

Epidemiology and temporal trends (2000–2012) of inflammatory bowel disease in adult patients in a central region of Spain

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Background and aim A growing incidence of inflammatory bowel disease (IBD) has been reported recently in southern Europe, with records of pediatric cases confirming these tendencies in Spain. Data on adult populations, however, have not been provided for over 10 years and need to be updated.

Patients and methods A multicenter retrospective registry of all adult patients with a diagnosis of IBD, including both Crohn's disease (CD) and ulcerative colitis (UC), attending five public hospitals covering a population of 514 368 inhabitants, was assessed.

Results In 2012, the prevalence of CD and UC in adults was 137.17/100 000 inhabitants (95% confidence interval 114–160) and 99.84/100 000 inhabitants (95% confidence interval 79–119), respectively. The mean incidence rate during the period 2000–2012 of CD and UC was 8.9 and 5.6/100 000 inhabitants per year, respectively. Most of our patients (75.55%) had been diagnosed during the last 13 years. CD affected both sexes equally; a trend toward a progressive increase in the age at diagnosis, ileal location, and inflammatory behavior was documented for CD patients. In contrast, UC affected male patients with a higher frequency (57.8%; $P = 0.015$), specifically those older

than 40 years of age. Age at UC onset tended to increase progressively from 2000 to 2012 ($P < 0.001$), but the extension on the disease remained unchanged.

Conclusion IBD is a highly prevalent disorder in our region, reaching the incidence of CD similar to the figures provided for Northern Europe. Changes in IBD localization, behavior, and age at diagnosis were documented during the period 2000–2012. *Eur J Gastroenterol Hepatol* 26:1399–1407
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European Journal of Gastroenterology & Hepatology 2014, 26:1399–1407

Keywords: burden of disease, Crohn's disease, epidemiology, incidence, inflammatory bowel disease, prevalence, Spain, temporal trends, ulcerative colitis

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Received 7 August 2014 Accepted 11 September 2014

Introduction

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as inflammatory bowel diseases (IBDs), are idiopathic chronic inflammatory disorders that affect different segments of the gastrointestinal tract. The reported epidemiology of IBD has increased markedly worldwide during the last decades. The geographical incidence varies widely, and the highest incidence figures for IBD have traditionally been found in western industrialized nations, including the northern parts of North America [1] and Europe [2,3]. However, an increasing incidence in the epidemiology of IBD worldwide is being observed, which now also affects developing countries as they become more developed and 'westernized' [4].

In Europe, there is significant evidence showing that incidence has increased in the southern region and other

Mediterranean countries [5]. An east–west gradient in IBD incidences has also been reported recently for Europe, where the incidences of both CD and UC were at least two-fold in all Western European Centers [6].

Recent studies, particularly for Spain, have clearly documented incidence trends in pediatric IBD [7,8] equivalent to the ones observed in Scandinavian countries, although the prevalence was markedly lower. The incidence of adult IBD in Spain has also been shown to increase over time [6,9–11], especially CD [6,12], with a prevalence of CD and UC that has been estimated in 87.5 and 110/100 000 inhabitants, respectively [13]. As there have been no studies in the last 10 years, current time trends for IBD in adult patients remain unknown.

Considering the high burden of IBD to the public health system [14], it is necessary that the incidence and prevalence estimates for IBD be updated to inform health

policies on the allocation of resources and provision of health services for affected individuals.

Objective

This study has two main objectives: (i) to estimate the current prevalence and incidence rates of IBD in central Spain, and (ii) to examine recent trends in disease prevalence. A further goal was to characterize changes in disease presentation over time.

Patients and methods

This is a collaborative, retrospective, multicenter study planned and carried out within the Ciudad Real province IBD working group, which represents all the adult IBD units in the region.

Study setting

The recruitment area for this study included five different public hospitals located in the Ciudad Real province, in the center of Spain, in the autonomous region of Castilla-La Mancha. The study areas are predominantly rural, with an overall reference population of roughly 514 368 inhabitants, of whom 402 369 (78.2%) are at least 16 years of age (average data from 2000 to 2012). No relevant demographic changes were noted in our region during the study period (with an average annual increase in 4849 inhabitants), the increase in the mean population age being 2.35 years in that period.

These hospitals are exclusive in their respective areas and offer universal coverage for adult specialist gastroenterology services as no additional private gastroenterology, endoscopy, or pathology clinics exist. The IBD units of these hospitals are considered referral centers for adult IBD patients in each area, and experienced gastroenterologists have been using commonly accepted diagnostic procedures and criteria during the entire study period.

Study design and data source

A population-based, multicenter retrospective study based on a registry of IBD patients cared for in the reference hospitals of our region was developed.

