
Torres 2010[53]	Brazil	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	hospital database	no excluded groups were specified	no / not applicable	yes
Torres 2012[54]	Puerto Rico	uncertain, only 1 registry reported information while the total number of registries serving the area is unknown	IBD registry	non-Hispanics were excluded	no / not applicable	yes
Vendrell 2013[55]	Puerto Rico	no, 1 insurance plan provided service to only low-income residents	insurance database	no excluded groups were specified	no / not applicable	yes
Victoria 2009[56]	Brazil	yes, the referral center is the only one in the area	hospital database	patients younger than 16 were excluded	no / not applicable	yes
Vivan 2017[57]	Brazil	no, only patients registered in an exceptional medicine program	not explicitly reported	no excluded groups were specified	no / not applicable	yes
Yamamoto-Furusho 2009[58]	Mexico	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	medical records	no excluded groups were specified	no / not applicable	yes

First Author and Publication Year	Country	Was the study population-based?	How were patients identified?	Were any groups excluded from the study for demographic reasons? (age, sex, ethnicity)	Was a control group included?	Was there a new outcome at the end of the study?
Yamamoto-Furusho 2015[59]	Mexico	uncertain, only 1 hospital reported information while the total number of hospitals serving the area is unknown	medical records	no excluded groups were specified	yes	yes
Yamamoto-Furusho 2018[60]	Mexico	yes, the claims database is national	hospital database	no excluded groups were specified	no / not applicable	yes
Yepes-Barreto 2010[61]	Colombia	uncertain, only 1 health promotion companies reported information while the total number serving the area is unknown	hospital database	patients 14 years old and younger were excluded	no / not applicable	yes

Appendix E: MOOSE Checklist.

Reporting Criteria	#	Reported (Yes/No)	Reported on Page Number
Reporting of Background			
Problem definition	1	yes	6
Hypothesis statement	2	no	not applicable
Description of study outcome(s)	3	yes	6
Type of exposure or intervention used	4	no	not applicable
Type of study design used	5	yes	6
Study population	6	yes	7
Reporting of Search Strategy			
Qualifications of searchers (e.g., librarians and investigators)	7	yes	7
Search strategy, including time period included in the synthesis and keywords	8	yes	Appendix A
Effort to include all available studies, including contact with authors	9	yes	7–8
Databases and registries searched	10	yes	7, Appendix A
Search software used, name and version, including special features used (e.g., explosion)	11	yes	Appendix A
Use of hand searching (e.g., reference lists of obtained articles)	12	yes	7, Appendix B
List of citations located and those excluded, including justification	13	yes	Appendix B
Method for addressing articles published in languages other than English	14	yes	7
Method of handling abstracts and unpublished studies	15	yes	7–8
Description of any contact with authors	16	yes	8
Reporting of Methods			

Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	17	no	not applicable
Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	18	yes	8–9
Documentation of how data were classified and coded (e.g., multiple raters, blinding, and interrater reliability)	19	yes	8
Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate	20	no	not applicable
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	21	yes	8
Assessment of heterogeneity	22	no	not applicable
Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	23	yes	8–9
Provision of appropriate tables and graphics	24	yes	Tables 1–2, Figures 1–4
Reporting of Results			
Table giving descriptive information for each study included	25	yes	Tables 1–2, Appendices C–D, G–J
Results of sensitivity testing (e.g., subgroup analysis)	26	no	not applicable
Indication of statistical uncertainty of findings	27	no	not applicable
Reporting of Discussion			
Quantitative assessment of bias (e.g., publication bias)	28	no	not applicable
Justification for exclusion (e.g., exclusion of non–English-language citations)	29	yes	Appendix B
Assessment of quality of included studies	30	yes	Appendix D
Reporting of Conclusions			
Consideration of alternative explanations for observed results	31	yes	14–17

Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	32	yes	14
Guidelines for future research	33	yes	14, 18
Disclosure of funding source	34	yes	2

Appendix F: PRISMA Checklist.

