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ORIGINAL ARTICLE

East–West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort

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ABSTRACT

Objective The incidence of inflammatory bowel disease (IBD) is increasing in Eastern Europe. The reasons for these changes remain unknown. The aim of this study was to investigate whether an East–West gradient in the incidence of IBD in Europe exists.

Design A prospective, uniformly diagnosed, population based inception cohort of IBD patients in 31 centres from 14 Western and eight Eastern European countries covering a total background population of approximately 10.1 million people was created. One-third of the centres had previous experience with inception cohorts. Patients were entered into a low cost, web based epidemiological database, making participation possible regardless of socioeconomic status and prior experience.

Results 1515 patients aged 15 years or older were included, of whom 535 (35%) were diagnosed with Crohn's disease (CD), 813 (54%) with ulcerative colitis (UC) and 167 (11%) with IBD unclassified (IBDU). The overall incidence rate ratios in all Western European centres were 1.9 (95% CI 1.5 to 2.4) for CD and 2.1 (95% CI 1.8 to 2.6) for UC compared with Eastern European centres. The median crude annual incidence rates per 100 000 in 2010 for CD were 6.5 (range 0–10.7) in Western European centres and 3.1 (range 0.4–11.5) in Eastern European centres, for UC 10.8 (range 2.9–31.5) and 4.1 (range 2.4–10.3), respectively, and for IBDU 1.9 (range 0–39.4) and 0 (range 0–1.2), respectively. In Western Europe, 92% of CD, 78% of UC and 74% of IBDU patients had a colonoscopy performed as the diagnostic procedure compared with 90%, 100% and 96%, respectively, in Eastern Europe. 8% of CD and 1% of UC patients in both regions underwent surgery within the first 3 months of the onset of disease. 7% of CD patients and 3% of UC patients from Western Europe received biological treatment as rescue therapy. Of all European CD patients, 20% received only 5-aminosalicylates as induction therapy.

Conclusions An East–West gradient in IBD incidence exists in Europe. Among this inception cohort—including indolent and aggressive cases—international guidelines for diagnosis and initial treatment are not being followed uniformly by physicians.

Significance of this study

What is already known on this subject?

- The incidence of inflammatory bowel disease (IBD) is increasing worldwide.
- Recent studies from Eastern Europe have reported sharp increases in incidence in some centres comparable with Western European incidence rates, whereas in other Eastern European centres IBD incidence has not been investigated. Whether these increases represent true increases in incidence remains unknown.
- Few population based inception cohorts in adults and paediatric onset IBD exist from Eastern Europe.

What are the new findings?

- A prospective, population based, web based inception cohort in 31 European centres covering a background population of 10.1 million people.
- A West–East gradient of 2 in IBD incidence exists in Europe. The highest incidence in the world is found on the Faroe Islands.
- The patient populations in Eastern and Western Europe are identical in terms patient characteristics, disease extent and phenotype, smoking habits and diagnostic delay.
- In this inception cohort, the initial surgery rates seemed unchanged despite the introduction of biological therapy in IBD treatment.

Significance of this study

How might it impact on clinical practice in the foreseeable future?

- In this European population based cohort, diagnostic procedures and initial medical treatment were not in accordance with current guidelines.
- Follow-up of the EpiCom cohort will reveal the impact of treatment choices on disease course.
- This web based epidemiological methodology has been shown to be feasible and affordable regardless of prior experience and cost constraints, and should be further developed.

INTRODUCTION

The incidence of inflammatory bowel diseases (IBDs), consisting of Crohn's disease (CD) and ulcerative colitis (UC), is subject to considerable variation worldwide. Incidences of UC and CD vary between 0 and 24.3/100 000 inhabitants and 0 and 20.2/100 000 inhabitants, respectively,[1] with IBD more common in industrialised countries than in non-industrialised countries. Until recently, few population based cohort data were available on the epidemiology of IBD in Eastern Europe. However, recent studies from Hungary and Croatia have reported sharp increases in IBD incidence that means they are now comparable with Western European countries.[2 3]

The reported increase could be due to methodological bias in previous studies from Eastern Europe, rising awareness of the disease, differences in diagnostic practices or they could reflect true changes in IBD incidence.[4] To investigate whether there is an East–West gradient in the incidence of IBD across European countries, 31 medical centres from Eastern and Western Europe participated in the European Crohn's and Colitis Organisation's (ECCO) Epidemiological Committee (EpiCom) study; a prospective population based cohort of unselected IBD cases diagnosed in 2010 within well described geographical areas was collated by capturing clinical data throughout a 5 year period (2010–2015). Epidemiological findings on incidence, phenotype and initial treatment are presented here.

METHODS

Study centres

Following an initial meeting in Vienna in 2006 and an announcement in an ECCO newsletter,[5] 31 centres from 14 Western and eight Eastern European countries covering a total background population of approximately 10.1 million people (6.8 million from Western and 3.3 million from Eastern Europe) agreed to participate in this study. The classification of centres as being situated in either Western or Eastern European countries was based on the socioeconomic status of that country before 1990. A well defined primary catchment area with up to date population data, including age and gender distribution, was a prerequisite for participation. Similarly, participation required an established network of gastroenterologists, colorectal surgeons and general practitioners within the uptake area to ensure complete coverage and inclusion of patients.

