Journal of Crohn's and Colitis, 2023, **XX**, 1–10
https://doi.org/10.1093/ecco-jcc/jjad094
Advance access publication 5 June 2023
Original Article

Fatigue in Patients with Newly Diagnosed Inflammatory Bowel Disease: Results from a Prospective Inception Cohort, the IBSEN III Study

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Abstract

Background and Aims: Although fatigue is common in inflammatory bowel disease [IBD], its pathogenesis remains unclear. This study aimed to determine the prevalence of fatigue and its associated factors in a cohort of patients newly diagnosed with IBD.

Methods: Patients ≥18 years old were recruited from the Inflammatory Bowel Disease South-Eastern Norway [IBSEN III] study, a population-based, observational inception cohort. Fatigue was assessed using the Fatigue Questionnaire and compared with data from a Norwegian general population. Univariate and multivariate linear and logistic regression analyses were performed to evaluate the associations of total fatigue [TF; continuous score] and substantial fatigue [SF; dichotomized score ≥4] with sociodemographic, clinical, endoscopic, laboratory, and other relevant patient data.

Results: In total, 983/1509 [65.1%] patients with complete fatigue data were included (ulcerative colitis [UC], 68.2%; Crohn's disease [CD], 31.8%). The prevalence of SF was higher in CD [69.6%] compared with UC [60.2%] [$p < 0.01$], and in both diagnoses when compared to the general population [$p < 0.001$]. In multivariate analyses, depressive symptoms, pain intensity, and sleep disturbances were associated with increased TF for both diagnoses. In addition, increased clinical disease activity and Mayo endoscopic score were significantly associated with TF in UC, whereas all disease-related variables were insignificant in CD. Similar findings were observed for SF, except regarding the Mayo endoscopic score.

Conclusions: SF affects approximately two-thirds of patients newly diagnosed with IBD. Fatigue was associated with depressive symptoms, sleep disturbances, and increased pain intensity in both diagnoses, while clinical and endoscopic activity were associated factors only in UC.

Key Words: Inflammatory bowel disease; fatigue; epidemiology

1. Introduction

Ulcerative colitis [UC] and Crohn's disease [CD] represent the two primary forms of inflammatory bowel disease [IBD], a condition characterized by inflammation of the gastrointestinal [GI] tract. IBD possibly arises due to inappropriate mucosal immune activation against commensal microbes in genetically susceptible hosts.[1,2] While inflammation in UC is limited to the mucosa and submucosa of the colon and rectum, inflammation in CD is transmural and may affect any part of the GI tract.[1]

Common symptoms of IBD include abdominal pain and diarrhoea, with the latter often with blood and mucus.[1] In addition, fatigue has also been reported as a prevalent symptom, affecting up to 80% of patients with active disease.[3] Fatigue differs from general tiredness, in both severity and duration. Barsevick et al. characterized fatigue as a 'subjective perception of lack of energy unrelieved by rest and unproportionable to activity, impacting the patient's function in life, often accompanied by emotional lability and decreased cognitive ability'.[4]

Fatigue is frequently observed as a concomitant symptom in chronic inflammatory diseases and cancer, as well as a sequala of infectious disease.[3,5] The pathogenesis of fatigue has yet to be determined; however, a correlation between the severity of fatigue and clinical activity in various inflammatory diseases has been reported in previous studies.[3,6] Several factors have been proposed to contribute to fatigue in IBD, including ongoing inflammation, medical treatment, microbiota composition, anaemia, and micronutrient deficiencies.[5–7] Furthermore, fatigue in patients with IBD is also associated with symptoms of depression, anxiety and sleep disturbances, independent of disease activity.[6,7]

Previous studies on fatigue in cohorts of patients with newly diagnosed IBD are scarce, providing limited possibilities for evaluating the factors influencing fatigue in treatment-naïve patients with IBD. In most studies investigating fatigue among patients with IBD, a positive association between disease activity and fatigue has been reported based on clinical disease activity indices and, in rare cases, additional biochemical tests such as C-reactive protein [CRP] and faecal calprotectin.[8] To the best of our knowledge, no published studies have assessed the association between fatigue and IBD-related disease activity, using complete endoscopic, biochemical, and clinical data. Thus, the present study aimed to determine the prevalence of fatigue, as well as to identify its associated factors at diagnosis, using data from an unselected population-based cohort of patients newly diagnosed with IBD.

2. Materials and Methods

2.1. Study design and sample population

The Inflammatory Bowel Disease in South-Eastern Norway III [IBSEN III] study is a prospective, population-based inception cohort study [Clinical Trials ID: NCT02727959] that included patients with newly diagnosed IBD during a 3-year period from 2017 to 2019. The patients were enrolled from the largest health region in Norway [the South-Eastern Health Region], with a catchment area of ~2.95 million inhabitants [56% of the Norwegian population in 2017]. The organization of the cohort and the inclusion process have been described elsewhere in detail.[9]

2.2. Data collection and handling

A comprehensive assessment of clinical, endoscopic, sociodemographic and patient-reported outcomes was undertaken, and faecal samples for calprotectin analysis were collected from the patients. All patients underwent a colonoscopy with biopsy at baseline. For CD, additional upper endoscopy, capsule endoscopy and magnetic resonance enterography were performed when clinically indicated. Blood sample analyses were performed at local laboratories as part of the routine follow-up, while comorbidities were assessed in the same manner as in the Trondelag Health Study [HUNT] database[10] and summarized into a continuous score.