A diagnosis of IBD was made according to standard clinical, endoscopic, histological, and radiological criteria [15–17]. Patients' data at the time of diagnosis were obtained from the private databases of the different hospitals.

To accurately estimate the incidence and prevalence figures in our region, all consecutive patients who were actively cared for in the IBD units or gastroenterology facilities of the participating hospitals over a 1.5-year period were included in the registry. All participating physicians at the different recruiting centers were provided with a computerized database and written instructions on how to include new registries. Only adult (≥ 16 years old) IBD patients who were followed at the end of 2012 in the adult gastroenterology department

were considered to provide the most reliable data, irrespective of the age at which IBD was diagnosed.

Every patient was identified in the registry with consecutive numbers, the patient's initials, and their date of birth. The epidemiological and clinical data at the time of diagnosis were obtained, which included age, sex, place of birth, current residence, data and hospital of diagnosis, type and location of the disease according to the Montreal classification system, smoking habit at diagnosis, and presence of complication from disease onset. The database was screened to avoid duplicated data, and an overlapping follow-up by different hospitals was excluded.

Statistical analyses

Results for continuous variables were expressed as mean and SD of medians and interquartile range; qualitative variables are presented as absolute and relative frequencies.

The reference population data of the area covered by every hospital and individual locations were obtained from the Instituto Nacional de Estadística (INE; National Institute of Statistics) (<http://www.ine.es>) for the entire 12-year study period.

The prevalence was estimated as the proportion of adult individuals with each disease diagnosed by 31 December 2012 along with a confidence interval (CI) of 95%.

We compared the qualitative variables using the χ^2 -test (Fisher's exact test, where appropriate) or the Mann–Whitney *U*-test to compare quantitative variables. CIs were estimated using the exact (binomial) method, on the basis of the Poisson distribution. A 0.05 significance level was used throughout.

Analyses and summaries were carried out using the PASW statistical program (version 18.0; SPSS Inc., Chicago, Illinois, USA) and EPIDAT (version 3.1) (Dirección Xeral de Innovación e Xestión da Saúde Pública, Xunta de Galicia, Spain).

Ethical considerations

The individual registries supporting this study were approved by the local ethics or research committees at the participating centers.

Results

Data from a total of 1047 adult patients diagnosed with IBD and actively cared for in our IBD or gastroenterology facilities were included in the IBD registry (Table 1). This represented 599 (57.21%) patients with CD, 436 (41.64%) with UC, and 12 (1.15%) with undetermined type IBD (IBDU), overall representing an average prevalence for IBD of 0.26%.

From 2000 to 2012, 791 new patients were diagnosed: 482 (60.94%) CD, 300 (37.93%) UC, and nine (1.14%) IBDU. This assumes that 75.55% of IBD patients from our region who are being actively attended to in our hospitals were diagnosed during the last 13 years. Demographics and the

Table 1 Cases of inflammatory bowel disease, including Crohn's disease and ulcerative colitis, diagnosed in centers participating in the study

Hospitals	n (%)								
	IBD	IBD		CD	CD		UC	UC	
		Before 2000	After 2000		Before 2000	After 2000		Before 2000	After 2000
Hospital Universitario de Ciudad Real	320 (30.6)	87 (27.2)	233 (72.8)	192 (32.1)	39 (20.3)	153 (79.7)	126 (28.9)	47 (37.3)	79 (62.7)
Hospital General Mancha Centro	248 (23.7)	60 (24.2)	188 (75.8)	152 (25.4)	36 (23.7)	116 (76.3)	92 (21.1)	23 (25)	69 (75)
Hospital General de Tomelloso	206 (19.7)	42 (20.4)	164 (79.6)	119 (19.9)	20 (16.8)	99 (83.2)	81 (18.6)	21 (25.9)	60 (74.1)
Hospital Santa Bárbara de Puertollano	148 (14.1)	44 (29.7)	104 (70.3)	65 (10.9)	15 (23.1)	50 (76.9)	83 (19)	29 (34.9)	54 (65.1)
Hospital Virgen de Altagracia	125 (11.9)	23 (18.4)	102 (81.6)	71 (11.9)	7 (9.86)	64 (90.1)	54 (29.6)	16 (29.6)	38 (70.4)
Total	1047	256 (24.5)	791 (75.5)	599	117 (19.5)	482 (80.5)	436	136 (31.2)	300 (68.8)

Proportions in columns 'IBD', 'CD', and 'UC' refer to the contribution of each center toward the complete registry of cases. Proportions in column 'before 2000' and 'after 2000' refer to cases within any participant center.

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

clinical characteristics of the patients are shown in Table 2. A trend toward a progressive increase in the incidence of IBD was documented over the 2000–2012 period, specifically at the expense of CD (Table 3).

