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The Influence of Breastfeeding, Cesarean Section, Pet Animals, and Urbanization on the Development of Inflammatory Bowel Disease: Data from the Swiss IBD Cohort Study

Severin A. Lautenschlager[a] Nicolas Fournier[b] Luc Biedermann[a] Valerie Pittet[b] Philipp Schreiner[a] Benjamin Misselwitz[a, c] Michael Scharl[a] Gerhard Rogler[a] Alexander R. Siebenhüner[d] on behalf of the Swiss IBD Cohort Study Group

[a]Department of Gastroenterology and Hepatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [b]Institute of Social and Preventive Medicine, Université de Lausanne, Lausanne, Switzerland; [c]Department of Visceral Surgery and Medicine, Inselspital Bern and Bern University, Bern, Switzerland; [d]Clinic for Medical Oncology and Hematology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Keywords
Inflammatory bowel disease · Environmental factors · Swiss IBD Cohort Study · Crohn's disease · Ulcerative colitis · Breastfeeding

Abstract
Introduction: The pathophysiology of inflammatory bowel disease (IBD) is incompletely understood. Current concepts imply that environmental factors (EFs) trigger disease onset as well as flares in genetically susceptible individuals. ***Objective:*** The objective of this study is to analyze the association between IBD and various EFs, which may influence the pathogenesis of the disease. ***Methods:*** 2,294 patients from the Swiss IBD Cohort Study (SIBDCS) received a questionnaire regarding EF including mode of delivery, breastfeeding, animals in household, and place of residence. The control group comprised patients' childhood friends, who grew up in a similar environment ("friends cohort"). ***Results:*** A total of 1,111 questionnaires were returned from SIBDCS patients (response rate: 48.4%). Breastfeeding for <6 months was associated with a decreased risk for ulcerative colitis/indeterminate colitis (UC/IC) (OR: 0.473, $p = 0.006$). IBD patients reported less pet animals in the household than the control group ($p = 0.004$). The presence of cats or dogs (OR: 0.688, $p = 0.015$) and pet rodents (OR: 0.598, $p = 0.001$) in the household before the age of 20 was inversely associated with the risk for UC/IC. ***Conclusion:*** The present study underlines the importance of EFs in the pathogenesis of IBD. Overall, the development of UC/IC seems to be more affected from environmental influences than from Crohn's disease. Our results imply a protective effect of possessing pet animals in household and short breastfeeding regarding the onset of UC/IC.

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Alexander R. Siebenhüner
Clinic for Medical Oncology and Hematology, University Hospital Zurich
Raemistrasse 100
CH– 8091 Zürich (Switzerland)
alexander.siebenhuener@usz.ch

Introduction

Inflammatory bowel diseases (IBD) are chronic immune-mediated diseases of the gastrointestinal tract, which can be subclassified into Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC).

In population-based studies, the incidence and prevalence of IBD in Europe and the USA have been on the rise since the beginning of the 20th century [1, 2]. Moreover, in Asian regions, for example, in countries like China, India, or Indonesia, both prevalence and incidence of CD and UC also increased continuously over the last 30 years [3].

Current concepts of IBD pathogenesis imply deregulation of host immune responses and changes in intestinal microbiota in genetically susceptible individuals [4, 5]. More than 240 single nucleotide polymorphisms associated with IBD risk have been identified, but even in combination, they only partially explain IBD risk [6–9]. Further, genetic susceptibility does not explain the increase of IBD in the last 100 years, because genetic risk factors have been present in humans since thousands of years.

A number of environmental factors (EFs) have been implicated in the pathogenesis of IBD [10]. There is an association between Westernized lifestyle and the increase in CD and UC in the Western world and in Asian countries [2, 3]. However, which factors of modern lifestyle really contribute to IBD risk remain to be elucidated. A frequently discussed concept, the "hygiene hypothesis," postulates that improvements in hygiene result in reduced microbial exposure, thus reducing the natural training of the immune system and enhancing the risk for immune-mediated diseases [11–14]. A non-exclusive concept, the "microflora hypothesis," suggests that changes in the composition of the microbiota, for instance, due to diet or use of antibiotics, disrupt microbial-mediated mechanisms of immunological tolerance [15].

Knowledge about environmental triggers of IBD might enable preventive efforts to reduce the incidence of IBD and enhance treatment of this disease. However, identifying causative EFs that influence the onset of IBD turned out to be challenging because potential risk factors may affect patients for years or decades before the diagnosis of the disease. In such a scenario, an early environmental insult would lead to a subclinical intestinal inflammation, which can be present long before occurrence of the first IBD symptoms [16]. Long-term prospective observational cohorts (e.g., the Swiss IBD Cohort Study, SIBDCS [17]) are well suited to identify or confirm potential environmental triggers.

Breastfeeding has been associated with protection from IBD, but some controversy remains in the literature [18–22]. A recently published review from Ananthakrishnan et al. [23] reported a protective effect of breastfeeding for both CD and UC. As Cesarean section (C-section) strongly affects the infant microbiota, an association between C-section and IBD risk has been postulated [24–26]. On the contrary, a population-based study of Bernstein et al. [27] reported no association between the mode of delivery and IBD. Further, having pets, exposure to farm animals, >2 siblings, and a shared bedroom are inversely associated with the risk of IBD [28].

