Inflammatory Bowel Diseases, 2025, **XX**, 1–10
https://doi.org/10.1093/ibd/izaf047
Advance access publication 10 March 2025
Original Research Article - Clinical

Prevalence of Irritable Bowel Syndrome Based on Rome IV Criteria in Patients in Biochemical and Endoscopic Remission From Newly Diagnosed Inflammatory Bowel Disease: One- and Three-Year Results (the IBSEN III Cohort)

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Background: Distinguishing irritable bowel syndrome (IBS) from inflammatory bowel disease (IBD) flare-ups is challenging. This study used objective remission markers to accurately determine IBS prevalence in a population-based cohort of patients with IBD.

Methods: Adults with ulcerative colitis and Crohn's disease were recruited from the IBD in South-Eastern Norway III cohort study. Irritable bowel-like symptoms were assessed using the Rome IV criteria for patients in remission from IBD at 1- and 3-year follow-ups. Remission was defined objectively using the biochemical marker fecal calprotectin (FC) ≤ 250 µg/g, and comparisons to remission based on endoscopic indices were made at 1-year follow-up.

Results: Among patients with FC ≤ 250 µg/g, IBS prevalences were 21.9% (n = 62/283) and 16.1% (n = 49/304) at the 1- and 3-year follow-ups, respectively, which were higher than that in the Norwegian population (9.5%; P < .005). Of patients in endoscopic remission at 1-year follow-up, 19.2% (n = 43/224) reported IBS-like symptoms, which was not significantly different from IBS prevalence for patients with FC ≤ 250 µg/g. Irritable bowel syndrome was independently associated with substantial fatigue (odds ratio: 3.05 [95% CI, 1.48-6.27]) and female sex (odds ratio: 2.67 [95% CI, 1.34-5.32]) at the 1-year follow-up. Patients with IBS reported significantly reduced health-related quality of life (HRQoL) scores.

Conclusions: The prevalence of IBS among patients in remission from IBD was approximately twice as common as that in the Norwegian population. Irritable bowel syndrome was independently associated with substantial fatigue, female sex, and reduced HRQoL.

Received for publication: November 14, 2024. Editorial Decision: February 10, 2025

Lay Summary

In this prospective cohort of newly diagnosed patients with inflammatory bowel disease (IBD), patients in remission from IBD reported irritable bowel-like symptoms 2 to 3 times more frequently than the general Norwegian population at both the 1- and 3-year follow-ups.

Key Words: irritable bowel syndrome, Rome IV, epidemiology

Key Messages

What is already known?

Distinguishing irritable bowel syndrome (IBS) from flare-ups of inflammatory bowel disease (IBD) remains difficult in patients with both conditions, and reported IBS prevalences in these patients vary significantly.

What is new here?

This is the first prospective cohort study of newly diagnosed patients with IBD to estimate IBS prevalence using the latest Rome IV criteria, while also objectively defining IBD remission with fecal calprotectin levels and endoscopic indices.

How can this study help patient care?

Utilizing objective disease activity markers to define remission from IBD may provide a more accurate assessment of IBS prevalence and could aid clinicians to consider IBS in patients in remission with persistent bowel symptoms.

Introduction

Irritable bowel syndrome (IBS) is one of the most common disorders of the gut-brain interaction, affecting an estimated 4%-5% of the global population when based on the Rome IV criteria for IBS.[1,2] Irritable bowel syndrome symptoms are similar to those of inflammatory bowel disease (IBD) and include abdominal discomfort or pain, changes in stool frequency and form, and bowel urgency.[2–4] Unlike IBD, however, IBS does not involve significant bowel inflammation.[3,5,6] Moreover, individuals with IBS report lower health-related quality of life (HRQoL) scores than healthy individuals, and IBS contributes significantly to healthcare costs.[2,5–8]

Irritable bowel syndrome may also develop in patients with established IBD, complicating the differentiation between IBS and active inflammation as the cause of bowel symptoms.[5,7,9] Consequently, reported prevalence estimates of IBS in patients with IBD vary, even among those in remission from IBD.[5,9–11] A recent systematic review and meta-analysis reported IBS prevalence rates ranging from 11.2% to 63.6% in patients with IBD,[10] suggesting differences in study methodology and/or populations. These variations may also be influenced by the different versions of the Rome criteria used to diagnose IBS. To date, only a few studies have used the latest Rome IV criteria to investigate the prevalence of IBS in patients in remission from IBD.[12–14]

The lack of consensus on defining remission in patients with IBD further complicates IBS prevalence estimations.[10] Numerous investigations concerning IBS in IBD have employed clinical disease activity metrics that depend on patient-reported symptoms to define remission from IBD, such as the Harvey-Bradshaw Index (HBI) for Crohn's disease (CD) and the Simple Clinical Colitis Activity Index (SCCAI) for ulcerative colitis (UC).[10,15–17] However, the Rome criteria, HBI, and SCCAI all incorporate abdominal pain and stool frequency, obscuring the distinction between IBS-like symptoms and those resulting from heightened IBD activity.