Descriptive epidemiology and temporary trends for Crohn's disease

The mean annual incidence of CD in our study group was 8.9/100 000/year (95% CI 8.1–9.8), age adjusted for the province population for each corresponding year (Fig. 1). The entire prevalence for CD in the region was 137.17/100 000 inhabitants (142.16 among men and 132.26 in women; $P=0.920$).

Age (A) at diagnosis

Considering the entire series of patients, CD affected both sexes equally, including 308 (51.42%) men and 291 (48.58%) women. Age at diagnosis was 35.9 ± 16.7 years (range 5–87 years). Age groups at diagnosis in our entire series were as follows: A1 (≤ 16 years old), 8.4% of patients; A2 (between 17 and 40 years old), 59.2% of patients; and A3 (disease onset > 40 years old), 32.4% of patients (Table 2). To analyze the temporal trend in the age of presentation of CD with the lowest risk of bias, only data of patients diagnosed in the period 2000–2012 were considered: age at diagnosis of CD showed a trend to increase progressively during the last 13 years [from 30.9 (13.6) to 37 (17.1) years old; $P < 0.001$] (Fig. 2a).

Table 2 Demographics and clinical characteristics of patients with inflammatory bowel disease in the Ciudad Real province area

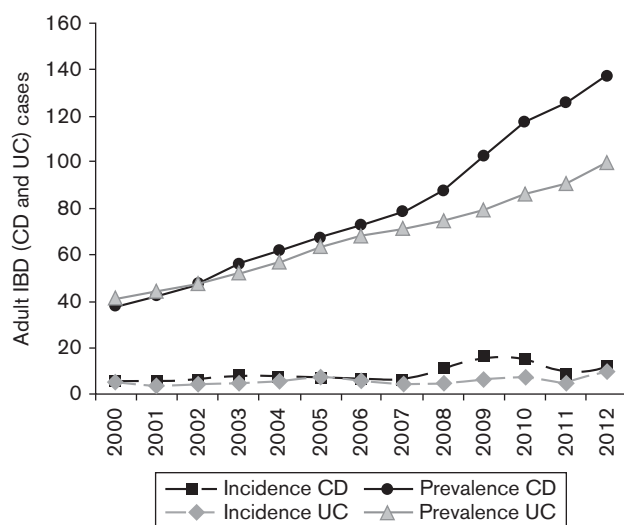
	n (%)			
	All IBD	Crohn's disease	Ulcerative colitis	IBD type undetermined
N	1047	599	436	12
Age [mean (SD) (range)]	38.8 (17) (5–87)	35.9 (16.7) (5–87)	42.4 (16.6) (5–83)	52.4 (16.9) (13–74)
Sex (male/female)	565 (54)/482 (46)	308 (51.4)/291 (48.6)	252 (57.8)/184 (42.2)	5 (41.74)/7 (58.3)
Age at diagnosis (A)				
A1	65 (6.3)	49 (8.4)	15 (3.5)	1 (8.3)
A2	554 (54)	347 (59.2)	206 (48.2)	1 (8.3)
A3	406 (39.6)	190 (32.4)	206 (48.2)	10 (83.3)
Disease location (L)				
L1	–	186 (35.7)	–	–
L2	–	126 (24.2)	–	–
L3	–	205 (39.3)	–	–
L4	–	4 (0.8)	–	–
Disease behavior (B)				
B1	–	387 (64.5)	–	–
B2	–	140 (23.4)	–	–
B3	–	72 (12)	–	–
Disease extension (E)				
E1	–	–	76 (20.2)	–
E2	–	–	176 (46.7)	–
E3	–	–	125 (33.2)	–
Complications at diagnosis	190 (18.2)	136 (22.8)	53 (12.2)	1 (8.3)
Year of diagnosis				
Before 2000	256 (24.5)	117 (19.5)	136 (31.2)	3 (25)
After 2000	791 (75)	482 (80.5)	300 (68.8)	9 (75)

A1, ≤ 16 years old; A2, between 17 and 40 years; A3, > 40 years old; B1, inflammatory behavior disease; B2, stricturing disease; B3, penetrating disease; E1, ulcerative proctitis; E2, left-sided ulcerative colitis; E3, extensive ulcerative colitis; L1, ileal disease; L2, colonic disease; L3, ileocolonic disease; L4, isolated upper disease. IBD, inflammatory bowel disease.