Interestingly, an increase in occurrence of CD and UC in closely inhabited areas is well described in a recent publication [29]. Urbanization describes a process of a population shift from a rural to an urban way of life and therefore expansions of cities and alterations in lifestyle, which constitute a predisposition to immune-mediated diseases, such as IBD. In this study, we analyzed SIBDCS data to test whether urbanism, breastfeeding, C-section, or pet animals are associated with the risk of developing IBD in Swiss patients.

Methods

Study Design

We used data from the SIBDCS and 2 related cohorts of patients' friends and mothers to evaluate the impact of various EFs on IBD risk. SIBDCS is a nationwide prospective cohort study established in 2006 and has included patients diagnosed with IBD from all parts of Switzerland.

Since the beginning of data collection, clinical and treatment data have been prospectively captured once a year and entered into a database. SIBDCS is funded by the Swiss National Science Foundation. Purposes and methodology of SIBDCS have been described by Pittet et al. [17].

Questionnaires in Swiss national languages were distributed to adult IBD patients (n = 2,294) addressing mode of delivery, duration of breastfeeding, pets in household, and places of residence since birth. Identical questionnaires were distributed to up to 3 matched childhood friends who grew up in a similar environment (i.e., "friends cohort"), which serves as a control group. Furthermore, questionnaires addressing the patient's early childhood were filled by the mothers of the patients.

In case of discrepancies between mothers' and patients' answers, the input from the mothers was used. Questionnaires were sent out between December 2015 and October 2016. We included all questionnaires returned until January 2018 in the present analysis.

Patients were asked in the questionnaire if they currently possess pet animals or owned pets in the past. As well, we asked the patients to declare in which timeframe they were obtaining animals and tried to pick those out who were in contact with pet animals before the age of 20. Thus, with an interquartile range of age of 20–38 years at the time of diagnosis for CD and 24–41 years for UC/IC, we get an insight into the period before the outbreak of the disease of most patients and try to identify if different sorts of domesticated animals influence the pathogenesis of IBD.

Table 1. Clinical characteristics of the study population

	CD (*n* = 617)	UC/IC (*n* = 494)	Controls (*n* = 352)
Gender			
Male	274 (44.4)	249 (50.4)	114 (32.4)
Female	343 (55.6)	245 (49.6)	238 (67.6)
Age, year (median, IQR, range)	48, 35–60 (19–87)	49, 38–59 (19–90)	35, 28–45 (18–75)
Age at diagnosis, year (median, IQR, range)	27, 20–38 (1–78)	31, 24–41 (8–78)	
Disease duration, year (median, IQR, range)	16, 9–25 (0–53)	13, 8–21 (0–59)	
Smoking status at diagnosis			
Non-smoker	364 (59.0)	371 (75.1)	
Smoker	230 (37.3)	96 (19.4)	
Unknown	23 (3.7)	27 (5.5)	
Current smoking status			
Non-smoker	461 (74.7)	419 (84.8)	
Smoker	153 (24.8)	69 (14.0)	
Unknown	3 (0.5)	6 (1.2)	
Therapy history (ever treated with)			
5-ASA	377 (61.1)	474 (96.0)	
Antibiotics	116 (18.8)	54 (10.9)	
Steroids	537 (87.0)	404 (81.8)	
Immunomodulators	499 (80.9)	304 (61.5)	
Anti-TNF	387 (62.7)	173 (35.0)	
Calcineurin inhibitors	13 (2.1)	47 (9.5)	
Extraintestinal manifestation			
Any	389 (63.0)	225 (45.5)	
Arthritis	338 (54.8)	176 (35.6)	
Uveitis/iritis	81 (13.1)	32 (6.5)	
Pyoderma gangrenosum	8 (1.3)	10 (2.0)	
Erythema nodosum	60 (9.7)	16 (3.2)	
Aphthous/oral ulcers	94 (15.2)	25 (5.1)	
Ankylosing spondylitis	38 (6.2)	17 (3.4)	
Primary sclerosing cholangitis	8 (1.3)	15 (3.0)	
Complications			
Perianal fistula	168 (27.2)	–	
Other fistula	113 (18.3)		
Abscess	140 (22.7)		
Stenosis	270 (43.8)		
Surgery history			
Intestinal surgery	260 (42.1)	47 (9.5)	
Fistula or abscess surgery	151 (24.5)	–	

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

To investigate if duration of breastfeeding has an impact on the onset of IBD, we created 2 subgroups of >6 months and <6 months being breastfed. For our analysis, we defined "urban" as living for ≥10 years in a city with at least 100,000 inhabitants, allowing the 6 biggest cities in Switzerland to be included. If not indicated otherwise, the time period before the age of 20 was considered.

In the final analysis, patients and friends were matched for age and sex. However, other potential confounders like socioeconomic status or place of residence have not been matched in the analysis. Further, for the analysis of a specific parameter, urban or rural living, breastfeeding, C-section or pet animals in household were also not matched for the remaining parameters as this would have decreased the sample size too much.

