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Environmental factors in a population-based inception cohort of inflammatory bowel disease patients in Europe — An ECCO-EpiCom study☆

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Abbreviations: CD, Crohn's disease; ECCO, European Crohn's and Colitis Organisation; EpiCom, Epidemiological Committee; GCS, glucocorticosteroids; IBD, inflammatory bowel disease; IBDU, inflammatory bowel disease unclassified; IOIBD, International Organisation of Inflammatory Bowel Diseases; OR, odds ratio; 95% CI, 95% confidence interval; UC, ulcerative colitis.

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Abstract

Background and Aims: The incidence of inflammatory bowel disease (IBD) is increasing in Eastern Europe possibly due to changes in environmental factors towards a more "westernised" standard of living. The aim of this study was to investigate differences in exposure to environmental factors prior to diagnosis in Eastern and Western European IBD patients.
Methods: The EpiCom cohort is a population-based, prospective inception cohort of 1560 unselected IBD patients from 31 European countries covering a background population of 10.1 million. At the time of diagnosis patients were asked to complete an 87-item questionnaire concerning environmental factors.
Results: A total of 1182 patients (76%) answered the questionnaire, 444 (38%) had Crohn's disease (CD), 627 (53%) ulcerative colitis (UC), and 111 (9%) IBD unclassified. No geographic differences regarding smoking status, caffeine intake, use of oral contraceptives, or number of first-degree relatives with IBD were found. Sugar intake was higher in CD and UC patients from Eastern Europe than in Western Europe while fibre intake was lower ($p < 0.01$). Daily consumption of fast food as well as appendectomy before the age of 20 was more frequent in Eastern European than in Western European UC patients ($p < 0.01$). Eastern European CD and UC patients had received more vaccinations and experienced fewer childhood infections than Western European patients ($p < 0.01$).
Conclusions: In this European population-based inception cohort of unselected IBD patients, Eastern and Western European patients differed in environmental factors prior to diagnosis. Eastern European patients exhibited higher occurrences of suspected risk factors for IBD included in the Western lifestyle.

1. Introduction

The occurrence of inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) is increasing in Europe[1] and across the rest of the world.[2] Recent studies from Eastern Europe[3,4] have reported incidence rates comparable with Western European countries; however, the overall regional incidence of both CD and UC is twice as high in Western Europe as compared to Eastern Europe.[5] Changes in lifestyle in Eastern Europe during the last two decades have resulted in a more "westernised" standard of living. With many aspects of westernisation associated with a risk of IBD,[6] such changes – including an altered diet[7,8] – could partly explain the observed increases in the incidence of UC and CD in this geographic region.

The European Crohn's and Colitis Organisation's (ECCO) Epidemiological Committee (EpiCom) study is a prospective population-based inception cohort of 1560 unselected IBD patients diagnosed within 31 centres from Eastern and Western Europe during 2010. In EpiCom-study it was shown that incidence rates for CD and UC in Western European centres are twice as high as in Eastern European centres.[5] The aim of this study was to investigate differences in exposure to environmental factors between Eastern and Western European patients and whether these differences could explain the observed incidence gradient. Furthermore, to investigate the possible influence of environmental factors on disease presentation at diagnosis and disease outcome within the first year.

2. Materials and methods

2.1. Study population

During a one-year inclusion period from January 1st to December 31st 2010, all incident IBD patients living in predefined, well-described geographical areas were recruited from 31 centres in 8 Eastern and 14 Western European countries in the EpiCom-cohort. A total number of 1560 adult and paediatric IBD patients were included out of a total background population of 10.1 million inhabitants (3.3 million in Eastern and 6.8 million in Western Europe). Diagnostic criteria, time period of inclusion, recorded patient data, and ascertainment methods were standardised and consistent.[5] All incident patients were included and followed-up carefully as previously described.[5,9] Patients aged <15 years at diagnosis were excluded from this paper.

