Sleep Disturbance and Risk of Active Disease in Patients With Crohn's Disease and Ulcerative Colitis

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BACKGROUND & AIMS: **Impairment of sleep quality is common in patients with inflammatory bowel diseases (IBDs) (eg, Crohn's disease [CD] and ulcerative colitis [UC]), even during clinical remission. Sleep impairment can activate inflammatory pathways. Few prospective studies have examined the role of sleep disturbance on risk of relapse in IBD.**

METHODS: **We analyzed data from 3173 patients with IBD (1798 in clinical remission at baseline) participating in the Crohn's and Colitis Foundation of America Partners study, a longitudinal, Internet-based cohort. Sleep disturbance was measured using a subset of questions from the Patient Reported Outcomes Measurement Information Systems sleep disturbance questionnaire. Disease activity was assessed using the short Crohn's Disease Activity Index and the simple clinical colitis activity index for CD and UC, respectively. Logistic regression was used to identify predictors of sleep quality and examine the effect of sleep quality at baseline among patients in remission on risk of active disease at 6 months.**

RESULTS: **Disease activity, depression, female sex, smoking, and use of corticosteroids or narcotics were associated with sleep disturbance at enrollment. Among 1291 patients whose CD was in remission at baseline, those with impaired sleep had a 2-fold increase in risk of active disease at 6 months (adjusted odds ratio, 2.00; 95% confidence interval, 1.45–2.76); however, no effect was observed in patients with UC (odds ratio, 1.14; 95% confidence interval, 0.75–1.74). These findings persisted in a number of sensitivity analyses.**

CONCLUSIONS: **Sleep disturbance was associated with an increased risk of disease flares in CD but not UC. These findings indicate that the evaluation and treatment of sleep disturbance in patients with CD might improve outcomes.**

Keywords: Intestinal Inflammation; Environment; PROMIS; Prospective Cohort Study.

See editorial on page 972.

Inflammatory bowel diseases (IBDs) (eg, Crohn's disease [CD] and ulcerative colitis [UC]) are chronic immunologically mediated diseases of the intestine that often have their onset during young adulthood and are characterized by a chronic relapsing and remitting course.[1,2] They are associated with considerable morbidity, need for surgery and hospitalizations, and impairment of health-related quality of life.[3,4] However, despite our understanding that external environment, behavior, and lifestyle play an important role in the pathogenesis and natural history of CD and UC,[5–8] such factors remain poorly studied. In particular, there has been little study of behavioral factors other than smoking that might influence disease activity, but that also could be modifiable and reduce the risk of active disease.

Sleep disturbances are common in the population and are associated with a spectrum of adverse outcomes including being a risk factor for obesity, weight gain, metabolic syndrome, depression, and mortality.[9–11] Prior studies have supported the biological plausibility that disturbed sleep may be a modifiable behavioral risk factor for disease relapse in IBD patients.[12–17] Patients with

Abbreviations used in this paper: CCFA, Crohn's and Colitis Foundation of America; CD, Crohn's disease; CI, confidence interval; DSS, dextran sodium sulfate; IBD, inflammatory bowel diseases; IL, interleukin; OR, odds ratio; PROMIS, Patient Reported Outcomes Measurement Information Systems; PSQI, Pittsburgh Sleep Quality Index; SCCAI, Simple Clinical Colitis Activity Index; SCDAI, Short Crohn's Disease Activity Index; TNF, tumor necrosis factor; UC, ulcerative colitis.

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IBD, even during periods of inactivity, have a higher prevalence of impaired sleep quality than healthy controls.[14] In animal models, acute or chronic sleep deprivation increases susceptibility to dextran sodium sulfate (DSS)-induced colitis, a widely used mouse model of IBD.[18] Key cytokines involved in chronic inflammation including tumor necrosis factor (TNF)-α, interleukin-1 (IL-1), and IL-6 affect sleep.[17] In human studies of juvenile idiopathic arthritis, administration of anti-TNF biological therapy improved sleep quality in addition to achieving disease remission.[19] There is limited literature examining the association between sleep quality in remission and risk of subsequent disease flare in patients with established CD or UC.

In the context of a large prospective IBD cohort, we performed this study with the following aims: to identify predictors of sleep quality among patients with CD and UC and to examine if sleep quality during remission is associated with a subsequent risk of symptomatic flares in patients with CD and UC.

