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Smoking, breastfeeding, physical inactivity, contact with animals, and size of the family influence the risk of inflammatory bowel disease: A Slovak case–control study

Tibor Hlavaty, Jozef Toth, Tomas Koller, Anna Krajcovicova, Stanislava Oravcova, Zuzana Zelinkova and Martin Huorka

Abstract

Background: The aetiology of inflammatory bowel disease (IBD) is not known but is likely to involve a combination of genetic predisposition and environmental risk factors. Smoking has been associated consistently with a higher risk of Crohn's disease (CD), while appendectomy and smoking appear to diminish the risk of ulcerative colitis (UC). The roles of other environmental factors are unclear. The aim of the present study was to evaluate the association of CD and UC with several environmental risk factors.

Methods: This case–control study included 338 patients (190 CD, 148 UC) and 355 controls. All subjects completed a detailed questionnaire regarding breastfeeding duration, history of helminthic infections, allergic diseases, appendectomy, household size, housing type, contact with specific domestic animals, physical activity, and smoking. Associations between risk factors and CD and UC were investigated by univariate and multivariate analysis.

Results: On multivariate analysis, CD associated with smoking at diagnosis (odds ratio, OR, 3.7, 95% CI 2.2–6.2; $p < 0.001$), being breastfed for <6 months (OR 2.7, 95% CI 1.7–4.4; $p < 0.001$), and less than two childhood sporting activities weekly (OR 2.7, 95% CI 1.5–5.0; $p < 0.001$) and inversely associated with frequent contact with cats in childhood (OR 0.6, 95% CI 0.4–0.9; $p < 0.03$). UC associated with less than two sporting weekly activities in childhood (OR 2.0, 95% CI 1.1–3.5, $p = 0.02$), fewer household members in childhood (OR 0.8, 95% CI 0.7–0.98, $p = 0.03$), and being breastfed for <6 months (OR 1.7, 95% CI 1.02–2.8, $p = 0.04$). A composite environmental risk index for CD revealed that 47 and 14% of the controls and patients with CD had no risk factors, respectively, and that 14 and 38% of the controls and patients with CD had at least two risk factors, respectively.

Conclusion: CD and UC associated with infrequent childhood sports activities and short breastfeeding. Furthermore, CD associated with smoking and infrequent contact with animals in childhood. UC associated with a smaller family size in childhood.

Background

Inflammatory bowel diseases (IBD) are chronic inflammatory conditions of the gastrointestinal tract and include Crohn's disease (CD) and ulcerative colitis (UC).

Despite extensive research into the aetiology of IBD, their cause remains unknown. At present, it is widely believed that IBD is induced by a multifactorial interplay of three elements, namely genetic susceptibility, mucosal immunity, and environmental risk

University Hospital Bratislava, Bratislava, Slovakia

Corresponding author:
Tibor Hlavaty, Gastroenterology Unit, Department of Internal Medicine V, University Hospital Bratislava, Ruzinovska 6, SK-82606 Bratislava, Slovakia.
Email: tibor.hlavaty2@gmail.com

factors.[1] Since the discovery of the NOD2 gene in 2001, there has been major progress in the research into IBD genetics.[2] Genetic studies have identified several dozens of susceptibility genes; these genes are mostly involved in the mucosal immune defence mechanisms against microorganisms that invade the mucosa.[3] Infectious aetiologies have also been studied extensively but a single causative microbial agent has never been confirmed.

The dramatic 4-fold increase in the incidences of both CD and UC in the past decades cannot be attributed solely to genetic predisposition because this cannot change that fast. It is more likely that environmental risk factors play an important role in triggering IBD in genetically predisposed individuals.

A number of environmental risk factors were suggested to be associated with CD and/or UC, including: smoking; appendectomy; oral contraception; insufficient breastfeeding; a diet rich in sugar, fat, and protein; a diet poor in vegetable and fruits; a fast food diet; dietary components, such as saccharin, carrageen, margarine, and cola; insufficient contact with farm animals; a sedentary lifestyle; left-handedness; psychosocial stress factors; dietary microparticles of aluminum, titanium, and silicon oxides, calcium phosphate; and refrigeration.[4–11]

The only replicated and widely recognized environmental risk factor for CD is smoking,[12] while only smoking and appendectomy have been shown consistently to protect from UC.[9,12] Further analysis of the other proposed environmental factors have yielded inconsistent or contradictory results. Thus, the environmental trigger(s) of IBD remain unresolved and further studies are needed.

The aim of the present study was to evaluate the association of CD and UC with several known and suspected environmental risk factors. To do so, a multifactorial analysis was performed.

Methods

This case–control study involved a cohort of patients who were followed up between 2008 and 2009 in the IBD Centre of the Department of Internal Medicine, Division of Gastroenterology and Hepatology, University Hospital Bratislava, Ruzinov.

