Sex-Related Differences in Patients With Inflammatory Bowel Disease: Results of 2 Prospective Cohort Studies

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Background: The understanding of gender differences in inflammatory bowel disease (IBD) patients is an important step towards tailored treatment for the individual patient. The aim of this study was to compare disease phenotype, clinical manifestations, disease activity, and healthcare utilization between men and women with Crohn's disease (CD) and ulcerative colitis (UC).

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EAMF, BO, RKW, LMS, and MS designed the study; LMS and MS gathered the data, interpreted the data, performed the statistical analysis, and codrafted the manuscript. All authors approved the final manuscript. Guarantor of the article: HH Fidder is accepting full responsibility for the conduct of the study. This author has had access to the data and had control of the decision to publish.

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Abbreviations: CD, Crohn's disease; EIMs, Extraintestinal manifestations; GI, gastro-intestinal; HrQoL, gealth-related quality of life; IBD, inflammatory bowel disease; IBD-I, inflammatory bowel disease indeterminate; IBD-U, inflammatory bowel disease unclassified; UC, ulcerative colitis; UMCs, university medical centers.

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Methods: Two multicenter observational cohort studies with a prospective design were used to explore the differences between men and women regarding demographic and phenotypic characteristics and healthcare utilization. Detailed data on IBD-phenotype was mainly available from the Dutch IBD Biobank, while the COIN cohort provided healthcare utilization data.

Results: In the Dutch IBD Biobank study, 2118 CD patients and 1269 UC patients were analyzed. Female CD patients were more often current smokers, and male UC patients were more often previous smokers. Early onset CD (<16 years) was more frequently encountered in males than in females (20% versus 12%, $P < 0.01$). Male CD patients were more often diagnosed with ileal disease (28% versus 20%, $P < 0.01$) and underwent more often small bowel and ileocecal resection. Extraintestinal manifestations (EIMs) were more often encountered in female IBD patients. In the COIN study, 1139 CD patients and 1213 UC patients were analyzed. Male CD patients used prednisone more often and suffered more often from osteopenia. IBD-specific healthcare costs did not differ between male and female IBD patients.

Conclusions: Sex differences in patients with IBD include age of onset, disease location, and EIM prevalence. No large differences in therapeutic management of IBD were observed between men and women with IBD.

Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, sex, gender

INTRODUCTION

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are immune-mediated chronic inflammatory diseases of the gastrointestinal tract. More than 1 million residents from the United States of America and 2.5 million Europeans are estimated to suffer from IBD.[1]

Treatment strategies for IBD are aimed at inducing and maintaining long-term remission.[2,3] In other chronic conditions, such as ischemic heart disease, it is recognized that the treatment of men and women requires a different approach.[4] Although incidence rates for male and female IBD patients are well established (approximately 1:1.5 in CD and 1:1.2 in UC, respectively), data on sex-specific differences with respect to disease characteristics of IBD are limited.[5–7] Female sex has been reported as a risk factor for extraintestinal manifestations (EIMs).[5] Studies focusing on predictors for postoperative recurrence of IBD have incorporated sex as a potential predictor, but these studies report conflicting outcomes regarding sex.[8–10] Data regarding differences in healthcare consumption between male and female IBD patients are very limited. One study that compared the use of treatment modalities between hospitalized female and male adolescent CD patients did not observe any significant difference regarding medical procedures, such as endoscopies and blood transfusions.[11] Also in pediatric IBD patients, no differences have been found between males and females regarding the risk for first gastrointestinal surgery.[11–13] The understanding of differences in disease characteristics and current clinical approach between female and male IBD patients is an important step toward tailored treatment in the individual patient.[14,15]

In this study, we aim to compare the phenotype, clinical manifestations, disease course, medical treatment, and other consumption of the healthcare system between adult male and female IBD patients, using 2 large independent multicenter observational cohorts.

METHODS

Dutch IBD Biobank

The Dutch IBD Biobank is part of the Parelsnoer Institute[16] and was founded in 2007 with the aim to facilitate basic science and clinical research by providing high-quality biomaterials and an extensive patient data collection. Every adult patient diagnosed with IBD and treated in one of the 8 university medical centers (UMCs) in the Netherlands is eligible for inclusion. Data are collected prospectively by using a standardized information model containing 225 IBD-related items. For the present study, demographic items, diagnosis, smoking status, disease location, disease behavior, surgery-related items, medication use, EIMs, and disease complications were used. Definitions of these items can be found in Supplementary Methods Table 1.

