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Original Article

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Gender Differences in Paediatric Patients of the Swiss Inflammatory Bowel Disease Cohort Study

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Purpose: Gender differences in paediatric patients with inflammatory bowel disease (IBD) are frequently reported as a secondary outcome and the results are divergent. To assess gender differences by analysing data collected within the Swiss IBD cohort study database since 2008, related to children with IBD, using the Montreal classification for a systematic approach.

Methods: Data on gender, age, anthropometrics, disease location at diagnosis, disease behaviour, and therapy of 196 patients, 105 with Crohn's disease (CD) and 91 with ulcerative or indeterminate colitis (UC/IC) were retrieved and analysed.

Results: The crude gender ratio (male : female) of patients with CD diagnosed at <10 years of age was 2.57, the adjusted ratio was 2.42, and in patients with UC/IC it was 0.68 and 0.64 respectively. The non-adjusted gender ratio of patients diagnosed at ≥ 10 years was 1.58 for CD and 0.88 for UC/IC. Boys with UC/IC diagnosed <10 years of age had a longer diagnostic delay, and in girls diagnosed with UC/IC >10 years a more important use of azathioprine was observed. No other gender difference was found after analysis of age, disease location and behaviour at diagnosis, duration of disease, familial occurrence of IBD, prevalence of extra-intestinal manifestations, complications, and requirement for surgery.

Conclusion: CD in children <10 years affects predominantly boys with a sex ratio of 2.57; the impact of sex-hormones on the development of CD in pre-pubertal male patients should be investigated.

Key Words: Gender difference, Paediatric inflammatory bowel disease, Male preponderance

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INTRODUCTION

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative and indeterminate (UC/IC) colitis. The paediatric incidence of these disorders varies from 3.1 to 7.1/100,000 children per year, with great regional variability [1,2]. CD in children has a male preponderance [1,3,4], which is in contrast to the female preponderance of CD in adulthood [5]. Studies in paediatric patients have suggested that female children with CD have more severe disease, a higher prevalence of extra-intestinal manifestations (EIM) and hypo-albuminemia at diagnosis [6], and an increased risk of surgery [7]. Furthermore, gender differences have been reported for weight at diagnosis, nutritional status and growth failure by some groups [8-11], but not by others [7]. To date, no such data on paediatric patients with IBD are available in Switzerland. In 2006, a nationwide multi-centre cohort study on patients with IBD, the Swiss IBD cohort study (SIBDCS) was initiated [12]. This study has established a registry, prospectively monitors patients, and has included a paediatric sub-cohort since 2008. The aim of our study was to evaluate gender differences in paediatric IBD patients registered within the SIBDCS database. In accordance with recent reports [6], we hypothesized that we would not find significant differences between female and male patients with CD and UC regarding disease location, disease behaviour and therapeutic interventions, but that male patients would outnumber female patients.

MATERIALS AND METHODS

Up to September 2012, 196 paediatric patients $\leq$16 years of age, diagnosed with CD, UC, or IC according to standard criteria [13], were included at least four months after diagnosis, and registered in the SIBDCS database. As described by Pittet et al. [12], patients were recruited from the following six university centres from western through eastern Switzerland: Geneva, Lausanne, Bern, Basel, Zurich, and St. Gallen, with the University of Lausanne as coordinating centre and data base location. After approval of the study protocol by the central ethics committee, we retrieved the following two types of data from the registry: 1. Information obtained from the patient chart at the moment of enrolment, such as date of birth, gender, age at first symptoms, age, weight and height at IBD diagnosis, type of IBD (CD, UC, IC), disease location and behaviour at diagnosis, recorded according to the Montreal classification [14], the necessity for surgery, defined as the sum of resectional and minor perianal surgery, excluding non-IBD related surgeries, the presence of EIM (articular, ocular, cutaneous, enoral, hepatic) or disease complications (anaemia, growth failure, osteoporosis), the cumulative exposure to medication at inclusion, and familial occurrence of IBD; and 2. Measured information, such as height and weight obtained by the study nurse at the visit of enrolment, using the wall stadiometers and weight scales available at the various study-centres.