Fecal calprotectin (FC) levels, endoscopic assessment, and histologic evaluation of bowel biopsies are considered objective and precise measures of disease activity in IBD, and therefore, they provide more accurate assessments of remission from IBD than clinical disease activity measures alone.[18,19] Endoscopic procedures, however, are costly and resource-intensive, and biopsies carry a low, but not negligible, risk of complications.[20] FC, an objective biomarker for bowel inflammation measured in stool samples, offers a safer and more cost-effective alternative for quantifying disease activity in patients with IBD.[20,21] FC levels ≤ 250 µg/g are associated with remission and are often used in clinical practice to define remission.[20–23]

Thus, defining IBD remission through objective measurements of disease activity is necessary to accurately determine IBS prevalence among these patients. A more accurate prevalence estimate may help clinicians better identify IBS in patients experiencing a high symptom burden despite optimal IBD treatment.

We conducted a prospective cohort study involving newly diagnosed patients with UC and CD in a well-defined health region of South-Eastern Norway. The primary aim was to estimate the prevalence of IBS in patients in remission from IBD (FC levels ≤ 250 µg/g) at the 1- and 3-year follow-ups and to compare this to IBS prevalence in the general Norwegian population. Secondary aims included identifying risk factors associated with IBS-like symptoms at each time point and comparing HRQoL between patients with and without IBS-like symptoms.

Materials and Methods

The study was approved by the South-East Regional Committee for Medical Research Ethics (reference number 2015/946-3) and the Norwegian Centre for Research Data (NSD, 498873). Study inclusion did not imply any changes in patient treatment, and all participants provided written informed consent before inclusion in the study. The study was conducted in accordance with the revised Declaration of Helsinki.

Study Population

Patients were recruited from the Inflammatory Bowel Disease in South-Eastern Norway (IBSEN) III study, an observational inception-based cohort with prospective follow-up (Clinical Trial ID: NCT02727959). The IBSEN III study monitors unselected patients with UC and CD diagnosed between 2017 and 2019 from the health region of South-Eastern Norway. This is the largest health region in Norway, with a catchment area of approximately 3 million inhabitants. A comprehensive account of the cohort has been published previously.[19]

Adult patients (≥18 years of age) were eligible for inclusion if they were diagnosed with UC or CD at inception, which was reconfirmed at the 1-year follow-up. The diagnosis of UC or CD was determined using the Lennard-Jones

Diagnostic criteria*: Recurrent abdominal pain, on average, at least 1 day pr week in the last 3 months, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

*Criteria must have been fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Figure 1. The Rome IV diagnostic criteria.

Criteria,[24] adapted from Moum et al.[25] All eligible patients underwent a clinical interview and a physical examination at the 1-year follow-up. Patients were also requested to provide a blood sample for analysis of C-reactive protein and a fecal stool sample for analysis of FC levels, and were instructed to complete electronic patient questionnaires at the 1-year follow-up. Endoscopic (eg, ileocolonoscopy) and/or radiological procedures (eg, small bowel magnetic resonance imaging) were performed at the 1-year follow-up if clinically indicated. In accordance with the IBSEN III study protocol, colonoscopy was not part of the 3-year follow-up. Instead, patients received a kit for fecal sampling and were asked to complete a set of patient-reported outcome measure questionnaires.

IBS Diagnosis: The Rome IV Criteria

Irritable bowel syndrome was diagnosed using the Rome IV criteria (Figure 1) developed by Lacy et al.,[4] and the Rome IV Diagnostic Questionnaire was administered to patients independently at the 1- and 3-year follow-ups.[26]

FC and the Definition of Remission From IBD

At the 1- and 3-year follow-ups, FC samples were obtained using a home-based sampling kit, delivered by mail, and preserved at −80 °C in a secure biobank. Fecal calprotectin levels were quantified using an enzyme-linked immunoassay (BÜHLMANN Calprotectin ELISA EK-CAL; BÜHLMANN Laboratories AG), with analysis performed at a single laboratory to minimize variance. Remission from IBD was defined as FC ≤ 250 µg/g, supported by empirical evidence and reflecting clinical practice.[21,22]

Criteria for Endoscopic Remission From IBD

For comparison, the IBS prevalence rate at the 1-year follow-up for patients who underwent colonoscopy and achieved endoscopic remission was calculated. Endoscopic remission was defined as a Mayo endoscopic score of 0 or 1 for UC, a modified Simple Endoscopic Activity score of 0-2 of the most affected bowel segment for CD, or no visible inflammation.[11,27]

Factors Associated With IBS-Like Symptoms

Demographic factors, including age (in years), sex (male/female), and diagnosis (UC/CD) were recorded. Clinical disease activity was measured using the SCCAI for UC and the HBI for CD.[15,17] Psychosocial measures were evaluated using the Hospital Anxiety and Depression Scale (HADS), the General Self-Efficacy Scale (GSE), and the Fatigue Questionnaire (FQ). HADS subscale scores for anxiety (HADS-A) and depressive symptoms (HADS-D) ≥ 8 were considered potential cases of anxiety or depression, respectively.[28] General self-efficacy total scores were analyzed, with higher scores representing greater self-efficacy.[29] A total dichotomized score of ≥ 4 on the FQ indicated substantial fatigue.[30] All the above-mentioned questionnaires have been translated into Norwegian and previously validated in a Norwegian population.[31–33]

Health-related quality of life

The Short Form 36 (SF-36), a generic HRQoL questionnaire comprising 36 questions, was utilized to assess generic HRQoL, with answers transformed into 8 dimensional scores: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health. Each dimension provides a possible score between 0 and 100, with higher scores indicating better HRQoL.[34]