Statistical Analysis

All statistical analyses were performed using the Stata Software (v. 14.2; Statacorp, College Station, TX, USA). Baseline demographics and clinical data were described. Continuous data distribution was assessed using Normal QQ-plot. Gaussian distributed data were summarized as mean, SD, and range, while non-Gaussian distributed data were summarized as median, interquartile range, and range. Categorical data were summarized as raw frequencies and relative percentages. Differences in means for Gaussian distributed data were assessed using the Student's *t* test. Differences in distribution for non-Gaussian distributed data were assessed using the Mann-Whitney-Wilcoxon rank sum test. Differences in distributions for categorical variables were assessed

Table 2. Frequency of environmental exposures in the study population

	CD (n = 617)	UC/IC (n = 494)	Controls (n = 352)	p value CD versus UC/IC	p value IBD versus controls
Breastfeeding					
No	112 (21.9)	114 (27.7)	80 (25.2)	0.042	0.803
Yes	400 (78.1)	298 (72.3)	238 (74.8)		
Breastfeeding duration					
<6 months	138 (62.4)	81 (56.6)	125 (71.0)	0.270	0.014
>6 months	83 (37.6)	62 (43.4)	51 (29.0)		
Cesarean section					
No	502 (91.4)	406 (93.1)	286 (85.4)	0.329	<0.001
Yes	47 (8.6)	30 (6.9)	49 (14.6)		
Any animals in household					
No	121 (20.3)	120 (25.2)	53 (15.3)	0.058	0.004
Yes	474 (79.7)	356 (74.8)	294 (84.7)		
Cats or dogs in household					
No	165 (27.5)	159 (32.9)	97 (28.0)	0.051	0.491
Yes	436 (72.6)	324 (67.1)	250 (72.0)		
Pet rodents in household					
No	346 (59.0)	291 (61.5)	168 (48.8)	0.413	<0.001
Yes	240 (41.0)	182 (38.5)	176 (51.2)		
Birds in household					
No	453 (77.6)	346 (73.5)	275 (80.7)	0.122	0.061
Yes	131 (22.4)	125 (26.5)	66 (19.3)		
Reptiles in household					
No	551 (95.3)	447 (96.1)	314 (92.4)	0.527	0.016
Yes	27 (4.7)	18 (3.9)	26 (7.6)		
Fish in household					
No	489 (84.2)	399 (85.4)	278 (81.5)	0.569	0.161
Yes	92 (15.8)	68 (14.6)	63 (18.5)		
At least 10 years in city >100,000 inhabitants					
No	492 (88.7)	402 (91.4)	333 (94.6)	0.159	0.007
Yes	63 (11.4)	38 (8.6)	19 (5.4)		

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

using the χ^2 test, or the Fisher exact test in case of smaller sample size.

To study the association between EFs and the incidence of IBD, a case-control analysis was done. IBD patients and controls were matched according to age and sex, and a logistic regression model was used. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. A p value <0.05 was considered as statistically significant.

Results

Clinical Characteristics of the Study Population

Out of 2,294 questionnaires sent to SIBDC patients, 1,111 questionnaires were returned (response rate: 48.4%). In addition, for 305 out of 1,111 responding patients, mother-filled questionnaires were available (response rate: 27.5%). Further, from 225 out of 1,111 responding patients, we received questionnaires from at least 1 patients' friend (response rate: 20.3%). As we accepted multiple friend-questionnaires per patient, 352 returned questionnaires from friends could be included.

In total, we received questionnaires from 466 patients with UC, 28 with IC, and 617 with CD. Epidemiological parameters and data for the clinical history of UC/IC and CD patients are depicted in Table 1 and are consistent with a mixed cohort of IBD patients with mild, moderate, and severe disease.

Breastfeeding

Breastfeeding was significantly lower for UC/IC patients than for CD patients (UC/IC: 298/494, 72.3% vs.

Table 3. Multivariate analysis of the association between environmental risk factors and IBD

	Outcome: IBD	Outcome: CD	Outcome: UC/IC
Breastfeeding	1.145 (0.789–1.660) $p = 0.476$	1.176 (0.810–1.707) $p = 0.393$	0.795 (0.558–1.134) $p = 0.206$
Breastfeeding duration			
None (ref)	1.000	1.000	1.000
<6 months	0.698 (0.464–1.051) $p = 0.085$	0.939 (0.577–1.530) $p = 0.800$	0.473 (0.278–0.807) $p = 0.006$
>6 months	1.231 (0.769–1.969) $p = 0.387$	1.453 (0.833–2.535) $p = 0.188$	1.024 (0.574–1.824) $p = 0.937$
Cesarean section	0.878 (0.561–1.374) $p = 0.569$	0.941 (0.565–1.567) $p = 0.814$	0.784 (0.421–1.458) $p = 0.442$
Any animals in household	0.914 (0.608–1.374) $p = 0.666$	0.767 (0.516–1.141) $p = 0.191$	0.602 (0.410–0.884) $p = 0.010$
Cats or dogs in household	1.155 (0.824–1.619) $p = 0.403$	1.215 (0.865–1.706) $p = 0.261$	0.825 (0.596–1.142) $p = 0.246$
Pet rodents in household	0.949 (0.703–1.280) $p = 0.732$	0.880 (0.652–1.187) $p = 0.402$	0.671 (0.496–0.907) $p = 0.009$
Birds in household	1.529 (1.066–2.192) $p = 0.021$	1.277 (0.885–1.844) $p = 0.192$	1.778 (1.247–2.536) $p = 0.001$
Reptiles in household	0.640 (0.340–1.202) $p = 0.165$	0.715 (0.388–1.318) $p = 0.282$	0.442 (0.219–0.891) $p = 0.022$
Fish in household	0.981 (0.665–1.445) $p = 0.921$	na	0.849 (0.570–1.263) $p = 0.418$
At least 10 years in urban areas >100,000 inhabitants	1.815 (1.011–3.259) $p = 0.046$	1.885 (0.981–3.625) $p = 0.057$	1.609 (0.759–3.409) $p = 0.215$

Odds ratio, 95% confidence interval, and p values are reported. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis.