Patients were grouped according to disease onset $<$10 and $\geq$10 years of age as proposed by Levine et al. [15], and disease characteristics were analysed according to the Montreal classification [14], in CD as involving the ileum alone, colon alone, or ileo-colonic and upper gastrointestinal tract involvement or perianal disease. Disease behaviour was stratified as inflammatory, stricturing, or penetrating. Disease extent in UC was analysed as involving pancolitis, left sided colitis and rectal disease; z-scores for height and weight for age were calculated according to World Health Organization 2007 growth charts [16], and diagnostic delay was defined as the interval between the manifestation of the first symptoms and diagnosis. Patients with change of diagnosis were included according to the second diagnosis (n=7). Patients with IC (defined as unclassified pan-colitis) with a disease duration $>$3 years and no change of diagnosis (n=6), as well as patients diagnosed with IC at $>$10 years of age at diagnosis only 6-12 months before enrolment (n=5) were included with the UC patients.

Statistical analysis

Continuous variables are presented as mean$\pm$ standard deviation (SD), or-if skewed-as median and range, and categorical variables are presented as proportions and percentages. Differences between

groups were quantified with the two-sample *t*-test, or with the Mann-Whitney U test for continuous variables, and categorical variables were compared using the chi-squared test or Fisher's exact test for small samples. To take into account disease duration when comparing treatment exposure, Finkelstein's modified log-rank test was used to handle left- and interval-censored data [17]. Pearson correlation was used to detect any correlation between gender and disease variables and linear regression was used to assess for gender associated predictors for growth outcome. All statistical examinations were performed with SPSS 11.0 (SPSS Inc., Chicago, IL, USA). R Core Team (2012; R Foundation for Statistical Computing, Vienna, Austria) has been used to perform Cox proportional hazard analysis.

RESULTS

Data from 196 patients were included (105 [53.6%] CD, 91 [46.4%] UC/IC, 11 IC, 10 female, 1 male patient). The overall sex ratio (male : female) for CD was 1.76, and for UC/IC 0.78. For the subgroup of children with disease onset < 10 years of age the crude sex ratio

Table 1. Characteristics of Patients with Ulcerative or Indeterminate Colitis

	<10 years of age at diagnosis			≥10 years of age at diagnosis		
	Female (25)	Male (17)	*p*-value	Female (26)	Male (23)	*p*-value
Age and intervals in months						
Age at diagnosis	87 (68.2-93.9)	64 (46.2-83.7)	0.44†	149.5 (144.5-159.3)	156.5 (150.4-170.3)	0.31†
Diagnostic delay	2 (2.0-5.1)	6 (3.2-14.2)	0.02†	2 (1.4-10.7)	3 (1.11-14.1)	0.61†
Disease duration	35.5 (29.9-61.1)	29 (27.6-99.4)	0.41†	12 (10.2-20.2)	10 (9.1-19.3)	0.61†
Age at inclusion	125 (110.8-142.4)	119 (98-158.6)	0.64†	167.5 (159.6-174.6)	176 (174.6-183.6)	0.17†
Growth						
Median Z-score for w/a at diagnosis	−0.4 (−0.82-0.17)	−0.59 (−0.87-0.08)	0.68†	−0.71 (−1.15-−0.37)	−0.92 (−1.18-−0.05)	0.97†
Median Z-score for w/a at inclusion	0.08 (−0.5-0.34)	−0.2 (−0.75-−0.08)	0.3†	0.1 (−0.47-0.4)	−0.3 (−1.04-0.24)	0.12†
Median Z-score for h/a at diagnosis	−0.21 (−0.58-0.4)	−0.04 (−0.31-0.61)	0.59†	−0.2 (−0.63-0.33)	0.02 (−0.76-0.53)	0.65†
Median Z-score for h/a at inclusion	0 (−0.8-0.34)	0.1 (−1.0-0.37)	0.6†	0.05 (−0.5-0.61)	−0.45 (−1.07-0.32)	0.21†
Median Z-score for BMI/a at diagnosis	−0.73 (−1.1-0.2)	−0.7 (−1.02-−0.2)	0.84†	−1.1 (−1.55-0.72)	−1.3 (−1.5-−0.6)	0.62†
Median Z-score for BMI/a at inclusion	0.3 (−0.07-0.5)	−0.1 (−0.5-0.43)	0.2†	−0.1 (−0.55-0.36)	−0.25 (−0.88-0.27)	0.63†
Localization at diagnosis						
Pancolonic	19 (76)	12 (70.6)	0.78*	16 (61.5)	20 (87)	0.17*
Left colon	4 (16)	2 (11.8)		6 (37.5)	1 (4.4)	
Proctitis	1 (4)	1 (5.9)		3 (18.8)	2 (8.8)	
Colectomy	2 (8)	3 (17.7)	0.3*	0	0	
EIMs	5 (20)	4 (23.5)	0.78*	7 (26.9)	4 (14.4)	0.4*
Complications	10 (40)	10 (58.8)	0.23*	14 (53.9)	11 (47.8)	0.67*
FH	8 (32)	4 (23.5)	0.55*	3 (18.8)	4 (14.4)	0.56*
Exposure to treatments						
Corticosteroids	21 (84)	17 (100)	0.13‡	20 (76.9)	16 (70)	0.88‡
Azathioprine	17 (68)	14 (82.4)	0.36‡	19 (73.1)	9 (39.1)	0.03‡
Anti-TNF α	3 (12)	6 (35.3)	0.45‡	1 (3.8)	4 (14.4)	0.17‡
Methotrexate	3 (12)	3 (17.7)	0.92‡	4 (15.4)	4 (14.4)	0.78‡