A study steering committee has organised twice yearly EpiCom group meetings since 2006 where participants have been educated in case ascertainment in order to achieve consistency of methods as well as being trained in how to enter data in the EpiCom database. Ten centres had previously organised population based cohorts. Furthermore, participants have been able to influence the development and improvement of the web based database, constructed by HD Support LLC, Denmark.[6] The low cost, web based epidemiological concept made participation possible for every country in Europe, regardless of socioeconomic status and prior experience.

Case definition

Incident cases diagnosed with IBD between 1 January and 31 December 2010 and living in the predefined catchment areas at the time of diagnosis were prospectively included. Cases were required to meet the Copenhagen Diagnostic Criteria for CD[7] and UC[8] (see web appendix available online only). Cases in which not of all criteria for either CD or UC were fulfilled and yet in which subsequent relevant IBD treatment was necessary were classified as IBD unclassified (IBDU).[7–9] Fulfilment of the aforementioned criteria was ensured by the participating physicians. Diagnostic criteria were locked into the database securing that the required criteria for CD, UC or IBDU were met. General practitioners, specialists, other IBD units and patient self-help groups in the study areas were contacted twice during the inclusion period to ensure complete prospective recruitment of patients. Patients younger than 15 years were included as paediatric patients in the paediatric centres, with the exception of the centre from the Czech Republic which included patients younger than 18 years. The age limit of 15 years was the referral age and was decided on by agreement between all centres. Disease phenotype classification by disease extent for UC, as well as disease location and behaviour for CD, were defined according to the Montreal classification[10] which has previously been shown to have overall good interobserver agreement.[11 12]

Induction therapy was defined as any medical or surgical treatment for IBD initiated within the first 3 months after diagnosis. Medical treatment was categorised as: 5-aminosalicylates (5-ASA) (oral and/or topical 5-ASA treatment±topical steroids), steroids (oral steroids±azathioprine, 6-mercaptopurine, 5-ASA or topical steroids), immunomodulators (azathioprine, 6-mercaptopurine, ciclosporin±steroids or methotrexate± steroids) or biological therapy (infliximab or adalimumab in combination with any of the above). Surgical treatment was defined as any surgery due to IBD within the first 3 months after diagnosis (regardless of medical treatment prior to surgery).

Data collection and validity

Data regarding demographics, disease course, therapy and blood samples were collected at diagnosis and every third month throughout the follow-up period, and data were prospectively entered by physicians and/or IBD specialist trained nurses into the EpiCom database,[13] a unique, tailor made and secure web based inception cohort database, facilitating remote data input from around the world in a cost effective way. Participants were trained in using the database at the biannual EpiCom meetings prior to and during the study. Furthermore, participants took part in the construction and validation process of the database. Built-in control and validation tests were used to enhance internal data validity. All data were standardised manually by JB to further improve data quality, and centres were asked to correct inconsistent information and to provide any missing data if necessary.

A running overview bar of the cumulative number of registered patients and corresponding annual incidence rates for each centre was implemented at the project website[14] to encourage researchers in entering the data and to meet the deadlines.

Audits of case ascertainment and data quality were performed randomly at 24 of 31 centres, followed by corrections if necessary. The centre from Finland was unable to supply full data on medical treatment due to local restrictions.

Ethical considerations

The study was approved by the local ethics committees according to local regulations.

Statistical methods

Statistical analyses were performed using SAS software V.9.2. Age and gender standardised annual incidence rates for the adult population were obtained using the European Standard population[15] with the age groups 0–14, 15–44, 45–64 and 65+years. The purchasing power parity (PPP) version of gross domestic product (GDP) was obtained for 2011 from the World Bank data service.[16] For analysis of a possible GDP effect on IBD incidence, for each centre the GDP (PPP version) of the corresponding country versus the centre wise standardised IBD incidence rate (per 100 000 population per year) was depicted. A p value of <0.05 was considered statistically significant. The incidence gradient was analysed using log linear (multiplicative) Poisson regression.

RESULTS

A total of 1515 patients aged 15 years or older were diagnosed with IBD in 2010. Of these, 535 (35%) patients were diagnosed with CD, 813 (54%) with UC and 167 (11%) with IBDU. In total, 1259 (83%) patients were diagnosed in Western European and 256 (17%) in Eastern European centres. Paediatric IBD was diagnosed in 45 patients (see web appendix available online only). Patient demographics (table 1) were similar in the two geographic regions, except for educational status. Nearly all cases of IBDU (96%) were diagnosed in Western European centres. Disease classification (figures 1, 2) and smoking habits at

Table 1 Demographic characteristics of incident adult and paediatric patients with inflammatory bowel disease