IBS in the General Population

The Trøndelag Health Study (HUNT) is a series of large, ongoing population-based health studies in Norway providing normative data on a wide range of health-related conditions, including IBS. During the HUNT4 survey, conducted between 2017 and 2019, a total of 42 669 respondents (response rate, 54%; mean age, 56.2 years; female, 57.2%) answered the Rome II questionnaire for IBS. The pooled prevalence of IBS reported from the HUNT4 survey was considered representative of the general Norwegian population in the current study.[35]

Data Handling and Missing Data

Clinical and demographic data were recorded in an electronic, secure case report form provided by Viedoc© (PCG Solutions AB). Patient-reported outcome data were submitted electronically via the internet-based system ViedocMe©. All study data were stored and analyzed on a secure, encrypted server (TSD Facilities, IT Department, University of Oslo). The prevalence of missing data for Rome IV, FC levels, disease activity measures, psychosocial, and HRQoL scores was analyzed for both the 1- and 3-year follow-ups. Potential differences in demographic, psychosocial, and disease-related factors between patients with and without available FC samples, including differences between responders and non-responders of the Rome IV Diagnostic Questionnaire, were recorded and analyzed to confirm sample representativeness. All demographic data, as well as data for psychosocial measures in patients in IBD remission and those with IBS, were fully complete (100%). Data on psychosocial measures were available for 98%-100% of patients without IBS. For disease-related measures, data were available for 72%-100% of patients with IBS and 88%-99% of patients without IBS.

Statistical Analysis

Patient characteristics at the 1- and 3-year follow-ups are presented as mean values with SDs for normally distributed data, median values with ranges for skewed data, or counts with percentages, as applicable. Chi-square tests were performed for categorical variables, independent samples *t*-tests for normally distributed continuous variables, and Mann-Whitney U-tests for continuous variables that were not normally distributed.

Proportions of individuals with IBS in the study population and the HUNT4 reference population were compared using 2-proportion Z-tests, and CIs were obtained by one-sample binomial testing with the Clopper-Pearson option. Associations between IBS and demographic, psychosocial,

and disease-related factors at the 1- and 3-year follow-ups were analyzed using binary logistic regression models, where a dichotomized variable for the Rome IV IBS criteria (IBS/no IBS) represented the dependent variable. All associations were analyzed using both univariable and multivariable logistic regression. Results from the regression analysis were checked for collinearity using Pearson correlation coefficients.

SF-36 dimensional scores were checked for normality and adjusted for potential confounding variables, including age, sex, GSE score, FQ score, HADS-D score, and HADS-A score. Mean SF-36 scores stratified by time and IBS status are presented with the SD and 95% CI, where appropriate. Owing to multiple tests, Bonferroni correction of CIs for estimated marginal means was performed. Differences in SF-36 scores between patients with and without IBS were evaluated with independent samples *t*-tests and Cohen's *d* effect sizes ([mean patient score—mean reference population score]/pooled SD), where < 0.2 indicated no difference, 0.2-0.5 indicated a small effect, 0.5-0.8 indicated a moderate effect, and > 0.8 indicated a large effect.[36] A moderate-to-large effect was considered clinically important.[37] We assumed homogeneity of variance in the study cohort.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29 (IBM Corp.) and MedCalc for Windows, version 22.016 (MedCalc Software). *P*-values < .05 were considered statistically significant.

Results

Study Cohort

The inclusion process for the study population is presented in Figure 2. Of the 1509 adult patients with IBD at diagnosis, 87.5% (*n* = 1320) attended the 1-year follow-up. Ten patients were colectomized prior to the 1-year follow-up and were consequently excluded. The remaining 1310 patients included 881 with UC (67.3%) and 429 with CD (32.7%). At the 1-year follow-up, 53.6% (*n* = 702/1310) of patients with UC/CD underwent colonoscopy. At the 1- and 3-year follow-ups, 38.6% (*n* = 506/1310) and 48.2% (*n* = 631/1310) submitted FC samples, respectively. Of these, 68.6% (*n* = 347/506) and 77.0% (486/631) at the 1- and 3-year follow-ups, respectively, had FC levels ≤ 250 µg/g and were considered to be in remission from IBD.