Methods

Study Cohort and Variables

The data source for this study was the Crohn's and Colitis Foundation of America (CCFA) Partners IBD cohort. The creation of this cohort has been described in detail in previous publications.[20,21] In brief, CCFA Partners is a longitudinal Internet-based cohort of patients with IBD. Participants with a self-reported diagnosis of UC, CD, or indeterminate colitis who were older than 18 years were invited to participate in the study through the CCFA e-mail roster, social media, and at educational events.[21] All participants completed a baseline survey comprising demographics and information about their IBD. Optional modules on various patient-reported outcomes were included with the baseline survey. They then were invited to complete a follow-up questionnaire 6 months after enrollment that ascertained disease activity as well as any changes in their treatment and repeated measures of patient-reported outcomes.

Assessment of Sleep Disturbance

Our main predictor variable of interest was sleep disturbance. This was ascertained using a subset of questions from the National Institutes of Health Patient Reported Outcomes Measurement Information Systems (PROMIS) sleep disturbance questionnaire.[22,23] The PROMIS sleep disturbance questionnaire was carefully developed within the PROMIS domain framework by first creating an initial pool of items identified from 535 candidate citations. Focus groups then were held among those with sleep disorders and normal sleepers, and the question bank was pilot tested in a national sample of 300 participants and a clinical sample. Subsequent psychometric testing using classic test theory and item response theory analyses were used to arrive at the final questionnaire that showed excellent measurement properties. The short form of the PROMIS questionnaire has comparable performance with the widely used Pittsburgh Sleep Quality Index (PSQI) and greater ability to discriminate between different levels of sleep disturbance.[23,24] Furthermore, the response burden to the PROMIS sleep questions is lower than for the 10-item PSQI, does not require participation of a sleeping partner, and is consistent with ascertainment of other patient-reported outcome measures in this cohort. In addition, each PROMIS question from the 29-item bank is designed as a stand-alone question with the same final score irrespective of the number of questions completed.[25]

For this study, patients were administered 4 questions that examined sleep quality. Respondents were asked if over the past 7 days: (1) their sleep quality was good, (2) their sleep was refreshing, (3) they had a problem with their sleep, or (4) they had difficulty falling asleep. Responses were scored on a 5-point Likert scale. The sum of the responses was normalized to a t-score with a mean of 50 and a standard deviation of 10 (http://www.nihpromis.org). Thus, a t-score of 50 refers to the median sleep quality, with higher scores indicating a greater degree of sleep disturbance. Patients with a sleep t-score greater than 50 were considered as having disturbed sleep, whereas t-scores less than 50 were considered normal. In sensitivity analyses, we defined disturbed sleep as requiring a t-score greater than 60 and as a continuous variable. To validate our use of the PROMIS questions, a subset of patients also were administered the PSQI. Correlation between the 2 questionnaires was examined using the Pearson correlation coefficient.

Other Variables

Self-reported disease location and behavior in CD and extent of involvement in UC was classified according to the Montreal classification.[26] Information was obtained about IBD-related hospitalizations or surgery, as well as medications for treatment of IBD including 5-aminosalicylates (oral), corticosteroids (oral), immunomodulators, and biological therapies (infliximab, adalimumab, certolizumab pegol, and natalizumab). Disease activity was assessed using validated measures: the Short Crohn's Disease Activity Index (SCDAI) for CD[27] and the Simple Clinical Colitis Activity Index (SCCAI) for UC.[28] An SCDAI less than 150 or an SCCAI of 2 or less indicated clinical remission for CD and UC, respectively, with values higher than this threshold indicating active disease.[21] Baseline depressive symptoms were ascertained using a PROMIS depression t-score scored similarly to the sleep t-score. Medication adherence was assessed using the Morisky Medication Adherence Scale.[29] Smoking status was stratified as never, past, or current smoking at the time of the baseline questionnaire with very few (<10 patients) describing a change in their smoking status at 6 months.

Outcomes

Our primary outcome was the presence of active disease at 6 months. This was defined as an SCDAI greater than 150 for CD or an SCCAI greater than 2 for UC on the 6-month follow-up questionnaire. As a secondary outcome, we assessed an expanded definition of disease flare, which included either a disease activity index greater than the threshold described earlier, or initiation of a new IBD medication, or a requirement for an IBD-related surgery or hospitalization between the baseline and follow-up visit. In the validation study, patient and physician reports matched 98% of the time for ever having bowel surgery and current pouch or ostomy status. In a sensitivity analysis, we used an alternate definition of active disease that included an SCDAI greater than 150 and a 100-point increase in SCDAI from baseline for CD and an SCCAI greater than 5 for UC.