	Western European centres			Eastern European centres**		
Adult patients (≥15 years)	**CD**	**UC**	**IBDU**	**CD**	**UC**	**IBDU**
No of patients (n (%))	430 (34)	668 (53)	161 (13)	105 (41)	145 (57)	6 (2)
Males (n (%))	220 (51)	375 (56)	78 (48)	63 (60)	82 (57)	4 (67)
Age (years) (median (range; IQR))	34 (16–89; 26)	39 (15–89; 27)	38 (16–84; 28)	32 (15–78; 21)	36 (18–81; 26)	30 (20–34; 5)
Time from symptoms to diagnosis (months) (median (range; IQR))	4.6 (0–31 years; 10 months)	2 (0–21 years; 4.2 months)	2.4 (0–30 years; 5.5 months)	3.4 (0–20 years; 6.5 months)	2.2 (0–5 years; 4.6 months)	2.7 (0–3 years; 8.6 months)
Never smoker (n (%))	170 (43)	311 (56)	70 (51)	39 (38)	77 (54)	4 (67)
Current smoker (n (%))	142 (36)	52 (9)	20 (15)	39 (38)	16 (11)	2 (33)
Former smoker (n (%))	88 (21)	196 (35)	46 (34)	25 (24)	51 (35)	0 (0)
Adult patients (≥15 years)	**Western European centres**			**Eastern European centres**		
Educational status (n (%))*						
Completed academic education	191 (18)			53 (21)		
Completed non-academic education	564 (55)			131 (52)		
Currently in education	151 (15)			57 (23)		
No education	128 (12)			12 (5)		
Employment status (n (%))**						
Employed	557 (53)			137 (54)		
Self-employed	63 (6)			12 (5)		
Unemployed	121 (11)			26 (10)		
Student	161 (15)			42 (17)		
Retired	157 (15)			36 (14)		
Extraintestinal complications at diagnosis (n (%))**						
None	1085 (88)			221 (85)		
Skin	19 (2)			3 (1)		
Eyes	18 (2)			3 (1)		
Joints	86 (7)			27 (10)		
Primary sclerosing cholangitis	5 (0)			2 (1)		
Pancreatitis	3 (0)			2 (1)		
Other	13 (1)			3 (1)		
	Western European centres			**Eastern European centres****		
Paediatric patients	**CD**	**UC**	**IBDU**	**CD**	**UC**	**IBDU**
No of patients (n (%))	9 (45)	9 (45)	2 (10)	6 (24)	18 (72)	1 (5)
Males (n (%))	5 (56)	3 (33)	1 (50)	3 (50)	8 (44)	1 (100)
Age (years) (median (range; IQR))	11 (6–14; 2.1)	12 (1–14; 1.9)	10 (7–14; 3.9)	10 (2–16; 6.2)	4 (1–16; 9.1)	9
Time to diagnosis (months) (median (range; IQR))	4.1 (0.3–12.4; 2.2)	2.3 (0.6–5.8; 1.9)	1.9 (1.5–2.2; 0.3)	3.6 (2.0–17.0; 2.6)	2.7 (1.2–104.3; 4.3)	3.5

*p<0.01; **NS. p Values are given for comparison between the geographic regions.
CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, IBD unclassified; UC, ulcerative colitis.

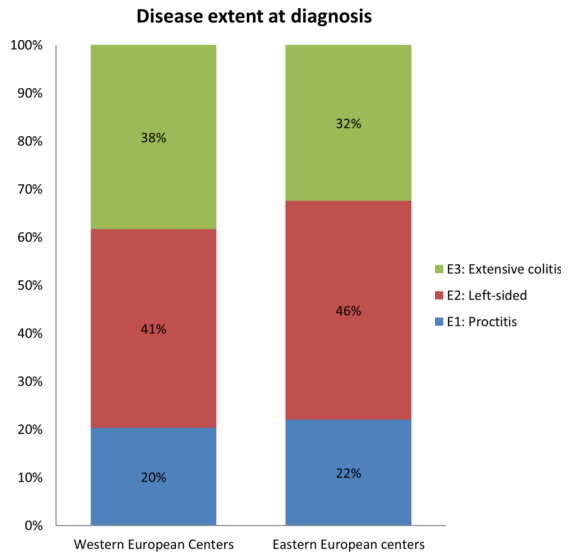

Figure 1 Extent of disease at diagnosis for adult patients with ulcerative colitis (UC) (NS).

diagnosis did not differ. In both Western and Eastern European centres, more CD patients (36% and 38%) than UC patients (9% and 11%) were current smokers at the time of diagnosis ($p<0.01$) while more UC patients (35% and 35%) than CD patients (21% and 24%) were former smokers ($p<0.01$).

Incidence in Europe

The crude as well as age and gender adjusted incidence rates (per 100 000 per year) for UC, CD and IBDU in the selected study areas are shown in table 2 and illustrated in figure 3. The regional annual incidence rates for IBD combined, and for CD, UC and IBDU separately, differed significantly between Eastern and Western Europe ($p<0.01$). The highest incidence of IBD was found on the Faroe Islands (81.5 per100 000). The overall annual incidence rates in all Western European centres were roughly twice as high as rates in all Eastern European centres for CD (incidence rate ratio (IRR)=1.9, 95% CI 1.5 to 2.4) and UC (IRR=2.1, 95% CI 1.8 to 2.6). The median crude annual incidence rate for CD was 6.5 (range 0–10.7) in Western European centres and 3.1 (range 0.4–11.5) in Eastern European centres whereas the median annual incidence rates for UC were 10.8 (range 2.9–31.5) and 4.1 (range 2.4–10.3), respectively, and the median annual rates for IBDU were 1.9 (range 0–39.4) and 0 (range 0–1.2), respectively.

The observed incidences correlated with the GDP of each country. The highest incidences were observed in countries with high GDP—that is, Western European centres (Northern Europe and the Mediterranean region)—compared with regions with lower GDP (Eastern European centres) (figure 4). Analysing incidence rates depending on age, gender, region and GDP, the IRR for IBD was 0.4 (95% CI 0.2 to 0.7) when comparing Eastern with Western European centres for the same age/gender group and GDP. High concordance prohibited the separation of the effects of GDP and geographic region in this analysis. The variation in rates could thus be ascribed to either factor.