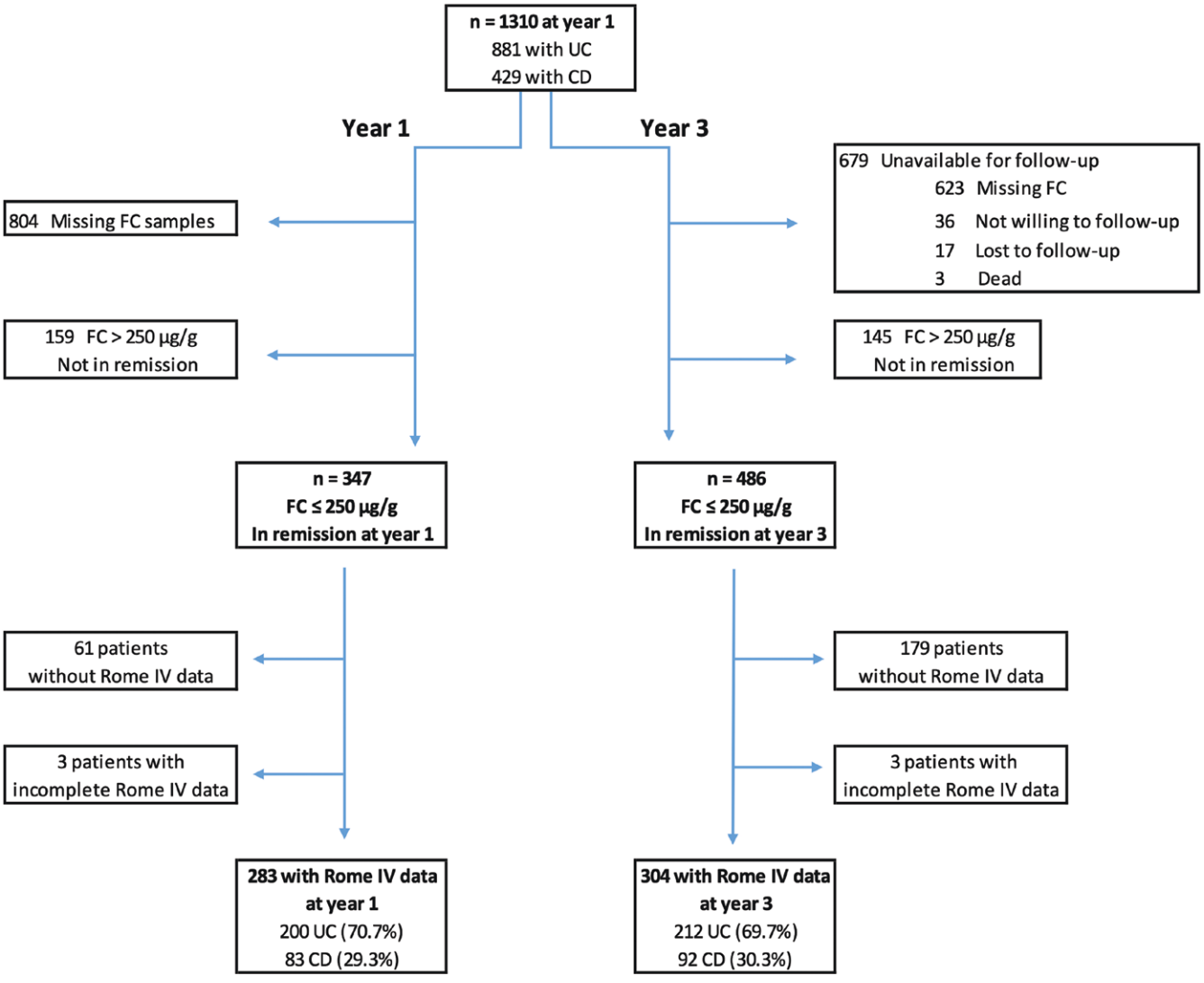

Figure 2. Study flowchart. CD, Crohn's disease; FC, fecal calprotectin; UC, ulcerative colitis.

At both the 1- and 3-year follow-ups, patients with UC/CD who submitted FC samples were significantly older than those with missing FC samples. Additionally, more female than male patients submitted FC samples at the 1-year follow-up. No other statistical differences were observed in terms of demographic, psychosocial, or disease-related factors between these 2 patient groups (Supplementary Data Content 1, Table showing the representability of patients with FC data compared to patients with missing calprotectin data).

Of patients in remission from UC/CD (FC levels ≤ 250 µg/g), complete Rome IV data were provided by 81.6% (n = 283/347) and 62.6% (n = 304/486) at the 1- and 3-year follow-ups, respectively. There were no significant differences in demographic, psychosocial, or disease-related factors between patients who completed the Rome IV questionnaire and those who did not at the 1-year follow-up (data not shown). At the 3-year follow-up, patients who completed the Rome IV questionnaire were significantly older than those who did not (mean age, 46 vs 41 years; P < .001).

Prevalence of IBS

The prevalence rates of IBS were 21.9% (n = 62/283) and 16.1% (n = 49/304) among patients with UC/CD in remission at the 1- and 3-year follow-ups, respectively (Table 1). There were no significant differences in IBS prevalence between patients with UC and CD at either follow-up. Among patients in remission at both time points and who reported IBS-like symptoms at least once, 27.5% (n = 11/40) experienced IBS-like symptoms at both the 1- and 3-year follow-ups.

In total, 62.4% (n = 438/702) of patients who underwent colonoscopy at the 1-year follow-up were in endoscopic remission (320 UC, 118 CD). Of patients in endoscopic remission, 51.1% (n = 224/438) completed the Rome IV questionnaire at the 1-year follow-up. Of these patients, 19.2% (n = 43/224) reported IBS-like symptoms. This was not significantly different from the prevalence of IBS among patients with FC levels ≤ 250 µg/g (difference 2.7%; CI, –4.5 to 9.6; P = .46).

A statistically significantly higher proportion of patients in remission at both follow-ups fulfilled the criteria for IBS compared to the general Norwegian population (9.5%; P < .005; Table 1). Although we observed a slight decrease in IBS prevalence from the 1-year to 3-year follow-up, this change was not statistically significant (21.9% vs 16.1%, P = .077).

Characteristics of Patients With and Without IBS

Demographic and psychosocial characteristics, as well as clinical disease activity measures, for patients in remission with or without IBS, are shown in Table 2. At the 1-year follow-up, patients with IBS were significantly younger and more often female than those without IBS. This was also observed at the 3-year follow-up, though not statistically significant. At both follow-ups, patients with IBS reported significantly higher median HADS-A, HADS-D, and FQ scores than non-IBS patients. They also reported higher HBI scores and SCCAI scores than those without IBS.

