Latin Americans and US Hispanics show differences in IBD phenotype: a systematic review with meta-analysis

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ABSTRACT

Latin America has experienced a rise in the prevalence and incidence of inflammatory bowel disease (IBD). Differences in IBD phenotype between Hispanics in Latin America and those in the USA have not been described. We conducted a systematic review with meta-analysis of population-based and cohort studies comparing the phenotype of ulcerative colitis (UC) and Crohn's disease (CD) in Latin Americans and US Hispanics. A systematic search was conducted up to March 2019 using MEDLINE, EMBASE and Google Scholar. Inclusion criterion includes studies describing IBD phenotype in Latin Americans or in US Hispanics. Exclusion criterion includes prevalence or incidence studies not describing phenotype. A random effects model was chosen "a priori" for analysis of pooled proportions. A total of 46 studies were included from Latin America and 7 studies from the USA. The predominant IBD subtype in Latin America was UC with a more balanced UC:CD ratio noted in Puerto Rico (0.53) and Brazil (0.56). UC-related extensive colitis was more common in US Hispanics (0.64) than in Latin Americans (0.38), p<0.001. CD phenotype was similar between US Hispanics and Latin Americans. UC is the predominant IBD subtype in Latin America, with the exception of Puerto Rico and Brazil which demonstrate a more balanced UC:CD ratio. In UC, extensive colitis was more frequently seen in US Hispanics than in Latin Americans. CD phenotype was similar in both US Hispanics and Latin Americans.

Significance of this study

What is already known about this subject?

- ► There is a growing incidence and prevalence of inflammatory bowel disease (IBD) in Latin America.
- ► Hispanics in the USA are more likely to have ulcerative colitis (UC).
- ► Based on a previous meta-analysis, Hispanics and non-Hispanic whites in the USA share a common IBD phenotype.

What are the new findings?

- ► Hispanics in Latin America have a predominance of UC except in Brazil and Puerto Rico where the UC to Crohn's disease (CD) ratio is nearly 1:1.
- ► US Hispanics are more likely to have extensive UC than Latin Americans.
- ► US Hispanics and Latin Americans share a common CD phenotype.
- ► US Hispanics and Latin Americans have a similar need for surgery in both UC and CD.

How might these results change the focus of research or clinical practice?

- ► Further research should be focused on identifying the different triggers for IBD within Latin American countries.
- ► Due to the low use of biologics in Latin America, efforts to provide these medications to this underserved community should be sought.

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INTRODUCTION

The incidence and prevalence of inflammatory bowel disease (IBD) is increasing in Latin America.[1–3] Concurrently, a growing number of academic centers have been reporting the phenotype of ulcerative colitis (UC) and Crohn's disease (CD) in this region. Environmental exposures[4] such as industrialization and a Western diet[5] have been considered to be influential in the development of this disease[6] and Latin America has experienced an increase in both industrialization[7] and westernization of the food industry.[8] There is a need to further understand the phenotype of IBD in this region as it is plausible that evolving environmental and dietary factors are shaping the phenotypic characteristics of IBD in Latin Americans. The Latin American population is a heterogeneous group comprised of a blend of indigenous, African and European descent. It is conceivable that IBD phenotype differs within Latin America and this was explored in a recent systematic review which included all types of cohort and cross-sectional studies.[2] Latin Americans also comprise the largest minority group[9] and largest migrant group to the USA.[10]

On migration to the USA, Latin Americans are exposed to the Western diet and environmental factors which have been long considered to be influential in the development of IBD.[4 5]

Based on a recent meta-analysis, US Hispanics were more likely to have UC but shared a similar IBD phenotype to non-Hispanic whites.[11] However, it remains unclear whether the phenotype seen in US Hispanics is similar to the one seen in Latin America. Thus, we also aimed to compare the pooled IBD Latin American phenotype with IBD phenotypes in US Hispanics. As secondary endpoints, we aimed to assess differences in age at diagnosis, presence of a family history of IBD, smoking status, medication use and surgical outcomes.

MATERIAL AND METHODS

Search strategy

Author (DJA) and a medical librarian conducted a systematic search up to March of 2019 using MEDLINE. The MESH and non-MESH terms used were as follows: (inflammatory bowel disease* OR ulcerative colitis OR crohn*) AND (Latin America OR Peru OR Ecuador OR Colombia OR Venezuela OR Brasil OR Brazil OR Argentina OR Uruguay OR Paraguay OR Bolivia OR El Salvador OR Panama OR Guatemala OR Mexico OR Honduras OR Nicaragua OR Chile OR Costa Rica OR Dominican Republic OR Puerto Rico OR Cuba). A similar search was conducted using EMBASE (online supplemental file 1). Google Scholar was used to gather unpublished data discovered during cross-referencing. We contacted authors if data were deemed pertinent but not accessible. Two authors (DJA, AC) performed a surveillance search from our group's recent meta-analysis to gather studies including US Hispanics with IBD.[11] The systematic review was reported according to the MOOSE guidelines (online supplemental file 2).[12]

Inclusion/Exclusion criteria

Two authors (DJA and AC) reviewed the studies for inclusion with an interobserver agreement of 94% and any disagreements in inclusion were resolved after a formal discussion. Authors JS and AC extracted the data from each study and compared it for accuracy. Disagreements were resolved with a third author (ST). Studies published in full, abstract form or unpublished work until March of 2019 were eligible for inclusion. Inclusion criterion includes population-based Latin American studies from countries where Spanish or Portuguese was the predominant language. The studies needed to describe IBD phenotype and there were no language restrictions. Each study was reviewed, and the following data were extracted when available: geographical location, study design, number of participants, location/behavior of disease, age at IBD diagnosis, family history of IBD, smoking history (former/current), medication use (eg, steroids, aminosalicylates, immunomodulators, biologics) and need for surgical intervention. Studies were excluded if IBD phenotype could not be integrated into the Montreal Classification. Incidence or prevalence studies which did not provide phenotype were also excluded. Authors JS and ST conducted the study appraisal using the AXIOS tool (online supplemental file 3).[13]

Outcomes assessed

The main outcome of this study was to assess the phenotypic characteristics of UC and CD in Latin America according to the Montreal Classification.[14] If the Montreal Classification was not reported among the authors, then the location of disease was grouped into the "best-fit" category that would approximate to the Montreal Classification. Particularly, proctosigmoiditis was commonly reported among Latin American studies and this was grouped with E1 disease (proctitis).

We also aimed to compare IBD phenotype between Latin Americans and US Hispanics. The term "US Hispanic" was used to define Hispanics residing in the USA, whereas "Latin Americans" defined Hispanics living in Latin America. Secondary outcomes were assessed when available and included age of IBD diagnosis as defined by the Montreal classification (A1: <17, A2: 17–40, A3: >40 years), smoking status, family history of IBD, aminosalicylate use, immunomodulator and biologic use.