2.3. Disease activity

Evaluation of disease activity was based on CRP and faecal calprotectin levels [Bühlmann Calprotectin ELISA EK-CAL; Bühlmann Laboratories AG], clinical disease activity indices (Harvey–Bradshaw index [HBI] for CD and Simple Clinical Colitis Activity Index [SCCAI] for UC). Active disease was defined as a SCCAI and HBI score of ≥3 and ≥5 respectively.[11,12] CRP ≥ 5 mg/L and faecal calprotectin >250 µg/g were considered as elevated and indicative of active inflammation.[13,14] Anaemia was defined as a haemoglobin level of <13 g/dL for males and <12 g/dL for females [World Health Organization definition].[15] For both UC and CD, disease phenotype was classified using the Montreal Classification System. Endoscopic activity was graded based on the Mayo endoscopic score in UC, and a modified version of the Simple Endoscopic score [SES-CD] with only scoring of the worst affected bowel segment in CD.[16–18]

2.4. The Fatigue Questionnaire

There are several questionnaires available for the assessment of fatigue in IBD, both disease specific as well as generic questionnaires which can be utilized for several different disorders. In the current study we used the generic Fatigue Questionnaire [FQ] as this has previously been translated and validated in Norwegian[19] as well as for Norwegian patients with IBD.[20] Moreover, FQ data from the Norwegian general population were available for comparison. The FQ was developed by Chalder et al.[21] and consists of 11 questions divided into two main dimensions: physical fatigue [PF] [questions 1–7] and mental fatigue [MF] [questions 8–11]. Each question presents four possible answers [0 = better than usual, 1 = no more than usual, 2 = worse than usual, and 3 = much worse than usual], with higher FQ scores implying higher fatigue levels. The PF and MF scores are combined to calculate the total fatigue [TF] score, with a maximum score of 33. In addition, scale scores were dichotomized into 0 = better than usual and no more than usual, and 1 = worse than usual and much worse than usual, where substantial fatigue [SF] is defined as a dichotomized FQ score ≥4, in accordance with prior studies.[19–21] Patients who had more than 50% missing values in one dimension were excluded.

2.5. Additional patient-reported outcome measures

To control for potential covariates, as well as to collect other patient-reported outcomes relevant to fatigue, the Hospital Anxiety and Depression Scale [HADS] was used to assess anxiety and depression,[22] the Norwegian version of the Pittsburgh Sleep Quality Index [PSQI] was used to assess

sleep quality and disturbances,[23] and the Brief Pain Inventory [BPI] was used to investigate pain intensity.[24]

The HADS was developed by Zigmond and Snaith in 1983 to screen for depression and anxiety among somatic patients.[22] The HADS has been translated into Norwegian and validated,[25] and consists of 14 items divided into two-dimensional subscales, HADS-D and HADS-A, with seven items each. Each item is scored from 0 to 3, with the total score ranging from 0 to 21.[22] A higher score indicates an increased level of psychological distress, where a dimensional sub-score ≥8 denotes levels of anxiety or depressive symptoms indicative of the need for further assessment.[26]

The Norwegian version of the PSQI is a standardized and validated instrument for assessing sleep quality and disturbances in clinical practice and research. It consists of 19 self-reported items that assess sleep patterns within the past month and is divided into seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The total of these scores yields one global score ranging from 0 to 21. A score >5 indicates poor sleep quality.[23]

The BPI was developed by Cleeland and colleagues,[24] and has been translated and validated for use in Norwegian and for patients with IBD.[27,28] The BPI consists of two domains: impact of pain on functioning [interference] and pain intensity [severity]. In the present study, only pain severity was assessed, which was supported by the recommendations for pain assessment provided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [IMMPACT].[24] Pain severity was evaluated using four components [BPI items 3–6], with a grading from 0 to 10 and a maximum total score of 40 points.[24]

2.6. Statistical analysis

Descriptive statistics were used to analyse patient characteristics. Normally distributed data are presented as mean and standard deviations [SD], while variables with skewed distributions are presented as median and interquartile range [IQR]. Categorical data are presented as counts and percentages. Crude differences between patient groups were assessed using independent sample t-test for pairs of normally distributed continuous data, Mann–Whitney U-test for pairs of variables with skewed distributions and chi-square test [χ^2] for pairs of categorical variables. The normality assumption was assessed using graphical presentations of the variables [histograms] combined with the Shapiro–Wilk's test. Level of fatigue and fatigue prevalence were compared with the Norwegian general population using a two-sample independent t-test and chi-square test using OpenEpi software. The Norwegian general population data from 1998 were used in the analysis owing to superior completeness and substantially unchanged levels of fatigue compared to the data from 2015.[20,29]

Fatigue was analysed as a continuous variable [TF] and as a dichotomized variable [SF]. Possible associations between fatigue and selected sociodemographic and clinical data were assessed using regression models, with fatigue as the dependent variable. The TF score was analysed using univariate and multivariate linear regression analyses, whereas binary logistic regression was used for SF. Only variables that reached p-values ≤0.1 in univariate regression analyses were included in the multivariate models. All analyses were considered exploratory so no correction for multiple testing was done, and p-values <0.05 were considered statistically significant. To assess which of the covariates demonstrated the strongest association with the outcome in the multivariate linear regression analyses, effect size [standardized coefficient beta] was calculated. An effect size [f^2] of 0.02 indicates a small effect, 0.15 a medium effect, and 0.35 a large effect.[30] Variables included in the multivariate linear regression analysis were evaluated for collinearity by calculating the correlation coefficients for all pairs using Pearson's correlation. The variable with the weakest association with fatigue, based on unstandardized B, was excluded from further analysis if the correlation coefficient was ≥0.6. Statistical analyses were performed using IBM SPSS Statistics version 28 and STATA/SE 16.0, both for Windows.

2.7. Ethical considerations

The IBSEN III study was approved by the Southeast Regional Committee for Medical and Health Research Ethics [Ref 2015/946-3] and signed informed consent was obtained from each patient before study inclusion.

3. Results

3.1. Study population

In total, 1561 adult [≥18 years old] patients with newly diagnosed IBD were included in the IBSEN III study, of whom 1003 [64.3%] and 506 [32.4%] were diagnosed with UC and CD, respectively. Patients with UC and CD who had complete FQ data were included in the current study (983/1509 [65.1%]) [Figure 1]. The baseline characteristics of the study population are presented in Table 1. In those with complete FQ data, a significantly higher proportion were females, had a higher Mayo endoscopic score [UC], and had an increased prevalence of perianal disease [CD] compared to patients without FQ data.

3.2. Prevalence and level of fatigue

The prevalence of substantial fatigue [SF], as well as level of total fatigue [TF] were significantly higher in CD compared to UC [Figure 2 and Table 2]. For both diagnoses, SF prevalence and fatigue scores were significantly higher than those of the Norwegian general population [Table 2]. At the time of inclusion, approximately half of the patients reported that their fatigue symptoms had been present for more than 1 week, but shorter than 6 months [49.5% of CD and 52.3% of UC patients].

3.3. Factors associated with fatigue

The univariate and multivariate regression analyses stratified by diagnosis are presented in Tables 3 and 4 for TF and SF, respectively.