CD: 400/617, 78.1%; $p = 0.042$; Table 2). However, breastfeeding rates for controls (238/352 individuals, 74.8%) was similar to those for IBD patients. While duration of breastfeeding did not differ between UC and CD patients, more controls reported a shorter duration of breastfeeding (<6 months) than IBD patients ($p = 0.014$).

In the multivariate analysis, breastfeeding was neither associated with the risk of IBD (OR: 1.145, 95% CI: 0.789–1.660, $p = 0.476$) nor with the risk of CD or UC/IC. There was also no significant association of long breastfeeding (>6 months) with a diagnosis of IBD, CD, or UC. Shorter breastfeeding (<6 months) was also not associated with IBD or CD but was a protective factor for the development of UC/IC (OR: 0.473, 95% CI: 0.278–0.807, $p = 0.006$).

Cesarean Delivery

A similar fraction of CD patients (47 out of 549 patients, 8.6%) and UC/IC patients (30 out of 436 patients, 6.9%) were born by C-section ($p = 0.329$). However, the number of control individuals born by C-section (49/335, 14.6%) was almost twice as high compared to IBD patients ($p < 0.001$). In a multivariate analysis, we observed no association between cesarean delivery and the development of IBD (OR: 0.878, 95% CI: 0.561–1.374, $p = 0.569$), UC/IC or CD (Table 2).

Pets and Other Household Animals

474 (79.7%) CD patients and 356 (74.8%) UC/IC patients reported any animal in the household. This number was even higher in the control group (IBD: 830/1,071, 77.5%; controls: 294/347, 84.7%; $p = 0.004$). In a multi-

Table 4. Multivariate analysis of the association between environmental risk factors and IBD before the age of 20

	Outcome: IBD	Outcome: CD	Outcome: UC/IC
Any animals in household	0.929 (0.662–1.301) $p = 0.667$	1.019 (0.724–1.435) $p = 0.914$	0.687 (0.495–0.954) $p = 0.025$
Cats or dogs in household	1.096 (0.808–1.487) $p = 0.555$	1.101 (0.812–1.493) $p = 0.534$	0.688 (0.510–0.930) $p = 0.015$
Pet rodents in household	0.934 (0.689–1.264) $p = 0.657$	0.866 (0.639–1.173) $p = 0.353$	0.598 (0.437–0.817) $p = 0.001$
Birds in household	1.737 (1.198–2.520) $p = 0.004$	1.399 (0.956–2.047) $p = 0.084$	1.671 (1.151–2.427) $p = 0.007$
Reptiles in household	0.681 (0.311–1.490) $p = 0.336$	0.935 (0.454–1.922) $p = 0.854$	0.551 (0.240–1.264) $p = 0.159$
Fish in household	1.054 (0.673–1.649) $p = 0.819$	1.191 (0.768–1.846) $p = 0.435$	0.793 (0.494–1.273) $p = 0.337$
At least 10 years in urban areas >10,000 inhabitants	1.267 (0.878–1.829) $p = 0.206$	1.169 (0.761–1.794) $p = 0.476$	1.412 (0.888–2.244) $p = 0.144$

Odds ratio, 95% confidence interval, and *p* values are reported. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis.

variate analysis, the presence of any animal or specific animals like cats or dogs, pet rodents, reptiles, or fish did not increase the risk for IBD. The presence of birds was associated with an increased risk for IBD compared to matched controls in the IBD group (OR: 1.529, CI: 1.066–2.192, $p = 0.021$). Interestingly, nearly all trends were stronger in the subgroup with UC/IC and reached statistical significance for any animal (OR: 0.602, CI: 0.410–0.884, $p = 0.01$) and in the subanalysis for pet rodents (OR: 0.671, CI: 0.496–0.907, $p = 0.009$) and reptiles (OR: 0.442, CI: 0.219–0.891, $p = 0.022$). The increased risk associated with birds was also stronger in the subgroup with UC (OR: 1.778, CI: 1.247–2.536, $p = 0.001$). No significant association was observed in the subgroup with CD.

These results remained robust when only animals in the household in infancy, childhood, or youth of the patient (i.e., <20 years) were considered (Table 4). For the IBD group, in the multivariate analysis, birds increased IBD risk compared to matched controls (OR: 1.737, CI: 1.198–2.520, $p = 0.004$), but no significant associations for other animals were observed. Most trends were also stronger in the subgroup with UC/IC (e.g., for any animal: OR: 0.687, CI: 0.495–0.954, $p = 0.025$; cats and dogs: OR: 0.688, CI: 0.510–0.930 $p = 0.015$; rodents: OR: 0.598, CI: 0.437–0.817, $p = 0.001$; and birds: OR: 1.671, CI: 1.151–2.427, $p = 0.007$), but no significant association in the subgroup with CD was observed.