Statistical analysis

STATA V.15 was used for statistical analysis. A random effects pooled proportion model was chosen as a priori for all analyses. The I^2 and p value tested for heterogeneity and an I^2 >70% or p value <0.05 was considered significant for high heterogeneity. Further sensitivity analysis was conducted when heterogeneity was present.

Categorical outcomes were analyzed using a prevalence rate and effect size (ES) between countries of origin. The pooled proportion of ES with 95% CIs were calculated for each outcome with respect to the Latin America country of origin and Hispanic American/Latin America. A meta-regression analysis was also conducted to determine the relationship between countries of origin. A pooled proportion (ES) was considered significant when the 95% CI did not include 1.00 and the meta-regression p value was less than 0.05.

RESULTS

The search yielded 1365 articles in MEDLINE and 4435 articles in EMBASE. A total of 4627 articles were left for screening after duplicates were removed. Description of further exclusion of studies is depicted in figure 1 (see the Search strategy section). A total of 46 of Latin American unique studies were used in the quantitative analysis for Latin America (tables 1 and 2). The following countries reported at least one study: Costa Rica,[15] Argentina,[16 17] Colombia,[18 19] Chile,[20–23] Cuba,[24–26] Mexico,[27–29] Puerto Rico,[30–32] Uruguay,[33–35] Peru,[36–40] and Brazil.[41–60] Seven US Hispanic studies[61–67] were included. The US-based studies were gathered from a previously published systematic review[11] with an updated surveillance search up to March 2019 which did not yield any new relevant studies.

Comparison of disease phenotype within Latin American countries

Predominant IBD subtype: Latin America

The predominant IBD subtype was UC and it was seen in nearly two-thirds of the IBD Latin American cohort (0.68) (figure 2) (see the Dominant IBD subtype in Latin American countries section). There were more balanced UC:CD

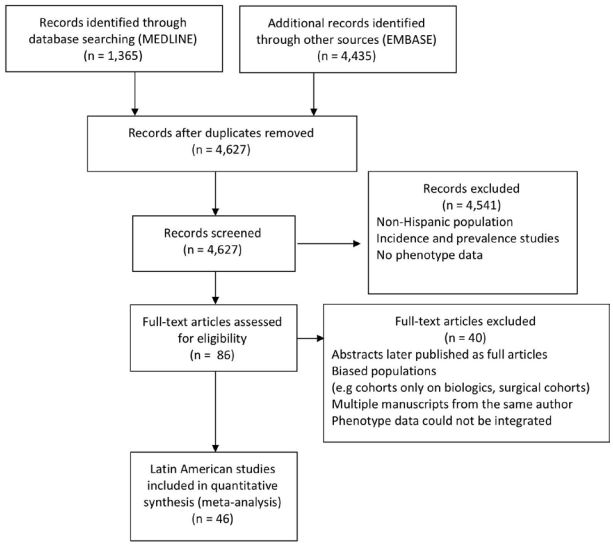

Figure 1 Flow diagram.

ratios (1:1) noted in Puerto Rico (0.53) and Brazil (0.56); however, these findings did not reach statistical significance, p=0.16 (table 3).

UC disease extension: Latin America

Extensive colitis was more frequent in Argentina (0.67) and Mexico (0.54), p=0.006. UC location of disease was otherwise similar across Latin American countries (table 3).

Location of luminal disease and disease behavior for CD: Latin America

The highest proportions for colonic disease were seen in nearly one-half of patients from Uruguay (0.43), Chile (0.46), and Puerto Rico (0.50), whereas the lowest proportions were seen in Cuba (0.15) and Colombia (0.17), p=0.002. The location of disease in CD was otherwise similar across Latin American countries. Similarly, there were no statistically significant differences in disease behavior (table 3).

Comparisons of disease phenotype in Latin Americans versus US Hispanics

Predominant IBD subtype: Latin Americans versus US Hispanics

In Latin America, two-thirds of the IBD population had UC (0.68) which was similar to US Hispanics (0.62), p=0.38 (table 4).

UC disease extension: Latin Americans versus US Hispanics

Proctitis was present in nearly one-third of patients in Latin America (0.37) but this was less common in US Hispanics (0.08), p=0.003 (figure 3) (see the IBD subtypes: Latin America vs United States section). The fewer incidence of proctitis in the US setting is likely due to the use of topical medications as most studies reported in the USA were from tertiary care centers and these patients likely had exposure to topical medications prior to presenting to the tertiary care center. Another explanation is that dietary and environmental exposures in the USA may contribute to differences in phenotype between Latin Americans and US Hispanics. Left-sided colitis was equally seen in one-fourth of patients from both groups, p=0.82. Extensive colitis was more common in US Hispanics (0.64) than Latin Americans (0.38), p<0.001 (table 4).

Location of luminal disease for CD: Latin Americans versus US Hispanics

The predominant phenotype in Latin America was ileocolonic disease (0.37), which was also the predominant disease location in US Hispanics (0.46), p=0.88. Ileal disease was more commonly seen among Latin Americans (0.31) than US Hispanics (0.19), but this difference did not reach statistical significance, p=0.13. Colonic disease was similarly seen in one-third of Latin and US Hispanics, p=0.42. Upper gastrointestinal involvement was infrequently seen in both groups. Overall, there were no statistically significant differences in location of disease between Latin Americans and US Hispanics (table 4).

Disease behavior for CD in Latin Americans versus US Hispanics

Inflammatory behavior (B1) was predominant for Latin America and US Hispanics (0.51) vs (0.64), p=0.24, respectively. Stricturing disease was nearly two times greater in Latin Americans (0.22) than US Hispanics (0.12), but this did not reach statistical significance, p=0.12. Stricturing CD was likely more common in Latin Americans due to less access to biologics. Penetrating disease was similarly seen in one-fourth of patients for both groups, p=0.94. Perianal involvement was also similar with nearly one-third of patients showing this phenotype in both groups, p=0.82 (table 4).

SECONDARY OUTCOMES

Age at IBD diagnosis

Latin Americans

In Latin America, Brazil, Colombia and Peru provided age of IBD diagnosis according to the Montreal Classification. In UC (0.52) and CD (0.58), the predominant age group was between 17 and 40 years. Among US-based studies, age of IBD diagnosis was not stratified according to IBD subtype and could not be determined.

Family history of IBD

Latin Americans

In Latin America, a family history of IBD was infrequent in both UC and CD (0.08) and (0.09), respectively, p=0.85 (table 4). Family history is likely infrequent given that this is a relatively new disease in Latin America. Among studies from the USA, family history data were not provided according to IBD subtype.