In the univariate analysis, increased TF was significantly associated with increased clinical disease activity and decreased haemoglobin levels for both diagnoses. However, no differences in fatigue scores were observed when the established cut-offs for anaemia were used. In UC, increased TF was associated with increased faecal calprotectin level [$p < 0.05$], but not when using >250 µg/g as a cut-off for active inflammation. Mayo endoscopic score, but not extension of disease, was significantly associated with TF, and further when analysed categorically, increased TF scores were only observed in

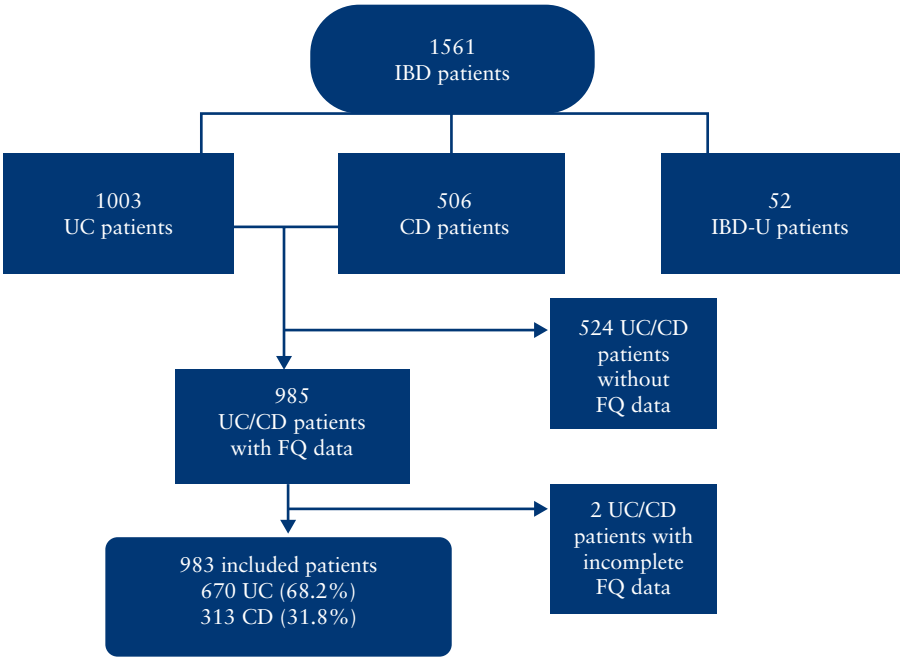

Figure 1. Flow chart illustrating the inclusion process from the IBSEN III cohort. Only patients ≥18 years old with ulcerative colitis and Crohn's disease were included for further analysis. Those without Fatigue Questionnaire [FQ] data, or with more than 50% missing values in one dimension, were excluded from our study. IBD: inflammatory bowel disease, UC: ulcerative colitis, CD: Crohn's disease, IBD-U: IBD unclassified.

those with a Mayo endoscopic score of 3 compared to endoscopic score of 2 (Unstandardized B 1.86, 95% confidence interval, CI [0.63, 3.1]). In CD, TF was not associated with disease location [except for colon affected], disease behaviour, fistulating disease, modified SES-CD, CRP, or calprotectin.

In the multivariate analysis, increased TF was significantly associated with depressive symptoms, pain intensity, and sleep disturbances, in both UC and CD. Younger age was associated with increased TF only in patients with CD. Because of its significantly positive association with depressive symptoms, anxiety was excluded from the multivariate analysis. Regarding disease activity, increased SCCAI and Mayo endoscopic scores were significantly associated with TF in UC, whereas in CD no disease-related variables were statistically significant.

When the potential factors associated with SF were investigated using binary logistic regression analyses, similar patterns were identified as that for TF [Table 4]. Due to an insufficient number of patients with HADS-D ≥ 8 among those without SF, the variable could not be analysed for CD and resulted in large 95% CIs for UC in the multivariate logistic regression analysis.

4. Discussion

In this large, unselected inception cohort of patients newly diagnosed with IBD, substantial fatigue affected approximately two-thirds of patients with UC and CD. Symptoms of depression, sleep disturbances and increased pain intensity were all independently associated with fatigue, regardless of the diagnosis. In UC, an increased clinical disease activity index and Mayo endoscopic score were both independently associated with increased fatigue, whereas none of the available disease activity variables showed any association with fatigue in CD.

Consistent with the findings of previous studies, the prevalence of substantial fatigue was ~10% higher in the CD group than in the UC group.[8] The prevalence of substantial fatigue in the present study was higher than that reported in recent publications in newly diagnosed IBD cohorts.[31,32] However, these results are not directly comparable because different instruments to assess fatigue were used. Among Norwegian patients with IBD controlled 20 years after diagnosis, those with current symptomatic IBD, defined by SCCAI > 2.5 and HBI > 4, were found to have mean TF scores and SF prevalence comparable to our cohort, while patients with quiescent disease had an SF prevalence of only 20–25%.[33] Moreover, when compared to data from the Norwegian general population, patients with IBD in the current cohort had substantially higher SF prevalence and fatigue scores.[20,29]

To the best of our knowledge, no previous studies on fatigue in patients with CD have included complete endoscopic data. In the present study, based on the evaluation of biochemical, radiological, and clinical data combined with endoscopic findings, we were unable to establish an association between the severity of CD inflammation and fatigue at the time of diagnosis. In patients with UC, the Mayo endoscopic score was independently associated with increased total fatigue score. However, the clinical significance of the Mayo endoscopic score remains uncertain considering that a higher Mayo endoscopic score, as well as affection of colon in CD patients, may due to common symptomatology with frequent bloody stools, yield an increased clinical disease activity index score and a decrease in haemoglobin.[34] These variables were both found to be associated with fatigue, regardless of the diagnosis, in univariate regression analysis.

In our study, haemoglobin levels were not independently associated with fatigue. The level of haemoglobin indirectly reflects the severity of IBD, where decreased levels are caused

Table 1. Baseline characteristics.