Section/topic	#	Checklist Item	Reported (Yes/No)	Reported on Page Number
Title				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	yes	1
Abstract				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	yes	5
Introduction				
Rationale	3	Describe the rationale for the review in the context of what is already known.	yes	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	yes	6
Methods				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	no	no protocol has been registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	yes	7, Appendix A
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	yes	7, Appendix A
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	yes	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in	yes	Appendix B

		systematic review, and, if applicable, included in the meta-analysis).		
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	yes	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	yes	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	yes	Appendix D
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	yes	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	yes	8–9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	no	not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	no	not applicable
Results				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	yes	9–10, Appendix B
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	yes	Tables 1–2, Appendices C–D, G–J
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	yes	Appendix D
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	yes	Tables 1–2, Figures 1–4, Appendices G–J
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and	yes	14

		measures of consistency.		
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	no	not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	no	not applicable
Discussion				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	yes	14–17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	yes	14, 17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	yes	18
Funding				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	yes	2

Appendix G: Phenotypic characteristics of Crohn's disease and ulcerative colitis, stratified by Montreal Classification (age at diagnosis, disease location, disease behavior, and perianal disease).

First Author and Publication Year	Country	Study Period	Age at Diagnosis A1 (<16 years) A2 (17 to 40 years) A3 (> 40 years)	CD Disease Location L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI tract)*	CD Disease Behavior B1 (inflammatory) B2 (fibrostenotic) B3 (penetrating)**	Perianal Disease in CD	UC Disease Location E1 (proctitis) E2 (left-sided) E3 (extensive)
Dolcini 1967[18]	Argentina	1946-1965	not reported	not applicable	not applicable	not applicable	26.00% 38.00% 36.00%
de la Cal 1999[15]	Argentina	1987-1993	not reported	not applicable	not applicable	not applicable	26.30% 50.00% 8.00%
Ruiz 2009[44]	Argentina	1988-2007	not reported	13.00% 31.00% 46.00% 11.00%	77.00% 5.00% 18.00%	not reported	6.00% 17.00% 77.00%
Edwards 2008[21]	Barbados	1980-2004	not reported	32.00% 45.00% 21.00% 2.00%	not reported	26.00%	13.00% 54.00% 33.00%
Gaburri 1998[23]	Brazil	1970-1998	not reported	58.50% 8.30% 24.90% 8.30%	not reported	not reported	not applicable
Souza 2002[51]	Brazil	1980-1999	not reported	not reported	not reported	not reported	32.40% 29.70% 28.30%

First Author and Publication Year	Country	Study Period	Age at Diagnosis A1 (<16 years) A2 (17 to 40 years) A3 (> 40 years)	CD Disease Location L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI tract)*	CD Disease Behavior B1 (inflammatory) B2 (fibrostenotic) B3 (penetrating)**	Perianal Disease in CD	UC Disease Location E1 (proctitis) E2 (left-sided) E3 (extensive)
Campos 2013[11]	Brazil	1984-2007	not reported	not reported	not reported	not reported	36.23% 24.65% 39.10%
Parente 2015[41]	Brazil	1988-2012	8.00% 71.00% 21.00%	15.00% 36.00% 17.00% 7.00%	69.00% 18.00% 13.00%	27.00%	9.20% 57.90% 29.60%
Torres 2010[53]	Brazil	1992-2007	7.70% 58.80% 33.30%	46.00% 10.00% 44.00% 0.00%	71.00% 8.00% 21.00%	31.10%	not applicable
Bechara 2015[6]	Brazil	1992-2012	4.80% 63.20% 32.00%	58.40% 17.60% 23.20% 0.80%	9.60% 44.80% 45.60%	26.40%	not applicable
Silva 2008[48]	Brazil	1996-2006	not reported	not applicable	not applicable	not applicable	28.34% 23.60% 48.00%
Hardt 2012[26]	Brazil	2000-2012	12.00% 58.30% 29.70%	24.00% 29.10% 46.30% 0.60%	33.70% 26.30% 40.00%	50.90%	not applicable

First Author and Publication Year	Country	Study Period	Age at Diagnosis A1 (<16 years) A2 (17 to 40 years) A3 (> 40 years)	CD Disease Location L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI tract)*	CD Disease Behavior B1 (inflammatory) B2 (fibrostenotic) B3 (penetrating)**	Perianal Disease in CD	UC Disease Location E1 (proctitis) E2 (left-sided) E3 (extensive)
de Barros 2017[14]	Brazil	2005-2012	11.20% 60.30% 28.50%	29.60% 28.00% 39.60% 2.80%	62.00% 24.60% 13.40%	31.80%	not applicable
Souza 2008[52]	Brazil	2006-2007	not reported	58.50% 9.80% 17.10% 2.44%	41.50% 12.20% 46.30%	12.22%	44.80% 16.40% 38.80%
Santana 2007[45]	Brazil	2006	69.20% 38.80% 0.00%	25.40% 23.70% 39.00% 11.90%	36.90% 7.70% 55.40%	not reported	not applicable
Arantes 2017[2]	Brazil	2008-2016	not reported	not reported	not reported	not reported	23.80% 35.60% 40.60%
da Silva 2015[13]	Brazil	2011-2012	not reported	not reported	not reported	not reported	16.20% 42.70% 41.10%
Delmondes 2015[17]	Brazil	2011-2014	not reported	5.00% 12.00% 17.00% 3.00%	64.00% 13.00% 23.00%	30.00%	71.00% 14.00% 12.00%