Smoking history

Latin Americans

In Latin America, a history of being a former or active smoker was greater in CD than UC, but this did not reach statistical significance (0.35) vs (0.25), respectively, p=0.35. Smoking status for US Hispanics was not stratified by IBD subtype.

Table 1 Summary of ulcerative colitis studies in Latin America

Country	Year	Author	Total	Age at diagnosis (years)	Predominant phenotype (%)	Use of ASA (%)	Use of thiopurines (%)	Use of biologics (%)	Need for surgery (%)	Predominant EIM (%)	Smoking (%)	Family history of IBD (%)
Argentina	2018	Torella	45		64.5% extensive	97.78%	31.11%	15.55%	6.66%		13.56%*	
Argentina	1967	Dolcini	100	59% between 20 and 40	35% extensive				6%	15% arthropathy		
Brazil	2018	Lima Martins	669	49% greater than 40	37.8% left sided	90.30%	62.50%	4.50%				
Brazil	2018	Nobrega	165	38	67% left sided							
Brazil	2017	Arantes	160	46*	40.6% extensive	84.30%	15.70%	10.80%				
Brazil	2017	Santos	152		35.6% extensive							
Brazil	2015	Cesar De Silva	267	39.4	42.7% left sided		19.50%	1.50%	3.40%	34.8% arthropathy	37.50%	7.90%
Brazil	2015	Delmondes	47	46% 31–45	71% distal/proctitis				0%	21% arthropathy	79%	17%
Brazil	2015	Parente	152	35.2*	36% colonic						21.10%	8.60%
Brazil	2011	Kleinubing-Junior	100	42.3*	26% extensive, 26% proctitis	82%	28%	2%				
Brazil	2010	Silva	27	41.0	33.3% colonic 33.3% proctitis				7.4%			
Brazil	2008	Machado de Souza	117	37.5*	44.8% proctosigmoiditis				20.5%		38.2%*	
Brazil	2007	Elia	10	36.7*	50% extensive				10%	40% arthropathy	16.3%*	
Brazil	2007	Lanna	59	40.9	30.5% proctosigmoiditis					38% arthropathy		
Brazil	2002	Souza	118	NA	32.4% proctosigmoiditis	64.70%	5.40%		21.90%	70.6% arthropathy		
Brazil	1991	Teixeira	123	31.6								
Chile	2016	Simian	508	36.9% 30–39	50% extensive	98%	33%	7%	5%	31% arthropathy	24%	12%
Chile	2006	Vergara	64	43.1	46.9% proctosigmoiditis				57.10%	12.5% arthropathy		
Chile	2005	Figueroa	181	48% 20–39*	30% proctosigmoiditis	56%	20%		18%	15% arthropathy		
Chile	1956	Donoso	82	19.5% 21–25	31.6% extensive					4.9% arthropathy, 4.9% dermatologic		
Colombia	2018	Reyes	125	39	46.4% extensive	83.20%	23.20%	16%	4.80%	23,2% arthropathy		
Colombia	2010	Juliao-Baños	163	38.46	45% left-sided colitis	88.30%	27.00%	7.40%	6.90%	18.4% arthropathy	25.10%	3%
Cuba	2016	Garcia	176	41.1	35.8% rectosigmoid	96.60%	4%	1.10%	35.30%	27.3% arthropathy	17.60%	
Mexico	2011	Bosques-Padilla	107	84% 20–59	50% extensive	96%			13%			
Mexico	2009	Yamamoto	848	31.3	59.1% extensive	89.80%	30%	1.17%	10.10%	24.4% arthropathy	8.60%	6.78%
Peru	2016	Paredes-Mendez	81	53.02	47% extensive	98.70%		0%	6.20%	17.3% arthropathy	9.9%%	2.50%

Continued

Table 1 Continued

Country	Year	Author	Total	Age at diagnosis (years)	Predominant phenotype (%)	Use of ASA (%)	Use of thiopurines (%)	Use of biologics (%)	Need for surgery (%)	Predominant EIM (%)	Smoking (%)	Family history of IBD (%)
Peru	2006	Cedron	30	33	36.7% left-sided colitis				3.33%			
Peru	2004	Vera Calderon	43	45	32.6% proctosigmoiditis	100%	9.20%		6.90%	32.5% arthropathy		
Peru	1999	Illescas	45	28.3% 30–39	60% distal	62.2%%			14.80%	4.05% ophthalmopathy		
Puerto Rico	2012	Torres	299	32.6	49.6% extensive				31.90%	19.4% arthropathy	10%	19.30%
Puerto Rico	1989	Moreno	59	27.1% 21–30	55.35% proctosigmoiditis	93.20%			13.50%	5.3% arthropathy, 5.3% pyoderma gangrenosum		
Puerto Rico	1983	Micames	102	22.5% 20–29					21.60%	12.7% arthropathy		
Uruguay	2018	Beatriz lade	59	57.6% 20–44	37.2% extensive				5%		10.4%*	10.4%*
Uruguay	2005	Beatriz-lade	121	30.5% 21–30	39.3% extensive				8.30%			4.10%

*Data for IBD: UC+CD combined.
†Age at diagnosis: mean or median.
ASA, aminosalicylates; CD, Crohn's disease ; EIM, extraintestinal manifestations; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Table 2 Summary of Crohn's disease studies in Latin America

