

# 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

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The copyright line for this article was changed on 6 November 2015 after original online publication.

## Publication data

Submitted 18 April 2013  
First decision 6 May 2013  
Resubmitted 23 January 2014  
Accepted 24 January 2014  
EV Pub Online 20 February 2014

*This article was accepted for publication after full peer-review.*

## SUMMARY

### Background

Fatigue is common in Crohn's disease (CD) and ulcerative colitis (UC). Data on fatigue in newly diagnosed patients are unavailable.

### Aim

To report prevalence of fatigue in newly diagnosed CD and UC patients and examine its association with health-related quality of life (HRQOL), depression and disability.

### Methods

The Ocean State Crohn's and Colitis Area Registry (OSCCAR) is a statewide cohort of newly diagnosed inflammatory bowel disease patients in Rhode Island. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue Scale. Patients were administered instruments measuring HRQOL, overall disability and work impairment, and depression.

### Results

Fatigue was prevalent in 26.4% of 220 subjects. Cohen's *d* effect sizes for fatigue were large: Short-Form 36 Health Survey mental health component (CD 1.5, UC 1.4) and physical health component (CD 1.4, UC 1.4), EuroQol-5D valuation of current health state (CD 1.2, UC 1.0), Inflammatory Bowel Disease Questionnaire (CD 1.9, UC 1.6) and Patient Health Questionnaire depression scale (CD 1.8, UC 1.7). Fatigued patients reported more work impairment (Score difference: CD 29.5%, UC 23.8%) and activity impairment (score difference: CD 32.3%, UC 25.7%) on the Work Productivity and Activity Impairment Questionnaire. Fatigue's association with all scores remained highly significant despite controlling for disease activity.

### Conclusions

Fatigue is strongly associated with poor HRQOL, disability and depression similarly in CD and UC even when controlling for disease activity. Fatigue's association with a wide range of patient-reported outcome measures suggests that monitoring fatigue is a simple way to screen for overall disruption in patient life.

*Aliment Pharmacol Ther* 2014; **39**: 811–822

## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory conditions that significantly impair the quality of life of over 1.5 million Americans.<sup>1</sup> Diarrhoea and fatigue have been reported as the two most common symptoms of individuals with inflammatory bowel disease (IBD) in a population-based cohort.<sup>2</sup> The fatigue associated with chronic conditions is often unrelieved by rest and may interfere with mental and physical activities.<sup>3</sup> Fatigue prevalence has been reported as nearly 40% in IBD even during periods of quiescent disease.<sup>4</sup> While the pathogenesis is likely multi-factorial, little is known about the causes of IBD-related fatigue.<sup>5</sup>

Fatigue has been associated with diminished health-related quality of life (HRQOL) in IBD.<sup>6–9</sup> Recent reports from Norway and the Netherlands demonstrated a strong association between both fatigue and chronic fatigue with generic (Short-Form 36, SF-36) and disease specific (Inflammatory Bowel Disease Questionnaire, IBDQ) HRQOL measures, which was independent of disease activity.<sup>4, 6, 10</sup> However, neither study specifically explored a potential relationship between fatigue and depression, which may be highly interrelated.<sup>11–14</sup> Fatigue's association with HRQOL has also never been explored in newly diagnosed IBD patients.

Disability differs from quality of life in that it pertains to objective difficulties in different domains of life as opposed to how a patient feels about the limitations and restrictions imposed by the disability.<sup>15</sup> Importantly, the association of IBD-related fatigue with disability has yet to be explored.

The aims of this study were twofold: (i) to report the prevalence of fatigue in a cohort of newly diagnosed CD and UC patients using the validated Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-F)<sup>16</sup>; and (ii) to explore the relationship of fatigue with quality of life, depression and overall disability in newly diagnosed IBD patients.

## METHODS

### Study population

The Ocean State Crohn's and Colitis Area Registry (OSCCAR) is a statewide cohort of newly diagnosed IBD patients established in Rhode Island in January 2008 with the goal of describing disease outcomes as well as factors that predict those outcomes.<sup>17</sup> All patients (adults and children) are enrolled within 12 months of their diagnosis. Diagnoses of CD, UC or indeterminate colitis are confirmed on endoscopy, pathology or imaging using

standard diagnostic criteria by health care professionals.<sup>18</sup> Detailed information is collected via home visits, telephone interviews and standardised chart review on patient history, disease activity and important patient-reported outcomes including fatigue, disability and quality of life on enrolment.

Between January 1, 2008 and December 31, 2011, 248 subjects 18 years and older were enrolled in OSCCAR. In this study, we excluded subjects with indeterminate colitis ( $n = 6$ ), insufficient data to support an IBD diagnosis ( $n = 9$ ) or insufficient data on fatigue ( $n = 13$ ). The remaining study population available for analysis was 220 patients (125 with CD, 95 with UC).