2.2. Definitions and disease classifications

Patients were diagnosed with CD, UC or IBD unclassified (IBDU) according to the *Copenhagen Diagnostic Criteria*.[10–12] Infectious gastroenteritis, endamoeba and cancer had to be ruled out in order to make the diagnosis. Patients who during follow-up ended up with not having IBD were excluded from the cohort. Disease classification of CD and UC regarding extent, localization and behaviour was defined using the *Montreal Classification*.[13] Medical treatment was grouped into five treatment groups of ascending potency of treatment: 5-aminosalicylates (5-ASA) (oral and/or topical 5-ASA treatment ± topical steroids), glucocorticosteroids (GCS) (oral steroids ± 5-ASA or topical steroids), immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine or methotrexate ± steroids), biologicals (infliximab or adalimumab in combination with any of the above), and surgery (major abdominal surgery due to IBD regardless of medical treatment prior to surgery). Immunomodulators were combined in one category due to the fact that 94% of patients received treatment with thiopurines. A severe disease course in UC was defined as any disease extent and a need of high dose GCS (0.5–1 mg/kg), and/or immunomodulators, and/or biologicals, and/or surgery, while severe CD was defined as the necessity for immunomodulators, and/or biologicals, and/or surgery within the first year after diagnosis.

2.3. Environmental factors questionnaire

Environmental factors prior to the development of IBD were assessed using a questionnaire developed by the International Organisation of Inflammatory Bowel Diseases (IOIBD). The questionnaire consists of 87 questions covering 25 different topics proposed to be environmental risk factors for CD and/or UC and has previously been used in IBD cohorts[14–16] and evaluated in a case–control study.[17] For statistical analysis items were grouped into fourteen parameters: smoking status at diagnosis, appendectomy before age 20, tonsillectomy before age 20, use of oral contraceptives, breastfeeding during infancy, childhood infections (measles, pertussis, rubella, chickenpox, mumps, and/or scarlet fever), vaccinations (tuberculosis, pertussis, measles, rubella, diphtheria, tetanus, and/or polio), high sugar consumption (≥2 of the following: sugar in coffee, sugar in tea, daily intake of soft drinks, sugar on breakfast cereals, sugar on porridge), high fibre intake (daily intake of ≥3 of the following categories: fruit, vegetables, whole meal bread, ≥4 pieces of bread, cornflakes, muesli), fast food consumption, high intake of caffeine (≥2 cups of coffee or tea per day), daily physical activity, access to running water at home, and IBD in first-degree relatives.

2.4. Data collection

Data regarding patient demographics and disease classification at diagnosis, as well as medical therapy including biological therapy, surgery, and hospitalizations, were collected at time of diagnosis and prospectively throughout the follow-up period. Validity of diagnostic and clinical data was secured by a variety of measures as previously described[5] including built-in control and validation tests, locked diagnostic criteria in the database, manual data standardisation, and random audits of case ascertainment and data quality at participating centres showing good consistency with the protocol. Patients were asked to complete the IOIBD environmental factors questionnaire either by themselves or, depending on educational level and whether local translations of the questionnaire exist, during an interview by the physician or IBD specialist trained nurses during an outpatient visit. Data were entered by physicians and/or IBD specialist trained nurses in the web-based EpiCom database.[18]

2.5. Statistical analysis

Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA). Demographics and disease classification between groups were compared with Chi-square test. The influence of environmental factors for CD and UC patients from both regions combined on disease classification at diagnosis, hospitalization, surgery, biological therapy, severe disease course, extra-intestinal manifestations at diagnosis, and highest treatment step reached during follow-up was analysed using multivariate logistic regression, while the impact on age of diagnosis was analysed with simple multivariate linear regression. Gender, age, and geographic region were included in the analysis, together with disease classification, when relevant, as these were considered confounding variables. Childhood infections and vaccinations were excluded from the analysis as they were highly correlated with year of birth. A p-value of <0.05 was considered statistically significant. Continuous variables are expressed as median (range) unless otherwise stated.

2.6. Ethical considerations

The study was approved by the local ethical committees according to local regulations. All patients gave written informed consent prior to answering the questionnaires.