Country	Year	Author	Total CD	Age at diagnosis (years)	Predominant phenotype (%)	Use of ASA (%)	Use of thiopurines (%)	Use of biologics (%)	Need for surgery (%)	Predominant EIM (%)	Smoking (%)	Family history of IBD (%)
Argentina	2018	Torella	14		57.15% colonic	78.57%	42.85%	50%	21.42%		13.56%*	
Brazil	2018	Lima Martins	357	58.3% 17–40	31.4% terminal ileum	70.90%	23.50%	43.40%				
Brazil	2018	Nobrega	141	36	55% colonic							
Brazil	2017	Arantes	208	46†	78.8% colonic	53%	35.30%	53.80%				
Brazil	2017	Santos	252		57.95% ileocolonic							
Brazil	2015	Del Mondes	40	40% 16–30	71% distal				14%	35% arthropathy	92%	28%
Brazil	2015	Parente	100	35.2†	61.2% colonic						21%	16%
Brazil	2013	Barros	179	32.7	26.8% ileocolonic		80.40%	29.60%	34.1%	29.9% arthropathy	19.80%	11.40%
Brazil	2011	Kleinubing-Junior	71	42.3†	47.9% ileocolonic	21.20%	57.70%	9%				
Brazil	2010	Silva	28	39.3	17.9% for each ileal +UGI, coloic, ileocolonic +UGI				29.1%			
Brazil	2010	Torres	90	33	46% ileal			18%	31%	specific EIM not specified	2%	19%
Brazil	2008	Machado de Souza	86	37.5†	58.5% ileal				59.3%		38.2%*	
Brazil	2007	Elia	30	36.7†	60% ileocolonic				44%	41.9% arthropathy	16.3%*	
Brazil	2007	Lanna	71	39.4	35.2% ileocolonic					38% arthropathy		
Brazil	2007	Poli	273	40.3	39.5% ileocolonic	69.60%	60.80%	9.60%	50.7%	64.10%	48.70%	13.20%
Brazil	2007	Santana	65	37.3	39% ileocolonic		43.10%		40%		16.90%	3.10%
Brazil	2004	Faria	100	33.7	50% ileal				50%		40.00%	
Brazil	2002	Souza	126	NA	43.1% small intestine and ileocecal				58%	83.3% arthropathy		
Brazil	1998	Gaburri	60	41.2	40% terminal ileum	80%	55.00%		40%		29.3%	6.70%
Chile	2016	Simian	196	27.6% 20–29	44% colonic	68%	67%	34%	38%	44% arthropathy	33%	10%
Chile	2005	Figueroa	57	48% 20–39†	47% colonic	56%	15.80%		28%	14% arthropathy		
Colombia	2018	Reyes	40	44	52.5% ileocolonic	30%	35%	35%	27.5%	20% arthropathy and 20% aphthous ulcers		
Colombia	2010	Juliao-Baños	202	50% >40	50% ileocolonic	53.30%	40.60%	46.90%	50%	31.3% arthropathy	47.80%	3%
Costa Rica	2016	Campos-Goussen	33	34–44	43% colonic	24%	79%	12%	42%		30%	3%
Cuba	2014	Garcia	80	35.1	45% ileocolonic	100%	6.30%	3.80%	100%	32.5% arthropathy	35%	
Cuba	1995	Jimenez-Mesa	83		59% ileal				80.50%			

Continued

Table 2 Continued

Country	Year	Author	Total CD	Age at diagnosis (years)	Predominant phenotype (%)	Use of ASA (%)	Use of thiopurines (%)	Use of biologics (%)	Need for surgery (%)	Predominant EIM (%)	Smoking (%)	Family history of IBD (%)
Mexico	2015	Yamamoto	132	79.5%<60	44.7% ileocolonic	28%	28%	1.50%	72.70%	19.7% arthropathy	43.20%	1%
Peru	2016	Paredes-Mendez	24	57.7	54.2% ileocolonic	70.80%	12.50%	33.30%	50%	25% arthropathy	8.30%	0%
Peru	2010	Bendano	17	39.9	47% ileocolonic	76.40%	11.80%	5.90%	70.50%	29.4 dermatologic		5.90%
Puerto Rico	2012	Torres	336	26.8	54.4% ileal				51.20%	22.8% arthropathy	13.70%	17.50%
Puerto Rico	1989	Moreno	11	36.3% 0–20 years	90% colonic	54.50%			36.30%	18% arthropathy		
Uruguay	2018	Beatriz lade	8	50% 20–44	62.5% ileal				12.50%		10.4%*	10.4%*
Uruguay	2005	Beatriz lade	48	Median 25, 54.2% between 15 and 29	43% colonic				31%	10.4% arthropathy		10.40%

*Data for IBD: UC and CD combined.
†Age at diagnosis: mean or median.
ASA, aminosalicylates; CD, Crohn's disease; EIM, extraintestinal manifestation; IBD, inflammatory bowel disease; UC, ulcerative colitis ; UGI, upper gastrointestinal.

Medication use

Latin Americans

In UC, steroids were used in nearly two-thirds of patients in Peru (0.65), Argentina (0.67) and Colombia (0.71). 5-Aminosalicylate (5-ASA) products were almost universally used, except in Peru where it was used in three-fourths of patients (0.76). Immunomodulators were used in one-fifth of patients from Brazil (0.20) and Chile (0.22); one-quarter of patients from Colombia (0.26) and Mexico (0.25), and nearly one-third of patients from Argentina (0.31). Colombia and Argentina had the highest use of biologics (0.10) and (0.16), respectively. Biologic use was the lowest in Cuba (0.01), Mexico (0.01), Peru (0.02), and Brazil (0.04) (table 5).

In CD, Argentina had the highest use of steroids (0.86). Steroids were used in nearly two-thirds of patients from Costa Rica (0.64) and Colombia (0.68). 5-ASA products were used in nearly three-quarters of patients from Chile (0.74) and Argentina (0.79) and two-thirds of patients from Peru (0.65) and Brazil (0.68). Immunomodulators were used in nearly one-half of patients from Brazil (0.50) and Chile (0.51); and three-fourths of patients from Costa Rica (0.79). Biologics were used in one-half of patients from Argentina (0.50) and infrequently used in Mexico (0.02) and Cuba (0.04) (table 5).

US Hispanics

In the USA, only one study stratified medication use according to Hispanic ethnicity and IBD subtype[62]; therefore, a pooled analysis for US Hispanics was not conducted.

Surgical outcomes

Latin Americans

In UC, Brazil (0.22), Puerto Rico (0.23) and Cuba (0.35) had the highest rates of need for surgery. In CD, need for surgery was highly prevalent across all Latin American countries but more pronounced in Peru (0.50), Puerto Rico (0.52), Mexico (0.73), and Cuba (0.81).

Latin Americans versus US Hispanics

In UC, surgery was needed in similar proportions in Latin America and US Hispanics (0.15) and (0.19), respectively, p=0.62. In CD, surgery was also needed in similar proportions between Latin America and US Hispanics (0.43) and (0.41), p=0.85, respectively (table 6).