### Ascertainment of fatigue

The FACIT-F Scale is a 13-item instrument (see Table S1) developed by combined expert and patient input assessing self-reported fatigue and its impact on daily activities and function.<sup>19</sup> The FACIT-F scale has been validated in the general population as well as many diseases including cancer, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, chronic immune thrombocytopenia and most recently IBD.<sup>16, 20–25</sup> The authors of the FACIT-F scale have proposed defining the cut-off score for fatigue as being less than or equal to 30, which we use in our study.<sup>19</sup>

### Ascertainment of patient-reported outcomes

Generic HRQOL was measured using the Medical Outcomes Study SF-36 Health Survey and the EuroQol (EQ-5D). The SF-36 is a validated generic HRQOL instrument useful for comparing quality of life of a specific disease population with that of the total US population.<sup>26, 27</sup> The EQ-5D is a simple generic HRQOL instrument that reflects the subjective valuation of health states based on respondents' preferences and has been validated for use in IBD.<sup>28, 29</sup> We calculated the proportion of patients reporting problems (moderate, extreme) for individual items of the EQ-5D and analysed the overall visual analogue scale (VAS) score according to fatigue status. Disease-specific quality of life was assessed using the validated, reliable 32-item IBDQ that assesses four dimensions: bowel symptoms (i.e. loose stools, frequency, abdominal pain or cramps); systemic symptoms (i.e. fatigue, lack of energy, altered sleep); social function (i.e. ability to attend work or social events); and emotional function (i.e. anger, frustration, depression, worry about surgery).<sup>30–32</sup>

The Work Productivity and Activity Impairment (WPAI) questionnaire assessed work time missed and

work productivity and activity impairment.<sup>33</sup> Four scores are derived from the WPAI: absenteeism (work time missed in employed subjects); presenteeism (reduced productivity while at work); overall work impairment (absenteeism + presenteeism); and activity impairment (reduced productivity in daily activities). The WPAI has been validated in a number of diseases including CD.<sup>34, 35</sup>

Presence of comorbid depression was assessed using the Patient Health Questionnaire Depression Scale (PHQ-8). The PHQ-8 is a standardised, validated instrument using eight of the nine criteria on which the DSM IV criteria of depression are based on a score  $\geq 10$  shown to represent clinically significant depression in population-based studies.<sup>36–38</sup> PHQ-8 data were available only for patients recruited into OSCCAR after October 2009, including 74 CD patients and 59 UC patients.

### Data analysis

We described CD and UC patients with and without fatigue by demographic characteristics, current medication use and clinical characteristics at study enrolment. Prevalence of fatigue was estimated at study enrolment.

We compared the various HRQOL outcomes according to patients' fatigue status (FACIT score  $\leq 30$ , FACIT score  $\geq 30$ ) at study enrolment. For continuous HRQOL outcomes (SF-36 domain scores, EQ-5D VAS score, IBDQ scores, PHQ-8 total score), we compared the mean scores of patients with and without fatigue using two-tailed *t*-tests and estimated the crude mean score differences and corresponding 95% confidence intervals (CI). Effect sizes were calculated for continuous HRQOL outcomes with Cohen's *d*.<sup>39, 40</sup> Cohen's guidelines for categorising effect sizes as small ( $d = 0.2$ ), medium ( $d = 0.5$ ) and large ( $d \geq 0.8$ ) were used.<sup>39</sup> We then ran linear regression models estimating mean score differences adjusting for selected demographic and clinical information at study enrolment including: sex, age at diagnosis (continuous variable), marital status (single, never married, married, divorced/separated, cohabitating, widowed, unknown), race (white, African American/black, more than one race, other), current steroid use (yes, no), smoking (never, former, current, unknown) and disease activity [continuous disease activity scores; Harvey Bradshaw Index (HBI) for CD, Simple Clinical Colitis Activity Index (SCCAI) for UC]. HBI  $\geq 5$  and SCCAI  $\geq 5$  were the parameters used to define active disease when categorical designations were used.<sup>41, 42</sup> One CD patient was missing HBI data.

For discrete HRQOL outcomes, i.e. reported problems on the EQ-5D dimensions and depression (PHQ-8 score  $\geq 10$ ), we estimated risks as well as risk ratios for compromised quality of life according to fatigue status. First, we estimated crude measures and corresponding 95% CI, using patients without fatigue as the reference group. We then controlled for sex, age at diagnosis, marital status, race, current steroid use, smoking and disease activity using the Mantel–Haenszel method. To adjust for all confounders simultaneously, we conducted a modified Poisson regression analysis.

Blood work at study enrolment was available for a sub-population of patients. We further controlled for haematocrit levels (continuous variable) for 140 patients in multivariable analyses. As an alternate analysis, we also restricted all analyses to non-anaemic patients (anaemia defined as having a value of  $\leq 36$  in women and  $\leq 39$  in men).<sup>43</sup>

We used PAWS Statistics (version 19; SPSS Inc, Chicago, IL, USA) and Excel spreadsheets (Microsoft, Redmond, WA, USA) to run analyses. The study protocol was approved by the Icahn School of Medicine at Mount Sinai and Rhode Island Hospital institutional review boards beginning August 29, 2007, and the approvals for use of HRQOL measures were obtained from the relevant copyright holders.