3. Results

3.1. Description of study population

In total, 1182 patients (76% of the original cohort) aged 15 years or older at diagnosis answered the questionnaire after a median time of 1.1 months from diagnosis (range: 0–16 months). Of these, 444 (38%) had CD, 627 (53%) UC, and 111 (9%) IBDU. A total of 249 (21%) patients came from Eastern European centres while 933 (79%) patients came from Western European centres. Patients' demographic characteristics are presented in Table 1; no differences were found between the geographic regions except for highest treatment step reached during follow-up for CD and UC patients. Of the 368 patients who did not answer the questionnaire, 45 (4%) were <15 years at diagnosis and not invited to participate in this study and 333 (96%) did not give consent. Non-responding patients differed only in the distribution of diagnosis (the fraction of CD patients was larger and the fraction of IBDU patients was smaller compared to responders), and in terms of extra-intestinal manifestations (fewer patients had extra-intestinal manifestations compared to responders).

3.2. Environmental factors in European IBD patients

Occurrences of environmental factors in Western and Eastern European IBD patients are shown in Table 2. Geographic differences were found in terms of childhood vaccinations (tuberculosis, pertussis, measles, rubella, diphtheria, and polio) as significantly more CD and UC patients in Eastern Europe had received vaccinations against these agents compared with Western European patients ($p < 0.01$). Furthermore, for both CD and UC more Western European patients had experienced infections (measles, pertussis, and mumps) during childhood ($p < 0.01$). Regarding dietary risk factors, more Western European CD and UC patients reported high daily fibre intake as well as low daily sugar intake ($p < 0.01$). More Eastern than Western European UC patients had a daily consumption of fast food ($p < 0.01$).

Multivariate linear regression revealed several factors predicting age of diagnosis in CD and UC patients, shown in Table 3. Significant environmental factors from logistic regression analysis predicting disease phenotype and extra-intestinal manifestations at diagnosis, as well as surgery, hospitalization, biological therapy, severe disease course, and treatment step reached during follow-up are shown in Tables 4 and 5.

For CD patients disease behaviour was associated with risk of surgery during the first year of disease (non-penetrating, non-stricturing vs. penetrating disease: OR: 0.08, 95% CI: 0.03–0.22; stricturing vs. penetrating OR: 1.0, 95% CI: 0.43–2.33), a severe disease course (non-penetrating, non-stricturing vs. penetrating disease: OR: 0.18, 95% CI: 0.08–0.44; stricturing vs. penetrating OR: 0.86, 95% CI: 0.31–2.41), treatment step (non-penetrating, non-stricturing vs. penetrating disease: OR: 0.23, 95% CI: 0.13–0.42; stricturing vs. penetrating OR: 0.73, 95% CI: 0.37–1.43), and hospitalization (non-penetrating, non-stricturing vs. penetrating disease: OR: 0.27, 95% CI: 0.14–0.54; stricturing vs. penetrating OR: 0.89, 95% CI: 0.41–1.93).

In UC patients disease extent was associated with hospitalization (proctitis vs. extensive colitis OR: 0.24, 95% CI: 0.10–0.61; left-sided vs. extensive OR: 0.54, 95% CI: 0.31–0.95), biological therapy (proctitis vs. extensive colitis OR: 0.11, 95% CI: 0.01–0.84; left-sided vs. extensive OR: 0.49, 95% CI: 0.21–1.11), severe disease course (proctitis vs. extensive colitis OR: 0.14, 95% CI: 0.08–0.24; left-sided vs. extensive OR: 0.42, 95% CI: 0.29–0.62), and treatment step (proctitis vs. extensive colitis OR: 0.33, 95% CI: 0.21–0.54; left-sided vs. extensive OR: 0.57, 95% CI: 0.40–0.81).

4. Discussion

In this population-based inception cohort of unselected IBD patients from Eastern and Western Europe we have shown that patients in the geographic regions differ in terms of environmental factors present prior to diagnosis. Eastern European patients reported more vaccinations against tuberculosis, pertussis, measles, rubella, diphtheria, and polio, as well as fewer childhood infections with measles, pertussis, and mumps than Western European patients. Eastern European CD patients consumed less fibre and more sugar than CD patients in Western Europe. Daily fast food consumption was more frequent in Eastern European than in Western European UC patients.