Assessment for heterogeneity

Overall, high levels of heterogeneity occurred across Latin America and the USA. In Latin America, Brazil contained the most population-based and cohort studies (n=20), thus, sensitivity analyses were conducted within this group. A sensitivity analysis was conducted and the common factors that appeared to differentiate these studies were sample size, large effect size, and incomplete phenotype data. Based on these criteria, five studies[45 50 52 55 58] from the UC analysis were removed from the meta-analysis. With this exclusion, heterogeneity was controlled (I^2=0.00%). The same concept was applied when reviewing Brazilian patients with CD. The initial analysis found a high level of heterogeneity (I^2=91.07%). The same five studies were removed from the analysis[45 50 52 55 58] which again controlled

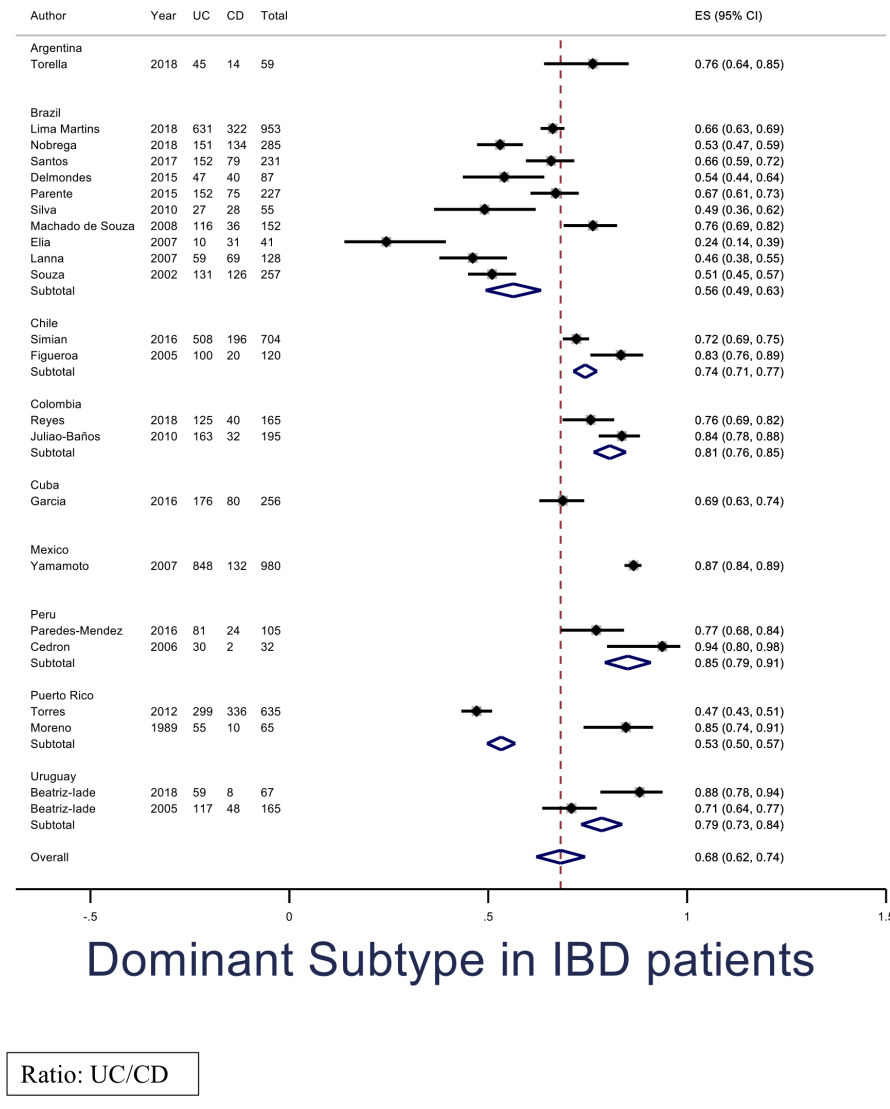

Figure 2 Inflammatory bowel disease (IBD) subtype by Latin American country. CD, Crohn's disease; ES, effect size; UC, ulcerative colitis.

the heterogeneity at I^2=0.00%. While reviewing the US Hispanic UC studies, they again showed a high level of heterogeneity (I^2=92.55%). Using the same selection/exclusion criteria, four studies were removed from the analysis.[62 65–67] With this exclusion, heterogeneity in patients with UC within the USA was reduced to I^2=47.73%. Studies that evaluated CD within the USA were also found to have high levels of heterogeneity (I^2=92.5%). Based on the previous selection/exclusion criteria, five studies were removed from the analysis.[61 62 64–66] With this exclusion, heterogeneity in US Hispanics with CD was controlled (I^2=0.00%). Results remained unchanged after sensitivity analyses.

DISCUSSION

Based on this meta-analysis, we found that the predominant IBD subtype in Latin America is UC; however, we found that Puerto Rico and Brazil had a more balanced UC to CD ratio (1:1). Within Latin America, Argentina and Mexico are more likely to have extensive UC, however, Latin Americans as a whole are less likely to have UC extensive disease as compared with US Hispanics. In UC, extensive colitis is associated with a higher need for biologics, hospitalizations, increased risk of colorectal cancer and higher rates for colectomy.[68] A plausible hypothesis for extensive UC being more common in US Hispanics than Latin Americans may stem from the environmental and dietary triggers found in the USA, which are often absent in Latin America.[4 5 69–71] The implication of this finding is that certain Latin American groups with UC (eg, Argentineans and Mexicans) and US Hispanics may have a more complicated course. This increased risk may serve as a prognostic factor which can aid in clinical decision-making for these cohorts.

We also found notable differences in CD phenotype within Latin American countries. Colonic CD was seen in nearly one-half of patients from Uruguay, Chile, and Puerto Rico, and these cohorts may be at a higher risk for the development of CRC.[72] Aside from colonic CD, there were no statistically significant differences in the location of disease nor disease behavior in Latin America. Latin America as a whole had a predominance of ileocolonic CD which was found to be similar to US Hispanics. Ileocolonic