## RESULTS

### Study population and fatigue prevalence

Baseline demographics and clinical characteristics of the study population at enrolment according to disease diagnosis and fatigue status are described in Tables 1 and 2. The median time to enrolment in OSCCAR from date of diagnosis for the included patients was 61 days (range 12–364).

At study enrolment, 58 (26%) of the 220 analysed subjects met FACIT-F criteria for fatigue. Prevalence of fatigue was similar in CD and UC (29.6% vs. 22.1%,  $P = 0.211$ ). However, significantly more women met fatigue criteria than men at enrolment (31.3% vs. 18.6%,  $P = 0.036$ ). Patients with active disease were more likely to have fatigue than those with inactive disease in CD (53.3% vs. 23.5%,  $P = 0.002$ ), but insignificantly in UC (33.3% vs. 18.8%,  $P = 0.144$ ).

### Fatigue and generic quality of Life (SF-36 and EQ-5D)

Crohn's disease and UC patients with fatigue had significantly worse scores across all domains of the SF-36 when

	Crohn's disease		Ulcerative colitis	
	Fatigue* n (%)	Non-fatigue† n (%)	Fatigue* n (%)	Non-fatigue† n (%)
<b>Total</b>	37 (100)	88 (100)	21 (100)	74 (100)
<b>Sex</b>				
Female	26 (70)	54 (61)	16 (76)	38 (51)
Male	11 (30)	34 (39)	5 (24)	36 (49)
<b>Age at Dx, years</b>				
18–34	24 (65)	42 (48)	8 (38)	34 (46)
35–64	13 (35)	38 (43)	9 (43)	31 (42)
65+	0 (0)	8 (9)	4 (19)	9 (12)
<b>Race</b>				
White	35 (95)	78 (89)	17 (81)	69 (93)
African American	0 (0)	7 (8)	2 (10)	2 (3)
One race	0 (0)	1 (1)	0 (0)	1 (1)
Other, unknown	2 (5)	2 (2)	2 (10)	2 (3)
<b>Hispanic or Latino origin</b>				
No	33 (89)	83 (94)	19 (91)	71 (96)
Yes	4 (11)	4 (5)	1 (5)	3 (4)
Unknown	0 (0)	1 (1)	1 (5)	0 (0)
<b>Occupational status</b>				
Paid	21 (57)	55 (63)	12 (57)	47 (64)
Unpaid/volunteer	7 (19)	14 (16)	2 (10)	5 (7)
Retired	0 (0)	6 (7)	3 (14)	7 (10)
Disabled	4 (11)	4 (5)	1 (5)	4 (5)
Student	5 (14)	9 (10)	3 (14)	11 (15)
<b>Marital status</b>				
Single, never married	19 (51)	31 (35)	10 (48)	24 (32)
Married	10 (27)	37 (42)	9 (43)	29 (39)
Divorced/separated	5 (14)	13 (15)	1 (5)	11 (15)
Cohabiting	3 (8)	3 (3)	0 (0)	6 (8)
Widowed	0 (0)	3 (3)	0 (0)	4 (5)
Unknown	0 (0)	1 (1)	0 (0)	0 (0)
<b>Smoking status</b>				
Never smoked	14 (38)	48 (55)	11 (52)	39 (53)
Former smoker	13 (35)	24 (27)	9 (43)	28 (38)
Current smoker	10 (27)	15 (17)	1 (5)	7 (10)
Unknown	0 (0)	1 (1)	0 (0)	0 (0)

Dx, diagnosis; GED, general equivalency degree.

\* FACIT score  $\leq 30$  at study enrolment.

† FACIT score  $>30$  at study enrolment.

**Table 1 |** Characteristics of study population at enrolment according to fatigue status

compared with patients without fatigue (Table 3). Patients without fatigue had mean SF-36 domain scores very similar to the US population mean of 50 for each, whereas patients with fatigue had mean SF-36 domain scores greater than one standard deviation below the US population mean for all but one domain (physical functioning) in CD and two domains (physical functioning and bodily pain) in UC. The mean score differences between patients with and without fatigue were greater than the reported minimal clinically important difference (MCID) for all but two domains of the SF-36 in CD. The mean score differences in the physical health and

mental health component scores were 2.7–4 times greater than the MCID for both CD and UC patients (MCID unknown for UC). Cohen's *d* effect sizes comparing fatigued with nonfatigued patients were greater than 0.8 for all SF-36 domains and largest for the Role Limitations Physical Problems, Vitality, and Social Functioning domains in both CD and UC and for mental health in CD (Table 3). Multivariable models controlling for sex, age at diagnosis, marital status, race, current steroid use and smoking did not significantly change the mean score difference between fatigued and nonfatigued CD or UC patients for the mental health or physical health