The rapid increase in CD and UC incidence during the last decades is unlikely to be explained by a change in genetic susceptibility in the population alone. Westernisation of lifestyle, including an increased consumption of refined sugar, fatty acids, fast food, and reduced consumption of fruit, vegetables and fibres,[19] in the societies experiencing an increasing occurrence of IBD may, at least in part, be responsible for the recent changes[20] as many aspects of a western diet have been linked with a risk of IBD.[21–24] The substantial political and economic changes in countries from

Table 1 Patient characteristics of 1,182 incident patients from the ECCO-EpiCom cohort.

	Western European centres			Eastern European centres		
	CD	UC	IBDU	CD	UC	IBDU
No. of patients (%)	345 (37%)	483 (52%)	105 (11%)	99 (40%)	144 (58%)	6 (2%)
Male (%)	181 (52%)	269 (56%)	51 (49%)	58 (59%)	82 (57%)	4 (67%)
Female (%)	164 (48%)	214 (44%)	54 (51%)	41 (41%)	62 (43%)	2 (33%)
Age at diagnosis, years	35 (16–89)	39 (15–89)	38 (17–79)	31 (15–78)	36 (18–81)	30 (20–34)
Time to diagnosis, months	4.6 (0–374)	2.5 (0–255)	2.5 (0–362)	3.3 (0–126)	2.2 (0–240)	2.7 (0–38)
First degree relative with IBD	34 (10%)	55 (11%)	18 (17%)	7 (7%)	10 (7%)	1 (17%)
Extra-intestinal complications						
None	299 (87%)	436 (90%)	90 (86%)	83 (84%)	127 (88%)	5 (83%)
Skin	3 (1%)	6 (1%)	2 (2%)	2 (2%)	0 (0%)	0 (0%)
Eyes	4 (1%)	3 (1%)	2 (2%)	0 (0%)	1 (1%)	0 (0%)
Joints	33 (10%)	32 (7%)	8 (8%)	13 (13%)	12 (8%)	1 (17%)
Primary Sclerosing Cholangitis	0 (0%)	2 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Pancreatitis	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Other	4 (1%)	4 (1%)	3 (3%)	2 (2%)	1 (1%)	0 (0%)
Disease extent at diagnosis						
E1: Proctitis		95 (20%)			29 (20%)	
E2: Left-sided		204 (42%)			67 (47%)	
E3: Extensive colitis		184 (38%)			48 (33%)	
Disease location at diagnosis						
L1: terminal ileum	101 (30%)			38 (39%)		
L2: colonic	88 (26%)			20 (20%)		
L3: ileo-colonic	79 (23%)			24 (24%)		
L4: upper gastro-intestinal tract	25 (7%)			1 (1%)		
L1+L4	22 (6%)			5 (5%)		
L2+L4	10 (3%)			3 (3%)		
L3+L4	16 (5%)			7 (7%)		
Disease behaviour at diagnosis						
B1: non-stricturing, non-penetrating	212 (61%)			67 (68%)		
B2: stricturing	70 (20%)			19 (19%)		
B3: penetrating	28 (8%)			5 (5%)		
B1p: B1 + perianal	15 (4%)			1 (1%)		
B2p: B2 + perianal	3 (1%)			0 (0%)		
B3p: B3 + perianal	17 (5%)			7 (7%)		
Highest treatment step reached during follow-up						
0: No treatment	9 (3%)*	3 (1%)*	0 (0%)	0 (0%)	2 (1%)	0 (0%)
1: 5-ASA	46 (13%)*	236 (49%)*	50 (48%)	27 (27%)	88 (61%)	4 (67%)
2: GCS	58 (17%)*	127 (26%)*	30 (29%)	23 (23%)	34 (24%)	1 (17%)
3: Immunomodulators	117 (34%)*	80 (17%)*	12 (11%)	34 (34%)	17 (12%)	1 (17%)
4: Biological therapy	67 (19%)*	23 (5%)*	10 (10%)	5 (5%)	1 (1%)	0 (0%)
5: Surgery	48 (14%)*	14 (3%)*	3 (3%)	10 (10%)	2 (1%)	0 (0%)