Patient cohort

The patient cohort consisted of 338 consecutive patients with IBD: 190 patients with CD and 148 patients with UC. The diagnosis of all patients was based on conventional clinical, endoscopic, radiological, and histological criteria. Before the next visit at our department, the patients completed a paper version of the questionnaire in our department ($n = 145$) or were asked during their visit to complete the same questionnaire via a secured internet site upon subsequent email notification (193 patients responded of 205 notified).

The demographic data and clinical characteristics of the patients were recorded. The clinical data were categorized according to the Montreal classification.[13]

Control group

The control group consisted of 355 healthy volunteers who were age- and sex-matched with the patient group. Family members of patients with IBD were excluded. The healthy volunteers were mostly recruited from the healthy accompanying persons of non-IBD patients or the medical students and staff members of our department and their acquaintances. The control group subjects completed the questionnaire discussed above.

The clinical and demographic characteristics of the patient and control groups are shown in Table 1.

The questionnaire

The questionnaire that was completed by both cohorts consisted of 44 questions concerning socioeconomic status, medical and surgical history, and exposure to environmental risk factors, namely the length of the breastfeeding period, history of helminth infections, history of allergic diseases, history of frequent respiratory diseases, history of appendectomy and tonsillectomy, concomitant medication, family history, number of older and total siblings, type of housing in childhood and at present, type of housing neighbourhood, contact with particular animals at least once weekly in childhood and at present (frequent contact), education level, profession, and frequency of sporting activities in childhood and at present. There were also questions on smoking at the time of diagnosis and at present.

Statistical analysis

Statistical analyses were performed by using appropriate statistical tests in the statistical software SPSS 18.0 (IBM SPSS, Chicago, IL, USA). In terms of nominal variables the patient group was compared to the control group by using the chi-squared test with Yate's correction. The parametric data were tested with Student's t-test or ANOVA techniques, while the nonparametric data were tested with a non-parametric test (Mann–Whitney U-test). Categorical ordinal variables were also tested with the Mann–Whitney U-test. Multivariate testing was performed in CD and UC cohorts separately by using multivariate logistic

Table 1. Demographic and clinical characteristics of the patient and control groups

Characteristic	Controls ($n = 355$)	Crohn's disease ($n = 190$)	Ulcerative colitis ($n = 148$)
Female/male	188/167 (53/47)	112/78 (59/41)	95/53 (64/36)
Age (years)	28 (16–81)	31 (16–87)	34 (14–73)
Age at diagnosis (years)	–	24.7 (4–63)	28.2 (5–71)
0–16 years	–	21 (12)	13 (9)
17–40 years	–	138 (78)	95 (68)
41 + years	–	17 (10)	31 (22)
Disease duration (years)	–	3.8 (0–40.9)	4.3 (0–38.8)
Location of disease			
Crohn's disease			
Ileum (L1)	–	63 (36)	–
Colon (L2)	–	39 (22)	–
Ileum and colon (L3)	–	71 (40)	–
Upper GIT (L4)	–	3 (2)	–
Perianal involvement	–	51 (27)	0
Ulcerative colitis			
Proctitis (E1)	–	–	27 (20)
Left-sided (E2)	–	–	63 (47)
Pancolitis (E3)	–	–	44 (33)
Behaviour in CD			
Inflammatory (B1)	–	103 (54)	–
Stenosing(B2)	–	34 (18)	–
Fistulizing (B3)	–	53 (28)	–
Abdominal IBD surgery	–	40 (21)	5 (3)
Total colectomy	–	2 (5)	3 (60)
Partial colectomy	–	5 (12)	1 (20)
Ileocaecal resection	–	28 (70)	0
Segmental ileal resection	–	4 (10)	0
Other	–	1 (3)	1 (20)

Values are median (range) or *n* (%). CD, Crohn's disease; IBD, inflammatory bowel disease.

regression method as well as classification tree method according to in-built algorithms in SPSS 18.0.[14] *p*-values <0.05 were considered to be statistically significant. In multiple univariate analyses, the *p*-values were adjusted using the Bonferroni correction.

Ethical considerations

All subjects provided written permission to use the collected data for research purposes.

Results

The associations between the potential risk factors and CD or UC were determined by performing univariate analyses and then by performing multivariate logistic regression and classification tree analyses.

Univariate analyses of childhood environmental risk factors

Univariate analyses of the childhood environmental factors (Table 2) revealed that the control group was significantly less likely to have been breastfed for less than 6 months than either the CD cohort ($p < 0.001$) or the UC cohort ($p = 0.04$). These data are displayed in Figure 1. The IBD patients were also more likely to have grown up in smaller families ($p = 0.03$). Correspondingly, the control subjects had an average family size sharing a household in childhood of 3.8 ± 1.4, whereas the equivalent family sizes in the CD and UC cohorts were 3.5 ± 1.4 ($p = 0.006$) and 3.3 ± 1.5 ($p < 0.001$), respectively. The third observation was that the CD cohort was less likely to have frequent contact with animals in childhood than the controls

Table 2. Comparison of the inflammatory bowel disease cohorts with the control group in terms of childhood factors