**Table 2 | Clinical characteristics of study population at enrolment according to fatigue status**

	Crohn's disease		Ulcerative colitis	
	Fatigue*	Nonfatigue†	Fatigue*	Nonfatigue†
<b>Total patients, n (%)</b>	37 (100)	88 (100)	21 (100)	74 (100)
<b>Disease activity</b>				
HBI, mean score (SD)‡	5.2 (3.9)§	2.6 (2.9)§	n.a.	n.a.
SCCAI, mean score (SD)	n.a.	n.a.	4.4 (2.7)§	2.8 (2.6)§
Active disease¶, n (%)	16 (44)‡	14 (18)**	8 (38)	16 (22)††
<b>Symptoms</b>				
Diarrhoea, n (%)	35 (95)	68 (77)	19 (95)‡	67 (91)
Bleeding, n (%)	21 (58)	47 (54)‡	18 (90)‡	65 (88)
Pain, n (%)	35 (95)	73 (86)‡‡	18 (95)††	58 (81)††
<b>Current medication use</b>				
Steroids, n (%)	18 (49)	41 (47)	11 (52)	34 (46)
Immunosuppressives, n (%)	6 (16)	4 (5)	2 (10)‡	1 (1)
5-ASA, n (%)	22 (60)	61 (69)	20 (100)‡	72 (97)
Anti-TNF, n (%)	5 (14)	6 (7)	1 (5) ‡	0 (0)
Anti-diarrhoeal, n (%)	2 (5)	6 (7)	3 (14)	5 (7)
Antibiotics, n (%)	11 (30)	23 (26)	2 (10) ‡	12 (16)
NSAIDS, n (%)	5 (14)	11 (13)	3 (14)	4 (6)
<b>Blood work</b>				
Haematocrit, mean (SD) N = 139	38.2 (4.5) n = 27	38.5 (4.8) n = 51	34.1 (8.6) n = 14	39.3 (5.2) n = 47

HBI, Harvey–Bradshaw index; n.a., not applicable; NSAIDS, nonsteroidal anti-inflammatory drugs; SCCAI, simple clinical colitis activity index; TNF, tumour necrosis factor; 5-ASA, 5-aminosalicylic acid.

\* FACIT score ≤30 at study enrolment.

† FACIT score >30 at study enrolment.

‡ One subject with missing scores.

§ *P* < 0.05 on each *t*-test for equality of means of disease activity scores, comparing fatigued vs. nonfatigued.

¶ Disease index score ≥5.

\*\* Nine subjects with missing scores.

†† Two subjects with missing scores.

‡‡ Three subjects with missing scores.

component scores. Further controlling for disease activity decreased the mean score differences between fatigued and nonfatigued CD and UC patients minimally. However, even when controlling for disease activity, the mean score differences in the physical health (CD: 9.9; 95% CI, 6.1–13.6; UC: 9.5; 95% CI, 5.4–13.5) and mental health (CD: 12.6; 95% CI, 8.1–17.0; UC: 12.8; 95% CI, 7.6–18.0) component scores were over two times the MCID of each for CD.

Both CD and UC patients with fatigue reported having problems with the usual activities, pain/discomfort and anxiety/depression domains of the EQ-5D significantly more often compared with patients without fatigue (Table 4). However, very few CD or UC patients reported problems with self-care irrespective of fatigue status. The association of fatigue and impairment in EQ-5D domains was strongest for usual activities, with a

fourfold increased risk of problems in fatigued CD patients (95% CI 2.36–6.89) and 4.9-fold increased risk in fatigued UC patients (95% CI 2.57–9.46). The increased risk of having impairment in usual activities, pain/discomfort and anxiety/depression did not vary significantly by sex. These estimates remained significantly greater in CD and UC patients with fatigue compared with patients without fatigue when adjusting for sex, age at diagnosis, marital status, race, corticosteroid use and smoking. Similarly, all associations remained significant when further controlling for disease activity with the exception of pain/discomfort in CD patients.

Patients with fatigue had significantly worse valuations of their current health state as measured with the EQ-5D compared with those without fatigue, both in CD (62.5 vs. 80.6, *P* < 0.001) and in UC (67.2 vs. 81.5, *P* < 0.001) (data not shown). The mean score differences between