Table 3 Annual incidences (cases/100 000 inhabitants/year) for the period 2000–2012 and cumulative prevalences (cases/100 000 inhabitants) for inflammatory bowel disease, including Crohn's disease, ulcerative colitis, and unclassified-type IBD at the Ciudad Real province (Spain)

Years	Population	IBD			CD			UC			UIBD		
		Cases	Incidence	Prevalence	Cases	Incidence	Prevalence	Cases	Incidence	Prevalence	Cases	Incidence	Prevalence
Before 2000	371 512	256	–	68.91	117	–	31.49	136	–	36.61	3	–	0.81
2000	373 645	42	11.24	79.75	22	5.89	37.20	19	5.09	41.48	1	0.27	1.07
2001	378 476	35	9.25	87.98	21	5.55	42.27	13	3.43	44.39	1	0.26	1.32
2002	384 834	41	10.65	97.18	24	6.24	47.81	17	4.42	48.07	0	0.00	1.30
2003	390 017	52	13.33	109.23	34	8.72	55.89	18	4.62	52.05	0	0.00	1.28
2004	396 629	53	13.36	120.77	28	7.06	62.02	23	5.80	56.98	2	0.50	1.76
2005	404 616	58	14.33	132.72	27	6.67	67.47	31	7.66	63.52	0	0.00	1.73
2006	411 259	50	12.16	142.73	27	6.57	72.95	23	5.59	68.08	0	0.00	1.70
2007	416 111	44	10.57	151.64	26	6.25	78.34	17	4.09	71.38	1	0.24	1.92
2008	426 712	69	16.17	164.04	48	11.25	87.65	21	4.92	74.52	0	0.00	1.87
2009	432 246	96	22.21	184.15	70	16.19	102.72	26	6.02	79.58	0	0.00	1.85
2010	434 363	98	22.56	205.82	66	15.19	117.41	31	7.14	86.33	1	0.23	2.07
2011	435 692	58	13.31	218.50	37	8.49	125.55	20	4.59	90.66	1	0.23	2.30
2012	436 679	95	21.76	239.76	52	11.91	137.17	41	9.39	99.84	2	0.46	2.75
(95% CI)				(225–254)			(114–160)			(79–119)			(2.2–3.3)
Mean	402 369.3	1047	14.69		599	8.92		436	5.60		12	0.17	
(95% CI)			(14.3–15.1)			(8.1–9.8)			(4.9–6.2)			(0.16–0.19)	

CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis; UIBD, unclassified-type inflammatory bowel disease.

Fig. 1

Diagnostic incidence and prevalence of IBD per 100 000 adult inhabitants per year in a central region of Spain during the period 2000–2012. CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Disease location (L)

Considering our overall CD population, an ileal disease (L1) was present in 186 (35.7%) of patients at the time of diagnosis; in 126 (24.2%) patients, CD presented with a colonic involvement (L2) at the onset. An ileocolonic disease was diagnosed in 205 (39.3%) patients and exclusive isolated upper CD (L4) was diagnosed in four (0.8%) patients. In addition, an upper disease involvement was also found in 19.9% of L1 patients, in 3.2% of

L2 patients, and in 11.7% of L3 patients (Table 2). During the 2000–2012 study period, a cumulative trend toward a progressive increase in the proportion of L1 patients (from 30.6 to 37%) was documented, but did not show statistical significance ($P=0.582$) (Fig. 2b).