Diagnostic procedures

All UC patients were diagnosed using endoscopy (see web appendix available online only). A full colonoscopy was performed in 524 (78%) UC patients from Western Europe compared with

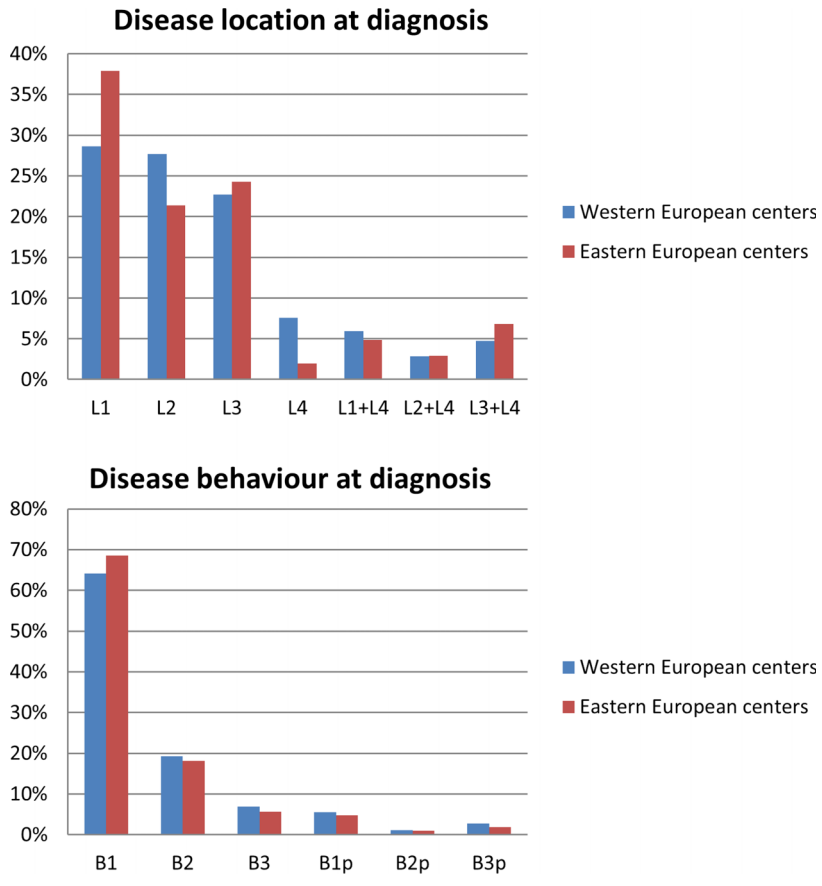

Figure 2 Disease location and behaviour at diagnosis for adult patients with Crohn's disease (NS).

Table 2 Incidence rates per 100 000 for inflammatory bowel disease, Crohn's disease, ulcerative colitis and inflammatory bowel disease unclassified in Europe for patients aged 15 years or older in 2010

	No of patients	IBD crude	IBD adjusted (SE)	CD crude	CD adjusted (SE)	UC crude	UC adjusted (SE)	IBDU crude	IBDU adjusted (SE)
Western European centres									
Cyprus, Nicosia	27	11.2	11.4 (2.2)	6.2	6.3 (1.6)	2.9	3.0 (1.1)	2.1	2.2 (1.0)
Denmark, Aarhus	55	21.2	20.7 (2.8)	8.5	8.2 (1.8)	10.8	10.6 (2.0)	1.9	1.8 (0.8)
Denmark, Amager	23	17.2	16.3 (3.4)	5.2	4.8 (1.8)	7.5	7.4 (2.4)	4.5	4.1 (1.7)
Denmark, Funen	123	30.7	33.4 (3.1)	10.7	11.4 (1.8)	18.7	20.1 (2.4)	1.2	1.4 (0.7)
Denmark, Herlev	48	22.4	24.4 (3.6)	6.5	7.0 (1.9)	7.5	8.3 (2.1)	8.4	9.2 (2.2)
Denmark, Herning	49	21.2	22.5 (3.3)	6.5	7.1 (1.9)	12.6	13.0 (2.5)	2.2	2.3 (1.1)
Denmark, Viborg	37	24.6	26.7 (4.5)	8.6	9.6 (2.7)	14.6	15.7 (3.4)	1.3	1.4 (1.0)
Faroe Islands	31	81.5	83.1 (15.0)	10.5	11.1 (5.6)	31.5	31.8 (9.3)	39.4	40.2 (10.5)
Finland, Pirkanmaa	107	26.2	27.7 (2.7)	4.4	5.0 (1.2)	17.1	18.0 (2.2)	4.7	4.7 (1.1)
Greece, Ioanninia	15	9.2	10.2 (2.6)	3.1	3.5 (1.6)	5.5	6.0 (2.0)	0.6	0.7 (0.7)
Greenland	9	24.0	19.6 (6.6)	0.0	0 (0)	24.0	19.6 (6.6)	0.0	0 (0)
Iceland	72	28.7	28.5 (3.4)	5.6	5.6 (1.5)	17.9	17.8 (2.7)	5.2	5.1 (1.4)
Ireland, Adelaide and Meath	36	13.2	12.9 (2.2)	4.8	4.3 (1.2)	4.4	4.2 (1.2)	4.0	4.4 (1.4)
Israel, Beer Sheva	51	13.2	13.0 (1.9)	8.6	8.4 (1.5)	4.4	4.4 (1.1)	0.3	0.2 (0.2)
Italy, Northern Italy	182	10.9	11.6 (0.9)	3.9	4.3 (0.5)	6.1	6.4 (0.7)	0.8	0.9 (0.3)
Portugal, Vale de Sousa	31	11.1	10.8 (2.0)	7.2	7.0 (1.6)	3.9	3.8 (1.2)	0.0	0 (0)
Spain, Vigo	102	20.4	21.4 (2.1)	10.2	10.8 (1.5)	9.0	9.4 (1.4)	1.2	1.2 (0.5)
Sweden, Linköping	55	38.3	40.0 (5.4)	9.8	10.1 (2.7)	16.0	16.5 (3.5)	12.5	13.5 (3.2)
Sweden, Örebro	39	26.5	28.3 (4.6)	7.5	8.3 (2.5)	15.6	16.1 (3.4)	3.4	3.9 (1.8)
UK, Brent and Harrow	76	19.9	19.3 (2.2)	2.6	2.4 (0.8)	15.9	15.6 (2.0)	1.3	1.3 (0.6)
UK, Hull and East Yorkshire	91	18.1	18.6 (2.0)	8.4	8.9 (1.4)	8.2	8.3 (1.3)	1.6	1.4 (0.5)
Eastern European Centres									
Croatia, Zagreb	12	6.3	6.6 (1.9)	3.1	3.3 (1.3)	3.1	3.3 (1.4)	0.0	0 (0)
Czech Republic, Prague	22	12.2	12.7 (2.8)	5.5	5.6 (1.8)	5.5	5.8 (1.9)	1.1	1.3 (0.9)
Czech Republic, South Bohemia	42	7.7	7.9 (1.2)	3.8	3.9 (0.9)	3.8	3.9 (0.9)	0.0	0 (0)
Estonia, Southern Estonia	30	10.3	11.0 (2.0)	5.2	5.4 (1.4)	5.2	5.7 (1.5)	0.0	0 (0)
Hungary, Veszprem province	58	23.0	24.0 (3.2)	11.5	12.0 (2.2)	10.3	10.7 (2.1)	1.2	1.3 (0.7)
Lithuania, Kaunas	32	8.5	9.1 (1.6)	2.4	2.6 (0.9)	6.1	6.5 (1.4)	0.0	0 (0)
Moldova, Chisinau	10	4.3	3.9 (1.2)	0.4	0.4 (0.4)	3.9	3.5 (1.2)	0.0	0 (0)
Romania, Timis	24	4.1	4.2 (0.9)	1.7	1.7 (0.5)	2.4	2.5 (0.7)	0.0	0 (0)
Russia, Moscow	26	5.1	5.3 (1.1)	0.8	0.9 (0.5)	4.1	4.2 (0.9)	0.2	0.2 (0.2)