* Difference between geographic regions, $p<0.05$

the former Soviet Union have e.g. resulted in an increased consumption of non-traditional, energy-dense processed foods[25,26] impacting on the risk of noncommunicable chronic diseases in these countries.[27] However, comparisons of dietary habits in Eastern and Western European countries are sparse and difficult to perform because of differences in methodology.[28] Dietary habits play an important role in shaping the microbiota of the human gut,[29] and a 'Westernised' diet is hypothesized to alter the intestinal microbiota towards a composition which increases the risk for the development of IBD.[8,30] However, most dietary studies have reported inconsistent findings regarding the role of dietary factors in the development of IBD.[31,32]

Previous studies have shown that a high consumption of dietary fibre, fruits and vegetables is inversely associated with the risk of CD.[17,21,23,24] In the present study significantly more Western European CD patients reported a high daily intake of all three food groups prior to the diagnosis. Additionally, more Eastern European CD and UC patients reported a high daily intake of sugar, including soft drinks. High daily sugar consumption was associated with an earlier age of diagnosis in CD and was inversely associated with the need for higher treatment steps during follow-up. Increased sugar intake has previously been linked to the development of CD[14,23,31] and soft drink consumption has been proposed as a possible risk factor for CD and UC,[33] although overall

Table 2 Environmental factors prior to diagnosis in Eastern and Western European patients with inflammatory bowel disease.

	Western Europe			Eastern Europe		
	CD	UC	IBDU	CD	UC	IBDU
Smoking status						
Never	141 (42%)	262 (56%)	50 (51%)	36 (37%)	77 (53%)	4 (67%)
Currently	120 (36%) **	38 (8%)	14 (14%)	37 (38%) **	16 (11%)	2 (33%)
Former smoker	76 (23%) **	168 (36%)	35 (35%)	25 (26%) **	51 (35%)	0 (0%)
Breastfeeding	223 (65%)	307 (64%)	64 (61%)	68 (69%)	92 (64%)	4 (67%)
Tonsillectomy	62 (18%)	82 (17%)	16 (15%)	21 (21%)	26 (18%)	3 (50%)
Appendectomy	45 (13%)	45 (9%) *	6 (6%)	12 (12%) **	3 (2%)	0 (0%)
Access to running water	312 (90%)	442 (92%)	90 (86%)	94 (95%)	126 (88%)	6 (100%)
Vaccinations:						
Tuberculosis	175 (51%) *	270 (56%) *	57 (54%)	78 (79%)	105 (73%)	5 (83%)
Pertussis	159 (46%) *	217 (45%) *	51 (49%)	75 (76%)	94 (65%)	4 (67%)
Measles	185 (54%) *	236 (49%) *	46 (44%)	67 (68%)	89 (62%)	5 (83%)
Rubella	177 (51%) *	226 (47%)	39 (37%)	63 (64%)	75 (52%)	3 (50%)
Diphtheria	184 (53%) * **	292 (60%) *	63 (60%)	75 (76%)	108 (75%)	5 (83%)
Tetanus	244 (71%)	361 (75%)	80 (76%)	79 (80%)	99 (69%)	4 (67%)
Polio	209 (61%) * **	342 (71%)	73 (70%)	73 (74%)	108 (75%)	4 (67%)
Childhood infections						
Measles	109 (32%) *	178 (37%) *	45 (43%)	14 (14%)	28 (19%)	0 (0%)
Pertussis	39 (11%) *	51 (11%) *	13 (12%)	1 (1%)	3 (2%)	0 (0%)
Rubella	82 (24%)	116 (24%)	26 (25%)	21 (21%)	26 (18%)	1 (17%)
Chicken pox	219 (63%)	319 (66%)	60 (57%)	68 (69%)	89 (62%)	5 (83%)
Mumps	64 (19%) **	131 (27%) *	33 (31%)	21 (21%)	23 (16%)	1 (17%)
Scarlet fever	32 (9%)	56 (12%)	7 (7%)	8 (8%)	10 (7%)	0 (0%)
Fruit daily	185 (54%) *	265 (55%)	57 (54%)	39 (39%)	67 (47%)	2 (33%)
Vegetables daily	204 (59%) *	287 (59%)	70 (67%)	41 (41%) **	79 (55%)	2 (33%)
Bread (≥4 slices/day)	159 (46%)	220 (46%) *	39 (37%)	49 (49%)	84 (58%)	3 (50%)
Eggs daily	24 (7%)	43 (9%) *	95 (90%)	13 (13%)	27 (19%)	1 (17%)
Muesli daily	28 (8%)	52 (11%) *	12 (11%)	6 (6%)	5 (3%)	0 (0%)
Cornflakes daily	41 (12%) *	39 (8%)	7 (7%)	5 (5%)	7 (5%)	0 (0%)
High fibre intake	148 (43%) *	223 (46%) *	57 (54%)	25 (25%)	48 (33%)	1 (17%)
High sugar intake	160 (46%) * **	188 (39%) *	36 (34%)	63 (64%)	99 (69%)	2 (33%)
Soft drink daily	80 (23%) * **	82 (17%) *	14 (13%) *	47 (47%)	68 (47%)	4 (67%)
Fast food daily	30 (9%)	33 (7%) *	4 (4%) *	10 (10%)	20 (14%)	3 (50%)
Juice daily	100 (29%)	131 (27%)	23 (22%)	21 (21%)	39 (27%)	3 (50%)
Coffee (≥2 cups/day)	126 (37%) *	206 (43%) *	39 (37%)	25 (25%)	39 (27%)	2 (33%)
Tea (≥2 cups/day)	95 (28%) *	128 (27%) *	29 (28%)	43 (43%)	73 (51%)	4 (67%)
Caffeine	182 (53%)	275 (57%)	56 (53%)	53 (54%)	81 (56%)	4 (67%)
Oral contraceptive use	49 (30%)	52 (24%)	11 (20%)	11 (27%) **	6 (10%)	1 (50%)
Daily physical activity	102 (30%)	176 (36%)	39 (37%)	39 (39%)	57 (40%)	3 (50%)