Factor	Controls (n = 355)	Cohort CD (n = 190)	UC (n = 148)
Breastfeeding duration (months)	8.0 ± 5.6	7.1 ± 7.4	8.0 ± 7.5
0–5 months	94 (32)	69 (53.5)**	42 (43.8)**
6–12 months	164 (56)	44 (34)	41 (43)
12 + months	35 (12)	16 (12)	13 (14)
Family			
People in family	3.8 ± 1.4	3.5 ± 1.4*	3.3 ± 1.5**
Children in family	1.9 ± 1.3	1.6 ± 1.3*	1.6 ± 1.1*
Older siblings	1.0 ± 1.1	1.0 ± 1.4	0.9 ± 1.0
Infections in childhood (yes/no)			
Frequent respiratory infection	127/187 (40/60)	61/88 (41/59)	40/78 (34/66)
Ascaris infection	83/212 (28/72)	40/105 (28/72)	35/82 (30/70)
Any parasitic infection	16/267 (6/94)	7/126 (5/95)	8/109 (7/93)
Settlement in childhood			
Village	122 (35)	61 (33)	54 (37)
Town <20,000	57 (16)	34 (18)	30 (20)
City >20,000	169 (49)	92 (49)	64 (43)
Frequent contact with animals in childhood	267 (75)	121 (64)**	107 (72)
Dogs	221 (62)	98 (52)*	87 (59)
Cats	161 (45)	68 (36)*	68 (46)
Poultry	157 (44)	70 (37)	54 (37)
Cattle	36 (10)	10 (5)*	11 (7)
Horses	19 (5)	6 (3)	9 (6)
Pigs	81 (23)	37 (20)	35 (24)
Small rodents	51 (14)	28 (15)	16 (11)
Sporting activity in childhood			
Never	21 (6)	19 (10)**	15 (10)*
Once per week or less	35 (10)	45 (24)**	25 (17)*
Twice and more per week	291 (84)	121 (65)**	106 (73)*

Values are mean ± SD or *n* (%). *Statistical difference vs. controls ($p < 0.05$). **Statistical difference vs. controls ($p < 0.001$). CD, Crohn's disease; UC, ulcerative colitis.

($p = 0.005$). The patients with CD had less frequent contacts with dogs ($p = 0.02$), cats ($p = 0.03$), and cattle ($p = 0.049$). Finally, the control subjects did more sports in childhood: i.e. were significantly less likely to undergo infrequent sporting activity (less than twice a week) than the CD ($p < 0.001$) and UC cohorts ($p = 0.02$). These data are shown in Figure 2.

Univariate analyses of socioeconomic environmental risk factors

The analysis of the socioeconomic environmental factors is shown in Table 3. The controls were more likely to have a university education than the CD and UC cohorts.

Univariate analyses of smoking and comorbidities

Finally, the smoking and medical comorbidities of the cohorts were analysed (Table 4). The patients in the CD and UC groups were more likely to have been smoking at the time of diagnosis than the control subjects ($p < 0.001$ for both comparisons). The patients in the CD cohort were also more likely to have undergone an appendectomy than the control subjects ($p < 0.001$). The UC cohort patients were also more likely to have depression than the control subjects ($p = 0.01$).

Multivariate analyses in CD

Next, the risk factors associated with CD were subjected to multivariate logistic regression analysis
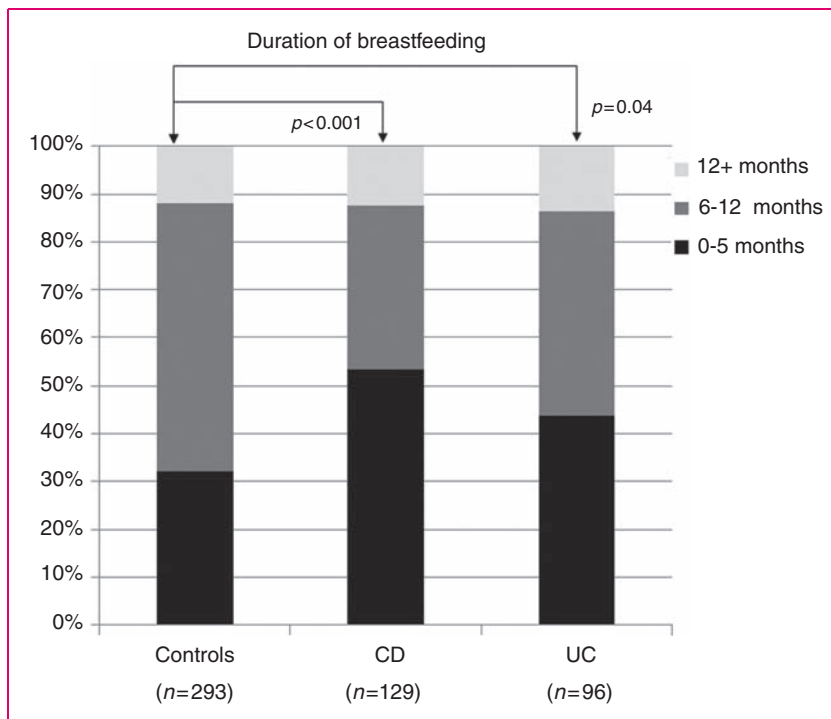
Figure 1. Breastfeeding duration in the inflammatory bowel disease cohorts and the control group.
p-values are relative to the control group. CD, Crohn's disease; UC, ulcerative colitis.