Table 3 Prevalence rates between Latin American countries

	Argentina	Brazil	Chile	Colombia	Cuba	Mexico	Peru	Puerto Rico	Uruguay	Meta regression
Phenotype	**ES (95% CI)**	**ES (95% CI)**	**ES (95% CI)**	**ES (95% CI)**	**ES (95% CI)**	**ES (95% CI)**	**ES (95% CI)**	**ES (95% CI)**	**ES (95% CI)**	**p value**
Predominant IBD subtype UC/CD*		0.56 (0.49 to 0.63)	0.74 (0.71 to 0.77)	0.81 (0.76 to 0.85)			0.85 (0.79 to 0.91)	0.53 (0.50 to 0.57)	0.79 (0.73 to 0.84)	0.16
E1: Proctitis	0.22 (0.15 to 0.29)	0.34 (0.26 to 0.43)	0.42 (0.21 to 0.63)	0.20 (0.15 to 0.25)		0.17 (0.15 to 0.20)	0.3 (0.11 to 0.49)	0.61 (0.11 to 1.10)	0.36 (0.29 to 0.43)	0.40
E2: Left-sided colitis		0.31 (0.23 to 0.38)	0.15 (0.07 to 0.22)	0.39 (0.34 to 0.45)		0.25 (0.22 to 0.28)	0.36 (0.29 to 0.44)	0.22 (0.18 to 0.26)	0.24 (0.18 to 0.30)	0.18
E3: Extensive colitis	0.67 (0.59 to 0.75)	0.34 (0.30 to 0.38)	0.43 (0.26 to 0.60)	0.40 (0.34 to 0.46)		0.54 (0.51 to 0.57)	0.42 (0.33 to 0.5)	0.23 (-0.10 to 0.54)	0.39 (0.31 to 0.46)	**0.006**
L1: Ileal		0.30 (0.23 to 0.36)	0.25 (0.20 to 0.31)	0.26 (0.16 to 0.36)	0.45 (0.38 to 0.53)		0.22 (0.09 to 0.35)		0.27 (0.16 to 0.39)	0.62
L2: Colonic		0.25 (0.20 to 0.29)	0.46 (0.39 to 0.52)	0.17 (0.09 to 0.26)	0.15 (0.10 to 0.21)		0.27 (0.13 to 0.40)	0.50 (0.45 to 0.55)	0.43 (0.30to 0.56)	**0.002**
L3: Ileocolonic		0.38 (0.32 to 0.44)	0.28 (0.22 to 0.34)	0.51 (0.40 to 0.63)	0.30 (0.23 to 0.37)		0.51 (0.36 to 0.66)			0.99
L4: Upper GI		0.05 (0.03 to 0.07)						0.08 (0.05 to 0.11)		0.98
B1: Inflammatory		0.49 (0.37 to 0.60)		0.48 (0.37 to 0.59)			0.46 (0.31 to 0.61)			0.97
B2: Stricturing		0.20 (0.15 to 0.26)	0.11 (0.07 to 0.15)	0.32 (0.21 to 0.43)			0.29 (0.15 to 0.43)			0.39
B3: Penetrating		0.32 (0.22 to 0.42)	0.10 (0.06 to 0.14)	0.03 (-0.01 to 0.08)			0.24 (0.11 to 0.37)			0.25
Perianal involvement in CD		0.31 (0.02 to 0.38)		0.08 (0.02 to 0.14)			0.27 (0.14 to 0.40)			0.22

p values in bold represent p<0.05.
*Predominant IBD subtype was calculated from studies that reported both UC and CD.
CD, Crohn's disease; ES, effect size; GI, gastrointestinal; UC, ulcerative colitis.

Table 4 Phenotype prevalence between Latin Americans and US Hispanics

Variables	Geographical location	N	ES	95% CI	I^2 (%)	ES p value	Meta regression p value
Predominant IBD subtype UC/CD*	Latin America	23	0.68	0.62 to 0.74	96.55	<0.001	0.38
	US Hispanic	7	0.62	0.48 to 0.75	92.55	<0.001	
EI: Proctitis	Latin America	33	0.37	0.28 to 0.45	98.20	<0.001	0.003
	US Hispanic	6	0.08	0.05 to 0.11	18.06	<0.001	
E2: Left-sided colitis	Latin America	30	0.27	0.23 to 0.32	91.11	<0.001	0.82
	U.S. Hispanic	5	0.26	0.15 to 0.38	82.01	<0.001	
E3: Extensive colitis	Latin America	34	0.38	0.32 to 0.44	95.26	<0.001	<0.001
	US Hispanic	6	0.64	0.52 to 0.77	84.01	<0.001	
LI: Ileal	Latin America	29	0.31	0.26 to 0.36	88.72	<0.001	0.13
	US Hispanic	4	0.19	0.12 to 0.27	51.86	<0.001	
L2: Colonic	Latin America	32	0.30	0.25 to 0.35	88.61	<0.001	0.42
	US Hispanic	6	0.37	0.21 to 0.52	86.67	<0.001	
L3: Ileocolonic	Latin America	28	0.37	0.32 to 0.41	81.77	<0.001	0.88
	US Hispanic	4	0.46	0.31 to 0.61	82.52	<0.001	
L4: Upper GI	Latin America	21	0.06	0.04 to 0.07	76.07	<0.001	
	US Hispanic	4	0.08	0.04 to 0.11	0.00	0.789	
B1: Inflammatory	Latin America	19	0.51	0.41 to 0.60	94.34	<0.001	0.24
	US Hispanic	4	0.64	0.42 to 0.87	91.73	<0.001	
B2: Stricturing	Latin America	20	0.22	0.17 to 0.27	82.82	<0.001	0.12
	US Hispanic	3	0.12	–0.04 to 0.28	–	0.15	
B3: Penetrating	Latin America	22	0.27	0.20 to 0.34	94.46	<0.001	0.94
	US Hispanic	4	0.26	0.20 to 0.32	15.36	<0.001	
Perianal involvement in CD	Latin America	19	0.30	0.24 to 0.36	88.32	<0.001	0.82
	US Hispanic	5	0.29	0.14 to 0.43	82.25	<0.001	
Need for surgery in UC	Latin America	24	0.15	0.11 to 0.19	92.76	<0.001	0.62
	US Hispanic	4	0.19	0.09 to 0.28	60.66	<0.001	
Need for surgery in CD	Latin America	23	0.43	0.34 to 0.51	94.78	<0.001	0.85
	US Hispanic	3	0.41	0.30 to 0.52	–	<0.001	
Latin America							
Age of diagnosis†							
A1 (<17)	Ulcerative colitis	3	0.04	0.02 to 0.05	–	<0.001	–
A2 (17–40)	Ulcerative colitis	3	0.52	0.46 to 0.59	–	<0.001	–
A3 (>40)	Ulcerative colitis	3	0.44	0.36 to 0.51	–	<0.001	–
A1 (<17)	Crohn's disease	9	0.07	0.05 to 0.09	20.50	<0.001	–
A2 (17–40)	Crohn's disease	9	0.58	0.52 to 0.64	68.53	<0.001	–
A3 (>40)	Crohn's disease	9	0.35	0.29 to 0.41	72.71	<0.001	–
Family history of IBD†	Ulcerative colitis	10	0.08	0.05 to 0.11	85.36	<0.001	0.85
	Crohn's disease	13	0.09	0.05 to 0.13	90.11	<0.001	
Smoking status (former/current smoker)†	Ulcerative colitis	9	0.25	0.16 to 0.34	97.07	<0.001	0.35
	Crohn's disease	13	0.35	0.23 to 0.47	96.95	<0.001	

p values in bold represent p<0.05.
*Predominant IBD subtype was calculated from studies that reported both UC and CD.
†Age of IBD diagnosis, family history and smoking status were only calculated for the Latin American group.
CD, Crohn's disease; ES, effect size; GI, gastrointestinal; IBD, inflammatory bowel disease; N, number of studies; UC, ulcerative colitis.