Urban versus Rural Life

A similar number of CD and UC/IC patients lived for at least 10 years in a city with >100,000 inhabitants (CD: 63, 11.4%; UC: 38, 8.6%, n.s.). In contrast, a significantly lower number of individuals from the control group reported to have lived in urban places (IBD: 101, 11.2%, control: 19, 5.4%, $p = 0.007$). This risk for IBD for urban individuals remained significant in a multivariate analysis (OR: 1.815, CI: 1.011–3.259, $p = 0.046$). A similar trend was observed for the subgroups of CD and UC/IC patients, which failed to reach statistical significance (Table 3).

Urban environment in infancy, childhood, and youth of the patient (before age 20) was not significantly associated with the risk of IBD, CD, or UC (Table 4). While all ORs for urbanism in young life also pointed toward an increased risk, effect sizes were much smaller than those in the previous analysis, considering the whole life (Table 3) and none of the associations were significant.

Discussion

Using data from 1,111 IBD patients, we aimed to identify EFs, which may have an impact on the risk to develop IBD. Our data confirm long-term residence in an urban environment as a risk factor for IBD. Breastfeeding for <6

months was associated with a lower risk of UC. The presence of various household animals especially within early life decreased the risk of IBD, especially in the UC subgroup, while opposite effects of household birds were observed.

The association between breastfeeding and IBD risk remains controversial [18–22, 30, 31]. Two meta-analyses support the hypothesis that breastfeeding is a protective factor for IBD [31, 32]. However, other studies observed that breastfeeding has no association with IBD or is even a risk factor for the development of the disease [33, 34]. Human milk contains, among others, lactoferrin, IgA, and lactadherin, which play an essential role in the defense against early enteric infections [35]. Maternal milk also contains human milk oligosaccharides, a group of various sugars with prebiotic effects including Bifidobacteria growth, which would affect the intestinal microbiota and may influence IBD risk [36]. In our study, we did not find a general effect of breastfeeding, but our data indicate an association of breastfeeding for <6 months with UC/IC. However, in our analysis, there was no information regarding breast milk substitution in any subgroup available, and we were unable to correct for many relevant confounders. Furthermore, the number of patients who have been breastfed for >6 months is quite low, and our study would be underpowered to detect effects in this subgroup. Therefore, additional studies are warranted.

The association between C-section and IBD is also under debate. A meta-analysis by Li et al. [26] implies an increased risk for CD but not for UC after C-section. On the other hand, a large population-based study of Bernstein et al. [27] reported no association of the mode of delivery with IBD. In our investigation, Cesarean delivery was also not associated with the risk for IBD. This is remarkable in light of evidence indicating an impact of C-section on the intestinal microbiota for up to 7 years of age [23]. However, investigations showed that differences in the intestinal flora of children delivered by C-section gradually diminish after the first year of life [25, 37].

The "hygiene hypothesis," first published by Strachan [38], implied that the number of children in the household is inversely associated with the risk of hay fever and eczema. This theory has been extended to other immune-mediated diseases such as IBD [14]. In line with the hygiene hypothesis, various risk factors related to microbial exposure such as exposure to household pets, farm animals, >2 siblings, sharing of bedrooms, or living in rural areas have been associated with protection from developing IBD [28, 39]. A higher exposure to pathobionts and microorganisms may lead to a better training of the immune system and therefore a lower predisposition to develop diseases with inappropriate immune activation [40].

Pets in the household would be one example for an EF related to increased microbial exposure and a protective effect of pets regarding IBD has been demonstrated [28, 41, 42]. Our investigation also indicates a similar inverse association of household pets and the risk for IBD, especially of the UC/IC subtype. Interestingly, possession of birds in the household has opposite effects, increasing the chances of an IBD and UC/IC diagnosis. Further, for CD, neither pet animals in general nor any subspecies were associated with the disease. When only exposure to animals in young life, before the age of 20 was considered, we found a highly similar picture: pet rodents and cats or dogs in household were inversely associated with the risk of UC/IC but not CD, with birds increasing UC/IC risk. The reasons for differential effects of birds and other animals and different susceptibility regarding the environment toward UC/IC and CD are unclear. Literature on this subject is rare, and we suggest further investigation with a bigger sample size and extended adjustment for confounders. In contrast to our findings, Castiglione et al. [43] reported no association of animals in household with CD and UC in a large case-control study. Another investigation from Han et al. [44] demonstrated even an increased risk of CD when owing pets at home during childhood period.

A positive correlation between urban environment and the risk for IBD is well established and was corroborated by a meta-analysis [39]. In an urban environment, potential risk factors for IBD, for example, smoking, intake of antibiotics, or lack of helminths exposure, are more prevalent [45–47]. Furthermore, in urban areas, infrastructure and sanitation would be better, resulting in reduced exposure to enteric pathogens or pathobionts [48, 49]. Our data support these findings, and we report a statistically significant positive association between living in urban areas and IBD. However, this association was not robust in the subanalysis regarding urban environment in young life. A possible explanation is the small sample size in this subgroup.