**Table 3 | Association between Fatigue and the Short-Form Health Survey (SF-36)**

SF-36	Crohn's disease					Ulcerative colitis			
	Mean score (s.d.)		Mean score difference (95% CI)	MCID	Cohen's <i>d</i> ‡	Mean score (s.d.)		Mean score difference (95% CI)	Cohen's <i>d</i> ‡
	Fatigue*	Nonfatigue†				Fatigue*	Nonfatigue†		
Physical functioning	41.5 (11.2)	51.2§ (10.3)	9.7 (5.6–13.9)	8.7	0.9	43.2 (10.7)	52.7 (7.4)	9.5 (5.5–13.6)	1.2
Role limitations physical problems	31.0 (7.9)	48.7 (10.4)	17.7 (13.9–21.5)	18.4	1.8	33.0 (7.5)	49.7 (10.1)	16.7 (12.0–21.5)	1.8
Bodily pain	35.9 (8.7)	48.5 (9.2)	12.7 (9.1–16.2)	11.8	1.4	41.9 (10.6)	51.5 (8.6)	9.6 (5.1–14.0)	1.1
General health	35.3 (9.7)	46.1 (9.1)	10.8 (7.2–14.4)	6.5	1.2	38.4 (10.1)	47.6 (9.0)	9.3 (4.8–13.8)	1.0
Vitality	31.6 (6.0)	48.8 (10.0)	17.2 (13.7–20.7)	9.3	1.9	34.7 (7.1)	51.3§ (9.4)	16.5 (12.1–20.9)	1.9
Social functioning	34.1 (13.0)	50.2 (8.4)	16.1 (12.3–20.0)	9.4	1.6	33.6 (11.6)	51.6 (7.4)	18.0 (13.9–22.2)	2.1
Role limitations emotional problems	35.7 (13.2)	47.8 (11.6)	12.1 (7.4–16.8)	15.6	1.0	39.3 (13.6)	50.4 (9.4)	11.1 (5.9–16.2)	1.1
Mental health	33.8 (11.7)	50.2 (9.4)	16.4 (12.4–20.3)	5.7	1.6	37.9 (15.7)	49.1 (8.5)	11.2 (6.1–16.3)	1.1
Physical health component	37.5 (7.6)	49.2§ (8.8)	11.7 (8.4–14.9)	4.1	1.4	40.1 (9.8)	51.1 (7.7)	11.0 (7.0–15.0)	1.4
Mental health component	33.2 (12.2)	48.8 (9.6)	15.6 (11.6–19.7)	3.9	1.5	36.1 (14.1)	49.8 (8.1)	13.7 (8.9–18.4)	1.4

CI, confidence interval; MCID, minimally clinically important difference (available for CD only); s.d., standard deviation.

Mean Domain and Component Score for US population (age ≥18) is 50.0 with a standard deviation of 10.0.

\* FACIT score ≤30 at study enrolment, *N* = 37 with Crohn's disease, *N* = 21 with ulcerative colitis.

† FACIT score >30 at study enrolment, *N* = 88 with Crohn's disease, *N* = 74 with ulcerative colitis. *P* < 0.005 on each *t*-test for equality of means, comparing fatigued vs. nonfatigued. Variance assumptions for 95% CI based on Levene's test for equality of variances.

‡ Cohen's *d* effect size: small (*d* = 0.2), medium (*d* = 0.5), and large (*d* ≥ 0.8).

§ One subject with missing scores.

**Table 4 | Association between Fatigue and the Euro Quality of Life Index (EQ-5D)**

EQ-5D	Crohn's disease			Ulcerative colitis		
	Problems % ( <i>n</i> )		RR‡ (95% CI)	Problems % ( <i>n</i> )		RR (95% CI)
	Fatigue*	Nonfatigue†		Fatigue*	Nonfatigue†	
Mobility	29.7 (11)	14.9 (13)	2.0 (0.99–4.02)	19.0 (4)	10.8 (8)	1.8 (0.58–5.28)
Self-care	5.4 (2)	0.0 (0)	–	4.8 (1)	2.7 (2)	1.8 (0.17–8.49)
Usual activities	64.9 (24)	16.1 (14)	4.0 (2.36–6.89)	66.7 (14)	13.5 (10)	4.9 (2.57–9.46)
Pain/discomfort	83.8 (31)	60.9 (53)	1.4 (1.10–1.71)	71.4 (15)	36.5 (27)	2.0 (1.31–2.93)
Anxiety/depression	73.0 (27)	26.4 (23)	2.8 (1.85–4.12)	64.9 (13)	35.1 (26)	1.8 (1.11–2.78)

CI, confidence interval.

\* FACIT score ≤30 at study enrolment, *N* = 37 with Crohn's disease, *N* = 21 with ulcerative colitis.

† FACIT score >30 at study enrolment, *N* = 87 with Crohn's disease, *N* = 74 with ulcerative colitis.

‡ RR, risk ratios with nonfatigued as the reference group (RR = 1.0). One CD patient failed to complete the EQ-5D.

patients with and without fatigue were greater than the published minimum clinically important difference for CD (MCID = 9.2).<sup>44</sup> The Cohen's *d* effect sizes for

fatigue were 1.2 for CD and 1.0 for UC. The mean score differences remained significant even when models were adjusted for sex, age at diagnosis, marital status, race,

corticosteroid use, smoking and disease activity [in CD 15.9 (95% CI, 9.61–22.27), in UC 12.4 (95% CI 4.74–20.21)]. Further controlling for haematocrit among patients for whom results were available (140 patients) did not significantly change the results.

### Fatigue and disease-specific quality of life (IBDQ)

Mean scores were significantly worse across all dimensions of the IBDQ in both CD and UC patients with fatigue compared with those without fatigue (Table 5). The overall IBDQ score was also significantly worse in fatigued CD (131.0 vs. 180.8,  $P < 0.001$ ) and UC (139.8 vs. 178.8,  $P < 0.001$ ) patients than those without fatigue. Importantly, the mean score differences between fatigued and nonfatigued in both CD (49.8) and UC (39.0) were more than double the published MCID for CD (MCID = 16). The mean score difference did not change significantly when controlling for sex, age at diagnosis, marital status, race, steroid use or smoking. Controlling for disease activity in addition to the other factors did modestly lower the overall IBDQ mean score difference to 34.5 (95% CI, 26.26–42.72) in CD and 31.6 (95% CI, 19.86–43.41) in UC. Further controlling for haematocrit in 74 CD patients and 60 UC patients for whom results were available did not change the results significantly. Cohen's  $d$  effect sizes for fatigue were large across all

domains of the IBDQ with the greatest effect seen in the Systemic Symptoms domain for both CD and UC (Table 5).