Figure 2. Sporting activity in childhood in the inflammatory bowel disease cohorts and the control group.
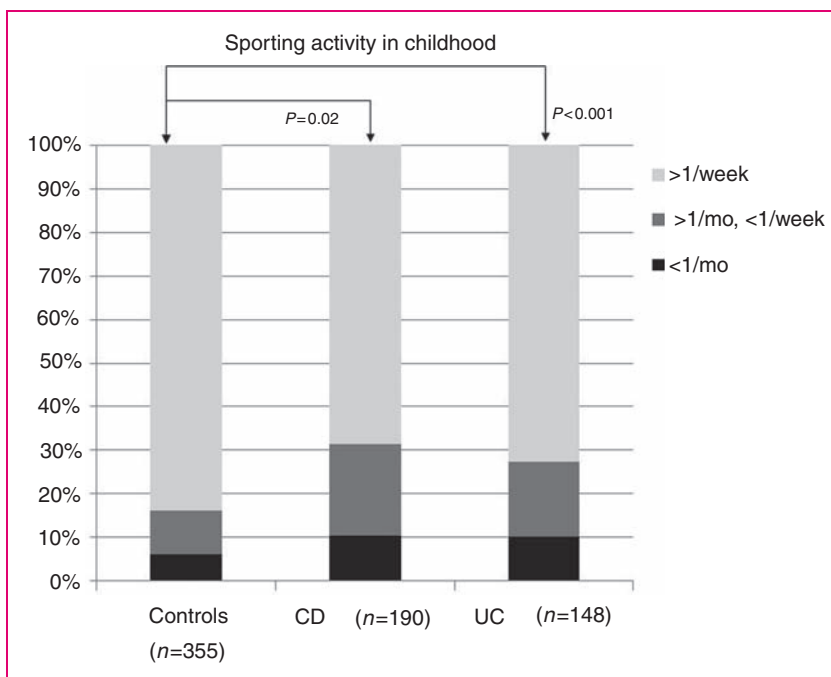*p*-values are relative to the control group. CD, Crohn's disease; UC, ulcerative colitis.

Table 3. Comparison of the IBD cohorts with the control group in terms of socioeconomic factors

Factor	Controls (n = 355)	Cohort CD (n = 190)	Cohort UC (n = 148)
Settlement			
Village	86 (24)	52 (28%	44 (30)
Town <20,000	33 (9)	33 (18)	17 (12)
City >20,000	235 (66)	103 (55)	87 (59)
Housing type			
Apartment	196 (57)	115 (64)	88 (61)
Family house	135 (39)	62 (34)	55 (38)
Other	13 (4)	4 (2)	2 (1)
Education			
Primary	55 (16)	32 (17)	27 (19)
Secondary	98 (28)	80 (44)	63 (43)
University	200 (57)	72 (39)**	56 (38)**
Profession			
Manual work	49 (15)	40 (23)*	39 (27)*
Sedentary work	290 (86)	136 (77)	108 (74)

Values are n (%). *Statistical difference vs. controls ($p < 0.05$). **Statistical difference vs. controls ($p < 0.001$). CD, Crohn's disease; UC, ulcerative colitis.

Table 4. Comparison of the IBD cohorts with the control group in terms of smoking and comorbidities

Factor	Controls (n = 355)	Cohort CD (n = 190)	Cohort UC (n = 148)
Smoking at diagnosis	69 (19)	80 (42)**	53 (36)**
Daily number of cigarettes at Dx	2.3 ± 6.0	4.3 ± 6.2**	4.1 ± 7.2*
Duration of smoking at Dx (years)	4.1 ± 8.6	2.5 ± 5.0	3.4 ± 6.9
Appendectomy	25 (7.0)	41 (21.6)**	10 (6.8)
Tonsillectomy	64 (18)	35 (18)	24 (16)
Depression	12 (3)	13 (7)	13 (9)*
Eczema	71 (20)	41 (22)	30 (20)
Allergic rhinoconjunctivitis	66 (19)	35 (18)	24 (16%
Allergy: self reported	112 (32)	67 (35)	51 (35)
Pollen	51 (14)	34 (18)	24 (16)
Dust mite	34 (10)	18 (10)	15 (10)
Food	21 (6)	15 (8)	10 (7)

Values are mean ± SD or n (%). *Statistical difference vs. controls ($p < 0.05$). **Statistical difference vs. controls ($p < 0.001$). CD, Crohn's disease; Dx, diagnosis; UC, ulcerative colitis.