Disease behavior (B) at the time of diagnosis

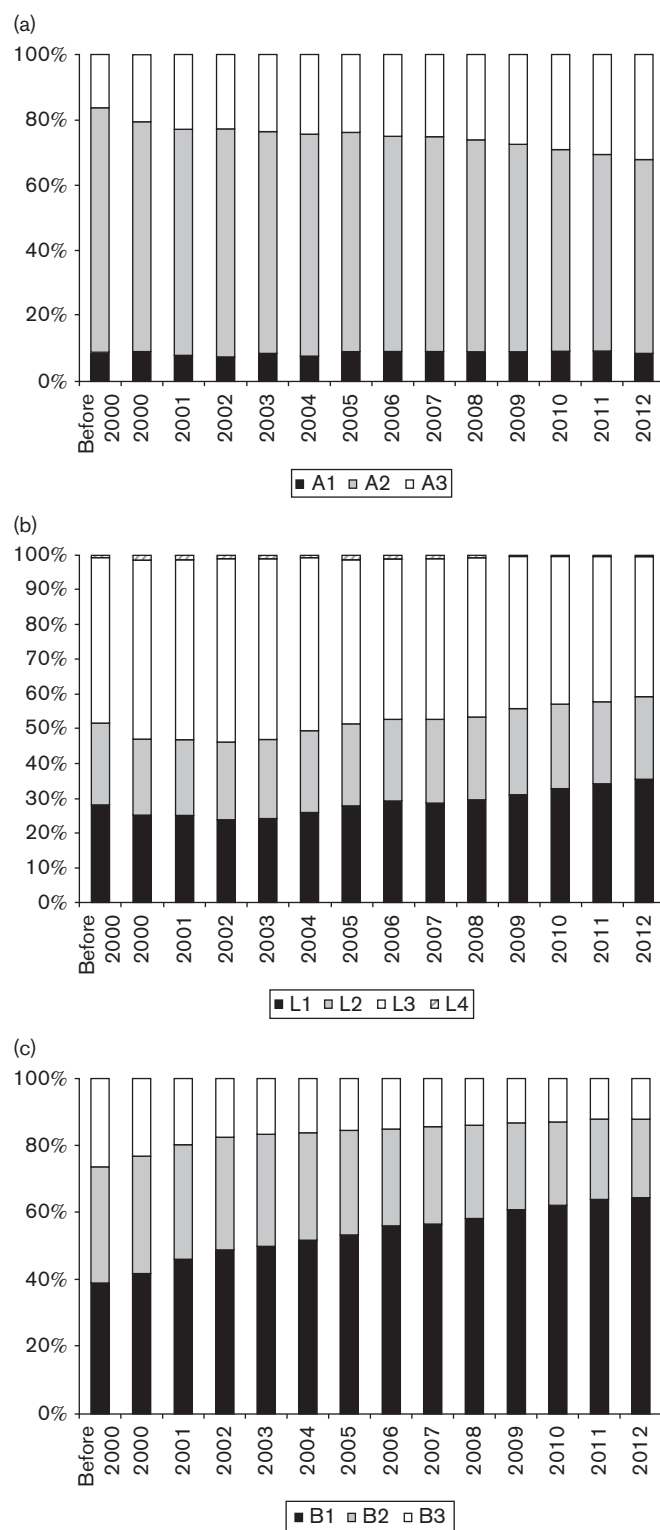
In terms of the pattern of the disease at the time of onset, most patients (387, 64.5%) presented an inflammatory (B1) (i.e. nonstricturing, nonpenetrating) pattern; 140 (23.4%) patients had a stricturing disease (B2) and the remaining 72 (12%) had a penetrating disease (B3) (Table 2). During the study period 2000–2012, a change in the behavior of the disease toward a progressive increase of a B1 pattern was documented (Fig. 2c).

Descriptive epidemiology and temporary trends for ulcerative colitis

For UC, the mean annual incidence was 5.6/100 000/year (95% CI 4.9–6.2), and the overall prevalence of UC in our region was 99.84/100 000 inhabitants (115.39 in men and 84.54 in women; $P=0.015$). The demographic and clinical data of UC patients are shown in Table 2).

In the overall IBD population from our province, UC was more frequently diagnosed among male (252, 57.8%) compared with female (184, 42.2%) patients ($P=0.042$). To ensure the most reliable estimation, the incidence of UC was calculated for the last 13 years: the mean incidence rates in men and women were 6.7 and 4.5 cases/100 000 inhabitants/year, respectively ($P=0.002$), during the period 2000–2012.

Fig. 2



Annual relative (over 100%) cumulative incidence for clinical characteristics of Crohn's disease (CD) cases newly diagnosed in a central region of Spain during the period 2000–2012. (a) Cumulative trends of age at CD diagnosis according to the Montreal classification system (A1, ≤ 16 years old; A2, between 17 and 40; and A3, disease onset > 40 years old); (b) cumulative trends for disease location (L1, an ileal disease; L2, colonic involvement; B3, ileocolonic disease; and L4, an isolated upper CD); and (c) cumulative trends for disease behavior (B1, an inflammatory – i.e. nonstricturing, nonpenetrating – pattern; B2, a stricturing disease; and B3, a penetrating disease).

Age (A) of patients at diagnosis

The mean age of UC adult patients at diagnosis in our entire IBD series was significantly older than for CD, being 42.4 ± 16.6 years (range 5–83 years) versus 35.9 ± 16.7 years (range 5–87 years), respectively ($P < 0.001$). The disease was diagnosed before 16 years of age in only 3.5% of patients (A1); 48.2% of UC patients were diagnosed between 17 and 40 (A2) years of age and in the remaining 48.2% patients, UC was diagnosed when they were older than 40 years of age (A3).

The temporary trends during the last 13 years for age at UC onset were characterized by a progressive increase in the age of UC patients in its onset when the cumulative prevalences in the 2000–2012 period were analyzed, from 36.9 ± 13.6 to 44.7 ± 17.3 ($P < 0.001$) (Fig. 3a).

Disease extension (E)

Ulcerative proctitis (E1) was present in 20.2% of patients. A left-sided UC (with disease involvement limited to the colorectal segment distal to the splenic flexure or E2) was documented at the time of diagnosis in 46.7% of patients and, finally, an extensive (E3) UC, with a disease extending past the splenic flexure, was documented in 33.1% of patients.