Statistical Analysis

All analyses were performed using Stata 11.0 (StataCorp, College Station, TX). Continuous variables were summarized using means and standard deviations and compared using the *t* test. Categoric variables, expressed as proportions, were

compared using the chi-square test. Univariate and multivariable logistic regression models were constructed to identify predictors of disturbed sleep at cohort entry. This analysis included the entire cohort of 3173 patients. Next, among participants who were in clinical remission at baseline (n = 1798), we evaluated the association between sleep disturbance during remission and risk of disease flare. Variables significant in the univariate analyses at a *P* value less than .10 were included in the final multivariable regression models, for which a *P* value less than .05 indicated independent statistical significance. The study was approved by the Institutional Review Board of Massachusetts General Hospital. The CCFA Partners cohort study was approved by the Institutional Review Board of the University of North Carolina, Chapel Hill.

Results

Study Cohort

A total of 4366 individuals who had both a baseline and a 6-month follow-up survey were eligible for inclusion in our study. The median interval between completion of the baseline and follow-up survey was 7 months (interquartile range, 6.5–7.8 mo). After excluding patients with a stoma or pouch (because standard symptom-based measures of disease activity are not applicable to these patients), indeterminate colitis, a change in their IBD diagnosis during the follow-up period, and those with missing data on sleep disturbance or disease activity scores, we arrived at the final cohort of 3173 patients (Figure 1). A total of 1798 patients (507 UC patients, 1291 CD patients) were in clinical remission at baseline. Patients excluded from the study were similar to the final cohort in age and sex, were slightly more likely to have UC, and had a lower frequency of prior hospitalizations or surgery.

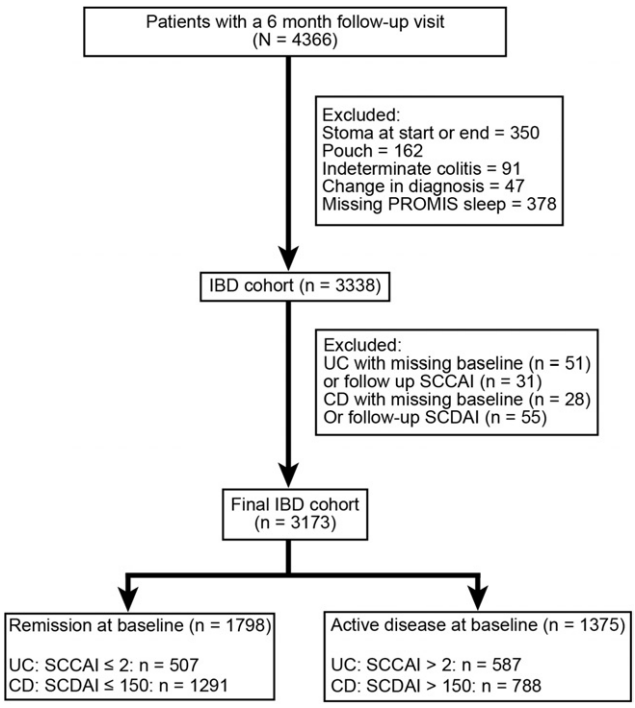

Figure 1. Flow chart establishing study cohort.

Validation of Assessment of Sleep Disturbance

A total of 773 patients completing the 6-month follow-up questionnaire completed both the PSQI and the PROMIS sleep questionnaire. Overall, there was a strong correlation between the 2 scores (correlation coefficient, 0.80; $P < .0001$). The correlation remained good for patients with active disease or in remission, and by IBD type. The mean PSQI for those without or with sleep impairment by the PROMIS sleep t-scores were 4 and 9, respectively ($P < .0001$). Four-fifths (82%) of patients with sleep t-scores higher than the median and 98% of those with sleep t-scores greater than 60 had a PSQI greater than 5.

Predictors of Sleep Disturbance at Baseline

Nearly two-thirds of patients (60%) in the study had sleep disturbance at baseline. Such patients were more likely to be female, have CD, or have a history of smoking ($P < .05$ for all) (Table 1). They were also more likely to be currently using systemic corticosteroids, narcotics, or anti-TNF biological therapies and were more likely to have ever required an IBD-related hospitalization or surgery. More than half the patients with sleep disturbance had active disease (55%), compared with a quarter of those with no sleep disturbance (26%) ($P < .001$). Conversely, 48% of those in remission at baseline had sleep t-scores greater than 50, compared with 76% of those with active disease ($P < .001$). On multivariable analysis, the strongest predictors of disturbed sleep were depressive symptoms (odds ratio [OR], 2.75; 95% confidence interval [CI], 2.34–3.23) and the presence of active disease (OR, 2.61; 95% CI, 2.19–3.11), whereas female sex, diagnosis of CD, and both past and current smoking conferred modest risks (Table 2). Current use of corticosteroids and narcotics, but not anti-TNF biologics or immunomodulators, also independently increased the risk of sleep disturbance.