COIN Study

The COIN study (costs of inflammatory bowel disease in the Netherlands) is a prospective multicenter study initiated in 2010, designed to assess costs and health-related quality of life (HrQoL).[17] CD and UC patients who were 18 years or older and attending the IBD units from 7 university medical centers (UMCs) and 7 general hospitals were eligible for participation. The study design has previously been described in detail.[17] In short, data were collected through a web-based baseline questionnaire, followed by quarterly questionnaires. For this study, data regarding demographics, smoking status, disease course and EIMs were collected at baseline. And IBD-specific healthcare consumption (medication use, use of diagnostics, outpatient clinic visits, hospital admissions, and surgical procedures) was measured after 3 months of follow-up. Healthcare costs were calculated by multiplying units of self-reported healthcare utilization during follow-up by their corresponding unit prices.[18] Total healthcare costs consisted of medication use, hospital admissions, surgeries, diagnostic procedures, and outpatient clinic visits. Costs were expressed in Euros for the year 2015. Definitions of all above-mentioned items can be found in Supplementary Methods Table 2.

Analyzing the Dutch IBD Biobank and COIN Cohort

To prevent duplicates, only patients in the COIN cohort that did not participate in the Dutch IBD Biobank cohort were included in the analysis. The 2 cohorts have a different study

aim. The Dutch IBD Biobank was founded to facilitate basic science and clinical research by providing high-quality biomaterials and an extensive patient data collection. The Dutch IBD Biobank is rigorous and detailed in phenotype collection (225 IBD items). The COIN study was designed to assess costs and health-related quality of life (HrQoL). Furthermore, the cohorts differ regarding patient inclusion, data collection, and selection of patients. In the Dutch IBD Biobank, patients were included and followed during hospital visits for IBD. Data in the COIN were collected through a web-based baseline questionnaire, followed by quarterly questionnaires. Patients were invited to participate at home. The Dutch IBD Biobank consisted entirely of IBD patients treated in tertiary referral centers (ie, university hospitals). Patients were included during a hospital visit for IBD. Data collection is based on electronic patient databases. Patients of the COIN study were self-reported through questionnaires and recruited from university hospitals and general hospitals. Because of the distinct features in each of the cohorts, analyses of the Dutch IBD Biobank study and the COIN study were performed separately.

Statistical Analysis

In all analyses, IBD-unclassified (IBD-U) and IBD-indeterminate (IBD-I) patients were included in the UC category. All analyses were repeated for CD and UC patients separately. Descriptive statistics were performed to describe differences between the male and female sex groups. Categorical variables were compared by a Pearson χ^2 test, and continuous variables by a Mann-Whitney-U test. Statistical analyses were performed with Stata Software V.13.1 (College Station, TX: Stata Corp LP) and SPSS version 21.0 (Armonk, NY: IBM Corp).

Ethical Considerations

The Dutch IBD Biobank was carried out with the approval of both a Central Medical Ethics Committee (MEC) and approval of local MECs of all participating centers. The COIN study was carried out with the approval of the MEC of the University Medical Center, Utrecht.

RESULTS

Patient Population and Male: Female Ratio

In the Dutch IBD Biobank, 2118 CD and 1269 UC patients were included. The male:female ratio was 1:1.7 in CD and 1:1.1 in UC (Table 1). In the COIN study, 1139 CD patients and 1213 UC patients were included. The male:female ratio in this study was 1:1.6 in CD and 1:1.1 in UC (Table 1).

Demographic Differences Between Female and Male CD and UC Patients

In the Dutch IBD Biobank, female CD patients were more often current smokers than male CD patients (43% versus 33%, $P < 0.01$). Male UC patients were more often previous smokers than female UC patients (51% versus 40%, $P < 0.01$) (Table 1). Comparable outcomes were observed in the COIN study (Table 1).

Differences in Disease Behavior Between Female and Male CD and UC Patients

In the Dutch IBD Biobank, men were diagnosed with CD with early onset (younger than 16 years old) more frequently than women with CD (20% versus 12%, $P < 0.01$) (Table 2). Also, UC was diagnosed more often in men older than 40 years in comparison with women (and 33% versus 22%, $P < 0.01$, respectively). Ileal disease (Montreal L1) was encountered more frequently in male CD patients, while colonic disease (Montreal L2) was more common in female CD patients. Proctitis (Montreal E1) was more frequent in female than in male UC patients. In the COIN study, men with CD or UC were diagnosed at 40 years or older more often than women (29% versus 17% in CD; 42% versus 26% in UC, both $P < 0.01$) (Supplementary Table S1). No differences in the incidence of flares were observed between males and females in either cohort.