	Patient diagnosis	
	UC [*n* = 670]	CD [*n* = 313]
Age, years (median [range])	37 [18–82]	37 [18–76]
Sex (*n* [%])		
Male	355 [53]	130 [41.5]
Female	315 [47]	183 [58.5]
Education level (*n* [%])		
Primary school [≤9 years]	65 [9.7]	28 [8.9]
High school [10–12 years]	277 [41.4]	143 [45.7]
University/higher education [>12 years]	326 [48.8]	142 [45.4]
Work status (*n* [%])		
Employed/student	568 [85.0]	255 [81.7]
Not working [unemployed/pensioner/homemaker]	62 [9.3]	28 [9.0]
Disabled	38 [5.7]	29 [9.3]
Civil status (*n* [%])		
Married/cohabitant	443 [66.1]	208 [66.5]
Single/divorced/widowed	223 [33.3]	105 [33.5]
Current smokers (*n* [%])	35 [5.2]	34 [10.9]
Number of comorbidities[a] (median/IQR [range])	1/1 [0–5]	1/2 [0–5]
Disease characteristics:		
HBI total score [median/IQR]		3.0/4.0
Missing (n [%])		*8 [2.6]*
CD localization: Montreal classification (*n* [%])		
L1 [ileal]		157 [50.2]
L2 [colonic]		50 [16]
L3 [ileocolonic]		106 [34]
L4 [upper gastrointestinal tract] + [L1/L2/L3]		8 [2.6]
CD behaviour: Montreal classification (*n* [%])		
B1 [inflammatory]		247 [78.9]
B2 [stricturing]		59 [18.8]
B3 [penetrating]		7 [2.2]
B4 [Perianal disease] + [B1/B2/B3]		17 [5.4]
SCCAI total score [median/IQR]	2.0/4.0	
Missing (n [%])	*22 [3.3]*	
UC extent: Montreal classification (*n* [%])		
E1 [Proctitis]	254 [37.9]	
E2 [Left-sided colitis]	157 [23.4]	
E3 [Extensive colitis]	257 [38.3]	
Mayo endoscopic score [*n* [%]]		
1: Mild disease	150 [22.4]	
2: Moderate disease	371 [55.4]	
3: Severe disease	143 [21.3]	
Faecal calprotectin [median/IQR]	195/733	225/739
Missing (n [%])	*108 [16.1]*	*51 [16.3]*
C-reactive protein (median/IQR [range])	3.0/6.0 [0–267]	4.0/ 11 [0–270]
Missing (n [%])	*41 [6.1]*	*7 [2.2]*
Haemoglobin (median [range])	14.0 [4.8–19.0]	13.7 [8.9–18.1]
Missing (n [%])	*15 [2.2]*	*5 [1.6]*
Anaemia[b] (*n* [%])	92 [14.0]	48 [15.6]

CD: Crohn's disease, UC: ulcerative colitis, HBI: Harvey–Bradshaw index, SCCAI: Simple Clinical Colitis Activity Index.
[a]Psychological disease, migraine, atopic eczema, asthma, hyper- and hypothyroidism, heart disease, atrial fibrillation, previous cerebral insult, COPD, psoriasis, kidney disease, rheumatoid arthritis, ankylosing spondylitis and podagra.
[b]Hb < 13 [males] and Hb < 12 [females].

primarily by varying degrees of intestinal bleeding, but also as a result of chronic inflammation, occasionally combined with decreased nutritional intake.[5,35] The association between fatigue in patients with IBD and anaemia or haemoglobin level based on previous studies is difficult to establish and possibly overestimated, owing to the utilization of different methodological approaches and IBD cohorts.[36]

The IBD symptom burden, commonly presented as disease activity, is known to be of consistently great importance for the presence and severity of fatigue in patients with IBD, which, in part, is supported by the findings of our study.[21,36–38] The use of clinical indices to define disease activity in clinical studies on patients with IBD, including studies of fatigue, is well established.[8] However, studies have shown that these indices are poorly correlated with the degree of intestinal inflammation determined by endoscopic and biochemical measures, especially for HBI in CD.[39–41] One explanation may be coexisting symptoms of irritable bowel syndrome [IBS], which is prevalent among patients with IBD, both at the time of diagnosis and after, regardless of whether IBD is in a remission or active phase.[42–46] However, we did not assess the presence of IBS in our cohort of newly diagnosed patients with endoscopically verified active inflammation.

Coexisting symptoms of depression and sleep disturbances, as described in previous studies on patients with IBD, are strongly associated with fatigue.[36,47–49] The strong association between depressive symptoms and fatigue may be caused by an overlap in symptomatology and, hence, their natural coexistence. However, it has also been theorized that the common symptomatology may be caused by common neuroendocrine and neurotransmitter pathways.[3,38] Although sleep disturbances are multifactorial, poor sleep quality is more prevalent in patients with IBD than in healthy controls.[50] Poor sleep quality is more prevalent among patients with active disease, owing to pain and nocturnal symptoms, but it has also been reported to be present among patients with IBD in remission.[50] Sleep deprivation is related to decreased functioning of the immune system, and studies have shown an increased risk of disease relapse in sleep-deprived patients with IBD.[5,51–53]

Pain in patients with IBD implies not only abdominal discomfort but also myalgia and arthralgia.[54,55] Even after adjusting for relevant covariates, pain was independently associated with fatigue, in contrast to findings from

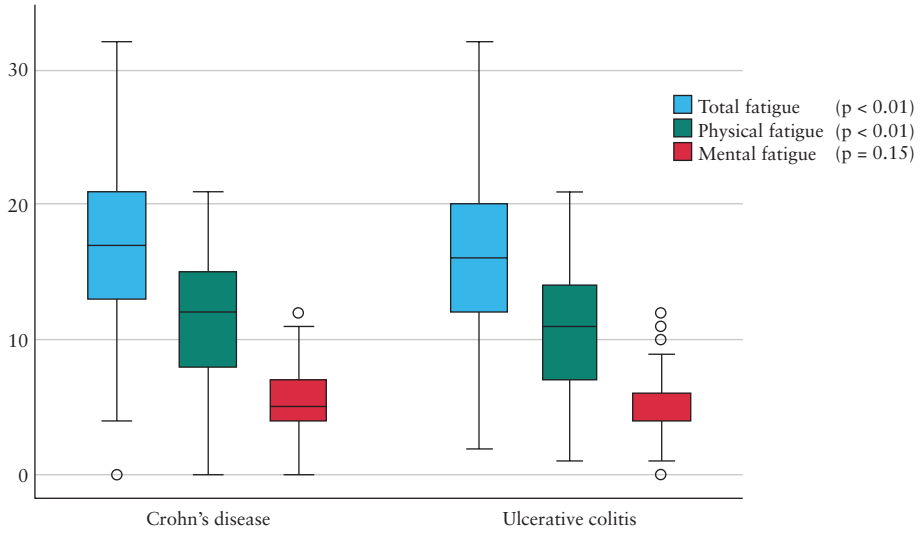

Figure 2. Comparison of total, physical, and mental fatigue scores between patients with ulcerative colitis [UC, *n* = 670] and Crohn's disease [CD, *n* = 313]. Combining the scores of physical [green] and mental [red] fatigue produces the total [blue] fatigue score, with a maximum scale score of 33 shown on the *y*-axis. Medians and the 25th and 75th percentiles are shown. Whiskers indicate the range. Outliers are marked as circles. Statistical differences between UC and CD were calculated using the independent sample t-test presented by *p*-values.