First Author and Publication Year	Country	Study Period	Age at Diagnosis A1 (<16 years) A2 (17 to 40 years) A3 (> 40 years)	CD Disease Location L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI tract)*	CD Disease Behavior B1 (inflammatory) B2 (fibrostenotic) B3 (penetrating)**	Perianal Disease in CD	UC Disease Location E1 (proctitis) E2 (left-sided) E3 (extensive)
Barros 2014[4]	Brazil	2012-2013	75.00% 5.00% 20.00%	not reported	55.00% 33.30% 11.10%	not reported	0.00% 38.50% 61.50%
Lima-Martins 2018[35]	Brazil	2013-2014	not reported	31.44% 28.89% 30.87% 3.11%	57.67% 21.02% 21.30%	25.85%	30.27% 37.76% 31.95%
dos Santos 2017[19]	Brazil	2016	not reported	12.50% 20.45% 51.13% 0.00%	25.00% 35.23% 23.86%	17.46%	30.99% 22.22% 35.67%
Lima 2017[34]	Brazil	not provided	6.70% 78.30% 15.00%	13.30% 31.70% 53.30% 1.70%	48.30% 21.70% 30.00%	33.30%	17.60% 39.70% 42.60%
Kleinubing-Junior 2011[32]	Brazil	2010	not reported	14.10% 25.40% 47.90% 0.00%	not reported	not reported	26.00% 33.00% 26.00%
Quintana 2012[42]	Chile	1963-2004	not reported	30.50% 23.00% 21.00% 10.80%	72.00% 13.00% 15.00%	14.70%	not applicable

First Author and Publication Year	Country	Study Period	Age at Diagnosis A1 (<16 years) A2 (17 to 40 years) A3 (> 40 years)	CD Disease Location L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI tract)*	CD Disease Behavior B1 (inflammatory) B2 (fibrostenotic) B3 (penetrating)**	Perianal Disease in CD	UC Disease Location E1 (proctitis) E2 (left-sided) E3 (extensive)
Figueroa 2005[22]	Chile	1990-2002	not reported	37.00% 47.00% 19.00% 4.00%	not reported	not reported	21.00% 51.00% 28.00%
Simian 2016[49]	Chile	2012-2015	not reported	27.00% 44.00% 28.00% 3.00%	80.00% 10.00% 9.00%	28.00%	28.00% 22.00% 50.00%
Juliao-Baños 2010[31]	Colombia	2001-2009	3.10% 46.90% 50.00%	18.80% 28.10% 50.00% 3.10%	34.40% 31.30% 6.30%	21.90%	19.50% 45.00% 35.50%
Rodríguez-Castro 2013[43]	Costa Rica	1990-2009	not reported	not reported	not reported	35.00%	not applicable
García 2014[24]	Cuba	2011-2012	not reported	36.25% 17.50% 45.00% 1.25%	not reported	not reported	not applicable
Arbelo 2002[3]	Cuba	1982-2002	not reported	not reported	not reported	not reported	15.00% 26.00% 59.00%

First Author and Publication Year	Country	Study Period	Age at Diagnosis A1 (<16 years) A2 (17 to 40 years) A3 (> 40 years)	CD Disease Location L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI tract)*	CD Disease Behavior B1 (inflammatory) B2 (fibrostenotic) B3 (penetrating)**	Perianal Disease in CD	UC Disease Location E1 (proctitis) E2 (left-sided) E3 (extensive)
Edouard 2005[20]	Guadeloupe and Martinique	1997-1999	not reported	4.25% 23.39% 48.91% 0.00%	not reported	19.14%	18.80% 25.42% 50.84%
Yamamoto-Furusho 2015[59]	Mexico	1983-2013	not reported	28.03% 21.96% 44.70% 6.83%	38.65% 35.60% 30.30%	not reported	not applicable
Yamamoto-Furusho 2009[58]	Mexico	1987-2006	not reported	not applicable	not applicable	not applicable	15.40% 25.50% 59.10%
Choquet 2004[12]	Mexico	1990-2000	not reported	not applicable	not applicable	not applicable	not reported not reported 54.94%
de la Cruz-Guillen 2011[16]	Mexico	1990-2008	not reported	not applicable	not applicable	not applicable	44.10% 30.80% 22.50%
Bosques-Padilla 2011[8]	Mexico	2004-2008	not reported	not applicable	not applicable	not applicable	29.00% 21.00% 50.00%
Sarmiento 2018[46]	Mexico	not provided	not reported	17.20% 34.50%	not reported	not reported	20.00% 17.40%