Extraintestinal Manifestations in Female and Male CD and UC Patients

In the Dutch IBD Biobank, skin- and joint-manifestations were more common in female CD and UC patients than in male CD and UC patients (Table 3). Osteopenia and osteoporosis were diagnosed more often in male than in female CD patients (28% versus 21% in females, $P < 0.01$). After correcting for smoking behavior, age at diagnosis, and disease duration, female sex was associated with EIMs with an adjusted odds ratio (OR) of 2.3 (95% CI: 1.9–2.8) in CD patients and an adjusted OR of 1.5 (95% CI: 1.1–2.3) in UC patients (Supplementary Table S2). In the COIN study,[19] a similar trend was observed, although it did not reach statistical significance (Supplementary Table S3).

Surgery Rates in Female and Male CD and UC Patients

In the Dutch IBD Biobank, more male CD patients underwent small bowel and ileocecal resection than female CD patients (16% versus 9%, and 40% versus 33%, respectively, both $P < 0.01$) (Table 4). No further differences in surgery rates between men and women (colon resection, ileostomy, colostomy, abscess/fistula surgery, and pouches) were observed. These observations were confirmed in the COIN study (Supplementary Table S4).

Medication Use, Healthcare Consumption, and Healthcare Costs in Female and Male CD and UC patients

In the Dutch IBD Biobank, no differences regarding the use of IBD-specific medication (anti-TNFα compounds and

TABLE 1: Demographic Differences Between Female and Male IBD Patients

DUTCH IBD BIOBANK	CD (n = 2118)			UC (n = 1269)		
	Male	Female	*P*	Male	Female	*P*
Age at inclusion median years (IQR)	42 (31–56)	41 (31–52)	0.13	49 (36–60)	42 (33–53)	<0.01
Employed at baseline n (%)	415 (73)	557 (58)	<0.01	335 (79)	334 (73)	<0.05
Low education n (%)	366 (48)	753 (58)	<0.01	297 (51)	335 (52)	0.77
Smoking status n (%)						
Current	138 (33)	351 (43)	<0.01	62 (21)	68 (17)	0.26
Never	283 (42)	471 (39)	0.23	235 (44)	321 (53)	<0.01
Previously	259 (48)	392 (45)	0.39	241 (51)	212 (40)	<0.01
Family history of IBD† n (%)	231 (30)	382 (28)	0.47	154 (26)	165 (25)	0.78
COIN STUDY	**CD (n = 1139)**			**UC (n = 1213)**		
	Male	Female	*P*	Male	Female	*P*
Age at inclusion mean years (SD)	51 (14)	45 (13)	<0.01	54 (13)	46 (13)	<0.01
Employed at baseline n (%)	230 (72)	322 (64)	0.02	347 (80)	337 (81)	0.65
Low education n (%)	266 (60)	479 (69)	<0.01	371 (59)	363 (62)	0.36
Smoking status n (%)	—	—	<0.01	—	—	<0.01
Current	72 (16)	180 (26)	<0.01	57 (9)	78 (13)	0.02
Never	233 (53)	331 (48)	0.10	334 (53)	339 (58)	0.12
Previously	138 (31)	185 (27)	0.10	235 (38)	170 (29)	<0.01
Family history of IBD n (%)	98 (22)	149 (21)	0.95	116 (19)	126 (22)	0.44

N: number; %: percentage of total; UC: ulcerative colitis; CD: Crohn's disease; IBD: Inflammatory Bowel Disease; SD: standard deviation; IQR: interquartile range; †: missing values were scored as non-present

immunomodulators) were observed between men and women (Supplementary Table S5).

In the COIN study, prednisone use was reported more frequently in male CD patients than in female CD patients (6.8% versus 3.7%, $P = 0.03$) (Table 5). No other differences regarding the use of IBD-specific medication, diagnostics, the number of hospitalizations, or the number of outpatient clinic visits between men and women with CD or UC were observed. Quarterly healthcare costs did not differ between male and female CD and UC patients (Table 6).

Additional Analysis: Including All patients in the COIN Cohort Without Removing Duplicates

By analyzing all variables described above in the COIN study without excluding patients who were also included in the Biobank study, no statistical differences were observed regarding the outcomes (data available on request).