Table 2. Fatigue measurements in patients with UC/CD compared to the Norwegian general population [NGP].

	UC vs. NGP			
	UC [*n* = 670]	**NGP [*n* = 2287]**	**Mean difference [95% CI]**	***p*-value**
Mental fatigue	5.15 [1.8]	4.3 [1.4]	1 [0.9, 1.1]	<0.001
Physical fatigue	11.42 [4.1]	7.9 [3.1]	4 [3.7, 4.3]	<0.001
Total fatigue	16.58 [5.4]	12.2 [4.0]	4 [3.6, 4.4]	<0.001
Total fatigue, males	15.49 [5.2]	11.9 [3.9]	4 [3.4, 4.6]	<0.001
Total fatigue, females	17.80 [5.3]	12.6 [4.0]	5 [4.4, 5.6]	<0.001
Substantial fatigue	403 [60.1]	503 [22]		<0.001
Substantial fatigue, males	176 [49.6]	-		
Substantial fatigue, females	227 [72.1]	-		
	CD vs NGP			
	CD [*n* = 313]	**NGP [*n* = 2287]**	**Mean difference [95% CI]**	***p*-value**
Mental fatigue	5.34 [2.0]	4.3 [1.4]	1 [0.8, 1.2]	<0.001
Physical fatigue	12.19 [4.2]	7.9 [3.1]	5 [4.5, 5.5]	<0.001
Total fatigue	17.53 [5.5]	12.2 [4.0]	5 [4.4, 5.6]	<0.001
Total fatigue, males	15.68 [5.2]	11.9 [3.9]	4 [3.1, 4.9]	<0.001
Total fatigue, females	18.84 [5.3]	12.6 [4.0]	6 [5.2, 6.8]	<0.001
Substantial fatigue	218 [69.6]	503 [22]		<0.001
Substantial fatigue, males	73 [56.2]	-		
Substantial fatigue, females	145 [79.2]	-		

The level of mental, physical, and total fatigue is presented as mean [SD], and the prevalence of substantial fatigue as *n* [%]. The Norwegian general population [NGP] compared to the results for patients with ulcerative colitis [UC] and Crohn's disease [CD] are presented as the difference in means with 95% confidence interval [95% CI] for mental, physical, and total fatigue, and *p*-value for difference in prevalence of substantial fatigue.

prior studies.[56] The main question that arises is whether the co-occurrence of depressive symptoms, sleep disturbance, and pain in fatigued patients with IBD should be regarded as a typical clinical presentation due to a shared underlying pathology, or whether it represents opportunities for separate targeted interventions to improve fatigue.

Our study is not without limitations. Given the 65% response rate for the FQ and the higher prevalence of patients with severe disease and female sex, selection bias cannot be completely excluded. However, given the multicentre design of our study and the inclusion of a large number of patients, we believe that our sample population is representative of

Table 3. Linear regression analysis of factors associated with total fatigue score as the dependent variable.

	Ulcerative colitis							
	Univariate analysis				**Multivariate analysis**			
Factors	**Unst. B**	**95% CI**	**Effect size**	***p*-value**	**Unst. B**	**95% CI**	**Effect size**	***p*-value**
Sex [ref. male]	−2.32	[−3.11, −1.52]	−0.22	<0.001	−0.89	[−2.11, 0.32]	−0.09	n.s.
Age, years	−0.02	[−0.05, 0.004]	−0.07	<0.1	0.02	[−0.03, 0.06]	0.04	n.s.
Comorbidities	1.08	[0.71, 1.45]	0.22	<0.001	−0.57	[−1.13, −0.08]	−0.11	<0.05
HADS-D	0.82	[0.72, 0.92]	0.55	<0.001	0.64	[0.48, 0.80]	0.46	<0.001
HADS-A	0.58	[0.49, 0.67]	0.45	<0.001	-	-	-	-
PSQI	0.68	[0.52, 0.84]	0.47	<0.001	0.28	[0.11, 0.46]	0.20	<0.01
BPI [pain intensity]	0.36	[0.27, 0.44]	0.45	<0.001	0.15	[0.05, 0.25]	0.18	<0.01
SCCAI	0.60	[0.47, 0.73]	0.33	<0.001	0.38	[0.18, 0.58]	0.22	<0.001
Haemoglobin [g/dL]	−0.62	[−0.86, −0.39]	−0.20	<0.001	−0.11	[−0.50, 0.29]	−0.03	n.s.
Calprotectin >250 µg/g	0.73	[−0.16, 1.59]	0.07	n.s.				
CRP ≥5 mg/L	1.13	[0.20, 2.05]	0.10	<0.05	−1.62	[−3.1, −0.13]	−0.13	<0.05
Albumin [g/L]	−0.15	[−0.20, −0.07]	−0.15	<0.001	−0.01	[−0.17, 0.15]	−0.01	n.s.
Mayo endoscopic score	0.93	[0.32, 1.54]	0.12	<0.01	1.32	[0.35, 2.30]	0.15	<0.01
	Crohn's disease							
	Univariate analysis				**Multivariate analysis**			
Factors	**Unst. B**	**95% CI**	**Effect size**	***p*-value**	**Unst. B**	**95% CI**	**Effect size**	***p*-value**
Sex [ref. male]	−3.17	[−4.35, −1.98]	−0.29	<0.001	−0.54	[−2.45, 1.36]	−0.05	n.s.
Age, years	−0.05	[−0.09, −0.01]	−0.14	<0.05	−0.07	[−0.12, −0.02]	−0.19	<0.01
Comorbidities	1.12	[0.60, 1.64]	0.23	<0.001	0.37	[−0.46, 1.20]	0.07	n.s.
HADS-D	0.75	[0.60, 0.89]	0.51	<0.001	0.61	[0.36, 0.87]	0.38	<0.001
HADS-A	0.57	[0.43, 0.70]	0.44	<0.001	-	-	-	-
PSQI	0.78	[0.55, 1.01]	0.51	<0.001	0.47	[0.17, 0.72]	0.29	<0.05
BPI [pain intensity]	0.34	[0.23, 0.45]	0.46	<0.001	0.17	[0.03, 0.31]	0.22	<0.05
HBI	0.47	[0.30, 0.64]	0.30	<0.001	−0.05	[−0.29, 0.20]	−0.03	n.s.
Haemoglobin [g/dL]	−0.60	[−1.03, −1.18]	−0.16	<0.01	−0.27	[−0.92, 0.39]	−0.06	n.s.
Calprotectin >250 µg/g	0.39	[−0.92, 1.69]	0.04	n.s.				
CRP ≥5 mg/L	0.31	[−0.96, 1.57]	0.03	n.s.				
Albumin [g/L]	0.01	[−0.03, 0.22]	0.09	n.s.				
Colon affected [L2]	1.68	[0.03, 3.34]	0.11	<0.05	−0.03	[−2.46, 2.40]	−0.002	n.s.
Modified SES-CD	0.03	[−0.26, 0.33]	0.01	<0.1	0.008	[−0.41, 0.43]	0.003	n.s.