The proportions of E1, E2, and E3 extensions in UC patients were maintained with no significant changes during the 2000–2012 study period (Fig. 3b).

Smoking habits in inflammatory bowel disease patients at diagnosis

Almost half of the CD patients (49.6%) were nonsmokers when diagnosed, 10.8% were past smokers (at least 6 months of habit discontinuation), and the remaining

36.6% were active smokers at disease onset. Among patients with UC, 68.1% were nonsmokers at the time of diagnosis, 15.5% were active smokers, and 16.4% smoked at least up to 6 months before the onset of the disease.

Complications and extraintestinal manifestations documented in inflammatory bowel disease patients at disease onset

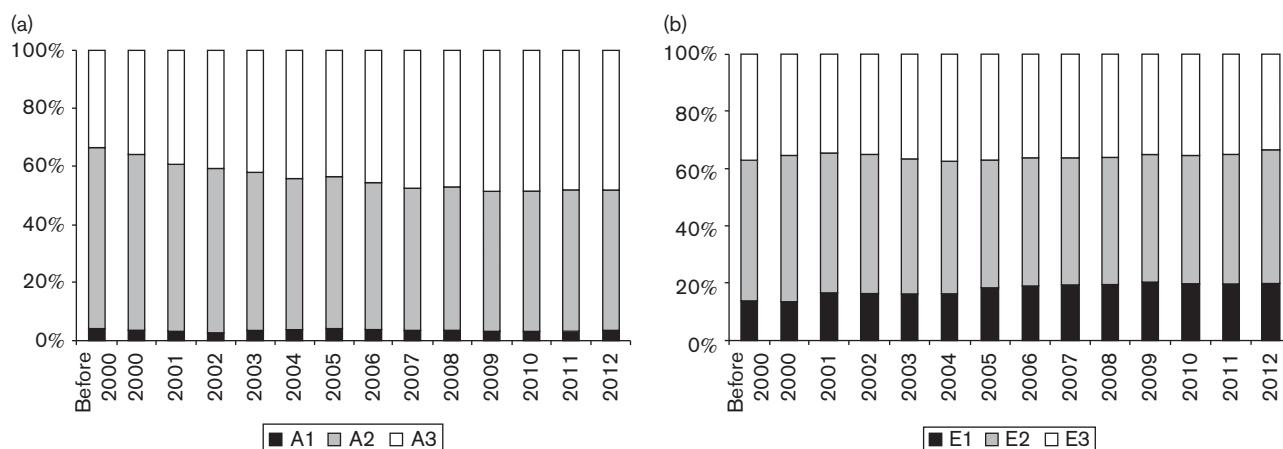
The presence of any kind of complication (including pelvic/perirectal abscesses, ocular disease, skin disorders, osteoarticular manifestations, and venous thromboembolic disease) at the time of IBD diagnosis was documented in 22.8% of CD and 12.2% of UC patients, respectively (Table 4). The prevalence of complications associated with IBD did not alter significantly during 2000–2012, with the exception of pelvic/perirectal abscesses in CD patients, which reduced from 13.6 to 6.3% ($P = 0.01$).

No significant relationship was observed between smoking (active or past habit) and the presence of complications at the time of CD diagnosis. Smokers, however, showed more complications at diagnosis than nonsmokers (30.5 vs. 25%, respectively; $P = 0.239$). In UC, an inverse association between smoking at diagnosis and a complicated disease at the onset was documented (14.5% in smokers vs. 20.4% in nonsmokers), which did not reach statistical significance ($P = 0.275$).

Discussion

The main finding of our study carried out in a central region of Spain is the significant increase over the last decade in the overall incidence of IBD in terms of the figures provided by previous studies for our country. We have documented that the incidence of IBD in our region

Fig. 3



Annual relative (over 100%) cumulative incidence for clinical characteristics of ulcerative colitis (UC) cases newly diagnosed in central Spain during the period 2000–2012. (a) Cumulative trends in the age at UC diagnosis according to the Montreal classification system (A1, ≤ 16 years old; A2, between 17 and 40 years; and A3, disease onset > 40 years); (b) annual cumulative trends for the extension of UC (E1, ulcerative proctitis; E2, left-sided UC; and E3, extensive UC).