### Fatigue and work productivity (WPAI)

In total, 25 of 83 (30%) employed CD patients and 16 of 66 (24%) employed UC patients completing WPAI questionnaires were categorised as having fatigue. Employed CD patients with fatigue showed significantly greater impairment in absenteeism, presenteeism and overall work impairment than employed CD patients without fatigue (Figure 1, upper panel). Employed UC patients with fatigue also showed significantly greater impairment in presenteeism and overall work impairment than non-fatigued patients (Figure 1, lower panel). Both employed and unemployed CD and UC patients with fatigue were significantly impaired in their daily activities compared with patients without fatigue. The difference in impairment for all WPAI scores far surpassed the reported minimum clinically important difference of 7%.

Associations between fatigue and WPAI scores in both CD and UC remained similar and statistically significant after adjusting for all available co-variables, although somewhat minimised when also adjusting for disease activity. Adjusted mean score differences in Overall Work Impairment and Overall Activity Impairment were

**Table 5 | Association between Fatigue and Inflammatory Bowel Disease Questionnaire (IBDQ)**

IBDQ	Crohn's disease				Ulcerative colitis			
	Mean score (s.d.)		Mean score difference (95% CI)	Cohen's $d$ §	Mean score (s.d.)		Mean score difference (95% CI)	Cohen's $d$ §
	Fatigue*	Nonfatigue†			Fatigue*	Nonfatigue†		
Bowel symptoms	42.6 (10.3)	55.8 (9.0)	13.3 (9.4–17.2)	1.4	44.8 (11.0)	54.7 (9.4)	9.9 (4.5–15.2)	1.0
Systemic symptoms	14.7 (4.4)	25.4 (5.1)	10.7 (8.9–12.5)	2.2	17.2 (5.3)	25.9¶ (4.9)	8.7 (6.0–11.3)	1.8
Social function	23.6 (7.4)	32.2 (4.7)	8.5 (6.3–10.7)	1.5	25.1 (8.8)	32.2 (3.6)	7.0 (4.5–9.6)	1.4
Emotional function	49.6¶ (13.5)	67.3 (9.4)	17.8 (13.6–22.0)	1.7	52.6 (12.5)	66.2 (8.6)	13.7 (7.7–19.7)	1.4
Total score	131.0¶ (30.6)	180.8 (24.1)	49.8‡ (39.6–60.0)	1.9	139.8 (30.8)	178.8¶ (22.0)	39.0 (24.2–53.8)	1.6

CI, confidence interval; s.d., standard deviation.

$P \leq 0.001$  on each  $t$ -test for equality of means, comparing fatigued vs. nonfatigued.

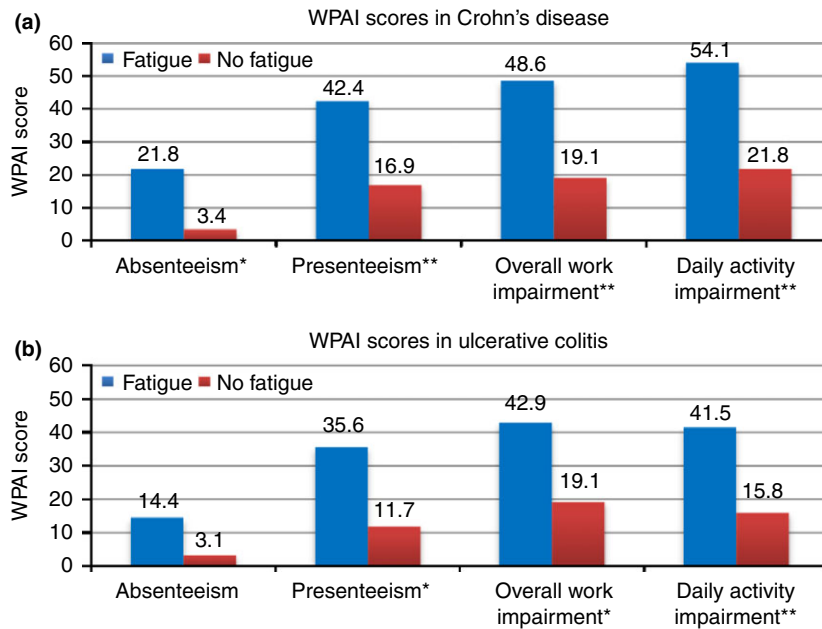
\* FACIT score  $\leq 30$  at study enrolment,  $N = 37$  with Crohn's disease,  $N = 21$  with ulcerative colitis.

† FACIT score  $> 30$  at study enrolment,  $N = 88$  with Crohn's disease,  $N = 74$  with ulcerative colitis.