Our study has strengths as well as limitations. A strength is the large patient number in our cohort with 1,111 returned questionnaires from IBD patients. Furthermore, inclusion of 344 confirmatory questionnaires from patients' mothers most likely reduced the "recall bias," which is invariably present in any retrospective study.

One limitation of our study is the low overall return of questionnaires (response rate for patients: 48.4%), potentially resulting in a "reporting bias." Response rates for the control group and for mothers were even lower (20.3 and 27.5%, respectively). Therefore, the size of the control group (352 persons) was rather small compared to the larger patient group. Low response rates for the control group might be explained by the difficulty for patients to find 3 childhood friends who grew up in a similar environment. Better strategies to increase sizes and coverage of friends and mothers cohorts are warranted for future studies. Probably further minimization of the effort to fill out questionnaires is needed. In addition to the printed questionnaires, the distribution of electronic questionnaires may increase the response rate and could be considered in further investigations. Obtaining a comparison between our control group and the baseline data of general Swiss population has been difficult, considering that with a median age of 35, quality data especially regarding C-section and breastfeeding are needed from the 1980s. Therefore, we were not able to receive a clear evidence whether our data from the control group were affected by bias. Another limitation regards controlling for confounders. In our analyses, cases and controls were matched for sex and age, but we were unable to adjust for other potential confounders such as socioeconomic status, place of residence, ethnicity, or education. Furthermore, we did not match for mode of delivery, breastfeeding, and urbanism in our study. This might be relevant since, for instance, rates of C-sections or household animals would be different in urban compared to rural areas.

Appendix: Members of the Swiss IBD Cohort Study Group

Karim Abdelrahman, Gentiana Ademi, Patrick Aepli, Amman Thomas, Claudia Anderegg, Anca-Teodora Antonino, Eva Archanioti, Eviano Arrigoni, Diana Bakker de Jong, Bruno Balsiger, Polat Bastürk, Peter Bauerfeind, Andrea Becocci, Dominique Belli, José M. Bengoa, Luc Biedermann, Janek Binek, Mirjam Blattmann, Stephan Boehm, Tujana Boldanova, Jan Borovicka, Christian P. Braegger, Stephan Brand, Lukas Brügger, Simon Brunner, Patrick Bühr, Bernard Burnand, Sabine Burk, Emanuel Burri, Sophie Buyse, Dahlia-Thao Cao, Ove Carstens, Dominique H. Criblez, Sophie Cunningham, Fabrizia D'Angelo, Philippe de Saussure, Lukas Degen, Joakim Delarive, Christopher Doerig, Barbara Dora, Susan Drerup, Mara Egger, Ali El-Wafa, Matthias Engelmann, Jessica Ezri, Christian Felley, Markus Fliegner, Nicolas Fournier, Montserrat Fraga, Yannick Franc, Pascal Frei, Remus Frei, Michael Fried, Florian Froehlich, Raoul Ivano Furlano, Luca Garzoni, Martin Geyer, Laurent Girard, Marc Girardin, Delphine Golay, Ignaz Good, Ulrike Graf Bigler, Beat Gysi, Johannes Haarer, Marcel Halama, Janine Haldemann, Pius Heer, Benjamin Heimgartner, Beat Helbling, Peter Hengstler, Denise Herzog, Cyrill Hess, Roxane Hessler, Klaas Heyland, Thomas Hinterleitner, Claudia Hirschi, Petr Hruz, Pascal Juillerat, Carolina Khalid-de Bakker, Stephan Kayser, Céline Keller, Christina Knellwolf-Grieger, Christoph Knoblauch, Henrik Köhler, Rebekka Koller, Claudia Krieger-Grübel, Patrizia Künzler, Rachel Kusche, Frank Serge Lehmann, Andrew Macpherson, Michel H. Maillard, Michael Manz, Astrid Marot, Rémy Meier, Christa Meyenberger, Pamela Meyer, Pierre Michetti, Benjamin Misselwitz, Patrick Mosler, Christian Mottet, Christoph Müller, Beat Müllhaupt, Leilla Musso, Michaela Neagu, Cristina Nichita, Jan Niess, Andreas Nydegger, Nicole Obialo, Diana Ollo, Cassandra Oropesa, Ulrich Peter, Daniel Peternac, Laetitia Marie Petit, Valérie Pittet, Daniel Pohl, Marc Porzner, Claudia Preissler, Nadia Raschle, Ronald Rentsch, Alexandre Restellini, Sophie Restellini, Jean-Pierre Richterich, Frederic Ris, Branislav Risti, Marc Alain Ritz, Gerhard Rogler, Nina Röhrich, Jean-Benoît Rossel, Vanessa Rueger, Monica Rusticeanu, Markus Sagmeister, Gaby Saner, Bernhard Sauter, Mikael Sawatzki, Michael Scharl, Martin Schelling, Susanne Schibli, Hugo Schlauri, Dominique Schluckebier, Daniela Schmid, Sybille Schmid-Uebelhart, Jean-François Schnegg, Alain Schoepfer, Vivianne Seematter, Frank Seibold, Mariam Seirafi, Gian-Marco Semadeni, Arne Senning, Christiane Sokollik, Joachim Sommer, Johannes Spalinger, Holger Spangenberger, Philippe Stadler, Peter Staub, Dominic Staudenmann, Volker Stenz, Michael Steuerwald, Alex Straumann, Bruno Strebel, Andreas Stulz, Michael Sulz, Aurora Tatu, Michela Tempia-Caliera, Joël Thorens, Kaspar Truninger, Radu Tutuian, Patrick Urfer, Stephan Vavricka, Francesco Viani, Jürg Vögtlin, Roland Von Känel, Dominique Vouillamoz, Rachel Vulliamy, Paul Wiesel, Reiner Wiest, Stefanie Wöhrle, Samuel Zamora, Silvan Zander, Tina Wylie, Jonas Zeitz, and Dorothee Zimmermann.