Values are presented as median (95% confidence interval) or number (%).
w/a: weight for age, h/a: height for age, BMI/a: body mass index (kg/m^2) for age, EIMs: extra-intestinal manifestations, FH: positive family history, TNF: tumor necrosis factor.
*Fisher's exact test, †Mann Whitney U test, ‡Cox proportional hazard analysis.

was 2.57, and the ratio adjusted for an age-matched Swiss population was 2.42 for CD, and 0.68, and 0.64, respectively, for UC. The sex-ratio for children ≥10 years at diagnosis could not be adjusted. It was 1.58 for CD, and 0.88 for UC.

The birth place of children diagnosed with CD <10 years of age was Switzerland in 16 of 25 (64%), United Kingdom in one (all 17 were Caucasian), and was unknown in eight (32%). All four grandparents of eight (1 girl, 7 boys; $p=0.67$) patients were born in Switzerland and nine patients had one to four grandparents of Italian, Spanish, English, Danish, German, Austrian or Syrian origin. The birth place of children with UC diagnosed <10 years of age was Switzerland in 24 of 42 (57%), Chile, Spain, Italy in one case each, and was unknown in 15 (35.7%). All four grandparents of 14 of 27 children (11 boys, 7 girls) were born in Switzerland and 13 of 27 children had one to four grandparents of French, Italian, Spanish, German, Dutch, Belgian, Turkish, Indian, Chilean, or Ecuadorian origin ($p=0.21$).