First Author and Publication Year	Country	Study Period	Age at Diagnosis A1 (<16 years) A2 (17 to 40 years) A3 (> 40 years)	CD Disease Location L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI tract)*	CD Disease Behavior B1 (inflammatory) B2 (fibrostenotic) B3 (penetrating)**	Perianal Disease in CD	UC Disease Location E1 (proctitis) E2 (left-sided) E3 (extensive)
				29.30% 2.90%			52.60%
de la Cal 1999[15]	Panama	1987-1993	not reported	not applicable	not applicable	not applicable	33.30% 60.00% 13.30%
Illescas 1999[29]	Peru	1944-1995	not reported	not applicable	not applicable	not applicable	60.00% 11.10% 28.80%
Bendano 2010[7]	Peru	1990-2010	11.80% 29.40% 58.80%	23.50% 29.40% 47.00% 29.40%	35.30% 35.30% 29.40%	53.00%	not applicable
Calderon 2004[10]	Peru	2001-2003	not reported	not applicable	not applicable	not applicable	6.90% 62.90% 30.20%
Paredes-Méndez 2016[40]	Peru	2004-2014	not reported	21.00% 54.00% 25.00% 0.00%	54.20% 25.00% 20.80%	16.60%	17.20% 35.80% 47.00%
Moreno 1989[39]	Puerto Rico	1980-1987	not reported	0.00% 90.00% 10.00%	not reported	40.00%	55.35% 18.57% 14.28%

First Author and Publication Year	Country	Study Period	Age at Diagnosis A1 (<16 years) A2 (17 to 40 years) A3 (> 40 years)	CD Disease Location L1 (ileal) L2 (colonic) L3 (ileocolonic) L4 (upper GI tract)*	CD Disease Behavior B1 (inflammatory) B2 (fibrostenotic) B3 (penetrating)**	Perianal Disease in CD	UC Disease Location E1 (proctitis) E2 (left-sided) E3 (extensive)
				0.00%			
Torres 2012[54]	Puerto Rico	1995-2009	not reported	not reported	not reported	15.60%	13.00% 37.20% 49.60%
Iade 2005a[27]	Uruguay	1951-2003	not reported	not applicable	not applicable	not applicable	17.40% 41.30% 38.00%
Iade 2005b[28]	Uruguay	1951-2003	not reported	23.00% 43.70% 16.70% 16.70%	not reported	52.20%	not applicable
Luciano 2018[36]	Uruguay	1954-2015	not reported	not applicable	not applicable	not applicable	18.90% 36.55% 31.51%
Sihues 2008[47]	Venezuela	2006	not reported	16.70% 50.00% 33.30% 0.00%	not reported	not reported	17.90% 28.60% 53.60%

*B1, B2, and B3 are mutually exclusive and add up to 100%.
**L1, L2, and L3 are mutually exclusive and add up to 100%. L4 is a modifier (i.e., presence or absence).

Appendix H: Proportion of medications prescribed for IBD in Latin America and the Caribbean.