Factors Associated With IBS

Factors associated with IBS in univariable and multivariable analyses are presented in Table 3. At the 1-year follow-up, female sex and substantial fatigue (FQ score ≥ 4) were independently associated with IBS in both univariable and multivariable analyses. At the 3-year follow-up, none of the selected factors were independently associated with IBS in the multivariable model.

IBS and HRQoL

SF-36 scores for patients in remission with or without IBS are shown in Table 4. Patients with IBS reported significantly lower mean HRQoL scores in 2 SF-36 dimensions at the 1-year follow-up, though the effect sizes were small. At the 3-year follow-up, patients with IBS reported significantly lower mean scores in 5 dimensions than those without IBS, with moderate effect sizes in 3 dimensions (physical function, bodily pain, and general health).

Discussion

In this prospective cohort study of unselected, newly diagnosed patients in remission from IBD, the prevalence of IBS as defined by the Rome IV criteria was 21.9% and 16.1% at the 1- and 3-year follow-ups, respectively. Female sex and substantial fatigue were independently associated with IBS at the 1-year follow-up but not at the 3-year follow-up. This is the first prospective study of patients with IBD to determine IBS prevalence using the Rome IV criteria, while also incorporating objective definitions of IBD remission based on FC levels and endoscopic indices.

The prevalence of IBS among patients in remission from IBD in our study was lower than the pooled prevalence of 32.5% reported in a recent systematic review and meta-analysis by Fairbrass et al.[10] The figure reported by Fairbrass et al. was based on a wide range of published rates (11.2%-63.6%), suggesting considerable methodical variation between studies. Most studies utilized Rome II and Rome III criteria to define IBS, neither of which are directly comparable to the Rome IV criteria since the latter may identify patients with more severe IBS-like symptoms.[10,38,39] In the systematic review and meta-analysis, only 2 studies used the Rome IV criteria. Nigam et

Table 1. Prevalence of IBS for patients in remission from IBD at the 1-and 3-year follow-ups, stratified by diagnosis.

	Year 1			Year 3		
	UC (n = 200)	CD (n = 83)	Total (n = 283)	UC (n = 212)	CD (n = 92)	Total (n = 304)
IBS	44 (22.0%)	18 (21.7%)	62 (21.9%)[a]	35 (16.5%)	14 (15.2%)	49 (16.1%)[a]
No IBS	156 (78.0%)	65 (78.3%)	221 (78.3%)	177 (83.5%)	78 (84.8%)	255 (83.9%)

[a]Statistically significantly higher prevalence compared to IBS in the general Norwegian population (9.5%; P < 0.005).
Abbreviations: CD, Crohn's disease; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Table 2. Demographic, psychosocial, and clinical disease activity measures for patients in remission at the 1-and 3-year follow-ups.

	Year 1			Year 3		
	IBS	No IBS	*P*-value	IBS	No IBS	*P*-value
	***n* = 62 (21.9%)**	***n* = 221 (78.3%)**		***n* = 49 (16.1%)**	***n* = 255 (83.9%)**	
Demographic						
Age in years (SD)	41 (14)	46 (15)	.030	45 (13)	47 (15)	.530
Sex						
Female, *n* (%)	47 (75.8)	109 (49.3)	<.001	31 (63.3)	126 (49.4)	.087
Male, *n* (%)	15 (24.2)	112 (50.7)		18 (36.7)	129 (50.6)	
Diagnosis						
UC, *n* (%)	44 (71.0)	156 (70.6)	1.000	35 (71.4)	177 (69.4)	.866
CD, *n* (%)	18 (29.0)	65 (29.4)		14 (28.6)	78 (30.6)	
Psychosocial measures						
HADS-A, median (range)	6 (0-16)	5 (0-18)	.009	7 (0-15)	4 (0-18)	<.001
Missing, n (%)	–	–		–	*2 (0.8)*	
HADS-D, median (range)	4 (0-14)	2 (0-14)	.001	4 (0-15)	2 (0-15)	.002
Missing, n (%)	–	–		–	*2 (0.8)*	
GSE, median (range)	29 (13-39)	30 (10-40)	.044	28 (18-40)	31 (10-40)	<.001
Missing, n (%)	–	–		–	*1 (0.4)*	
FQ, median (range)	7 (0-11)	2 (0-11)	<.001	4 (0-11)	2 (0-11)	<.001
Missing, n (%)	–	*1 (0.5)*		–	*4 (1.6)*	
Clinical disease activity measures						
CRP, median (range)	2.0 (0-15)	1.8 (0-31)	.662			
Missing, n (%)	*7 (11.3)*	*28 (12.7)*				
HBI CD, median (range)	5 (0-11)	1 (0-6)	<.001	4 (1-11)	2 (0-12)	.002
Missing, n (%)	*5 (27.8)*	*8 (12.3)*		–	*1 (1.3)*	
SCCAI UC, median (range)	2.0 (0-11)	0 (0-8)	<.001	2 (0-8)	1 (0-12)	<.001
Missing, n (%)	*4 (9.1)*	*12 (7.7)*		*1 (2.9)*	*4 (2.3)*	

Results are presented as percentages for categorical variables, mean (SD) for age, and median values with ranges for all other continuous variables. The number of study participants with missing data are also shown for each variable.
Abbreviations: CD, Crohn's disease; CRP, C-reactive protein; FQ, fatigue questionnaire; GSE, general self-efficacy; HADS, Hospital Anxiety and Depression Scale; HADS-A, anxiety subscale; HADS-D, depression subscale; HBI, Harvey-Bradshaw Index; IBS, irritable bowel syndrome; SCCAI, Simple Clinical Colitis Activity Index; UC, ulcerative colitis.