* Difference between geographic regions, $p < 0.05$.
** Difference between Crohn's disease and ulcerative colitis patients, $p < 0.05$.

evidence is inconsistent and subject to important methodological limitations such as the lack of prospective studies.[34] Furthermore, the question remains whether the high sugar intake is in fact a consequence of CD symptoms and patients are simply trying to counteract weight loss or fatigue.[35]

Overall, incidence rates for CD and UC were in this cohort found to be twice as high in Western Europe than in Eastern Europe,[5] but it would seem that Eastern European patients are exposed to a greater number of risk factors – some who have been confirmed in a Danish population-based inception cohort[17] – prior to diagnosis than Western European patients, thus supporting the hypothesis of Western diet as part of the explanation for the increasing incidence. However, due to the lack of a control group in this study the true impact of dietary habits in disease risk needs to be confirmed in further prospective studies. Also, since no previous study on the diet of Eastern European IBD patients pre-diagnosis is available for comparison we are not able to assess the changes in diet over time.

In a Swedish population-based case control study the consumption of fast food was associated with an increased risk of CD and UC.[36] In the present study more Eastern European than Western European patients reported daily consumption of fast food among those with UC but not CD, and daily consumption of fast food was associated with young age at diagnosis in both CD and UC as well as increased risk for surgery and severe disease extent in UC patients. Additionally, the proportion of patients reporting a high

Table 3 Factors predicting a young age at diagnosis for patients with Crohn's disease (CD) and ulcerative colitis (UC) in a European inception cohort.

	CD	UC
Male gender	p = 0.034	–
Current smoker	p = 0.004	–
Previous smoker	–	p < 0.001
Ever smoked	p < 0.001	–
No tonsillectomy < 20 yr	–	p = 0.013
No appendectomy < 20 yr	p = 0.002	p < 0.001
Breastfeeding during infancy	–	p = 0.014
Running water at home	p < 0.001	p < 0.001
Oral contraceptives	p < 0.001	p < 0.001
High sugar intake consumption	p = 0.006	–
Low daily caffeine intake	–	p < 0.001
Daily fast food consumption	p < 0.001	p < 0.001

caffeine intake was similar in both geographic regions for CD and UC, but high caffeine consumption was associated with the risk of surgery and a severe disease course during follow-up in CD and with the presence of extra-intestinal manifestations at diagnosis in UC patients. However, high caffeine intake was also inversely associated with young age at diagnosis. This is in conflict with other studies that mostly did not find a relationship between caffeine and IBD.[37] Whether fast food and caffeine directly influence the risk and course of IBD or are surrogate markers for e.g. psychological stress[38,39] or a higher consumption of bacteria in food remains to be proven.