Regional incidence rates	No of patients	IBD (95% CI)	CD (95% CI)	UC (95% CI)	IBDU (95% CI)
All Western European centres	1259	18.5 (17.5 to 19.5)*	6.3 (5.7 to 6.9)*	9.8 (9.1 to 10.6)*	2.4 (2.0 to 2.8)*
All Eastern European centres	256	8.1 (7.2 to 9.2)	3.3 (2.7 to 4.0)	4.6 (3.9 to 5.4)	0.2 (0.1 to 0,4)
All centres	1515	15.2 (14.4 to 16.0)	5.4 (4.9 to 5.8)	8.2 (7.6 to 8.7)	1.7 (1.4 to 1.9)

*Difference in incidence between the geographic regions p<0.01.
CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, IBD unclassified; UC, ulcerative colitis.

130 (90%) from Eastern European countries (p<0.01) while the remaining patients had a sigmoidoscopy performed as part of their diagnostic investigations (proctosigmoiditis patients, where the investigator reached normal tissue). For CD, 402 (93%) patients in Western and 101 (96%) in Eastern European countries had a colonoscopy performed, while 1% in both Western and Eastern European countries only had a sigmoidoscopy performed during the diagnostic investigation (NS). For patients with IBDU, 119 (74%) from Western Europe had a colonoscopy compared with six (100%) from Eastern Europe.

Treatment

The initial treatment in Western and Eastern European centres during the first 3 months of disease is shown in figure 5. The observed regional differences for UC and CD patients were significant (p<0.01). 5-ASA monotherapy was chosen as the initial treatment for 75 (18%) CD patients in Western Europe and for 33 (31%) in Eastern Europe, with most patients receiving oral 5-ASA only (66 (92%) and 29 (88%), respectively, NS). Of these patients, 25 (35%) in Western Europe and six (18%) in Eastern Europe had colonic CD (NS). Of CD patients receiving steroids as the initial