There was no gender difference for maternal age at

Table 2. Characteristics of Patients with Crohn's Disease

	<10 years of age at diagnosis			≥10 years of age at diagnosis		
	Female (7)	Male (18)	*p*-value	Female (31)	Male (49)	*p*-value
Age and intervals in months						
Age at diagnosis	89 (−2.0-151)	91 (63.1-102.5)	0.88†	155 (150.4-166.1)	153 (146.8-160.1)	0.48†
Diagnostic delay	11.5 (1.6-20.9)	5 (3.4-24.4)	0.8†	4 (1.5-14.7)	4 (4.6-8.6)	0.42†
Disease duration	9 (−32.9-87.5)	24 (12.7-36.4)	0.5†	13 (11.1-23.7)	14 (14.4-23.7)	0.77†
Age at inclusion	110.5 (−2.6-206.7)	112 (82.7-107.3)	0.33†	174 (168.3-183.0)	177 (166.0-179.0)	0.71†
Growth						
Z-score for w/a at diagnosis	−0.2 (−2.5-2.1)	−0.3 (−1.0-0.5)	0.81†	−1.26 (−1.5-−0.4)	−1.1 (−1.3-−0.5)	0.55†
Z-score for w/a at inclusion	0.15 (−2.1-2.1)	−0.2 (−0.7-0.5)	0.62†	−0.2 (−0.6-0.35)	−0.5 (−1.0-−0.3)	0.35†
Z-score for h/a at diagnosis	−0.84 (−2.8-1.6)	0.15 (−0.7-0.3)	0.66†	−0.42 (−1.0-−0.1)	−0.56 (−0.8-−0.1)	0.89†
Z-score for h/a at inclusion	−0.25 (−2.6-2.3)	−0.2 (−0.9-0.2)	0.75†	−0.3 (−0.8-0.1)	−0.7 (−0.9-−0.2)	0.29†
Z-score for BMI/a at diagnosis	−1.33 (−2.4-0.31)	−0.6 (−1.26-0.14)	0.18†	−1.1 (−1.7-−0.6)	−1.36 (−1.7-−1.0)	0.99†
Z-score for BMI/a at inclusion	0.25 (−1.9-1.8)	−0.3 (−0.5-0.7)	0.72†	−0.1 (−0.6-0.3)	−0.5 (−0.9-−0.3)	0.63†
Localization at diagnosis						
Ileal	0	2 (11.1)	0.14*	3 (9.7)	5 (10.2)	0.83*
Colonic	3 (42.9)	3 (16.7)		5 (16.1)	5 (10.2)	
Ileo-colonic	3 (42.9)	13 (72.2)		22 (71)	36 (73.5)	
Upper GI	2 (28.6)	1 (5.6)	0.16*	9 (29)	16 (32.7)	0.53*
Behavior at inclusion						
Non-stricturing, non-penetrating	5 (71.4)	9 (50)	0.33*	20 (64.5)	32 (65.3)	0.94*
Stricturing	2 (28.6)	1 (5.6)	0.11*	4 (12.9)	3 (6.1)	0.3*
Penetrating intern	1 (14.3)	0	0.1*	2 (6.5)	2 (4.1)	0.64*
Penetrating perineal	1 (14.3)	8 (44.4)	0.16*	10 (32.3)	15 (30.6)	0.88*
Surgical interventions	1 (14.3)	2 (11.1)	0.83*	6 (19.4)	8 (16.3)	0.73*
EIMs	2 (28.6)	6 (33.3)	0.82*	9 (29)	15 (30.6)	0.88*
Complications	4 (57.1)	9 (50)	0.75*	13 (41.9)	20 (40.8)	0.92*
FH	0	4 (22.2)	0.17*	8 (25.8)	10 (20.4)	0.57*
Exposure to treatments						
Corticosteroids	5 (71.4)	14 (77.8)	0.65‡	22 (71)	42 (85.7)	0.13‡
Azathioprine	4 (57.1)	17 (94.4)	0.02‡	27 (87.1)	45 (91.8)	0.51‡
Anti-TNF α	4 (57.1)	6 (33.3)	0.20‡	13 (41.9)	11 (22.5)	0.14‡
Methotrexate	3 (42.9)	2 (11.1)	1.00‡	7 (22.6)	9 (18.4)	0.89‡

Values are presented as median (95% confidence interval) or number (%).
w/a: weight for age, h/a: height for age, BMI/a: body mass index (kg/m^2) for age, GI: gastrointestinal tract, EIMs: extra-intestinal manifestations, FH: positive family history, TNF: tumor necrosis factor.
*Fisher's exact test, †Mann Whitney U test, ‡Cox proportional hazard analysis.

birth (mean 33.3 years [SD 4.1] in boys and 29.5 [2.9] in girls with CD, 30.8 [4.5] in boys, 30.9 [5.3] in girls with UC/IC diagnosed <10 years of age, 29.1 [3.1] in boys and 30.1 [5.4] in girls with CD, and 29.3 [3.2] in boys and 30.6 in girls with UC/IC diagnosed ≥10 years of age , p=not significant [NS] in all), nor for birth order (6/18 boys [six unknown] and 1/7 girls [two unknown] with CD, 5/17 boys [eight unknown] and 7/25 girls [eight unknown] with UC/IC diagnosed <10 years of age, were firstborn, and 10/49 boys [20 unknown] and 7/31 girls [seven unknown] with CD, and 10/23 boys [11 unknown] and 11/26 girls [seven unknown] with UC/IC diagnosed ≥10 years of age were firstborn, p=NS for all). The interval between first symptoms and diagnosis was significantly longer in boys compared to girls with disease onset <10 years of age. Azathioprine was more often required by female patients with UC/IC diagnosed after ≥10 and by male patients with CD diagnosed <10 years of age.

No gender difference was found after comparison of median age at diagnosis, median disease duration before inclusion, median age at inclusion, growth parameters, disease localization and behaviour at diagnosis, requirement for surgical interventions, EIM and complications before inclusion and family history of IBD (Tables 1 and 2) in patients with CD or UC/IC.