CI: confidence interval, Unst. B: unstandardized B, n.s.: not significant, HADS: Hospital Anxiety and Depression Scale [D = Depression, A = Anxiety], PSQI: Pittsburg Sleep Quality Index, BPI: The Brief Pain Inventory, HBI: Harvey–Bradshaw index, SCCAI: Simple Clinical Colitis Activity Index, CRP: C-reactive protein, L2: CD localization, Montreal classification. Effect size: small effect = 0.02, medium effect = 0.15, large effect = 0.35.

patients newly diagnosed with IBD. Quantification of inflammatory changes in IBD is complex, and disease severity is not sufficiently reflected by the available endoscopic scores or inflammatory markers [CRP and calprotectin].[57,58] In our study, the influence of faecal calprotectin may have been underestimated because of the delay in obtaining samples from patients after colonoscopy and the subsequent initiation of medical treatment.[14,59] Furthermore, a modified, non-validated version of the SES-CD was used, which may have reduced the possibility of assessing the full impact of inflammation on fatigue in patients with CD. We performed a large number of statistical tests so some of our findings might be by chance, and all the results should be interpreted with caution and preferably repeated in new studies. However, our findings are in line with our clinical experiences and thus supported by empirical evidence.

In conclusion, the burden of substantial fatigue in patients newly diagnosed with IBD is considerable, affecting approximately two-thirds of patients. Depressive symptoms, sleep disturbances, and increased pain intensity were strongly associated with fatigue in both patients with UC and CD, while objective variables reflecting the severity of inflammation were found to be only independently associated with fatigue in patients with UC.

Table 4. Binary logistic regression analysis of factors associated with substantial fatigue as the dependent variable.

Factors	Ulcerative colitis			
	Univariate analysis		Multivariate analysis	
	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Sex [ref. male]	0.38 [0.28, 0.562]	<0.001	0.58 [0.25, 1.33]	n.s.
HADS-D ≥ 8	12.04 [5.49, 26.40]	<0.001	16.79 [2.03, 139.25]	<0.01
HADS-A ≥ 8	5.49 [3.59, 8.41]	<0.001		
PSQI > 5	6.20 [3.46, 11.10]	<0.001	4.60 [1.86, 11.40]	<0.001
BPI [pain intensity]	1.13 [1.07, 1.18]	<0.001	1.04 [0.97, 1.12]	n.s.
SCCAI ≥ 3	2.65 [1.91, 3.68]	<0.001	3.51 [1.52, 8.13]	<0.01
Anaemia[a]	1.21 [0.77, 1.92]	n.s.		
Calprotectin >250 µg/g	1.42 [1.01, 1.99]	<0.05	1.16 [0.49, 2.72]	n.s.
CRP ≥ 5 mg/L	1.61 [1.11, 2.31]	<0.05	0.62 [0.23, 1.67]	n.s.
Mayo endoscopic score ≥2	1.42 [0.98, 2.05]	<0.1	1.70 [0.54, 5.41]	n.s.
	Crohn's disease			
	Univariate analysis		**Multivariate analysis**	
Factors	**OR [95% CI]**	***p*-value**	**OR [95% CI]**	***p*-value**
Sex [ref. male]	0.34 [0.29, 0.55]	<0.001	0.74 [0.22, 2.52]	n.s.
HADS-D ≥ 8	12.72 [3.87, 41.75]	<0.001	-	
HADS-A ≥ 8	3.92 [2.14, 7.18]	<0.001		
PSQI > 5	5.85 [2.45, 13.98]	<0.001	4.75 [1.32, 17.13]	<0.05
BPI [pain intensity]	1.20 [1.11, 1.30]	<0.001	1.28 [1.11, 1.47]	<0.001
HBI ≥ 5	2.64 [1.52, 4.57]	<0.001	0.29 [0.07, 1.20]	n.s.
Anaemia[a]	0.96 [0.49, 1.87]	n.s.		
Calprotectin > 250 µg/g	1.21 [0.71, 2.07]	n.s.		
CRP ≥ 5 mg/L	1.12 [0.68, 1.84]	n.s.		
Colon affected [L2]	1.91 [0.91, 4.0]	<0.1	1.69 [0.33, 8.64]	n.s.

OR: odds ratio, CI: confidence interval, n.s.: not significant, HADS: Hospital Anxiety and Depression Scale [D = Depression, A = Anxiety], PSQI: Pittsburg Sleep Quality Index, BPI: The Brief Pain Inventory, HBI: Harvey–Bradshaw index, SCCAI: Simple Clinical Colitis Activity Index, CRP: C-reactive protein, L2: CD localization, Montreal classification.
[a]Haemoglobin <13 [males] and <12 [females].

Funding

This work was supported by the Østfold Hospital Trust. In addition, the IBSEN III study was supported by an investigator-initiated research grant from Takeda Pharmaceuticals and non-restricted research grants from Ferring Pharmaceuticals, Pfizer, Tillotts Pharma, the Dam Foundation, and the Southeastern Health Authorities in Norway. The funding bodies played no role in the design of the study; collection, analysis, and interpretation of data; or writing of the manuscript.