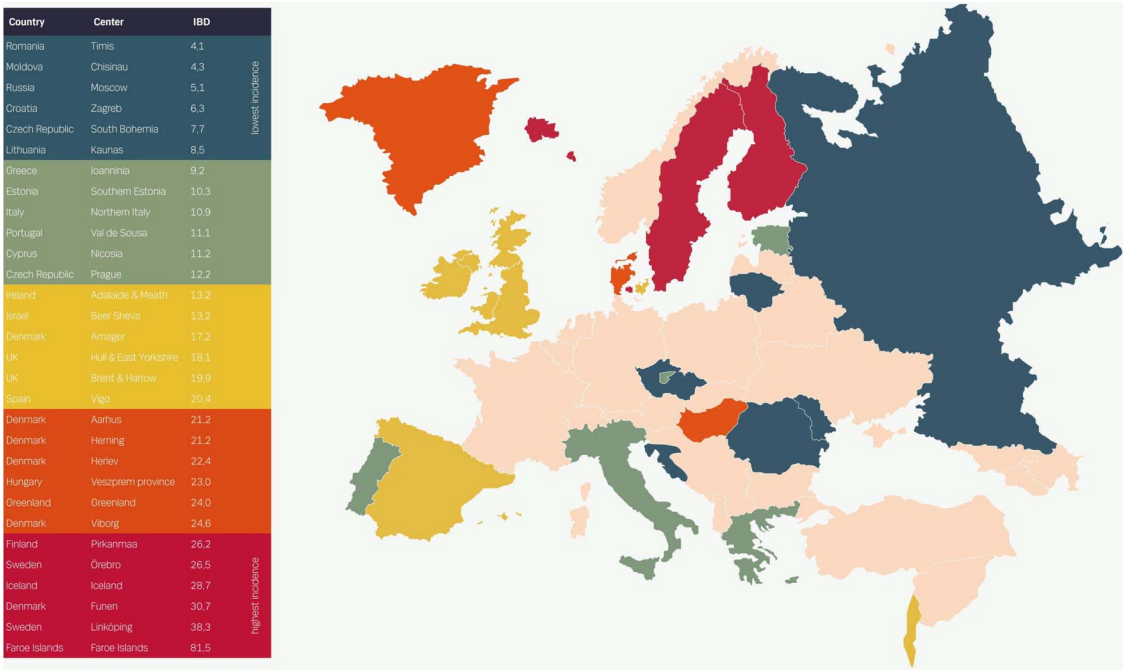

Figure 3 Incidence rates (/100 000) of cases aged 15 years or older for inflammatory bowel disease (IBD) in selected areas in Europe in 2010.

treatment, 152 (67%) in Western Europe and 53 (93%) in Eastern Europe received prednisolone while the remaining patients were treated with budesonide ($p<0.01$). Of patients receiving budesonide, 44 (58%) in Western Europe and two (50%) in Eastern Europe had disease located in the terminal ileum (NS). For patients treated with prednisolone, these numbers were 45% in Western Europe and 51% in Eastern Europe (NS). Most patients with UC were treated with 5-ASA monotherapy as the initial treatment. Sixty-nine (44%) patients with left-sided colitis and 19 (23%) with extensive colitis in Western Europe received combination therapy with oral and topical 5-ASA compared with 21 (42%) and six (22%), respectively, in Eastern Europe. Of UC patients with proctitis, 11 (11%) in Western Europe and five (19%) in Eastern Europe received oral 5-ASA only.

Biological therapy

Biological treatment was administered to 29 (7%) CD patients from Western European centres: 24 (83%) were treated with infliximab and five (17%) with adalimumab. Five (17%) patients were treated 'top down', with no medical treatment preceding biological therapy, while the remaining patients were treated with combinations of steroids and either azathioprine and/or 5-ASA. An equal proportion of six (21%) patients had stricturing or penetrating disease. In 20 (69%) cases, biological treatment was initiated due to refractoriness to other treatments. Only two (2%) CD patients from Eastern Europe received infliximab due to refractoriness to other treatments. Of the 16 (3%) UC patients from Western European centres who received biological treatment, all received infliximab: three (19%) did not receive any treatment before starting on biologicals while the remaining patients were treated with combinations of steroids and either azathioprine and/or 5-ASA or azathioprine alone. The indication for starting biological treatment was refractoriness to other treatments in 14 (88%) cases. Most patients (10 (63%)) had extensive colitis at diagnosis while the remaining patients had left-sided colitis. Four (3%) patients with IBDU received infliximab because of refractoriness to other treatments (two patients), maintenance of remission (one patient) or steroid dependency (one patient). Three patients received steroids prior to starting biological treatment while one patient received 5-ASA monotherapy. No association between smoking status at diagnosis and biological treatment was observed in any patient.

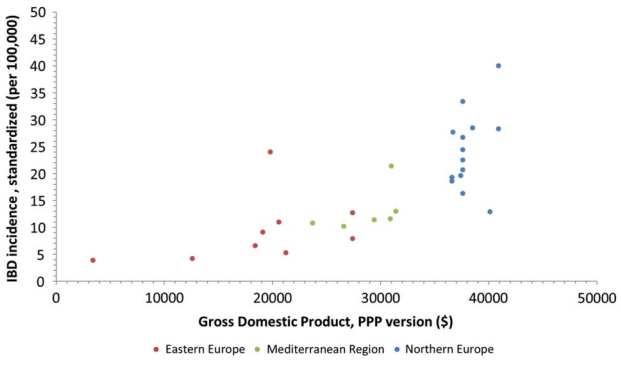

Figure 4 Inflammatory bowel disease (IBD) (Crohn's disease/ulcerative colitis/inflammatory bowel disease unclassified) standardised incidence rates versus 2010/2011 purchasing power parity (PPP) version of gross domestic product (GDP).

Surgery

Resections were performed in 34 (8%) Western European CD patients (including three hemicolectomies and one total colectomy) compared with eight (8%) Eastern European CD patients (one hemicolectomy). Stricturing disease occurred in 14 (41%) Western European patients and penetrating disease in 14 (41%) compared with two (26%) and five (63%), respectively, for Eastern European patients (NS). The majority of patients (24 (73%) and 7 (88%)) received no medical treatment before undergoing surgery (NS). Seven (1%) Western European UC patients (one with left-sided colitis and six with extensive colitis) underwent a colectomy at diagnosis or during the first 3 months of disease compared with one (1%) patient with