Sleep Disturbance and Risk of Disease Flare in Crohn's Disease

Half of the 1291 patients with CD in remission at baseline had disturbed sleep (n = 651; 50%). Participants with sleep disturbance while in clinical remission were more likely to be women, have CD, or have a history of smoking. Neither corticosteroids nor narcotic use were associated with disturbed sleep in this cohort, likely owing to their low frequency of use among those in remission (Table 3). Among those with disturbed sleep, 22% of those in remission had active disease at month 6 compared with 12% of those without disturbed sleep (OR, 1.96; 95% CI, 1.45–2.65). On multivariable analysis, the presence of sleep disturbance was associated with a 2-fold increase in risk of disease flare at 6 months (OR, 2.00; 95% CI, 1.45–2.76) (Table 4). By using the expanded definition of disease flare, incorporating either active symptoms or initiation of new therapies, we found a similar effect of sleep disturbance on disease flare (OR, 1.64; 95% CI, 1.27–2.11). Defining disease flare as requiring both an SCDAI greater than 150 and a 100-point increase in the score from baseline also yielded a similar effect size (OR, 1.70; 95% CI, 1.09–2.65). To explore the possibility of subclinical symptoms at baseline that were lower than our remission threshold influencing sleep status and likelihood of flare, in a sensitivity analysis we defined remission as an SCDAI of 200 or less, and we defined active disease on follow-up evaluation as values greater than this threshold.

Table 1. Baseline Characteristics of the Study Cohort

	No sleep disturbance, % (n = 1267)	Disturbed sleep, % (n = 1906)	*P* value
Median age, *y* (IQR)	43 (31–57)	45 (32–56)	.90
Median age at diagnosis, *y* (IQR)	26 (20–39)	27 (20–39)	.94
Female	70	75	.005
IBD type			.003
CD	62	68	
UC	38	32	
Smoking status			< .001
Never	68	61	
Past	28	32	
Current	4	7	
Family history of IBD	24	22	.06
Depressive symptoms[a]	33	63	< .001
Current medication use			
Steroids	10	17	< .001
5-aminosalicylates	52	49	.10
Immunomodulators	32	30	.41
Anti-TNF biologics	31	34	.04
Narcotics	4	11	< .001
Prior IBD surgery	30	35	.005
Prior hospitalization	59	63	.01
Crohn's phenotype			.05
Inflammatory	42	37	
Stricturing	38	39	
Penetrating	19	23	
Crohn's location			.004
Ileal	34	30	
Colonic	17	13	
Ileocolonic	47	56	
Upper gastrointestinal only	2	1	
Perianal Crohn's	26	30	.09
UC extent			.65
Proctitis	5	5	
Left-sided colitis	43	42	
Pancolitis	37	40	
Unavailable	15	13	
Active disease[b]	26	55	< .001

IQR, interquartile range.
[a]Depressive symptoms were defined as having a PROMIS depression t-score greater than 50.
[b]Active disease was defined as an SCCAI greater than 2 for patients with UC and an SCDAI greater than 150 for patients with CD.

The association with sleep impairment and subsequent active disease was strengthened further in this analysis (OR, 1.95; 95% CI, 1.37–2.79). Participants who had no impaired sleep at baseline but sleep impairment on follow-up surveys were significantly more likely to have active disease at the follow-up evaluation (OR, 2.37; 95% CI, 1.46–3.86) than those whose sleep remained unimpaired. Adjusting for baseline body mass index did not influence our results. Similar results were found after adjusting for medication adherence using the Morisky Medication Adherence Scale (data available for 832 patients) (OR, 1.63; 95% CI, 1.10–2.42) or depressive symptoms (data available for 1206 patients) (OR, 1.77; 95% CI, 1.27–2.45). On a continuous scale, each 10-point (1 standard deviation) increase in the PROMIS sleep t-score was associated with a 50% increase in risk of disease flare (OR, 1.46; 95% CI, 1.19–1.79) (Table 5). Patients with the greatest disturbance in sleep quality (PROMIS t-score >60) had an OR of 2.21 (95% CI, 1.30–3.77) compared with those with t-scores of 50 or less (Table 5). We did not find a statistically significant interaction by age, sex, disease phenotype, depressive symptoms, or medication adherence in susceptibility to the effect of sleep disturbance ($P > .05$ for all interactions).