Conflict of Interest

B.C.O., C.L., G.H.H., G.P., I.J., M.H., R.O., R.B.C., S.V., M.B.B., Ø.H., V.S., T.B.A., M.C.S., T.B., L.P.J.J., and K.A.H. declare that they have no conflicts of interest. M.L.H. received investigator-initiated research grants from Takeda, Pfizer, Tillotts, Ferring, and Janssen. M.L.H. served as the speaker honoraris for Takeda, Tillotts, Ferring, AbbVie, and Meda. M.L.H. received support from the advisory board of Takeda, AbbVie, and MSD. V.A.K. received consultant fees from Janssen-Cilag. V.A.K. also received advisory board and consultant fees from Takeda. The advisory board of Tillotts Pharma supported V.A.K. A.W.M. received an unrestricted research grant from Takeda. T.E.D. is a speaker, consultant, and advisory board member for AbbVie, Ferring, Pfizer, Pharmacosmos, Tillotts, and Vifor Pharma. T.E.D. is also a recipient of unrestricted research grants from AbbVie and Pharmacosmos. S.O.F. has received personal fees from Takeda, Galapagos, Jansen-Cilag, Abbvie, Pharmacosmos, and Bristol-Myers-Squibb.

Acknowledgments

The authors would like to thank all members of the IBSEN III study group, including the study nurses, local study personnel, and the local principal investigators: R. Torp, A. Hasund, S. Sagosen, C.M. Ystrøm, J. Pallenschat, O. Høie, and T. Tønnessen, who have contributed to the enrolment of patients and collection of patient data in the IBSEN III study. The authors also thank the Unger-Vetlesen Institute for analysing the faecal samples. We would like to thank Editage [www.editage.com] for English language editing.

Author Contributions

M.L.H., G.H.H., R.O., G.P., T.E.D., V.A.K., A.W.M., T.B., M.H., L.P.J.J., and K.A.H. conceived and designed the study. M.L.H., G.H.H., R.O., M.H., M.B.B., R.B.C., S.V., S.O.F., T.B.A., T.E.D., V.A.K., V.S., Ø.H., B.C.O., I.J., and C.L. participated in patient data collection. M.C.S., L.P.J.J., and K.A.H. analysed and interpreted the results. T.B., M.H., G.H.H., L.P.J.J., and K.A.H. drafted the manuscript. All authors critically reviewed the final version of the manuscript for important intellectual content and provided consent for its publication.

Data Availability

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

References

1. Robbins SL, Kumar V, Cotran RS. *Robbins and Cotran pathologic basis of disease: The gastrointestinal tract*, 8th edn. Philadelphia: Saunders/Elsevier; 2010: 807–13.
2. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011;**474**:307–17.
3. van Langenberg DR, Gibson PR. Systematic review: fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther* 2010;**32**:131–43.
4. Barsevick AM, Cleeland CS, Manning DC, *et al*; ASCPRO (Assessing Symptoms of Cancer Using Patient-Reported Outcomes). ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. *J Pain Symptom Manage* 2010;**39**:1086–99.
5. Nocerino A, Nguyen A, Agrawal M, Mone A, Lakhani K, Swaminath A. Fatigue in inflammatory bowel diseases: etiologies and management. *Adv Ther* 2020;**37**:97–112.
6. Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nat Rev Gastroenterol Hepatol* 2019;**16**:247–59.
7. McGing JJ, Radford SJ, Francis ST, Serres S, Greenhaff PL, Moran GW. Review article: The aetiology of fatigue in inflammatory bowel disease and potential therapeutic management strategies. *Aliment Pharmacol Ther* 2021;**54**:368–87.
8. Grimstad T, Norheim KB. Fatigue in inflammatory bowel disease. *Tidsskr Nor Laegeforen* 2016;**136**:1721–4.
9. Kristensen VA, Opheim R, Perminow G, *et al*. Inflammatory bowel disease in South-Eastern Norway III (IBSEN III): a new population-based inception cohort study from South-Eastern Norway. *Scand J Gastroenterol* 2021;**56**:899–905.
10. Krokstad S, Langhammer A, Hveem K, *et al*. Cohort profile: the HUNT study, Norway. *Int J Epidemiol* 2013;**42**:968–77.
11. Best WR. Predicting the Crohn's disease activity index from the Harvey–Bradshaw Index. *Inflamm Bowel Dis* 2006;**12**:304–10.
12. Higgins PD, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut* 2005;**54**:782–8.
13. Maaser C, Sturm A, Vavricka SR, *et al*; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR guideline for diagnostic assessment in IBD part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis* 2019;**13**:144–64.
14. D'Haens G, Ferrante M, Vermeire S, *et al*. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:2218–24.
15. World Health Organization. *Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers*. Geneva: World Health Organization, 2001. Accessed March 27, 2023. https://www.who.int/publications/m/item/iron-children-6to23--archived-iron-deficiency-anaemia-assessment-prevention-and-control.
16. Daperno M, D'Haens G, Van Assche G, *et al*. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;**60**:505–12.
17. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
18. Paine ER. Colonoscopic evaluation in ulcerative colitis. *Gastroenterol Rep [Oxf]* 2014;**2**:161–8.
19. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res* 1998;**45**:53–65.
20. Jelsness-Jorgensen LP, Bernklev T, Henriksen M, Torp R, Moum BA. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. *Inflamm Bowel Dis* 2011;**17**:1564–72.
21. Chalder T, Berelowitz G, Pawlikowska T, *et al*. Development of a fatigue scale. *J Psychosom Res* 1993;**37**:147–53.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
23. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;**28**:193–213.
24. Cleeland CS. *The Brief Pain Inventory: User Guide*, 2009. Accessed March 27, 2023. https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.
25. Mykletun A, Stordal E, Dahl AA. Hospital anxiety and depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. *Br J Psychiatry* 2001;**179**:540–4.
26. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the hospital anxiety and depression scale. an updated literature review. *J Psychosom Res* 2002;**52**:69–77.
27. Klepstad P, Loge JH, Borchgrevink PC, Mendoza TR, Cleeland CS, Kaasa S. The Norwegian brief pain inventory questionnaire: translation and validation in cancer pain patients. *J Pain Symptom Manage* 2002;**24**:517–25.
28. Jelsness-Jorgensen LP, Moum B, Grimstad T, *et al*. Validity, reliability, and responsiveness of the brief pain inventory in inflammatory bowel disease. *Can J Gastroenterol Hepatol* 2016;**2016**:5624261.
29. Dahl AA, Grotmol KS, Hjermstad MJ, Kiserud CE, Loge JH. Norwegian reference data on the fatigue questionnaire and the patient health questionnaire-9 and their interrelationship. *Ann Gen Psychiatry* 2020;**19**:60.
30. Cohen J. *Statistical Power Analysis for the Behavioral Sciences: Multiple Regression and Correlation Analysis*, 2nd edn. New York: Routledge, 1988.
31. Grimstad T, Norheim KB, Isaksen K, *et al*. Fatigue in newly diagnosed inflammatory bowel disease. *J Crohns Colitis* 2015;**9**:725–30.
32. Cohen BL, Zoega H, Shah SA, *et al*. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther* 2014;**39**:811–22.
33. Huppertz-Hauss G, Hoivik ML, Jelsness-Jorgensen LP, *et al*. Fatigue in a population-based cohort of patients with inflammatory bowel disease 20 years after diagnosis: The IBSEN study. *Scand J Gastroenterol* 2017;**52**:351–8.
34. Atreya R, Siegmund B. Location is important: differentiation between ileal and colonic Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2021;**18**:544–58.
35. Bager P, Befrits R, Wikman O, *et al*. The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. *Scand J Gastroenterol* 2011;**46**:304–9.