Table 4 Major complications at diagnosis of Crohn's disease and ulcerative colitis (before and after 2000)

	n (%)								
	CD					UC			
	All	CD	Before 2000	After 2000	P	UC	Before 2000	After 2000	P
Complication	190 (18.1)	136 (22.8)	30 (25.6)	106 (22.1)	0.411	54 (12.2)	20 (14.8)	34 (11)	0.260
Pelvic/perirectal abscesses	41 (3.9)	41 (6.9)	15 (13.6)	26 (6.3)	0.010	—	—	—	—
Ocular disease	15 (1.4)	9 (1.5)	1 (0.9)	8 (1.9)	0.692	6 (1.4)	4 (3.4)	2 (0.8)	0.078
Skin disorders	18 (1.7)	16 (2.3)	2 (1.8)	12 (2.9)	0.744	4 (0.9)	1 (0.8)	3 (1.1)	> 0.999
Venous thromboembolic disease	5 (0.5)	1 (0.2)	0	1 (0.2)	> 0.999	4 (0.9)	3 (2.5)	1 (0.4)	0.091
Sclerosing cholangitis	3 (0.3)	—	—	—	—	3 (0.7)	1 (0.8)	2 (0.8)	> 0.999
Osteoarticular manifestation	132 (12.6)	87 (14.6)	16 (14.5)	71 (17.1)	0.520	45 (10.3)	18 (15.3)	27 (10.3)	0.167

CD, Crohn's disease; UC, ulcerative colitis.

has reached values similar to those provided for Northern European countries, whereas the prevalence has not reached that for these countries as yet.

During the last decade, the incidence figures for CD in Spain have repeatedly been estimated to be between 5.9 and 7.5 new cases/100 000 inhabitants/year in different studies [8–10]. A single study reported an incidence rate for CD in 2010 of 10.2 new cases/100 000 in the northwest region of the country [6]. Taken together, these data may represent a progressive and considerable increase over time that has occurred in parallel with the growing social–economic development of our country; thus, speculation on the relationship between the two events is tempting as has been suggested similarly in other European regions. Our annual mean incidence rate of 8.9 patients/100 000 inhabitants surpasses most of the previous estimates provided for other populations in our country, and places our region in similar rates to those currently provided for North European countries (9.9–8.6/100 000) [3,18,19] and Hungary [20]. This is parallel to the prevalence in our region (with 137 CD patients/100 000 inhabitants), which has also increased to approach Scandinavian prevalence figures (141–151 patients/100 000) [21–23], although still not close to the rates reported in the USA (241/100 000) [1]. Our research shows a notable increase in new patients diagnosed with CD during the last decade and is significantly beyond the last estimates provided for the Spanish population in 1997 (87 cases/100 000) [13]. In fact, three of four new patients in our region were diagnosed with CD during the last 13 years.

In contrast, the trend of the incidence of UC in our study was found to be the opposite, with an annual mean incidence in our region for the period 2000–2012 of only 5.6 new cases/100 000 inhabitants per year. This is lower than the incidence figures available for the last decade for different regions of Spain, which provided incidence rates from 7.1 to 9.6 [6,9–11]. Although direct comparisons among our incidence rates and those provided by previous studies from other Spanish regions are not fully appropriate, our low incidence is striking. As a consequence, the population prevalence of UC in our region for 2012 (99.84 cases/100 000) has also decreased in terms of the previous Spanish estimate in 1997 (109.96 cases/100 000

inhabitants). The decreasing trend in the incidence of UC on the basis of our data can be interestingly supported by a previous study, which showed that the incidence of UC in northern France decreased 17% over a 12-year period, in parallel to a 23% increase in new CD patients during the same period [24]. This contrasting evolution for the two major forms of IBD has already been documented in various Nordic regions during the 1990s [25,26], and had been observed in our country as well [12]. Genetic or environmental causes to explain this trend change must be investigated, but we should consider that the growing incidence of CD and the higher care costs associated when compared with UC [14] could enhance the burden of IBD for the public health systems in our country. In fact, although a UC/CD relationship of 1.6 was estimated in 1997 [13] and 1.3 in 2002 [10], our current observation in 2012 is 0.73.

Our research has also examined the developmental aspects of IBD patterns over a period of 13 years; thus, in the case of CD, a male/female ratio of around 1 remained, as traditionally described in Spain [13], with a progressive increase in the patients' age at diagnosis (Fig. 2a), which exceeded the rate of aging in the reference population of our province for the same period. In fact, the average age of CD onset in our study was 35.9 years, whereas in previous studies, patients were diagnosed with CD between 31 and 33 years of age [10,11]. The distribution or disease location (L) for CD constitutes one of the most stable and homogeneously described aspects reported, with an ileal involvement (L1) at the onset, the most frequently described location in several Spanish and European studies [10,27], in agreement with ours. Moreover, the proportion of patients with ileal involvement of CD (L1) increased progressively during 2000–2012 at the expense of a reduction in ileocolonic locations (L3). The behavior and complication rate (Table 3) of the disease showed no relevant changes throughout the study period (Fig. 2b). Only a significant reduction for pelvic/perirectal abscesses was documented, which could be related to the reduction in the fistulizing behavior (B3) observed in the same period (Fig. 2c). We do not know whether a reduction in the diagnostic delay could have been the cause of this change as our study did not

determine the date of onset of symptoms associated with IBD.