CD has also been found to be the predominant CD disease location in Caucasians, Asians and African Americans.[73] While CD was overall less common in Latin America, it initially appears to carry the same disease behavior as US Hispanics. However, a confounding factor is that disease modifying drugs (eg, biologics) are not readily accessible in Latin America as compared with the USA.[74]

In Latin America, there was wide use of 5-ASA products in CD despite their questionable efficacy in inducing and maintaining remission.[75] Biologics were used in 5% of patients with UC and 25% of patients with CD. In contrast, between the years of 2007 and 2015, the USA has increased biologic use from 5.1% to 16.2% in UC and from 21.8% to 43.8% in CD.[76] A likely reason for the disparity in the use of biologics between the USA and Latin America is the cost, which has been estimated to be $41,109 per year.[76] Private insurance companies in Brazil, Mexico and Argentina do not cover biologics or biosimilars.[74] In our meta-analysis, we found that within Latin America, biologic use was inversely proportional to need for surgery in both UC (eg, Cuba,

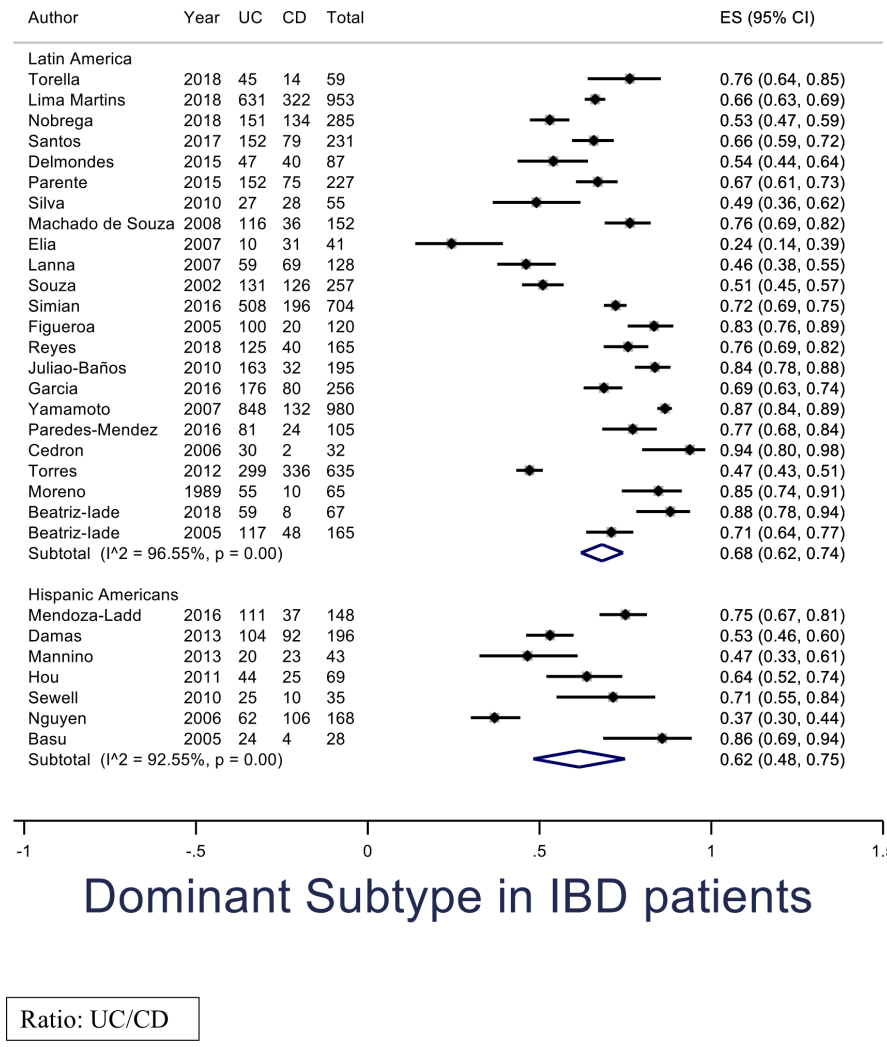

Figure 3 Inflammatory bowel disease (IBD) subtype: Latin America vs USA. CD, Crohn's disease; ES, effect size; UC, ulcerative colitis.

Brazil) and CD (eg, Mexico, Cuba). We hypothesize that a subset of IBD Latin American patients with moderate to severe disease are living with suboptimal controlled disease due to lack of access to biologics. However, Latin America as a whole had similar surgical outcomes in both UC and CD when compared with US Hispanics. It is conceivable that with greater biologic use in Latin America, the surgical outcomes would have been better in the Latin American group.[77] More importantly, the low access to biologics seen in Latin America should raise a public health concern. While biologics have been shown to improve outcomes in IBD,[77] the costs associated with them make them highly inaccessible to a poorer Latin America healthcare system.[78]

In Latin America, the predominant age of diagnosis was between 17 and 40 years for both UC and CD. This is similar to the age of IBD diagnosis seen in the Caucasian population.[79] However, the time lag between symptom onset and IBD diagnosis could not be answered with this meta-analysis and it could be a confounder if Latin Americans are having delays in diagnoses. Among Latin Americans, the presence of a family history of IBD was infrequent in both UC 8% and CD 9%, whereas a recent systematic review estimated the proportion to be 12% in Caucasians.[73] It is plausible that IBD in Latin Americans and US Hispanics is driven primarily by environmental factors rather than genetics, as a positive family history of IBD was infrequent in this meta-analysis. In our previous meta-analysis, we also found that a family history of IBD was less frequently seen in US Hispanics as compared with non-Hispanic whites.[11] Smoking habits (current/former smoker) were greater in Latin American patients with CD as compared with patients with UC, but this did not reach significance.

A strength of this meta-analysis is we analyzed the Latin American population per country which allowed us to bring out differences within Latin America. We also compared Latin Americans as a whole as compared with US Hispanics. This has not been previously done. Limitations of this meta-analysis include the high degree of heterogeneity seen across the Latin American countries. We were able to determine certain factors that increased heterogeneity which were sample size, large effect size, and a few studies had incomplete phenotype descriptors. After the sensitivity analysis, the heterogeneity was reduced. Other potential contributors to heterogeneity include variations in environmental exposures, and the admixed background of Latin Americans. There are focal concentrations of European ancestry