DISCUSSION

In this large nationwide multicenter study based on 2 IBD cohorts, we aimed to identify clinical relevant differences in disease characteristics and current clinical approach between female and male IBD patients. We observed that early onset CD (<16 years old) was more prevalent in male patients. Ileal disease and small bowel surgery were more common in male than in female CD patients. Both female CD and UC patients suffered more often from EIMs than male patients. Prednisone use was higher in male CD patients compared to female CD patients. The use of other IBD-specific medication, outpatient clinic visits, diagnostic procedures, and hospitalizations did not differ between female and male IBD patients.

Although correction for gender is frequently performed in the analysis of clinical parameters in IBD studies, results of previous studies usually did not correct for sex.[20–22] Our finding in the Dutch IBD Biobank that male sex was associated with a CD diagnosis before the age of 16 years seems to have some base in previous literature.[23] However, this observation was not confirmed in the COIN cohort. Differences in exposure to hormonal changes during pubertal development could underlie the sex-related differences of early onset CD,[24] but environmental differences (such as diet and smoking behavior) between males and females in puberty may also contribute.[25]

In the Dutch IBD Biobank, the ileum was more frequently affected in men with CD than in women. Prior data on this subject are scarce, with only 1 other study confirming our observation (ie, ileitis terminal) in 33% of males versus 29% of females with CD.[10] It is likely that the increased prevalence of ileal involvement translated into more small bowel and ileocecal resections in men with CD. One could argue that higher resection rates reflect more severe disease behavior in men. However,

TABLE 2: Disease Behavior in Female and Male IBD Patients in the Dutch IBD Biobank

	CD (n = 2118)			UC (n = 1269)		
N (%)	**Male**	**Female**	***P***	**Male**	**Female**	***P***
Type of IBD	—	—	<0.01	—	—	<0.01
CD	773 (37)	1345 (63)		—	—	
UC	—	—		604 (48)	665 (52)	
Disease duration at baseline median, years (IQR)	13 (6–22)	12 (6–21)	0.16	11 (5–20)	10 (5–18)	0.19
Montreal classification						
A1: diagnosis ≤16 years	153 (20)	166 (12)	<0.01	54 (9)	80 (12)	0.07
A2: diagnosis 17–40 years	487 (63)	980 (73)	<0.01	348 (58)	437 (66)	<0.01
A3: diagnosis >40 years	133 (17)	199 (15)	0.14	202 (33)	148 (22)	<0.01
L1: ileal disease[a]	169 (28)	210 (20)	<0.01	—	—	—
L2: colon disease[a]	162 (26)	356 (33)	<0.01	—	—	—
L3: ileocolon disease[a]	280 (46)	500 (47)	0.67	—	—	—
L4: upper GI disease†	76 (10)	101 (8)	0.06	—	—	—
P: peri-anal disease†	221 (29)	342 (25)	0.11	—	—	—
E1: proctitis[b]	—	—	—	26 (5)	59 (10)	<0.01
E2: left-sided colitis[b]	—	—	—	179 (36)	197 (35)	0.86
E3: extensive colitis[b]	—	—	—	299 (59)	307 (55)	0.11
Disease behavior CD						
Fistulising†	102 (13)	236 (18)	<0.01	—	—	—
Stricturing†	216 (28)	341 (25)	0.19	—	—	—
Penetrating†	110 (14)	159 (12)	0.11	—	—	—

N: number; %: percentage of total; UC: ulcerative colitis; CD: Crohn's disease; IBD: Inflammatory Bowel Disease; IQR: interquartile range; †: missing values were scored as non-present
a.These percentages are calculated for 1677 CD patients (1066 female CD patients and 611 male CD patients)
b.These percentages are calculated for 1067 UC patients (563 female UC patients and 504 male UC patients)

TABLE 3: Extra-Intestinal Manifestations in the Dutch IBD Biobank

	CD (n = 2118)			UC (n = 1269)		
N (%)	**Male**	**Female**	***P***	**Male**	**Female**	***P***
Skin manifestations†	47 (6)	203 (15)	<0.01	31 (5)	55 (8)	0.03
Arthropathy†	95 (12)	272 (20)	<0.01	55 (9)	95 (14	<0.01
Arthritis†	27 (3)	119 (9)	<0.01	25 (4)	43 (6)	0.07
Ocular† manifestations†	31 (4)	73 (5)	0.15	16 (3)	27 (4)	0.17
Osteopenia†	219 (28)	277 (21)	<0.01	93 (15)	87 (13)	0.24