The risk of CD and UC has consistently been reported to be increased by the use of oral contraceptives,[40] with the mechanism hypothesized to be multifocal, microvascular gastrointestinal infarctions.[41] In the present study the use of oral contraceptives was significantly associated with a young age at diagnosis. This conclusion, however, is biased due to the lack of a control group. Patients in this cohort are young and a high frequency of oral contraceptive use is expected. Furthermore, oral contraceptives in UC were inversely associated with requiring the highest necessary treatment step during follow-up as well as severe disease extent at diagnosis. The influence of oral contraceptives on disease course in IBD patients remains unclear.[42,43] However, a Danish inception cohort study found a similar relationship between use of oral contraception and disease localisation of UC.[15]

Appendectomy is thought to be inversely associated with the development of UC.[44,45] In this cohort significantly more Western than Eastern European UC patients reported an appendectomy before the age of 20. Additionally, in Eastern Europe more CD patients had an appendectomy prior to diagnosis than UC patients, in accordance with a Danish population-based cohort.[15] The association of appendectomy with CD is still unclear.[46] Interestingly, appendectomy decreased the odds of a severe disease course in CD patients as well as the need for biological therapy, whereas others have reported a worsened disease course.[47] Appendectomy was inversely associated with young age at diagnosis, in accordance with a previous Australian study.[48] No difference in the occurrence of breastfeeding during infancy between Eastern and Western Europe was found. Breastfeeding is thought to have a protective effect against CD and UC.[49] In this study we could not confirm this observation, since breastfeeding during infancy was found to be associated with young age at diagnosis as well as with the risk of presenting with extra-intestinal manifestations at diagnosis in CD.

In terms of childhood infections and vaccinations we observed significant geographic differences in both CD and UC patients. Vaccinations against tuberculosis, pertussis, measles, rubella, diphtheria, and polio occurred more frequently, while childhood infections with measles, pertussis, and mumps had occurred less frequently in Eastern European CD and UC patients compared to Western European patients. It has been hypothesized that a lack of exposures to enteric pathogens

Table 4 Environmental factors and Crohn's disease patients' subsequent risk (odds ratio, 95% CI) of hospitalization, surgery, biological therapy, severe disease course, extra-intestinal manifestations, high treatment step, and behaviour in a European inception cohort.

	Hospitalization	Surgery	Biological therapy	Severe disease course	Extra-intestinal manifestations	Treatment step	Disease behaviour
Age at diagnosis, per year	–	–	0.98 (0.96–1.0)	0.97 (0.96–0.99)	–	0.98 (0.97–0.99)	–
Being Eastern European	–	–	0.11 (0.03–0.36)	0.33 (0.19–0.58)	–	0.37 (0.23–0.60)	–
Current smoking	–	–	–	–	–	–	1.59 (1.03–2.44)
High intake of caffeine	–	2.18 (1.01–4.71)	–	1.86 (1.15–2.99)	–	1.84 (1.24–2.72)	–
Appendectomy	–	–	0.25 (0.07–0.83)	0.34 (0.17–0.66)	–	0.48 (0.27–0.86)	–
High daily sugar intake	–	–	–	0.53 (0.33–0.86)	–	–	–
Breastfeeding during infancy	–	–	–	–	2.34 (1.17–4.67)	–	–

Table 5 Environmental factors and ulcerative colitis patients' subsequent risk (odds ratio, 95% CI) of hospitalization, surgery, biological therapy, severe disease course, extra-intestinal manifestations, high treatment step, and extent in a European inception cohort.