Table 5 Medication use in Latin America

	Ulcerative colitis			Crohn's disease		
Country	**I^2 (%)**	**ES**	**95% CI**	**I^2 (%)**	**ES**	**95% CI**
Steroids						
Brazil		0.46	(0.09 to 0.82)	96.76	0.49	(0.29 to 0.69)
Peru		0.65	(0.29 to 1.00)		0.73	(0.60 to 0.86)
Mexico		0.33	(0.30 to 0.36)		0.22	(0.16 to 0.30)
Costa Rica					0.64	(0.47 to 0.78)
Argentina		0.67	(0.52 to 0.79)		0.86	(0.60 to 0.96)
Chile		0.52	(0.48 to 0.55)		0.61	(0.55 to 0.67)
Cuba		0.12	(0.08 to 0.18)		0.13	(0.07 to 0.22)
Colombia		0.71	(0.66 to 0.76)		0.68	(0.59 to 0.77)
Puerto Rico		0.53	(0.40 to 0.65)		0.45	(0.21 to 0.72)
Overall	97.9	0.51	(0.39 to 0.63)	96.46	0.52	(0.39 to 0.65)
5-Aminosalicylates						
Brazil		0.84	(0.75 to 0.94)	98.62	0.68	(0.47 to 0.89)
Peru		0.76	(0.52 to 1.00)		0.65	(0.51 to 0.79)
Mexico		0.91	(0.90 to 0.93)		0.28	(0.21 to 0.36)
Costa Rica					0.24	(0.13 to 0.41)
Argentina		0.98	(0.88 to 1.00)		0.79	(0.52 to 0.92)
Chile		0.97	(0.96 to 0.98)		0.74	(0.69 to 0.79)
Cuba		0.97	(0.93 to 0.98)		*	*
Colombia		0.86	(0.83 to 0.90)		0.39	(0.28 to 0.50)
Puerto Rico		0.93	(0.84 to 0.97)		0.55	(0.28 to 0.79)
Overall	93.01	0.88	(0.85 to 0.92)	97.79	0.60	(0.46 to 0.73)
Immunomodulators						
Brazil	14.56	0.20	(0.18 to 0.23)	97.97	0.50	(0.32 to 0.68)
Peru		0.10	(0.05 to 0.18)		0.10	(0.01 to 0.19)
Mexico		0.25	(0.23 to 0.28)		0.29	(0.22 to 0.37)
Costa Rica					0.79	(0.62 to 0.89)
Argentina		0.31	(0.20 to 0.46)		0.43	(0.21 to 0.67)
Chile		0.22	(0.19 to 0.24)		0.51	(0.45 to 0.56)
Cuba		0.05	(0.02 to 0.09)		0.06	(0.03 to 0.14)
Colombia		0.26	(0.21 to 0.31)		0.37	(0.26 to 0.49)
Puerto Rico		*	*		*	*
Overall	94.19	0.20	(0.15 to 0.26)	97.96	0.41	(0.27 to 0.55)
Biologics						
Brazil	86.04	0.04	(0.01 to 0.07)	97.93	0.25	(0.10 to 0.41)
Peru		0.02	(0.01 to 0.09)		0.13	(0.03 to 0.23)
Mexico		0.01	(0.01 to 0.02)		0.02	(0.00 to 0.05)
Costa Rica		*	–		0.12	(0.05 to 0.27)
Argentina		0.16	(0.08 to 0.29)		0.50	(0.27 to 0.73)
Chile		0.07	(0.05 to 0.09)		0.34	(0.28 to 0.41)
Cuba		0.01	(0.00 to 0.04)		0.04	(0.01 to 0.10)
Colombia		0.10	(0.06 to 0.13)		0.40	(0.29 to 0.51)
Puerto Rico		*	*–		*	*
Overall	87.63	0.05	(0.03 to 0.07)	97.45	0.24	(0.15 to 0.34)

*I^2 could not be calculated if less than two studies were reported for that outcome
ES, effect size

in certain parts of Brazil[80 81] and more widespread predominance of European ancestry in countries like Uruguay[82] and Argentina.[83] In contrast, countries such as Peru and Mexico have a predominant indigenous population.[84] In addition, the number of published studies were variable per country, and this may have created a selection bias; however, we accounted for this by searching for unpublished articles. The US studies were also not stratified according to first-generation or second-generation Hispanic but this was not feasible as only one study performed this stratification in the USA.[61] The US studies also did not differentiate between Latin American Hispanics as compared Hispanics from Spain. This is unlikely to have affected the results as Spaniards only make up 1.3% of the total Spanish-speaking

Table 6 (a) Need for surgery among patients with UC and CD: Latin Americans vs US Hispanics. (b) Need for surgery among patients with UC and CD in Latin American countries

(a)

	Ulcerative colitis				Crohn's disease			
Group	I^2 (%)	ES	95% CI	Meta regression p value	I^2 (%)	ES	95% CI	Meta regression p value
Latin America	92.76	0.15	(0.11 to 0.19)	0.62	94.80	0.43	(0.34 to 0.51)	0.85
US Hispanics	60.66	0.19	(0.09 to 0.28)		0.00	0.41	(0.30 to 0.52)	
Overall	91.94	0.16	(0.12 to 0.19)		94.10	0.42	(0.34 to 0.51)	

(b)

	Ulcerative colitis			Crohn's disease		
Group	I^2 (%)	ES	95% CI	I^2 (%)	ES	95% CI
Brazil	95.61	0.22	(0.08 to 0.35)	95.48	0.42	(0.29 to 0.55)
Uruguay		0.07	(0.03 to 0.11)		0.27	(0.15 to 0.38)
Peru		0.09	(0.04 to 0.13)		0.50	(0.31 to 0.69)
Mexico		0.11	(0.09 to 0.13)		0.73	(0.65 to 0.80)
Costa Rica		–	–		0.42	(0.27 to 0.59)
Argentina		0.06	(0.02 to 0.10)		0.21	(0.08 to 0.48)
Chile		0.11	(0.02 to 0.20)		0.36	(0.30 to 0.42)
Cuba		0.35	(0.29 to 0.43)		0.81	(0.71 to 0.88)
Colombia		0.05	(0.03 to 0.08)		0.36	(0.25 to 0.47)
Puerto Rico		0.23	(0.12 to 0.34)		0.52	(0.47 to 0.58)
Overall	92.76	0.15	(0.11 to 0.19)	94.78	0.43	(0.34 to 0.51)

CD, Crohn's disease; ES, effect size; UC, ulcerative colitis.

population in the USA.[85] While there are dietary and environmental variations within Latin America, these components are often balanced via meta-analysis.

CONCLUSION

Hispanics in Latin America have a predominance of UC over CD, except in Brazil and Puerto Rico, where the UC:CD ratio is more evenly balanced. Countries such as Argentina and Mexico are more likely to have extensive UC, but US Hispanics as a whole are more likely to have extensive UC than Latin Americans. CD colonic disease is more likely to affect Uruguay, Chile, and Puerto Rico but Latin Americans as a whole have a similar CD phenotype when compared with US Hispanics. There is great variability in the use of biologics in Latin America and many countries with low access to biologics have a higher need for surgery. Future studies should be aimed at studying the genetic and environmental factors accounting for the phenotypic differences in Latin Americans and US Hispanics.

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