N: number; %: percentage of total; UC: ulcerative colitis; CD: Crohn's disease; †: missing values were scored as non-present

TABLE 4: Surgery Rates in Female and Male IBD Patients in the Dutch IBD Biobank

	CD (n = 2118)			UC (n = 1269)		
N (%)	**Male**	**Female**	***P***	**Male**	**Female**	***P***
Small bowel resection†	127 (16)	115 (9)	<0.01	—	—	—
Ileocaecal resection†	308 (40)	450 (33)	<0.01	—	—	—
Colon resection†	124 (16)	244 (18)	0.22	102 (17)	121 (18)	0.54
Strictureplasty†	44 (6)	45 (3)	0.01			
Ileostomy/colostomy†	90 (12)	193 (14)	0.08	56 (9)	75 (11)	0.24
Surgery for abscesses or fistula†	160 (21)	307 (23)	0.26	13 (2)	14 (2)	0.95
Stoma†	90 (12)	180 (13)	0.25	63 (10)	69 (10)	0.98
Pouch†	13 (1.7)	25 (1.9)	0.77	52 (9)	65 (10)	0.47
Post operative stricture†	47 (6)	60 (4)	0.10	—	—	—

N: number; %: percentage of total; UC: ulcerative colitis; CD: Crohn's disease; †: missing values were scored as non-present

TABLE 5: Medication Use and Other Healthcare Use in Female and Male IBD Patients in the COIN Study

	CD (n = 940)*			UC (n = 1023)*		
N (%)	**Male**	**Female**	***P***	**Male**	**Female**	***P***
Anti-TNF	81 (22)	118 (21)	0.63	18 (3)	21 (4)	0.37
Adalimumab	35 (10)	67 (12)	0.28	8 (2)	5 (1)	0.54
Infliximab	47 (13)	51 (9)	0.06	10 (2)	16 (3)	0.13
Azathioprine	98 (27)	126 (22)	0.11	80 (15)	58 (12)	0.22
Mercaptoprine	25 (7)	46 (8)	0.47	35 (6)	27 (6)	0.59
Methotrexate	10 (3)	12 (2)	0.54	2 (0)	3 (1)	0.56
Budesonide	16 (4)	31 (5)	0.46	17 (3)	9 (2)	0.20
Prednisone	25 (7)	21 (4)	0.03	32 (6)	24 (5)	0.54
Sulfazalazine	6 (2)	8 (1)	0.79	3 (1)	6 (1)	0.23
Mesalazine	92 (25)	134 (23)	0.60	329 (61)	283 (59)	0.62
Use of diagnostics	89 (24)	123 (22)	0.36	92 (17)	73 (15)	0.45
Hospitalization due to IBD	19 (5)	17 (3)	0.09	14 (3)	18 (4)	0.28
Outpatient clinic visit due to IBD	171 (77)	281 (82)	0.11	234 (82)	197 (77)	0.12

N: number; %: percentage of total; UC: ulcerative colitis; CD: Crohn's disease; *: At t = 3 months of follow-up

TABLE 6: Mean healthcare costs in female and male patients in the COIN, calculated in Euros for the year 2015, calculated over 3 months of follow-up

Mean € (95% CI)	Male	Female	*P-value*
M. CROHN (369 males and 572 females)			
Total healthcare costs	1,768 (1,502 – 2,075)	1,520 (1,298 – 1,746)	0.19
Medication costs	1,205(1,006– 1,411)	1,118 (953 – 1,286)	0.52
Hospitalization costs	370 (224 – 540)	198 (107 – 300)	0.08
Surgery costs	3 (0 – 11)	14 (3 – 29)	0.27
Diagnostics costs	48 (35 – 62)	46 (34 – 58)	0.89
Outpatient clinic costs	125 (100 – 153)	127 (100 – 165)	0.94
ULCERATIVE COLITIS (544 males and 480 females)			
Total healthcare costs	538 (429 – 646)	608 (480 – 739)	0.45
Medication costs	299 (234 – 365)	353 (269 – 447)	0.37
Hospitalization costs	113 (50 – 183)	122 (50 – 195)	0.87
Surgery costs	5 (0 – 12)	12 (0 – 24)	0.37
Diagnostics costs	32 (24 – 42)	36 (25 – 47)	0.61
Outpatient clinic costs	82 (71 – 95)	75 (62 – 88)	0.39