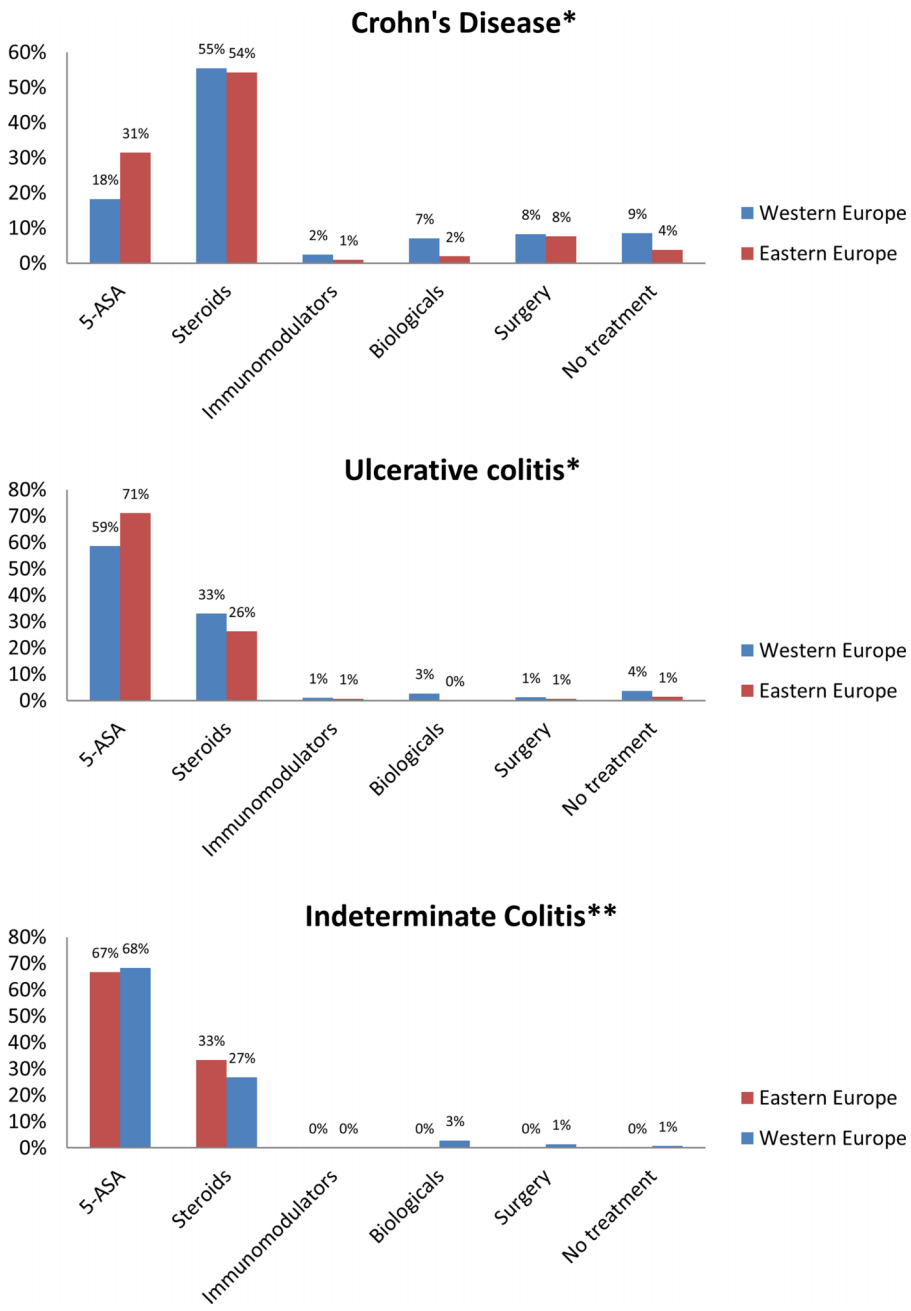

Figure 5 Initial treatment during the first 3 months of disease in Eastern and Western European centres.

extensive colitis from Eastern Europe. All UC patients were treated medically with steroids with or without immunomodulators before undergoing surgery. No association between smoking status at diagnosis and risk of surgery was observed for either CD or UC patients (NS). Two (1%) patients with IBDU from Western Europe had a total colectomy at diagnosis or during the first 3 months of disease.

DISCUSSION

We have presented what we believe is the first multicentre web based inception cohort study of the incidence of IBD in Europe. The overall age and gender adjusted annual incidence rates per 100 000 per year were 5.4 for CD, 8.2 for UC and 1.7 for IBDU. The combined annual incidence rates for CD and UC in all Western European centres were twice as high as the rates in all Eastern European centres. This gradient was smaller than originally expected compared with the North–South gradient previously observed[17]; this might be explained by a bias concerning case ascertainment in previous Eastern European studies.

All 31 participating centres performed a population based study capturing all incident IBD patients in the catchment area during 2010. Several measures were used in order to secure the quality and validity of the incidence rates recorded. Diagnostic criteria used for case definition, the time period of inclusion, the recorded patient data and the method of case ascertainment were standardised and consistent, and catchment areas were precisely defined. The unification of methods constitutes a major strength of population based inception cohorts compared with, for example, Health Administrative Databases, where issues of data incompleteness compared with clinical records and coding errors of diagnoses exist.[18 19] Furthermore, by contacting all departments of gastroenterology, practising gastroenterologists and general practitioners in the uptake areas during the inclusion period, prospective inclusion of all patients in the regions diagnosed with IBD was ensured. Audit visits and built-in data

control in the database guaranteed project protocol adherence, as well as extensive training of participating physicians and nurses in methodology prior to and during the study period at the biannual EpiCom group meetings.