Table 3. Binary logistic regression analysis of factors associated with IBS at the 1- and 3-year follow-ups.

Factor	Year 1				Year 3			
	Univariable		Multivariable		Univariable		Multivariable	
	OR (CI)	*P*-value	OR (CI)	*P*-value	OR (CI)	*P*-value	OR (CI)	*P*-value
Age, for every year	0.98 (0.96-1.0)	.03	0.99 (0.97-1.01)	.20	0.99 (0.97-1.01)	.51	1.00 (0.98-1.02)	.82
Female sex (ref. male)	3.22 (1.70-6.10)	<.001	2.66 (1.33-5.32)	.005	1.76 (0.94-3.31)	.08	1.47 (0.76-2.84)	.26
UC (ref. CD)	1.02 (0.55-1.89)	.95	1.12 (0.58-2.17)	.74	1.10 (0.56-2.16)	.78	1.13 (0.57-2.27)	.72
HADS-D ≥ 8	2.21 (1.11-4.40)	.02	1.88 (0.78-4.56)	.16	2.96 (1.37-6.40)	.006	1.78 (0.71-4.50)	.22
HADS-A ≥ 8	1.66 (0.92-2.98)	.09	0.68 (0.31-1.46)	.32	2.18 (1.14-4.16)	.02	1.27 (0.59-2.71)	.54
GSE, for every unit increase	0.95 (0.90-0.99)	.02	0.99 (0.94-1.05)	.74	0.94 (0.89-0.98)	.007	0.97 (0.91-1.02)	.23
Substantial fatigue	3.97 (2.10-7.53)	<.001	3.05 (1.48-6.27)	.003	2.06 (1.11-3.82)	.02	1.35 (0.67-2.71)	.41

Exp (β) values are shown as odds ratios (OR) with 95% CIs in parentheses.
Substantial fatigue: ≥ 4 on the Fatigue Questionnaire.
Abbreviations CD, Crohn's disease; GSE, general self-efficacy: HADS, Hospital Anxiety and Depression Scale; HADS-A, anxiety subscale; HADS-D, depression subscale; IBS, irritable bowel syndrome; UC, ulcerative colitis.

Table 4. HRQoL scores for patients in remission with and without IBS at the 1- and 3-year follow-ups.

	Year 1			Year 3		
	IBS (n = 60-62)	No IBS (n = 218-220)	Effect size	IBS (n = 49)	No IBS (n = 250)	Effect size
SF-36 dimension						
Physical function	88.3 (84.8-91.8)	88.7 (86.9-90.5)	−0.03	85.1 (81.5-88.7)[a]	91.6 (90.0-93.1)[a]	−0.51
Role physical	58.2 (50.2-66.2)[a]	70.4 (66.3-74.5)[a]	−0.39	62.3 (53.9-70.6)[a]	73.0 (69.4-76.6)[a]	−0.36
Bodily pain	65.9 (60.7-71.2)	70.9 (68.3-73.6)	−0.24	62.0 (56.4-67.5)[a]	74.6 (72.2-77.0)[a]	−0.64
General health	57.8 (53.3-62.3)[a]	63.5 (61.2-65.8)[a]	−0.32	55.2 (50.3-60.2)[a]	64.8 (62.7-67.0)[a]	−0.55
Vitality	48.1 (44.2-52.0)	50.3 (48.3-52.3)	−0.14	52.0 (47.5-56.0)	53.1 (51.3-55.0)	−0.07
Social functioning	77.8 (73.4-82.1)	80.3 (78.1-82.5)	−0.15	79.3 (74.6-84.0)	82.9 (80.8-84.9)	−0.22
Role emotional	66.1 (58.2-74.1)	73.1 (69.0-77.1)	−0.22	65.8 (57.0-74.5)[a]	76.0 (72.1-79.7)[a]	−0.33
Mental health	75.0 (72.4-77.4)	75.2 (73.9-76.5)	−0.02	75.0 (72.5-77.6)	75.4 (74.3-76.5)	−0.04

[a]Significant difference between IBS patients and non-IBS patients, $P < .05$.
Shown are mean SF-36 scores adjusted for age, sex, total general health efficacy score, total fatigue score, and total Hospital Anxiety Depression Scale scores, with 95% CIs in parentheses. Since the total number of respondents for each SF-36 dimension varied, the range of responses is reported.
Cohen's d effect sizes: < 0.2, no difference; 0.2-0.5, small; 0.5-0.8, moderate; > 0.8, large. Moderate and large effects were considered clinically important.
Abbreviations: SF-36, Short Form 36; IBS, irritable bowel syndrome.

al. reported an IBS prevalence rate of 23% among patients in remission from UC,[13] which is comparable to our results. In a case-control study, Ozer et al. found that 34% of patients with IBD in remission had IBS-like symptoms, which was 2 to 3 times higher than that in the Turkish reference population.[14] Both authors used clinical disease activity indices to define remission from IBD, potentially affecting the prevalence of IBS.