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Statement of Ethics

The SIBDCS protocol has been approved by the local ethics committees (EK13-16). All patients provided written informed consent for participation in SIBDCS and data collection. Patients' mothers and friends signed individual informed consent forms prior to filling the respective questionnaires.

Conflict of Interest Statement

B.M. has consulted to Gilead and Novigenix; received speaking and/or traveling fees from MSD, Vifor, Takeda, and Novartis; and an unrestricted research grant from MSD. G.R. has consulted to Abbvie, Augurix, BMS, Boehringer, Calypso, Celgene, FALK, Ferring, Fisher, Genentech, Gilead, Janssen, MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions, and Zeller; G.R. has received speaker's honoraria from Astra Zeneca, Abbvie, FALK, Janssen, MSD, Pfizer, Phadia, Takeda, Tillots, UCB, Vifor, and Zeller; G.R. has received educational grants and research grants from Abbvie, Ardeypharm, Augurix, Calypso, FALK, Flamentera, MSD, Novartis, Pfizer, Roche, Takeda, Tillots, UCB, and Zeller. L.B. has consulted to Abbvie, Janssen, MSD, Pfizer, Takeda, and Vifor; L.B. has received speaker's honoraria from Astra Zeneca, Abbvie, FALK, MSD, Takeda, and Vifor; L.B. has received educational grants and research grants from Abbvie, MSD, and Takeda. A.R.S. has no disclosures in association with the manuscript. All other authors have nothing to disclose.

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Author Contributions

S.A.L. and A.R.S.: organization, data interpretation, and manuscript preparation; N.F.: statistical data analysis and critical review of the manuscript; A.R.S., G.R., L.B., and V.P.: study design and critical review of the manuscript; and P.S., B.M., and M.S.: manuscript preparation and critical review of the manuscript.

References

1 Foster A, Jacobson K. Changing incidence of inflammatory bowel disease: environmental influences and lessons learnt from the South asian population. Front Pediatr. 2013;1:34.
2 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54.e42; quiz e30.
3 Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. Gastroenterology. 2013;145(1):158–65.e2.
4 Ek WE, D'Amato M, Halfvarson J. The history of genetics in inflammatory bowel disease. Ann Gastroenterol. 2014;27(4):294–303.
5 Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet. 2007;369(9573):1627–40.
6 Knights D, Lassen KG, Xavier RJ. Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. Gut. 2013;62(10):1505–10.
7 Graham DB, Xavier RJ. From genetics of inflammatory bowel disease towards mechanistic insights. Trends Immunol. 2013;34(8):371–8.
8 Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet. 2015;47(9):979–86.
9 de Lange KM, Moutsianas L, Lee JC, Lamb CA, Luo Y, Kennedy NA, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. Nat Genet. 2017;49(2):256–61.
10 Ananthakrishnan AN. Environmental triggers for inflammatory bowel disease. Curr Gastroenterol Rep. 2013;15(1):302.
11 de Silva HJ, de Silva NR, de Silva AP, Jewell DP. Emergence of inflammatory bowel disease 'beyond the West': do prosperity and improved hygiene have a role? Trans R Soc Trop Med Hyg. 2008;102(9):857–60.
12 Hafner S, Timmer A, Herfarth H, Rogler G, Schölmerich J, Schäffler A, et al. The role of domestic hygiene in inflammatory bowel diseases: hepatitis A and worm infestations. Eur J Gastroenterol Hepatol. 2008;20(6):561–6.
13 Klement E, Lysy J, Hoshen M, Avitan M, Goldin E, Israeli E. Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2008;103(7):1775–82.
14 Koloski NA, Bret L, Radford-Smith G. Hygiene hypothesis in inflammatory bowel disease: a critical review of the literature. World J Gastroenterol. 2008;14(2):165–73.
15 Noverr MC, Huffnagle GB. The 'microflora hypothesis' of allergic diseases. Clin Exp Allergy. 2005;35(12):1511–20.
16 Rogler G, Vavricka S. Exposome in IBD: recent insights in environmental factors that influence the onset and course of IBD. Inflamm Bowel Dis. 2015;21(2):400–8.
17 Pittet V, Juillerat P, Mottet C, Felley C, Ballabeni P, Burnand B, et al. Cohort profile: the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). Int J Epidemiol. 2009;38(4):922–31.
18 Hansen TS, Jess T, Vind I, Elkjaer M, Nielsen MF, Gamborg M, et al. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. J Crohns Colitis. 2011;5(6):577–84.
19 Guo AY, Stevens BW, Wilson RG, Russell CN, Cohen MA, Sturgeon HC, et al. Early life environment and natural history of inflammatory bowel diseases. BMC Gastroenterol. 2014;14:216.
20 Jakobsen C, Paerregaard A, Munkholm P, Wewer V. Environmental factors and risk of developing paediatric inflammatory bowel disease: a population based study 2007-2009. J Crohns Colitis. 2013;7(1):79–88.
21 Biedermann L, Rogler G, Vavricka SR, Seibold F, Seirafi M. Pregnancy and breastfeeding in inflammatory bowel disease. Digestion. 2012;86(Suppl 1):45–54.
22 Moffatt DC, Ilnyckyj A, Bernstein CN. A population-based study of breastfeeding in inflammatory bowel disease: initiation, duration, and effect on disease in the postpartum period. Am J Gastroenterol. 2009;104(10):2517–23.
23 Ananthakrishnan AN, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, Ali RAR, et al. Environmental triggers in IBD: a review of progress and evidence. Nat Rev Gastroenterol Hepatol. 2018;15(1):39–49.
24 Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107(26):11971–5.