(Table 5). Four independent environmental risk factors for CD were identified: smoking at the time of diagnosis (OR 3.7, 95% CI 2.2–6.2), being breastfed for less than 6 months (OR 2.7, 95% CI 1.7–4.4), doing sporting activities less than twice a week in childhood (OR 2.7, 95% CI 1.5–5.0), and infrequent contact with cats in childhood (OR 1.7, 95% CI 1.1–2.8).

Classification tree analysis is a multivariate statistical analysis that is based on the classification of cohorts into subgroups according to significant input variables at each node. This maximizes the composite predictive value. The results of the classification tree analysis are shown in Figure 3. The data showed that 39% of the control cohort subjects did not have any risk factors; only 9% of the CD cohort patients had no risk factors.

Multivariate analyses in UC

The risk factors associated with UC were subjected to multivariate logistic regression analysis (Table 6). Three independent environmental risk factors for UC were identified: being breastfed for less than months (OR 1.7, 95% CI 1.02–2.8), less than two sporting activities per week in childhood (OR 2.0, 95% CI 1.1–3.5), and the number of household members in childhood (OR 0.8, 95% CI 0.7–0.98).

Environmental risk index

The three significant variables that associated with CD in multivariate analyses, namely smoking at diagnosis (OR 3.7), being breastfed for less than 6 months (OR 2.7), and less than two sporting activities per week in childhood (OR 2.7), were then combined into a new composite index called the environmental risk index (ERI). In this index, the presence of each particular risk factor adds one point for the subject. Thus, when a subject has no risk factors, the ERI is 0, whereas the presence of all three risk factors yields an ERI of 3. In the ERI = 0 group, there were 137 (47%) controls and 18 (14%) patients with CD. In the ERI = 1 group, there were 112 (39%) controls and 60 (48%) patients with CD. In the ERI = 2 group, there were 37 (13%) controls and 42 (33%) patients with CD. In the ERI = 3 group, there were three (1%) controls and six (5%) patients with CD. The data are shown in Figure 4.

Finally, the theoretical prevalence of CD in particular ERI subgroup was calculated on the basis of the data observed in this study. The calculated theoretical prevalence of CD in particular ERI subgroups are shown in Table 7. The increasing prevalence of risk factors in the population increased the theoretical prevalence of CD from 30 in the no-risk population to 124 (one risk factor), 259 (two risk factors), and 505 (all three risk factors).

Table 5. Multivariate logistic regression of environmental factors associated with Crohn's disease

Step	Variable	B	SE	*p*-value	OR (Exp(B))	95% CI for EXP(B) Lower	95% CI for EXP(B) Upper
1a	Smoking at diagnosis	1.290	0.266	0.000	3.634	2.156	6.127
	Breastfeeding for less than 6 months	0.961	0.252	0.000	2.615	1.596	4.287
	Frequent contact with animals in childhood	0.212	0.421	0.615	1.236	0.541	2.823
	Contact with dogs in childhood	0.070	0.368	0.850	1.072	0.521	2.207
	Contact with cats in childhood	0.604	0.328	0.065	1.829	0.962	3.478
	Contact with poultry in childhood	−0.511	0.330	0.121	0.600	0.314	1.145
	Contact with cattle in childhood	0.918	0.578	0.112	2.505	0.807	7.779
	Less than two sporting activities per week in childhood	0.999	0.322	0.002	2.717	1.445	5.106
	Number of siblings	−0.049	0.104	0.636	0.952	0.776	1.168
	Number of household members	−0.067	0.093	0.467	0.935	0.779	1.121
	Constant	−2.586	0.705	0.000	0.075		
7a	Smoking at diagnosis	1.314	0.260	0.000	3.722	2.235	6.200
	Breastfed for less than 6 months	0.999	0.247	0.000	2.716	1.674	4.409
	Contact with cats in childhood	0.549	0.253	0.030	1.732	1.054	2.845
	Less than twosporting activities per week in childhood	1.004	0.314	0.001	2.730	1.477	5.048
	Constant	−2.186	0.270	0.000	0.112		

Step 1a, input-independent variables; Step 7a, output-independent variables; B, coefficient in the correlation equation; SE, standard error of B; *p*, level of statistical significance for a particular factor; OR, odds ratio, CI, confidence interval for the odds ratio.

Discussion

In the present study, a wide range of potential environmental risk factors (48 in total) were analysed in CD and UC cohorts and an age- and sex-matched control group. Multivariate analyses revealed that CD associated with four independent environmental risk factors, namely smoking at the time of diagnosis, less than two sporting activities per week in childhood, being breastfed for less than 6 months, and frequent contact with cats in childhood. In addition, UC associated significantly with three independent environmental risk factors, namely less than two sporting activities per week in childhood, the number of household members in childhood, and being breastfed for less than 6 months.