36. Artom M, Czuber-Dochan W, Sturt J, Norton C. Targets for health interventions for inflammatory bowel disease-fatigue. *J Crohns Colitis* 2016;**10**:860–9.
37. Hoivik ML, Moum B, Solberg IC, *et al*; IBSEN Study Group. Health-related quality of life in patients with ulcerative colitis after a 10-year disease course: results from the IBSEN study. *Inflamm Bowel Dis* 2012;**18**:1540–9.
38. Czuber-Dochan W, Ream E, Norton C. Review article: description and management of fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;**37**:505–16.
39. Cellier C, Sahmoud T, Froguel E, *et al*. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. a prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gut* 1994;**35**:231–5.
40. Schoepfer AM, Beglinger C, Straumann A, Trummler M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009;**15**:1851–8.
41. Zittan E, Kabakchiev B, Kelly OB, *et al*. Development of the Harvey–Bradshaw index-pro [HBI-PRO] core to assess endoscopic disease activity in Crohn's disease. *J Crohns Colitis* 2017;**11**:543548.
42. Gajula P, Quigley EM. Overlapping irritable bowel syndrome and inflammatory bowel disease. *Minerva Gastroenterol Dietol* 2019;**65**:107–15.
43. Quigley EM. Overlapping irritable bowel syndrome and inflammatory bowel disease: less to this than meets the eye? *Therap Adv Gastroenterol* 2016;**9**:199–212.
44. Jelsness-Jørgensen LP, Bernklev T, Moum B. Fatigue and disease-related worries among inflammatory bowel disease patients in remission; is it a reflection of coexisting IBS-like symptoms? A short report. *J Psychosom Res* 2012;**73**:469–72.
45. Henriksen M, Hoivik ML, Jelsness-Jorgensen LP, Moum B, Group IS. Irritable bowel-like symptoms in ulcerative colitis are as common in patients in deep remission as in inflammation: results from a population-based study [the IBSEN Study]. *J Crohns Colitis* 2018;**12**:389–93.
46. Burgmann T, Clara I, Graff L, *et al*. The Manitoba inflammatory bowel disease cohort study: prolonged symptoms before diagnosis--how much is irritable bowel syndrome? *Clin Gastroenterol Hepatol* 2006;**4**:614–20.
47. Frigstad SO, Høivik ML, Jahnsen J, *et al*. Fatigue is not associated with vitamin D deficiency in inflammatory bowel disease patients. *World J Gastroenterol* 2018;**24**:3293–301.
48. Chavarria C, Casanova MJ, Chaparro M, *et al*. Prevalence and factors associated with fatigue in patients with inflammatory bowel disease: a multicentre study. *J Crohns Colitis* 2019;**13**:996–1002.
49. Graff LA, Clara I, Walker JR, *et al*. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. *Clin Gastroenterol Hepatol* 2013;**11**:1140–6.
50. Ranjbaran Z, Keefer L, Farhadi A, Stepanski E, Sedghi S, Keshavarzian A. Impact of sleep disturbances in inflammatory bowel disease. *J Gastroenterol Hepatol* 2007;**22**:1748–53.
51. Ananthakrishnan AN, Long MD, Martin CF, Sandler RS, Kappelman MD. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol* 2013;**11**:965–71.
52. Ali T, Madhoun MF, Orr WC, Rubin DT. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. *Inflamm Bowel Dis* 2013;**19**:2440–3.
53. Canakis A, Qazi T. Sleep and fatigue in IBD: an unrecognized but important extra-intestinal manifestation. *Curr Gastroenterol Rep* 2020;**22**:8.
54. Bielefeldt K, Davis B, Binion DG. Pain and inflammatory bowel disease. *Inflamm Bowel Dis* 2009;**15**:778–88.
55. Palm O, Bernklev T, Moum B, Gran JT. Non-inflammatory joint pain in patients with inflammatory bowel disease is prevalent and has a significant impact on health related quality of life. *J Rheumatol* 2005;**32**:1755–9.
56. Jelsness-Jørgensen LP, Frigstad SO, Moum B, *et al*. Pain may be an important factor to consider in inflammatory bowel disease patients troubled by fatigue. *United European Gastroenterol J* 2017;**5**:687–93.
57. Mosli MH, Zou G, Garg SK, *et al*. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. *Am J Gastroenterol* 2015;**110**:802–19; quiz 820.
58. Kyle BD, Agbor TA, Sharif S, *et al*. Fecal calprotectin, CRP and leucocytes in IBD patients: comparison of biomarkers with biopsy results. *J Can Assoc Gastroenterol* 2021;**4**:84–90.
59. Khaki-Khatibi F, Qujeq D, Kashifard M, Moein S, Maniati M, Vaghari-Tabari M. Calprotectin in inflammatory bowel disease. *Clin Chim Acta* 2020;**510**:556–65.