‡ MCID for Crohn's disease = 16.0. Remission defined as total score  $\geq 170$ .<sup>30</sup>

§ Cohen's  $d$  effect size: small ( $d = 0.2$ ), medium ( $d = 0.5$ ) and large ( $d \geq 0.8$ ).

¶ One subject with missing scores.



**Figure 1** | Work productivity and activity impairment (WPAI) according to fatigue status among patients with newly diagnosed (a) Crohn's disease and (b) ulcerative colitis. Only employed patients (CD: 83/125; UC: 66/90) considered for the first three items of the WPAI (absenteeism, presenteeism, overall work impairment). All patients (CD 125; UC 90), including unemployed patients, were considered for the fourth item of the WPAI (daily activity impairment). Two employed CD patients did not complete absenteeism questions. \* $P < 0.01$  for difference between patients with fatigue vs. no fatigue. \*\* $P < 0.001$  for difference between patients with fatigue vs. no fatigue.

24.3% (95% CI, 10.3–38.2) and 25.7% (95% CI, 15.1–36.2) for CD and 25.5% (95% CI, 9.9–41.2) and 18.9% (95% CI, 7.9–30.0) for UC respectively.

### Fatigue and depression (PHQ-8)

Among 133 patients completing the PHQ-8, 26 CD and 13 UC patients met criteria for fatigue (data not shown). The mean PHQ-8 score was significantly greater among patients with fatigue than among those without, both in CD (10.4 vs. 3.1,  $P < 0.001$ ) and UC (8.8 vs. 2.7,  $P < 0.001$ ). The Cohen's *d* effect size for fatigue was 1.8 in CD and 1.7 in UC. The association between fatigue and depression in CD and UC patients was not significantly altered when controlling for sex, age at diagnosis, marital status, race, corticosteroid use, smoking and disease activity. In addition, fatigued patients were far more likely than nonfatigued to meet the criteria for depression, both in CD (42.3% vs. 6.4%,  $P < 0.001$ ) and UC (41.7% vs. 4.3%,  $P = 0.006$ ).

## DISCUSSION

We have reported the association of fatigue with generic HRQOL, IBD disease-specific HRQOL, work disability and depression in a prospective cohort of newly

diagnosed IBD patients in Rhode Island. Fatigue was prevalent in 26% of newly diagnosed patients in the OSCCAR cohort. The associations of fatigue with impairment in patient-reported outcomes were highly significant even when controlling for factors such as disease activity, age, smoking, steroid use and haematocrit. Although some studies have suggested that CD patients may suffer from more impaired HRQOL than UC patients,<sup>4, 45</sup> the fatigue effects on all patient-reported outcome measures in our study were remarkably consistent across disease states. The association of fatigue with worse HRQOL has been demonstrated in other chronic inflammatory diseases,<sup>46–48</sup> but only a few studies<sup>4, 6</sup> have reported on the association of fatigue with generic and disease-specific HRQOL in IBD despite its high prevalence and none has explored this problem in newly diagnosed patients.<sup>2, 49, 50</sup>

Fatigue is a particularly challenging symptom because it appears to affect the HRQOL of IBD patients even when their disease is not active.<sup>2, 4, 5, 51, 52</sup> Fatigue and HRQOL have been shown to correlate closely in patients with confirmed mucosal healing.<sup>53</sup> However, it is difficult to conclude whether fatigue is involved directly in the patient's poor perception of their health state or a



consequence of coexisting anxiety/depression. Several publications have previously suggested an overlap between depression and fatigue.<sup>5, 11–14</sup> While we have demonstrated a strong association of fatigue with depression, fewer than half the fatigued patients in the OSCCAR cohort met clinical criteria for depression. It is difficult to make determinations on causation in a cross-sectional analysis, but this suggests that depression is the basis of fatigue in only a subset of patients with IBD. Prospective studies to better define this relationship are needed.

The impact of persistent fatigue was demonstrated in a Norwegian study of the association of chronic fatigue with impaired HRQOL.<sup>6</sup> Jelsness-Jørgensen *et al.* reported Cohen's *d* effect sizes for chronic fatigue ranging from 0.32 to 1.48 for CD and 0.30 to 0.92 for UC across all domains of the SF-36. Only 2/8 UC domains and 5/8 CD domains met criteria for large effect sizes (Cohen's  $d \geq 0.8$ ) in their study. In contrast, we have reported larger Cohen's *d* effect sizes for fatigue in newly diagnosed patients ranging from 0.9 to 1.9 for CD and 1.0 to 2.1 for UC. It appeared that effect sizes were more similar between acute and chronic fatigue for the physical health component domains than for the mental health component domains in CD. A possible explanation of this may be that patients dealing with fatigue for a prolonged period of time learn to deal with the mental impact, while the physical effects persist.

A study of disability in another Norwegian IBD cohort showed that the most strongly associated factor with HRQOL was IBD-related sick leave and that sick leave most often occurred in the first 4 weeks of illness.<sup>54</sup> We have shown that newly diagnosed IBD patients with fatigue exhibited significantly more absenteeism than patients without fatigue. Even when present at work, fatigued IBD patients exhibited greater presenteeism than nonfatigued patients. These results suggest that disease-related fatigue may be a driving force behind their decreased productivity. Disability represents an important measure of dysfunction distinct from HRQOL, which has been inadequately explored in IBD.<sup>15</sup> In response to this, there is now an international effort to create a disability index for IBD.<sup>55, 56</sup> Our results suggest that screening for fatigue may represent another way to identify those IBD patients most at risk for disability.