Most patients changed the z-score for weight, height and body mass index (BMI) between diagnosis and study inclusion, and there was no gender difference between male and female patients (Table 3). However, a significant correlation between disease duration before inclusion and the amplitude of z-score change was found for the BMI of males >10 years of age at diagnosis of CD (rho=0.337, p=0.022), for the BMI of males <10 years (rho=0.61, p=0.02), and for the height of females ≥10 years of (rho=0.4, p=0.037) of

Table 3. Predictive Value of Disease Duration on Change of Z-Scores between Diagnosis and Study Inclusion

UC/IC (n)	<10 years of age at diagnosis			≥10 years of age at diagnosis		
	Female (25)	Male (17)	p-value	Female (26)	Male (23)	p-value
Median change of z-score (95% CI) for						
Weight for age	0.05 (−0.4-0.8)	0.13 (−0.8-0.4)	0.4	0.52 (0.1-1.1)	0.1 (−0.8-0.7)	0.06
Height for age	−0.01 (−0.4-1.2)	−0.2 (−1.4-0.3)	0.76	0.13 (−0.2-1.1)	−0.18 (−1.1-0.22)	0.06
BMI for age	0.94 (0.3-1.3)	0.6 (0.2-1.0)	0.24	0.8 (0.4-1.2)	1.2 (0.1-1.5)	0.8
Estimated effect size R (95% CI; p-value) of duration on						
Delta z-score w/a	−0.0063 (−0.2-0.006; 0.29)	0.0004 (−0.01-0.01; 0.93)		0.0129 (−0.02-0.04; 0.40)	−0.0201 (−0.06-0.02; 0.31)	
Delta z-score h/a	−0.0093 (−0.23-0.004; 0.17)	−0.0089 (−0.02-0.001; 0.08)		0.0244 (0.002-0.05; 0.04)	0.0001 (−0.04-0.04; 0.99)	
Delta z-score BMI/a	−0.0031 (−0.02-0.01; 0.64)	0.0065 (0.001-0.012; 0.02)		0.0004 (−0.06-0.06; 0.99)	−0.0228 (−0.07-0.02; 0.30)	
CD (n)	Female (7)	Male (18)	p-value	Female (31)	Male (49)	p-value
Median change of z-score (95% CI) for						
Weight for age	0.17 (−0.03-0.34)	0.01 (−1.7-1.2)	0.7	0.2 (−1.1-2.2)	0.18 (−1.2-1.0)	0.16
Height for age	0.27 (−1.7-2.1)	−0.1 (−1.2-1.0)	0.52	0.28 (−1.0-1.9)	−0.24 (−0.5-0.14)	0.33
BMI for age	1.1 (−0.5-2.7)	0.7 (−1.3-2.8)	0.4	−0.1 (−0.8-0.9)	0.6 (−0.22-1.3)	0.63
Estimated effect size R (95% CI; p-value) of duration on						
Delta z-score w/a	0.0051 (−0.01-0.02; 0.37)	−0.0222 (−0.05-0.003; 0.08)		−0.0023 (−0.03-0.02; 0.85)	0.0021 (−0.02-0.03; 0.86)	
Delta z-score h/a	−0.0009 (−0.04-0.03; 0.95)	−0.0051 (−0.24-0.01; 0.56)		−0.0015 (−0.02-0.02; 0.9)	−0.0025 (−0.02-0.01; 0.75)	
Delta z-score BMI/a	−0.0166 (−0.05-0.02; 0.25)	−0.0001 (−0.03-0.03; 0.99)		−0.0019 (−0.03-0.03; 0.88)	0.0286 (0.004-0.05; 0.02)	

UC/IC: ulcerative and indeterminate colitis, CI: confidence interval, BMI: body mass index, w/a: weight for age, h/a: height for age, BMI/a: BMI for age, CD: Crohn's disease.

age at diagnosis of UC/IC. The duration of the disease under treatment had a significant impact on the z-score change of BMI in males with UC diagnosed <10, of height in females with UC, and of BMI in males with CD diagnosed ≥ 10 years of age (Table 3).

DISCUSSION

The only major gender difference found in our cohort was the marked preponderance of boys with CD, and especially of boys with CD diagnosed <10 years. Several previous studies on the incidence or prevalence of paediatric IBD, which also included gender data of patients <17 or ≤ 16 years of age, such as those from Ohio [18], Hungary [19], and United Kingdom [20], Spain [21] and Scotland [22] reported just a small male excess, whereas others, such as studies from Toronto [23], the United Kingdom [24], Wisconsin [2], and Japan [25], reported a similarly high overall male excess as was seen in our cohort. However, only a few studies coming from Canada [3], Netherlands [26], and Sweden [27], separately report gender ratios for children with CD younger or older than 10 years of age at diagnosis, and they found either no, or a much lower male excess than was found in our study.