For UC, we found that it affected a significantly high proportion of male patients (57.3%) who were diagnosed at an average age of 42.4 years, in agreement with the same age range reported previously for our country by previous studies [9,10]. In our series of patients, a significant change was documented for age at diagnosis (A) during 2000–2012 at the expense of the A3 group of patients, surpassing the aging index for our reference area. However, this result should be considered with caution as it could include biases derived from the lower survival rate in 2012 of those cases diagnosed at an older age. In our study, the onset of UC before 16 years of age (A1) remains incidental, as reported previously by others. Left-sided colitis (E2) remains the predominant location at diagnosis (46.7%), and does not show significant changes over time, as described previously in most of the studies available [10,20,27].

Our research has attempted to exhaustively include all patients with IBD (including CD, UC, and UIBD) who were actively cared for in the gastroenterology/IBD units of every participating public hospital in our region. We consider that some of the features shown by our region could have facilitated the collection of reliable data on IBD epidemiology, including broad coverage of our rural population through a network of public hospitals and the absence of parallel private healthcare resources, ensuring patient treatment in our centers. Our rural population is basically stable and is characterized by low geographical mobility. It also showed no relevant variations over the study period (variation coefficient of 10% from 2000 to 2012), which lends additional strength to our results. Finally, patients with IBD are cared for by identifiable physicians, on the basis of common criteria, and who are part of a working group that holds regular meetings. Despite this, the external validity of our results should be researched further as we cannot assume our region's characteristics to be representative for the entire country.

Our work also has some limitations. We cannot assume that, in the 1.5-year period of data collection, all patients with IBD in our region have been cared for at our hospitals; thus, our figures may underestimate the true magnitude of the problem, and perhaps patients with prolonged remission and milder forms of the disease may not have been properly accounted for. However, a longer recruitment period of patients could have minimized this problem. Moreover, retrospective collection of the characteristics of each patient at the time of IBD onset represents an additional limitation that we have attempted to control through the systematic recording of the variables considered, and the most intensive analysis of the cases diagnosed in the last 13 years, to establish the clinical and epidemiological trends in IBD.

Finally, although we could not ensure the exhaustive inclusion of pediatric IBD cases from our region because not all of our hospitals offer pediatric gastroenterology services (some cases may have been treated in referral centers in neighboring provinces and no pediatric gastroenterologists are integrated into our working group), we preferred to exclude the study of the epidemiology of IBD in patients younger than 16 years old. However, the epidemiology of child CD and UC in our country and its trends have been analyzed by recent research [7,8] in which we had the opportunity of collaboration, and the data may also be extrapolated to our region.

This study has provided clues toward a progressive increase in the epidemiology of IBD in central Spain, and specifically for CD, which today reach figures similar to those reported for the Scandinavian countries. Despite the limitations of our retrospective design and the exclusive inclusion of adult IBD cases, our results and their comparison with the epidemiological figures provided previously for IBD in other Spanish regions suggest a growing trend and considerable expansion of IBD in our country over the past decades to resemble the rates observed in other European areas.

The existence of a progressive reduction in the epidemiology of UC, as has been documented in other European regions, must be confirmed by further prospective research. However, the overall burden of IBD seems to be increasing at a potentially enormous level. Taking into account that IBD now affects 0.26% of the adult population in our region, the health system should consider the costs associated with treatment, the high long-term disability rate, and the social impact of IBD to strategically design sustainable health policies [28]. Further epidemiological studies should assess the impact of current disease management alternatives, including interventions to modify the disease behavior and its long-term outcomes, to improve patients' quality of life towards the development of a normal life [29,30], making them compatible with the sustainability of the healthcare system.

Acknowledgements

The Ciudad Real province IBD working group is sponsored by AbbVie Laboratories. The sponsor did not participate in the design, data collection, analysis, writing, or in the scientific content of this study.

The study conception and design was of Alfredo J. Lucendo. Alfredo J. Lucendo, Rufo Lorente, Óscar Roncero, Daniel Hervías, Abdelmouneim Bouhmid, Teresa Angueira, Cristina Verdejo, Irina Salueña, and Sonia González-Castillo contributed in the acquisition of data. Statistical analyses were carried out by Ángel Arias. Alfredo J. Lucendo and Ángel Arias carried out the analysis and interpretation of data. Alfredo J. Lucendo wrote the manuscript. Rufo Lorente, Óscar Roncero, Daniel Hervías, Abdelmouneim Bouhmid, Teresa Angueira,

Cristina Verdejo, Irina Salueña, Sonia González-Castillo, and Ángel Arias contributed in the critical review of the manuscript, providing relevant intellectual content. All of the authors approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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