Although clinical disease activity indices like the HBI, SCCAI, Modified Mayo Scores, and IBD-control scores are practical measures of clinical remission, their accuracy in defining IBD remission in studies on IBS is uncertain. These indices, as well as the Rome IV questionnaire, include bowel pain, the number of daily stools, and/or bowel symptoms to determine score severity. Patients with frequent bowel symptoms may receive high clinical index scores, classifying them as having active IBD and subsequently excluding them from IBS studies when the cause can be severe IBS. This phenomenon is underlined by the results of our study, where patients diagnosed with IBS reported significantly higher clinical disease activity scores than those without IBS. The opposite can also occur; patients with low-grade symptoms, especially in CD, may fulfill the Rome IV criteria for IBS, even though the symptoms are more likely to be caused by unrecognized bowel inflammation.[5,10,12,22] Therefore, we advocate for the use of objective measures of remission from IBD in IBS studies.

Yet, the preferred method of defining remission from IBD remains debatable. Although endoscopic and ultimately histologic remission likely provides the most accurate definition, FC measurements are considered more practical, simple, and cost-effective. In agreement with several previous studies and clinical practice, remission from IBD in our study was defined as FC levels ≤ 250 µg/g.[11,13,20,22,23] Correlations between FC levels ≤ 250 µg/g, mucosal healing, and endoscopic remission have been reported in both UC and CD studies, supporting our definition for the purpose of this study.[20,21]

We did not find a statistically significant difference between IBS prevalence rates with remission defined endoscopically and those with remission defined by FC levels ≤ 250 µg/g, suggesting that IBS prevalence remains mainly unaffected by these remission definitions. In this observational cohort, colonoscopy at the 1-year follow-up was only performed if clinically indicated, and not performed as part of the study at 3-year follow-up. Thus, approximately half of eligible patients were referred to ileocolonoscopy at 1-year follow-up. Unsurprisingly, patients who underwent ileocolonoscopy at 1-year follow-up also had statistically significantly higher median FC levels compared to patients without ileocolonoscopy, which likely represented a selection bias. Defining remission using FC levels ≤ 250 µg/g avoided this, since all patients received fecal sampling kits. Additionally, FC samples were available at both follow-ups, simplifying the comparison of IBS prevalence rates over time. Future endoscopic data from the cohort at 5-year follow-up will hopefully complement these results.

Normative IBS data based on the Rome IV criteria in a Norwegian population have not been published. We therefore referenced the IBS prevalence rate of 9.5% from the HUNT4 normative cohort, where the Rome II criteria were applied.[35] However, differences between the 2 versions of the Rome criteria must be noted. Unlike the Rome II criteria where both abdominal discomfort and abdominal pain were considered relevant to diagnose IBS, the term "abdominal discomfort" was removed in the revised Rome IV criteria. Also, the minimum frequency of abdominal pain was increased to at least 1 day per week in the Rome IV criteria.[2,4] Comparisons between the 2 Rome versions are therefore difficult, which should be regarded as a limitation of our study. Even so, the pooled global prevalence of IBS based on several studies has been reported to be 9.4% and 3.8%-4.8% based on the Rome II and IV criteria, respectively, suggesting that the Rome IV criteria identify patients with more severe IBS and result consistently in a lower IBS prevalence than the Rome II criteria.[1,2,6] We are therefore confident that IBS prevalence for patients in remission from IBD was at least 2 to 3 times higher than IBS in the general Norwegian population.

Associations between IBS-like symptoms, female sex, and increased fatigue have been well documented both globally and in a Norwegian population.[1,2,6,35,38] This coincides with the results of our study, where female sex and substantial fatigue

were independently associated with IBS in multivariable analysis at the 1-year follow-up. Since a significantly larger proportion of female than male patients provided FC samples at the 1-year follow-up overall, the association between female sex and IBS may have been influenced by a response bias. Further statistical analysis of the study population, however, showed no significant male/female differences between patients with FC levels ≤ 250 µg/g and patients with FC levels > 250 µg/g, which would be expected if a response bias was present among FC sample responders.

Previous studies have demonstrated reduced HRQoL among patients with IBS compared with those without IBS, which aligns with our study's results.[2,6,12] Our findings are also consistent with other similar studies on IBS defined by the Rome IV criteria, notably by Ozer et al. and Lin et al., where patients with IBS-like symptoms reported significantly lower HRQoL scores.[12,14] We adjusted SF-36 scores by potential confounding factors, including age, sex, GSE score, FQ score, and HADS scores, in order to accurately determine the effects of IBS on HRQoL. In our cohort, differences in HRQoL between patients with and without IBS were most pronounced at the 3-year follow-up, where patients with IBS reported markedly reduced SF-36 scores of moderate Cohen's effect size. Since increased bowel symptoms are associated with reduced HRQoL in patients with IBD,[5,12] the observed HRQoL impairment in patients with IBS at the 3-year follow-up may be a mark of more chronic or relapsing IBS.

This study has several strengths. The study design allowed us to follow a well-defined cohort of unselected patients with IBD within a specific geographical area and with uniform diagnostic criteria. The IBSEN III cohort consists of all patients newly diagnosed with IBD within a 3-year period, reducing selection bias. Furthermore, FC levels were used to objectively define remission.[21] We also calculated IBS prevalence using ileocolonoscopy results as a definition of remission from IBD to evaluate potential effects on IBS prevalence rates. Further, we defined IBS based on the latest Rome IV criteria, which only a few similar studies have done previously. Finally, for patients who submitted fecal samples for calprotectin analysis and answered the Rome IV questionnaire, data completeness was high (72%-100%).