Limitations

This study had three major limitations. Firstly, there were only 190 and 148 patients with CD and UC, respectively. While this size is comparable to those in similar studies[15–18] and allows for good univariate analyses, it limits the scope of multivariate analyses to study interactions between factors to a maximum of two or three factors. The second limitation was the recall bias of the data, especially with regard to the early childhood data and multiple questions. It is difficult to design a retrospective study that solves this type

of error.[19] However, we believe there is no reason to think that the recall bias was different in the control and study cohorts. The third possible source of error was interaction bias of particular factors.[20] In the present study, a strong interaction was observed between contact with different animals in childhood; there was also covariance between the number of siblings and the size of the family in childhood.

Smoking

Smoking was the strongest CD-associated risk factor in the present study. Our observation is in line with those of several studies, including a recent meta-analysis.[12] The effects of smoking on IBD have been reviewed extensively elsewhere.[6] It is possible that smoking promotes CD by suppressing immune functions and/or reducing intestinal motility.[21,22] Contrary to most published data, we have found also more smokers in the UC cohort than among controls. Although we do not have a clear explanation, it might be that the UC patients were older at diagnosis or had longer duration of disease and that in the past the smoking rate in Slovakia was much higher than today.

Sporting activity

Less than two sporting activities per week in childhood was a risk factor for both CD and UC in the
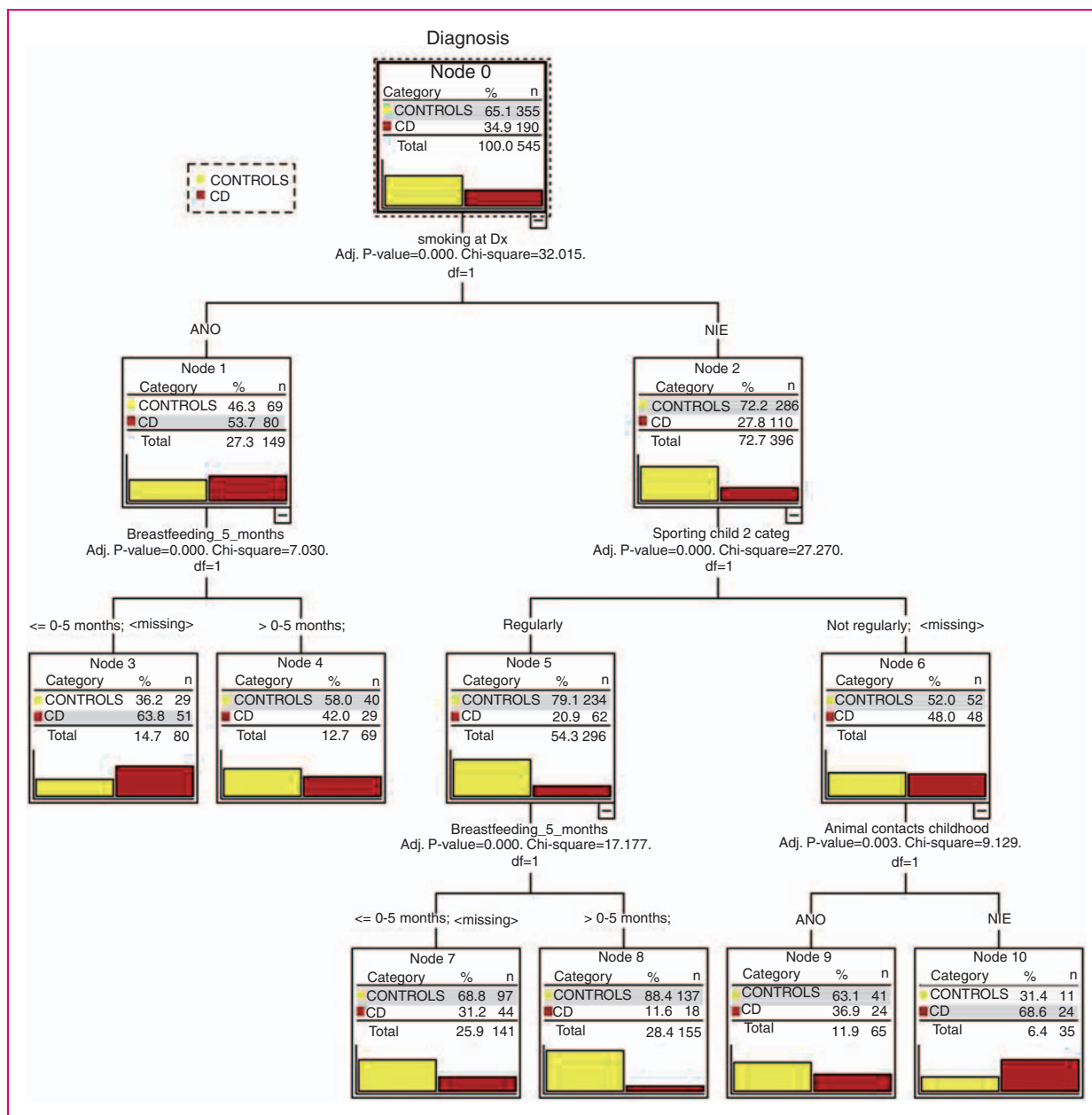
Figure 3. Results of multivariate classification tree analysis of the Crohn's disease and control groups.
ANO, yes; CD, Crohn's disease; Adj. P value, *p*-value adjusted after Bonferroni correction; df, degrees of freedom; Dx, diagnosis; NIE, no; Breastfeeding_5_months, Breastfed for less than or equal to 5 months (less than 6 months); Sporting child 2 categ, less than two sporting activities per week in childhood; Animal contacts childhood, contact with animals in childhood at least once per week.