CI: confidence interval

no other arguments for a more severe course in men were found in the Dutch IBD Biobank, since comparable numbers of male and female patients used anti-TNFα compounds and immunomodulators. Therefore, our data suggests that gender may be a potential risk factor for ileal disease involvement and subsequent ileal surgery. Prior reports regarding the role of gender in relation to (overall abdominal) surgery are conflicting.[13, 26]

A multivariable analysis for EIMs in the COIN study has previously been published.[19] In both cohorts, an association was found between female sex and EIMs in IBD patients.[27–30] Smoking is strongly associated with EIMs,[19] and one could hypothesize that the female association with EIMs is explained by the fact that women with IBD were more often smokers than men with IBD.[31] However, multivariable analysis suggests that female sex is an independent risk factor for EIMs, in both CD and UC patients. Similarly, many rheumatic diseases, including rheumatoid arthritis (RA) are more common in women than in men.[32] Sex hormones are thought to underlie this gender difference. In RA, disease activity is found to be correlated with prolactin plasma levels.[33] Prolactin levels have been found to rise in women with RA post-partum, corresponding with a higher incidence of flares.[34] Other suggested mechanisms include a lower level of serum androgens resulting in an increased production of interleukin-2 and suppression of the synthesis of autoantibodies.[35, 36] The same mechanisms might explain the higher incidence of EIMs in female IBD patients.

In the COIN study, prednisone was more often prescribed to male CD patients, but since the numbers were small, results need to be interpreted with caution. In regard to the use of other IBD-specific medication, diagnostic procedures, outpatient clinic visits, hospitalizations, and associated costs, we found no gender differences in the COIN study. Only very few previous studies have reported on differences in IBD-related healthcare utilization in men and women. One study did not find a significant difference with respect to procedures (endoscopy, surgery, and blood transfusions) and the use of corticosteroids or biologic agents by comparing treatment between hospitalized male and female adolescent CD patients.[11] Another study found that female IBD patients were treated with immunosuppressive agents less frequently than male IBD patients.[31] The authors hypothesize that this difference results from the tendency to prescribe less medication to women of child-bearing potential. However, a sub-analysis did not substantiate this assumption. Apart from more ileal and ileocolonic surgery in male CD patients in the Dutch IBD Biobank cohort, no differences in the management of male and female IBD patients were detected. Interestingly, in other immune-mediated diseases, female patients have been postulated to be less responsive to anti-TNFα therapy.[37–39] The current study was not designed to assess response to therapy, therefore we cannot confirm nor refute this finding.

Strengths of this study include the large sample size (n > 5700) and the corroboration of two independent cohorts. Most of the observed differences between men and women were encountered in both cohorts or showed a similar trend, which supports the validity of both the separate cohorts and our conclusions of this current study. Moreover, the same results were obtained when repeating analyses for the complete COIN cohort, (ie, including the duplicates from the IBD Biobank cohort). Specific strengths of the Dutch IBD Biobank are the standardized and concise method of phenotyping of the included patients. Strengths of the COIN study include the diversity of

the case mix and the comprehensive and prospective way consumption of healthcare and associated healthcare costs were studied. Some differences between the 2 cohorts warrant comment. First, the Dutch IBD Biobank study exclusively recruited patients from university medical centers, whereas the COIN study included patients from both academic medical centers and general hospitals. Data collection in the Dutch IBD Biobank was predominantly conducted from medical records, while the data in the COIN study was self-reported. Self-reported information is generally less objective, and this could be considered a limitation. However, self-report is a validated method to study healthcare consumption and incurred healthcare costs in IBD patients.[40] In addition, a non-responder analysis showed no relevant statistical significant differences regarding demographic data (including gender) and disease course items between self-reported responders and non-responders.[17] Therefore, it was concluded that self-report reliably reflects consumption of health care in patients with IBD. With regard to disease characteristics, our findings were primarily based on the rigorous phenotyping from the Dutch IBD Biobank study.

In summary, our study revealed several sex differences between male and female IBD patients regarding age of onset, smoking behavior, disease location, and EIMs. For example, both cohorts showed that smokers were most often female patients with CD. As smoking is a clinical parameter associated with severe disease course, clinicians should discuss this with every patient. This is an example where our results could aid toward the development of tailored treatment for the individual IBD patient.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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