A strength of this study is that patients were enrolled shortly after their initial IBD diagnosis. In addition, a greater variety of patient-reported outcome measures encompassing generic HRQOL, disease-specific HRQOL, work disability and depression were used than in any of the prior studies assessing fatigue in IBD. We have also

assessed fatigue using the FACIT-F, which is validated for use in IBD. A recent review of the IBD fatigue literature by Czuber-Dochan *et al.* reported that all but one study did not use validated fatigue scales.<sup>5</sup>

Limitations of the study include the fact that full laboratory, radiology and surgical data were not yet available on many of the patients in the study. This limited our ability to fully assess how the association of fatigue with the patient-reported outcomes may be influenced by factors such as anaemia, iron deficiency, vitamin D deficiency, inflammatory markers and Montreal Classification. We assessed patients for fatigue at or close to their initial IBD diagnosis. Therefore, nearly half of patients were on steroids and relatively few patients were on immunosuppressive or biological medications. Other studies have shown possible associations between immunosuppressive use and fatigue,<sup>4–6, 57</sup> but the small number of patients in our cohort using these medications made this difficult to assess. We also did not have data on functional GI disorders that may impact fatigue in IBD patients.<sup>5, 58</sup> Lastly, the data presented represent the population of IBD patients in Rhode Island and may not be generalisable to other areas of the United States.

In conclusion, we have shown that fatigue is highly associated with poor generic and disease-specific HRQOL, disability and depression in newly diagnosed IBD patients even when controlling for demographic variables and disease activity. This association with fatigue appeared very similar for both CD and UC. While fatigue is multi-factorial, it was found to be highly impactful in this cohort of newly diagnosed IBD patients. Fatigue's strong association with a wide range of patient-reported outcome measures suggests that monitoring fatigue may in itself be a simple way to screen for overall disruption in a patient's life. More investigation is needed to understand the aetiology of IBD fatigue and ultimately introduce fatigue-specific treatments, which can improve patients' overall well-being.

## AUTHORSHIP

*Guarantor of the article:* Bruce E. Sands.

*Author contributions:* Benjamin L. Cohen contributed to conception of the study, analysis and interpretation of data, and drafted the manuscript. Helga Zoëga contributed to analysis and interpretation of data and drafting and critical revision of the manuscript. Samir A. Shah contributed to patient and data acquisition and critical revision of the manuscript. Neal LeLeiko contributed to patient and data acquisition and critical revision of the manuscript. Renee Bright contributed to patient and data

acquisition and critical revision of the manuscript. Sheldon Lidofsky contributed to patient and data acquisition and critical revision of the manuscript. Nicole Flowers contributed to conception of the study and critical revision of the manuscript. Meaghan Law contributed to patient and data acquisition and critical revision of the manuscript. Heather Moniz contributed to patient and data acquisition and critical revision of the manuscript. Marjorie Merrick contributed to critical revision of the manuscript. Bruce E. Sands contributed to conception of the study, patient and data acquisition, analysis and interpretation of data, and critical revision of the manuscript. All authors approved the final version of the manuscript.

## ACKNOWLEDGEMENTS

*Declaration of personal interests:* Dr Bruce Sands (the Icahn School of Medicine at Mount Sinai Principal Investigator in this study) receives financial compensation as a consultant and lecturer to several companies which either develop or assess medicines used for the treatment of inflammatory bowel disease. These companies include Pfizer, Millennium Pharmaceuticals/Takeda, Bristol-Myers Squibb, Abbott Immunology, Abbvie, Immedex, Amgen, Prometheus Laboratories, Centocor/Janssen Biotech, Elan Pharmaceuticals, Strategic Consultants,

Inc., Avaxia Biologics (of which he owns stock options), Immune Pharmaceuticals Corporation, Puretech Ventures, LLC, Sigmoid Biotechnologies, Teva Pharmaceuticals, Baxter Healthcare, Creative Educational Concepts, Curatio CME/Huntsworth Health North America, Focus Medical Communications, AstraZeneca LP, Luitpold Pharmaceuticals, Salix Pharmaceuticals, Vedanta Biosciences, Dainippon Sumitomo Pharma, Shire. Benjamin L. Cohen has served as a speaker for AbbVie. Samir A. Shah has served as a speaker for AbbVie, Janssen, and Santarus. Helga Zoëga, Neal LeLeiko, Sheldon Lidofsky, Renee Bright, Nicole Flowers, Meaghan Law, Heather Moniz, and Marjorie Merrick have no personal interests to declare.

*Declaration of funding interests:* The Ocean State Crohn's and Colitis Area Registry (OSCCAR) is supported by grants from the Center for Disease Control and Prevention (CDC) (5U01DP000340 and 3U01DP002676) and the Crohn's and Colitis Foundation of America (CCFA).

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F).

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