25 Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5(7):e177.
26 Li Y, Tian Y, Zhu W, Gong J, Gu L, Zhang W, et al. Cesarean delivery and risk of inflammatory bowel disease: a systematic review and meta-analysis. Scand J Gastroenterol. 2014;49(7):834–44.
27 Bernstein CN, Banerjee A, Targownik LE, Singh H, Ghia JE, Burchill C, et al. Cesarean section delivery is not a risk factor for development of inflammatory bowel disease: a population-based analysis. Clin Gastroenterol Hepatol. 2016;14(1):50–7.
28 Cholapranee A, Ananthakrishnan AN. Environmental hygiene and risk of inflammatory bowel diseases: a systematic review and meta-analysis. Inflamm Bowel Dis. 2016;22(9):2191–9.
29 Benchimol EI, Kaplan GG, Otley AR, Nguyen GC, Underwood FE, Guttmann A, et al. Rural and urban residence during early life is associated with risk of inflammatory bowel disease: a population-based inception and birth cohort study. Am J Gastroenterol. 2017;112(9):1412–22.
30 Rigas A, Rigas B, Glassman M, Yen YY, Lan SJ, Petridou E, et al. Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. Ann Epidemiol. 1993;3(4):387–92.
31 Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. Am J Clin Nutr. 2004;80(5):1342–52.
32 Xu L, Lochhead P, Ko Y, Claggett B, Leong RW, Ananthakrishnan AN. Systematic review with meta-analysis: breastfeeding and the risk of Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther. 2017;46(9):780–9.
33 Ekbom A, Adami HO, Helmick CG, Jonzon A, Zack MM. Perinatal risk factors for inflammatory bowel disease: a case-control study. Am J Epidemiol. 1990;132(6):1111–9.
34 Thompson NP, Montgomery SM, Wadsworth ME, Pounder RE, Wakefield AJ. Early determinants of inflammatory bowel disease: use of two national longitudinal birth cohorts. Eur J Gastroenterol Hepatol. 2000;12(1):25–30.
35 Goldman AS. The immune system in human milk and the developing infant. Breastfeed Med. 2007;2(4):195–204.
36 Akram W, Garud N, Joshi R. Role of inulin as prebiotics on inflammatory bowel disease. Drug Discov Ther. 2019;13(1):1–8.
37 Grönlund MM, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. J Pediatr Gastroenterol Nutr. 1999;28(1):19–25.
38 Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259–60.
39 Soon IS, Molodecky NA, Rabi DM, Ghali WA, Barkema HW, Kaplan GG. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. BMC Gastroenterol. 2012;12:51.
40 Amre DK, Lambrette P, Law L, Krupoves A, Chotard V, Costea F, et al. Investigating the hygiene hypothesis as a risk factor in pediatric onset Crohn's disease: a case-control study. Am J Gastroenterol. 2006;101(5):1005–11.
41 Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for IBD. Am J Gastroenterol. 2006;101(5):993–1002.
42 Niewiadomski O, Studd C, Wilson J, Williams J, Hair C, Knight R, et al. Influence of food and lifestyle on the risk of developing inflammatory bowel disease. Intern Med J. 2016;46(6):669–76.
43 Castiglione F, Diaferia M, Morace F, Labianca O, Meucci C, Cuomo A, et al. Risk factors for inflammatory bowel diseases according to the "hygiene hypothesis": a case-control, multicentre, prospective study in Southern Italy. J Crohns Colitis. 2012;6(3):324–9.
44 Han DY, Fraser AG, Dryland P, Ferguson LR. Environmental factors in the development of chronic inflammation: a case-control study on risk factors for Crohn's disease within New Zealand. Mutat Res. 2010;690(1–2):116–22.
45 Korzenik JR. Past and current theories of etiology of IBD: toothpaste, worms, and refrigerators. J Clin Gastroenterol. 2005;39(4 Suppl 2):S59–65.
46 Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. Dig Dis Sci. 1989;34(12):1841–54.
47 Card T, Logan RF, Rodrigues LC, Wheeler JG. Antibiotic use and the development of Crohn's disease. Gut. 2004;53(2):246–50.
48 Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. Gut. 2008;57(9):1185–91.
49 Shanahan F, Bernstein CN. The evolving epidemiology of inflammatory bowel disease. Curr Opin Gastroenterol. 2009;25(4):301–5.