present study. While Sonnenberg[10] found that IBD associated with sedentary professions, such as administrative work, sales work, hair dressing, or health professions,[10] this observation was not confirmed in a large prospective Danish population study.[23] A study by Persson et al.[24] revealed that the relative risk (RR) of CD related inversely to regular physical activity: for weekly and daily exercise, the estimated RRs were 0.6 (95% CI 0.4–0.9) and 0.5 (95% CI 0.3–0.9),

respectively. Similar observations were reported also by Klein et al. in an Israeli study.[25] Regular physical activity has a complex positive effect on a person's health: it increases the muscular mass and strength, improves bone density, improves cardiovascular and pulmonary functions, enhances immune system parameters, and eliminates the negative effects of stress on the organism.[26,27] The mechanism by which sporting protects from IBD is not known.

Table 6. Multivariate logistic regression of environmental factors associated with ulcerative colitis

Step	Variables	B	SE	p-value	OR (Exp(B))	95% CI for EXP(B) Lower	Upper
Step 1a	Breastfed for less than 6 months	0.500	0.258	0.053	1.650	0.994	2.740
	Less than two sporting activities per week in childhood	0.670	0.295	0.023	1.953	1.095	3.484
	Number of siblings	−0.037	0.102	0.716	0.964	0.789	1.177
	Size of the family in childhood	−0.200	0.095	0.036	0.819	0.680	0.987
	Appendectomy	0.022	0.535	0.967	1.023	0.358	2.919
	Number of cigarettes per day at diagnosis	0.027	0.019	0.170	1.027	0.989	1.067
	Constant	0.179	0.679	0.792	1.196		
Step 4a	Breastfed for less than 6 months	0.526	0.257	0.041	1.692	1.022	2.801
	Less than two sporting activities per week in childhood	0.687	0.293	0.019	1.988	1.119	3.534
	Size of the family in childhood	−0.202	0.095	0.033	0.817	0.679	0.984
	Constant	0.244	0.380	0.520	1.277		

Step 1a, input-independent variables; Step 4a, output-independent variables; B, coefficient in the correlation equation; SE, standard error of B; p, level of statistical significance for a particular factor; OR, odds ratio, CI, confidence interval for the odds ratio.
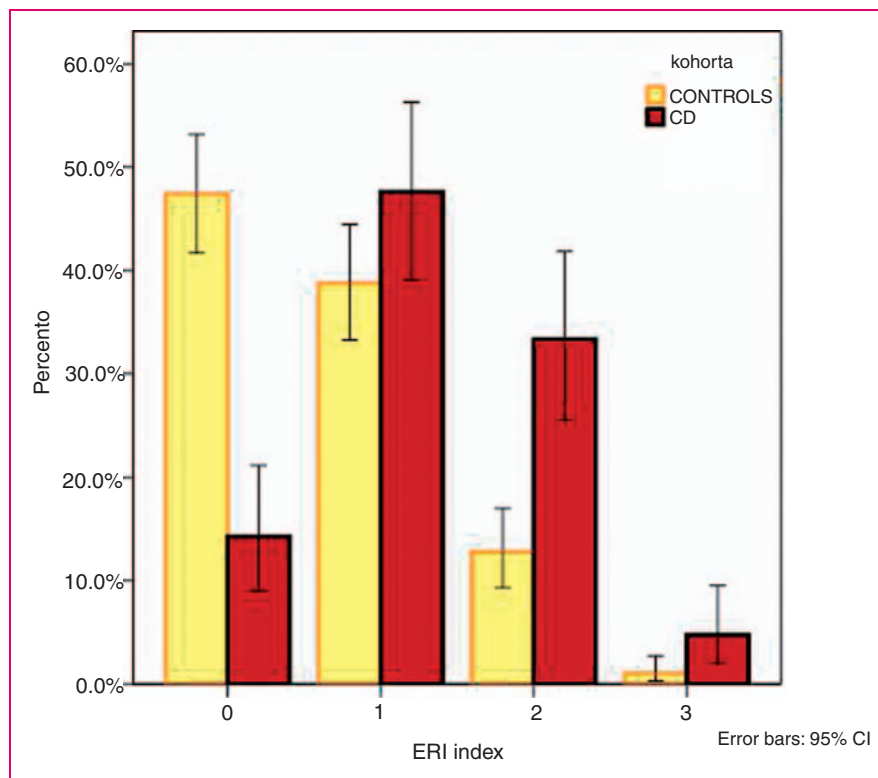
Figure 4. Frequencies of environmental risk indices (ERI) 0, 1, 2, and 3 in the control and Crohn's disease (CD) cohorts.