First Author and Publication Year	Country	Study Period	Corticosteroids (%)	Immunomodulators (%)*	5-ASA (%)	Infliximab (%)	Adalimumab (%)	Anti-TNF (%)
Gaburri 1998[23]	Brazil	1970-1998	CD: 68.3%	CD: 8.3%	CD: 81.6%			
Souza 2002[51]	Brazil	1980-1999	CD: 85.3% UC: 81.2%	CD: 6.9% UC: 5.4%	CD: 64.7% UC: 93.2%			
Bechara 2015[6]	Brazil	1992-2012	CD: 33.6%	CD: 22.8%	CD: 31.2%			CD: 4.8%
de Barros 2017[14]	Brazil	2005-2012		CD: 80.4%				CD: 29.6%
Santana 2007[45]	Brazil	2006	CD: 70.8%	CD: 43.1%				
Arantes 2017[2]	Brazil	2008-2016		CD: 35.3% UC: 20.2%	CD: 53.0% UC: 84.3%	CD: 20.2% UC: 5.4%	CD: 33.6% UC: 5.4%	
da Silva 2015[13]	Brazil	2011-2012	UC: 62.8%	UC: 19.5%				UC: 1.5%
Lima-Martins 2018[35]	Brazil	2013-2014		CD: 71.70% UC: 19.40%	CD: 31.46% UC: 56.36%			CD: 43.40% UC: 4.50%
Vivan 2017[57]	Brazil	2016-2017	IBD: 20.68%	IBD: 62.3%	IBD: 32.75%			IBD: 37.93%
Lima 2017[34]	Brazil	not reported	CD: 13.3% UC: 17.6%	CD: 61.7% UC: 11.8%	CD: not reported UC: 88.2%	CD: 18.3% UC: not reported		CD: 18.3% UC: not reported
Kleinubing-Junior 2011[32]	Brazil	not reported	CD: 35.2% UC: 17.0%	CD: 57.7% UC: 28.0%	CD: 21.2% UC: 82.0%			CD: 8.5% UC: 2.0%
Figueroa 2005[22]	Chile	1990-2002	CD: 29.7% UC: 20.9%	CD: 16.2% UC: 20.9%	CD: 94.5% UC: 91.3%			
Simian 2016[49]	Chile	2012-2015	CD: 68%	CD: 67%	CD: 68%			CD: 34%

First Author and Publication Year	Country	Study Period	Corticosteroids (%)	Immunomodulators (%)*	5-ASA (%)	Infliximab (%)	Adalimumab (%)	Anti-TNF (%)
			UC: 58%	UC: 33%	UC: 98%			UC: 7%
Juliao-Baños 2010[31]	Colombia	2001-2009	IBD: 73.8% CD: 87.5% UC: 71.8% IBDU: 57.1%	IBD: not reported CD: 40% UC: 27% IBDU: not reported	IBD: not reported CD: not reported UC: 88.3% IBDU: not reported	IBD: 77.8% CD: not reported UC: not reported IBDU: not reported		IBD: 13.4% CD: 46.9% UC: 7.4% IBDU: not reported
Rodríguez-Castro 2013[43]	Costa Rica	1990-2009	CD: 53%	CD: 64%	CD: 85%	CD: 25%		CD: 25%
García 2014[24]	Cuba	2011-2012	CD: 15.2%	CD: 6.3%	CD: 100%	CD: 3.8%		CD: 3.8%
Yamamoto-Furusho 2015[59]	Mexico	1983-2013	CD: 21.96%	CD: 28.78%	CD: 28.03%			CD: 1.51%
Yamamoto-Furusho 2009[58]	Mexico	1987-2006	UC: 33.3%	UC: 28%	UC: 89.8%			UC: 0.0%
de la Cruz-Guillen 2011[16]	Mexico	1990-2008	UC: 7%		UC: 100%	UC: 7.35%		UC: 7.35%
Bosques-Padilla 2011[8]	Mexico	2004-2008	UC: 32%	UC: 13%	UC: 96%			
Sarmiento 2018[46]	Mexico	not reported	CD: 28.7% UC: 46.0%	CD: 42.0% UC: 24.9%	CD: 65.5% UC: 66.3%			CD: 37.4% UC: 16.2%
Bendano 2010[7]	Peru	1990-2010	CD: 35.3%					
Paredes-Méndez 2016[40]	Peru	2004-2014	CD: 16.6% UC: 33.3%	CD: 37.5% UC: 9.8%	CD: 54.3% UC: 88.8%	CD: 33.3% UC: 2.4%		CD: 33.3% UC: 2.4%

First Author and Publication Year	Country	Study Period	Corticosteroids (%)	Immunomodulators (%)*	5-ASA (%)	Infliximab (%)	Adalimumab (%)	Anti-TNF (%)
Melendez 2011[37]	Puerto Rico	1995-2007	CD: 74.1% UC: 71.7%	CD: 44.3% UC: 14.5%	CD: 81.9% UC: 74.6%			CD: 9.7% UC: 0.8%
Luciano 2018[36]	Uruguay	2015-2017 (Anti-TNF introduced in 2016)	UC: 53.4%	UC: 17.8%	UC: 95.0%			UC: 1.4%

*Immunomodulators represent azathioprine, 6-mercaptopurine, and methotrexate.