The current hypothesis for the adult female predominance of CD suggesting the cumulative exposure to endogenous and exogenous oestrogen following puberty as a possible trigger [28] cannot explain neither the pre-pubertal male preponderance nor the geo-epidemiological variability. Most of our patients with CD diagnosed <10 years of age were born in Switzerland, but only half of them had four grand-parents who were natives of Switzerland. Thus, the prevalence of X-linked polymorphisms including those of the DLG 5 gene, of members of the Toll-like receptor family [29], or of the IL-6 promoter [30] may, as in populations of other countries, not suffice to explain the important male excess of our CD patients. Local factors, including pre- or postnatal exposure to xeno- or phyto-oestrogens [31], and/or the administration of antibiotics causing a change of the intestinal microflora and thereby of the metabolism of sex-steroids [32,33] will have to be investigated. Furthermore, it is unknown whether there is a relation between adrenarche and the age at which antibiotics or oestrogens are administered.

The gender ratio of our patients with UC/IC was balanced in both age categories, and it was similar to the ratios reported by others [3,20,22], even though these patients shared the same environment as our CD patients. The lack of male excess in the UC/IC group may be explained by susceptibility loci that do not favour inflammation in a sex-steroid dependent way [34], including genes that regulate intestinal epithelial barrier function, encode for cytokines and inflammatory mediators, or involve the HLA-DQA1 locus.

Besides the important male excess in CD patients diagnosed <10 years of age, we only found minor gender differences. In UC/IC patients, boys <10 years of age had a longer diagnostic delay, and girls ≥ 10 years at diagnosis more often needed azathioprine therapy. These results differ from those reported by others [6,18] and require confirmation by the analysis of larger groups.

Older maternal age at pregnancy as a risk factor for CD in girls [27] or in boys [35] has previously been reported [27]. No gender difference for maternal age at pregnancy was found in our cohort. First-born rather than second-born twins have been reported to be at higher risk of CD, but no association between birth order of singletons and CD risk was found in previous studies [36]. No gender difference for CD was observed in the first-born children of our cohort.

Because of the widely variable disease durations of our patients, though without gender difference, we asked whether this variability could mask gender differences related to growth. We effectively found that catch-up growth, expressed as a z-score change, was dependant on disease duration in boys diagnosed with UC/IC <10 years, in girls with UC/IC diagnosed ≥ 10 years of age, and in boys diagnosed with CD ≥ 10 years of age. In these groups the z-score change was duration-dependent, whereas the growth dynamics of the remaining groups were independent of the disease duration, either because there was no growth im-

pairment or because of persistent growth abnormalities, as already described by Pfefferkorn et al. [35].

No other gender-related differences were found in either disease or age group, and this finding is in accordance with the reports of other groups [6,18].

There are several potential limitations of our study. Firstly, the cross-sectional nature of this study did not allow us to assess disease course, or growth and nutrition status over time. Furthermore, the Tanner stage was not uniformly assessed, and therefore not adjusted for growth and nutrition status. Additionally, we were not able to adjust for medication use in analyzing the BMI and height, as longitudinal use of medications was not assessed. Secondly, our study was retrospective and not population-based. In Switzerland, pubertal and post-pubertal children with IBD may be followed by adult gastroenterologists in private practice. Only pre-pubertal children are regularly followed by the paediatric gastroenterologists of the major regional medical centres such as those represented by the SIBDCS; therefore, the findings of these younger children are representative. Lastly, the relatively small number of patients <10 years of age at diagnosis required the use of non-parametric tests, which led to lower statistical power.

In conclusion, except for the marked male prevalence in pre-pubertal CD patients, we could not observe any gender difference in clinical phenotypes, disease behaviour, or treatment, and our results are in line with those of previous studies reporting a lack of gender difference. Future studies should investigate whether unique or repeated antibiotic treatments during the pre-pubertal period result in detectable changes of serum sex-steroids and/or of the quantity and function of invariant natural killer T cells in the intestinal mucosa, thereby favouring the development of CD, and whether there is an age at which antibiotic treatment confers a special risk of the development of CD.

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