Breastfeeding

Being breastfed for less than 6 months was a risk factor for both CD (OR 2.7) and UC (OR 1.7). This finding is in line with that of a meta-analysis of 17 published studies on breastfeeding and IBD that showed protective effect of breastfeeding with a cumulative OR of 0.67 (95% CI 0.52–0.86) for CD and an OR of 0.77 (95% CI 0.61–0.96) for UC.[28] However, in a subgroup of studies that were of the highest methodological quality, the observed protective effect was even higher: the OR for CD was 0.45 (95% CI 0.26–0.79), while that for UC was 0.56 (95% CI 0.38–0.81). Another two recent studies have also confirmed the link between short breastfeeding and IBD.[29,30] However, another recent large multicentre study from southern Italy found no

Table 7. Theoretical prevalence of CD in ERI subgroups on the basis of the observed ERI index frequencies and the prevalence of CD in Slovakia

| ERI index | Frequency of ERI[a] | | In ERI subgroup | | |
	Healthy controls	CD group	Healthy controls[b]	CD patients[b]	Calculated prevalence of CD[c]
0	47	14	47,385	14	30
1	39	48	38,762	48	124
2	13	33	12,762	33	259
3	1	5	991	5	505
Total	100	100	99,900[d]	100[d]	

[a]Frequencies (%) based on the observed frequencies among controls and CD group in this study.
[b]Calculated number of persons in ERI subgroup, which is based on the frequencies of ERI and prevalence of CD in Slovakia.
[c]*n* per 100,000.
[d]Estimated prevalence of Crohn's disease in Slovakia per 100,000.
CD, Crohn's disease; ERI, environmental risk index.

association whatsoever.[31] The mechanism by which breastfeeding protects from IBD is not precisely known. It may help to optimize the gut microflora of the infant, promote the maturation of the mucosal immune system and intestinal mucosa, and have positive psychological and emotional effects.

Contact with animals

Infrequent contact with animals in childhood (defined as less than once per week) was another independent risk factor for CD (OR 1.7), but not for UC, in the present study. In the univariate analyses, this association was significant for contact with cats, dogs, and cattle. These observations are consistent with the results of several large studies. A large German paediatric study on 444 patients with CD, 304 patients with UC, and 1260 control subjects revealed that contact with animals in early childhood had a significant protective effect (for CD: OR 0.5, 95% CI 0.3–0.8; for UC: OR 0.3, 95% CI 0.2–0.6). This effect was even stronger in the subgroup of children who had frequent contact with animals in the first year of life. Similar to the present results, particularly contact with cats and cattle had a significant protective effect. Another case–control study from Canada on 581 patients with IBD and 433 controls also revealed that contact with animals, particularly cats, was protective in CD (OR 0.66, 95% CI 0.46–0.96) but not UC.[32]

Size of family

The remaining risk factor that associated significantly with UC, but not CD, was the size of the household in childhood (OR 0.81 per person of the family, 95% CI 0.68–0.98). Bernstein et al.[32] made similar observations and recorded an OR of 0.87 (95% CI 0.79–0.96). This association may reflect the fact that larger families impose more intensive antigenic stimulation in early childhood due to more interpersonal contacts. This may promote the maturation of the immune system.

Combination of environmental risk factors

In this study, we designed a composite environmental index called the ERI that was composed of the three variables that associated most significantly with CD in multivariate analyses, namely smoking at diagnosis, being breastfed for less than 6 months, and less than two sporting activities per week in childhood. The use of this index revealed that 47% of the controls but only 14% of the patients with CD had no risk factors, whereas 14% of the controls and 38% of the patients with CD had at least two risk factors. These differences were highly statistically significant. Furthermore, calculation of the theoretical prevalence of CD based on the observed ERI prevalence in the controls and the ORs revealed that the prevalence of CD rose as the number of risk factors increased, namely, from 30 (ERI = 0) to 124 (ERI = 1), 259 (ERI = 2), and 505 (ERI = 3). This suggests that the increase in CD prevalence in Western countries may be attributable to the increased prevalence of several (possibly three) environmental risk factors. ERI was a working tool in our study and its composition may but does not have to reflect a definite true combination of environmental risk factors resulting in CD. Further studies are necessary.

Clinical implications

The clinical significance of the present study lies in its contribution to explaining the causes of IBD. If these factors are confirmed prevention strategies in high-risk groups (such as children with a positive family history or genetic or serological surrogate markers) may reduce their development of IBD. Indeed, the present study suggests that modifying all four environmental risk factors (namely, smoking, breastfeeding, sporting activity, and contact with animals) may reduce the risk of developing IBD very significantly (by 10–30 times). Further research is needed to confirm and expand the models presented in this study.

Conflict of interest

The authors declare that there is no conflict of interest.

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