The study also has some limitations. First, only one-third of patients were in biochemical remission and fulfilled IBS criteria at both the 1- and 3-year follow-ups, which could imply a non-representative study population or fluctuations in IBS-like symptoms over time. In a longitudinal study of IBS using Rome III criteria at 3-month intervals over a period of 12 months, Barberio et al. found that 25.6% of patients in remission from IBD had IBS-like symptoms at 2 points in time, which is very similar to 27.5% found in our study. The authors also reported that 61.5% of patients developed IBS-like symptoms at only 1 of 4 measurement points and that 63.6% of patients with IBS-like symptoms at baseline reported fluctuating symptoms during the 12-month follow-up period.[5] These findings suggest that the severity of IBS-like symptoms in these patients may vary over time. To ensure the overall representativeness of our study population, we compared the distribution of demographic, psychosocial, and disease-related factors between those who answered the Rome IV questionnaire and those who did not at the 1- and 3-year follow-ups and found no differences. In this regard, we concluded that the study population was representative.

Secondly, many potential study participants were excluded due to lacking FC data, both at the 1- and 3-year follow-ups, leading to possible bias in estimating IBS prevalence, as well as in the multivariable analysis. Consequently, subgroup analyses stratified by diagnosis (UC/CD) and sex (male/female) were not possible.

Thirdly, the Covid-19 pandemic likely led to fewer submitted calprotectin samples than expected. Furthermore, patients who provided FC samples at both follow-ups were older than those with missing FC samples. Since IBS-like symptoms are often reported more frequently among younger individuals, IBS prevalence rates may have been underestimated, but not overinflated.[2]

Fourthly, although patients who underwent colectomy during the first year of follow-up were excluded from the study, additional surgical outcomes and disease extent were not investigated, which represents a limitation. Since ileocolonoscopy and/or other investigations were performed at the 1-year follow-up only if clinically indicated, updated data on disease extent and location were available for only about half of the study population. As expected, analysis of patients who underwent ileocolonoscopy at 1-year follow-up revealed increased disease activity on a group level, indicated by significantly higher median FC levels compared with patients who did not undergo ileocolonoscopy. This suggests potential bias in the available data on disease extent and location, contributing to study uncertainty. Therefore, we did not include disease extent and location as variables in the analysis of 1-year follow-up data.

Finally, due to the limited size of the study population, we had to restrict the number of variables included in the multivariable analysis and limit sub-analyses.

In conclusion, the prevalence of IBS based on the Rome IV criteria among patients in remission from IBD was approximately 2 times more common than in the general Norwegian population and stable at both 1- and 3-year follow-up. Defining IBD remission using FC levels ≤ 250 µg/g or with endoscopic indices did not significantly influence the prevalence of IBS. Female sex and substantial fatigue were significantly associated with IBS at the 1-year follow-up. Compared with patients without IBS, those with IBS reported both statistically and clinically important HRQoL reductions in 3 SF-36 dimensions at the 3-year follow-up.

Supplementary Data

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

Acknowledgments

The authors would like to thank the members of the IBSEN III study group, including members of the IBSEN III board, local study nurses, principal investigators, and all study participants. We would also like to thank the Unger-Vetlesen Institute for analyzing the fecal biomarker calprotectin and Editage (www.editage.com) for English language editing and assistance in creating the graphical abstract.

Author Contributions

R.O., V.A.K., M.L.H., P.R., T.E.D., S.O.F., T.B., L.P.J.-J., G.H.-H., and B.C.O. contributed to study conception and

design. R.O., V.A.K., M.L.H., C.L., T.B.A., I.J., K.A.H., V.S., I.F.G., M.-B.B., P.R., T.E.D., A.W.M., R.B., R.T., S.V., S.O.F., J.V., M.H., T.B., L.P.J.-J., G.H.H., and B.C.O. participated in the acquisition of study data. L.P.J.-J., T.B., G.H.-H., and B.C.O. analyzed the data and interpreted the results. L.P.J.-J., T.B., G.H.-H., and B.C.O. wrote the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version for submission. Guarantor of the article: B.C.O.

Funding

This work was supported by funding from the Telemark Hospital Trust [project number 3092.03]. The IBSEN III study is fully investigator-initiated and has received funding from Takeda Pharmaceuticals, Pfizer, Ferring Pharmaceuticals, Tillotts Pharma, Dam Foundation, and the South-Eastern Health Authorities. The funding bodies have not influenced study design, study implementation, interpretation of data, or reporting of findings in any way.

Conflicts of Interest

A.W.M.: investigator-initiated research grant from Takeda. M.L.H.: investigator-initiated research grants from Takeda, Pfizer, Tillotts, Ferring, and Janssen. Speaker honoraria from Takeda, Tillotts, Ferring, AbbVie, Galapagos, MSD, and Meda. Advisory board position at Takeda, Galapagos, MSD, Lilly, Janssen, Pfizer, and AbbVie. S.O.F.: personal fees from Takeda, Galapagos, Jansen-Cilag, AbbVie, Pharmacosmos, Norgine, and Bristol Myers Squibb. V.S.: sponsored by funds from Takeda. All other authors report no conflicts of interest.

Data Availability

The data underlying this article cannot be shared publicly owing to the privacy of individuals who participated in the study. The data will be shared upon reasonable request to the corresponding author.

Ethical Considerations

The study was approved by the South-East Regional Committee for Medical Research Ethics (reference number 2015/946-3) and the Norwegian Centre for Research Data (NSD, 498873). Study inclusion did not imply any changes in patient treatment, and all participants provided written informed consent before inclusion in the study. The study was conducted in accordance with the revised Declaration of Helsinki. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was reviewed before submission to improve the quality of the work.

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