Appendix I: Proportion of hospitalization of patients with IBD in Latin America and the Caribbean.

First Author and Publication Year	Country	Study Period	CD Hospitalization (%)	UC (IBDU) Hospitalization (%)
Souza 2002[51]	Brazil	1980-1999	83.30%	63.00%
de Barros 2017[14]	Brazil	2005-2012	59.40%	
Santana 2007[45]	Brazil	2006	29.20%	
da Silva 2015[13]	Brazil	2011-2012		43.80%
Simian 2016[49]	Chile	2012-2015	55.10%	35.64%
Juliao-Baños 2010[31]	Colombia	2001-2009	75.00%	42.90% (28.60%)
Paredes-Méndez 2016[40]	Peru	2004-2014	75.00%	51.80%
Micames 1983[38]	Puerto Rico	1974-1980		82.35%

Appendix J: Proportion of intestinal resections for Crohn's disease and colectomy for ulcerative colitis in Latin America and the Caribbean.

First Author and Publication Year	Country	Study Period	IBD Surgery (%)	CD Surgery (%)	UC (IBDU) Surgery (%)
Dolcini 1967[18]	Argentina	1946-1965			15.00%
Sobrero 2009[50]	Argentina	2007		41.00%	31.00%
Gaburri 1998[23]	Brazil	1970-1998		40.00%	
Souza 2002[51]	Brazil	1980-1999		57.80%	21.90%
Torres 2010[53]	Brazil	1992-2007		31.00%	
Silva 2008[48]	Brazil	1996-2006			10.23%
de Barros 2017[14]	Brazil	2005-2012		34.10%	
Santana 2007[45]	Brazil	2006		20.00%	
Souza 2008[52]	Brazil	2006-2007	35.00%	23.18%	10.91% (0.09%)
da Silva 2015[13]	Brazil	2011-2012			3.40%
Barros 2014[4]	Brazil	2012-2013	32.50%		
dos Santos 2017[19]	Brazil	2016		12.69%	
Vivan 2017[57]	Brazil	2016-2017		31.70%	5.88%
Lima 2017[34]	Brazil	not reported		31.60%	2.90%
Quintana 2012[42]	Chile	1963-2004		22.6%	

First Author and Publication Year	Country	Study Period	IBD Surgery (%)	CD Surgery (%)	UC (IBDU) Surgery (%)
Figueroa 2005[22]	Chile	1990-2002		57.00%	18.00%
Simian 2016[49]	Chile	2012-2015		38.00%	5.00%
Juliao-Baños 2010[31]	Colombia	2001-2009	12.90%	50.00%	5.90%
Rodríguez-Castro 2013[43]	Costa Rica	1990-2009		68.00%	
Arbelo 2002[3]	Cuba	1982-2002		46.60%	1.30%
Lee 1988[33]	Jamaica	1968-1988		25.00%	
Yamamoto-Furusho 2009[58]	Mexico	1987-2006		72.70%	10.10%
Choquet 2004[12]	Mexico	1990-2000			28.00%
de la Cruz-Guillen 2011[16]	Mexico	1990-2008			10.30%
Bosques-Padilla 2011[8]	Mexico	2004-2008			13.00%
Sarmiento 2018[46]	Mexico	not reported		17.80%	1.90%
Bendano 2010[7]	Peru	1990-2010		70.50%	
Calderon 2004[10]	Peru	2001-2003			6.90%
Paredes-Méndez 2016[40]	Peru	2004-2014	16.20%	50.00%	6.20%
Micames 1983[38]	Puerto Rico	1974-1980			21.56%
Moreno 1989[39]	Puerto Rico	1980-1987		13.63%	13.5%
Melendez 2011[37]	Puerto Rico	1995-2007	39.00%	53.00%	22.00%

First Author and Publication Year	Country	Study Period	IBD Surgery (%)	CD Surgery (%)	UC (IBDU) Surgery (%)
Torres 2012[54]	Puerto Rico	1995-2009		51.20%	31.90%
Bartholomew 1979[5]	Trinidad and Tobago	1968-1978	35.29%		
Iade 2005ab[27,28]	Uruguay	1951-2003		31.20%	8.30%
Luciano 2018[36]	Uruguay	1985-2015			10.50%

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