	Hospitalization	Surgery	Biological therapy	Severe disease course	Extra-intestinal manifestations	Treatment step	Disease Extent
Age at diagnosis, per year	0.98 (0.96–1.0)	–	0.95 (0.92–1.0)	0.99 (0.98–1.0)	–	–	–
Female vs. male	–	–	–	–	2.14 (1.25–3.68)	–	0.68 (0.49–0.95)
Being Eastern European	0.31 (0.14–0.69)	–	0.08 (0.01–0.62)	0.55 (0.36–0.84)	–	0.43 (0.29–0.64)	–
IBD in 1st degree relatives	0.29 (0.09–0.95)	–	–	–	2.22 (1.10–4.51)	–	1.76 (1.07–2.89)
Never smoked	–	–	2.86 (1.21–6.75)	–	–	–	–
Oral contraceptive	–	–	–	–	–	0.51 (0.29–0.92)	0.56 (0.33–0.98)
Daily fast food intake	–	5.78 (1.88–17.76)	–	–	–	–	2.03 (1.17–3.52)
High intake of caffeine	–	–	–	–	2.86 (1.55–5.26)	0.67 (0.50–0.95)	–

during childhood is a risk factor for CD especially[50,51] and that multiple childhood infections and poor hygiene are protective against IBD.[52] In light of this hypothesis one could suggest that Eastern European patients in this cohort carried a risk for developing IBD due to more vaccinations and fewer infections during childhood, however, the observed differences could be skewed by recall bias. Furthermore, studies have focused on specific infectious agents like paromyxoviral infection and vaccination with inconsistent findings.[53–55] In this study the prevalence of childhood infections and vaccinations was highly correlated with year of birth, as the vaccination pattern apparently has changed during the lifetime of the patients included. Therefore only age at diagnosis was included in the analysis.

Finally, the impact of smoking on the risk and severity of CD and UC has been thoroughly investigated. Active smoking is a risk factor for developing CD while being protective against UC.[56,57] In accordance with this, in both regions more CD patients than UC patients were current smokers at diagnosis, while more UC than CD patients were previously smokers. The frequency of smokers and former smokers was similar to estimations from the European Union.[58] Current smoking at diagnosis was positively associated with more severe disease behaviour and young age at diagnosis in CD, while previous smoking was associated with young age at diagnosis in UC patients. UC patients who had never smoked prior to diagnosis had higher odds of needing biological therapy during the first year of disease.

The primary strength of this study was that the EpiCom cohort is population-based, that patients were prospectively included and followed up, and that the cohort consists of unselected IBD patients thus representing the broad spectrum of disease from mild to severe cases. Data quality and validity as well as consistency between centres were ensured by various measures described elsewhere.[5] Furthermore, a short duration from onset of symptoms to diagnosis,[5] as well as the fact that patients answered the questionnaire very close to the date of diagnosis to some extent reduced the risk of recall bias concerning e.g. dietary habits prior to the IBD diagnosis. However, a number of important limitations need to be considered. The IOIBD questionnaire, although previously used,[14–17] has never been validated or, to our knowledge, properly forward/backward translated into languages other than English. Because of the cost of such a validation and translation process and since the IOIBD questionnaire was constructed by an expert group and never tested in other specialist group, patients or IBD nurses it was decided in the EpiCom-group not to include a validation in the protocol. Also, in this study if patients were not able to fill out the questionnaire by themselves the doctor or IBD specialist nurse completed the questionnaire together with the patient and this could have introduced bias in the results. Questions regarding factors from early life such as vaccinations and infections are most likely subject to reporting and recall bias, while questions regarding dietary factors could be biased by misclassifications by the patients. Furthermore, some questions in the questionnaire are broad and might not capture the intended exposure of the environmental factor. Also, by including this large number of risk factors in the analysis, some associations found might be due to chance alone. Additionally, the study is limited by the fact that information on regional dietary habits and vaccination status was unavailable in several participating centres and a comparison of dietary habits between IBD patients and the background population therefore was not possible. Last and most important, since no control group was included in this study it remains to be investigated whether environmental factors influencing the IBD patients in this cohort differ from the background population, and the associations with disease presentation and course need to be further investigated.

To conclude, in this population-based inception cohort of unselected IBD patients from Eastern and Western Europe the

geographic regions differed in terms of environmental factors prior to diagnosis. The observed differences could not explain the West–East gradient in IBD incidence in Europe, but Eastern European patients exhibited higher occurrences of suspected risk factors included in the Western lifestyle for IBD, which lends support to the theory of Westernisation of lifestyle having a main role in the recent increases in IBD incidence in Eastern Europe. However, these findings demand further investigation through controlled trials.

Conflict of interest

No authors reported any conflict of interest.

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