The reported IBD incidence rate on the Faroe Islands (81.5 per 100 000 per year) is, to our knowledge, the highest reported incidence rate to date. Median age at diagnosis and time to diagnosis did not differ from other Western European centres (data not shown) and incidence rates for 2011 and 2012 in the Faroe Islands did not differ significantly from the incidence rate found in 2010 (K Nielsen, personal communication). A previous study found a mean incidence rate of 23.9 per 100 000 for 1981–1988[20] on the Faroe Islands. The present major increase in incidence could have been caused by environmental factors[21] (eg, special dietary habits) in combination with a genetic burden.[22] Another interesting observation was the Hungarian incidence of IBD (23 per100 000), which was the highest Eastern European incidence and equalled Western European incidences. This finding is in line with previous reports,[2] and as Hungary is one of the wealthier Eastern European countries in terms of GDP, may be the result of a more westernised way of life. The analysis suggests that lifestyle variations, expressed by geographic lifestyle differences combined with PPP, influence IBD incidence and suggests that the risk of IBD is linked to the developmental status of the geographic region/country.

Additionally, previous population based studies have shown that 5–7% of all cases of IBD occur in children <15 years of age.[23 24] In this inception cohort, however, only 45 (3%) out of 1560 IBD cases were paediatric onset IBD cases. As many centres participating in the study are low incidence areas, and since the paediatric incidence rates observed during 2010 do not differ from previously reported rates from the same countries or regions,[25 26] the observed number of incident paediatric onset IBD patients is likely to resemble the true number of cases.

The geographic regions of Eastern and Western Europe were surprisingly similar in terms of sociodemographic characteristics, time to diagnosis and smoking habits. In accordance with the available literature, more CD patients were smokers at the time of diagnosis and more UC patient were former smokers,[27 28] and this was the case in both regions. In addition, the anatomical location, disease extent and behaviour at the time of diagnosis showed little overall difference. The diagnostic approach for CD and UC seemed similar in Eastern and Western Europe and in accordance with the international guidelines for IBD[29–34] as almost 90% of all IBD patients had a full colonoscopy performed as part of the diagnostic workup. However, only 78% of Western European UC patients and 73% of IBDU patients had a full colonoscopy performed, compared with 90% and 100% in Eastern Europe.

The IBD patients included in this population based inception cohort were unselected and represented the broad spectrum of disease from indolent to severe cases. It is therefore unsurprising that international guidelines for the diagnosis and treatment of IBD are not being followed at 'the clinical frontier'. The observation that 21% of CD patients were treated with 5-ASA monotherapy for induction offers one such example: the efficacy of 5-ASA for inducing remission in CD patients remains uncertain[35] and consequently current guidelines do not recommend 5-ASA for CD.[34 36] In a Danish cohort of CD patients, a mild phenotype of patients was recognised as responders to 5-ASA and were furthermore characterised as dependent on 5-ASA treatment, thus benefiting from monotherapy for a median of 3 years.[37 38] Also, budesonide, recommended as the first choice of treatment for ileocaecal CD,[36] has recently not shown superiority to 5-ASA,[38] and 5-ASA is recommended during pregnancy due to its low toxicity,[39 40] which could partly explain the observed high frequency of 5-ASA as the initial treatment in CD patients.

With regards to steroid treatment in CD, 33% of Western European and 7% of Eastern European patients were treated with budesonide. Yet only 62% and 50%, respectively, had the disease located in the terminal ileum. Furthermore, although current guidelines recommend topical therapy with 5-ASA for active proctitis, and combined therapy with both oral and topical 5-ASA for mildly to moderately active left-sided and extensive colitis,[41] these were not followed uniformly by participating physicians. Socioeconomic considerations regarding treatment options influence the choice of treatment, just as patient preferences do, and these might be influenced by psychological distress, patient beliefs about medication or a discordant doctor–patient relationship.[42] Also, differences in disease management are strongly linked to extra-medical considerations and not necessarily linked to the disease itself, while the comparison might be further complicated by major differences between health systems across Europe.

Surgery rates for CD have been declining in the past two decades.[43] In a Danish population based cohort, 12% of CD patients diagnosed between 2003 and 2005 had a resection performed within the first year after diagnosis.[9] Similarly, in a population based study from Hungary, CD patients diagnosed between 2002 and 2006 reported a surgery rate of 9.8% after 1 year.[44] The present study found that surgery rates within the first 3 months were already close to what is seen at 1 year of diagnosis, representing unavoidable surgeries. Biological treatment within the first 3 months of disease was administered in 7% of CD and 3% of UC patients from Western Europe. This rapid escalation of therapy might be the result of the 'era of mucosal healing' as an important treatment goal[45] as well as the use of biological as medical rescue therapy.[46] Almost 20% of both CD and UC patients treated with biologicals were treated 'top down' and did not receive any other treatment prior to biologicals.

In the present study we have shown that it is possible to perform a large, entirely web based, epidemiological population based cohort study throughout Europe in 31 centres. The database is inexpensive with low maintenance costs, is easy to use and facilitates direct remote data input. Most centres had not performed population based inception cohort studies before but this innovative methodology enabled participation regardless of prior experience and cost constraints. The web based epidemiological concept is feasible and the data it generates are valid, robust and consistent.

The EpiCom study has created this inception cohort, as well as the related database, as a framework for more epidemiological studies to further analyse the impact of treatment choices on disease course during follow-up observation in 2010–2015 of the EpiCom cohort, as well as the impact of environmental factors.

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East–West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort

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Notes