Sleep Disturbance and Risk of Disease Flare in Ulcerative Colitis

In contrast to its effect on CD, we observed no effect between sleep disturbance at baseline and risk of disease flare in UC using either our primary (OR, 1.14; 95% CI, 0.75–1.74) or expanded definitions of disease flare (OR, 1.14; 95% CI, 0.75–1.74) (Table 4).

Discussion

Sleep impairment is common in chronic inflammatory diseases.[13–17,30–37] Biological mechanisms support a potential role for sleep impairment in disease relapse in IBD[15–17]; never-

Table 2. Predictors of Disturbed Sleep at Baseline in the Full Cohort (n = 3173)

Parameter	OR	95% CI
Sex		
Male	Reference	
Female	1.18	0.99–1.41
IBD type		
CD	Reference	
UC	0.74	0.61–0.90
Smoking status		
Never	Reference	
Past	1.28	1.09–1.50
Current	2.17	1.55–3.03
Steroid use		
No	Reference	
Yes	1.33	1.04–1.70
Anti-TNF use		
No	Reference	
Yes	1.03	0.87–1.23
Narcotics		
No	Reference	
Yes	1.65	1.17–2.35
Prior IBD hospitalization		
No	Reference	
Yes	1.06	0.88–1.28
Prior IBD surgery		
No	Reference	
Yes	0.87	0.71–1.07
Active disease[a]		
No	Reference	
Yes	2.61	2.19–3.11
Depressive symptoms[b]		
No	Reference	
Yes	2.75	2.34–3.23

NOTE. Disturbed sleep was defined as having a PROMIS sleep t-score of greater than 50.
[a]Active disease was defined as an SCCAI greater than 2 for patients with UC and an SCDAI greater than 150 for patients with CD.
[b]Depressive symptoms were defined as having a PROMIS depression t-score greater than 50.

Table 3. Characteristics of the Cohort of Patients in Remission at Baseline, Stratified by Sleep Disturbance

	No sleep disturbance, % (n = 932)	Disturbed sleep, % (n = 857)	*P* value
Age, *y*	45 (16)	45 (15)	.67
Age at diagnosis, *y*	30 (14)	30 (13)	.80
Female	69	74	.04
IBD type			.001
CD	68	75	
UC	32	25	
Smoking status			.015
Never	70	64	
Past	26	31	
Current	4	5	
Family history of IBD	24	24	.96
Depressive symptoms[a]	27	50	< .001
Current medication use			
Steroids	7	9	.10
5-aminosalicylates	51	49	.59
Immunomodulators	32	30	.27
Anti-TNF therapy	32	33	.64
Narcotics	3	5	.06
Prior IBD surgery	68	63	.06
Prior hospitalization	40	38	.34
Crohn's phenotype			.11
Inflammatory	42	41	
Stricturing	39	36	
Penetrating	19	24	
Crohn's location			.16
Ileal	36	34	
Colonic	17	13	
Ileocolonic	46	52	
Upper gastrointestinal only	1.6	1.4	
Perianal Crohn's	26	28	.61
UC extent			.33
Proctitis	5	4	
Left-sided colitis	38	45	
Pancolitis	40	38	
Unavailable	16	12	

NOTE. Disturbed sleep was defined as having a PROMIS sleep t-score greater than 50.
[a]Depressive symptoms were defined as having a PROMIS depression t-score greater than 50.

theless there are few published studies examining this hypothesis. By using a large IBD cohort, we showed that CD patients who have impaired sleep quality while in clinical remission have a greater risk of disease flare. We did not identify this effect in UC.

There has been limited research on sleep disturbances in patients with IBD. Ranjbaran et al[15] administered the PSQI to 205 patients with IBD, IBS, or healthy controls and found that patients with IBD, despite being in remission, had significantly prolonged sleep latency, sleep fragmentation, decreased daytime energy, and poor overall sleep quality compared with healthy controls. Sleep quality was associated with lower health-related quality of life.[15] However, the assessment of sleep quality and health-related quality of life was cross-sectional (ie, at the same time point). A larger study of 318 patients with CD and UC showed that 77% of those with active and 49% of those with inactive disease experienced poor sleep as measured with the PSQI.[33] This is nearly identical to our proportion of 76% and 48% of those with active disease or in remission, respectively, using the PROMIS sleep questions.

Sleep impairment in patients with IBD likely is multifactorial. During periods of active disease, the need for nocturnal bowel movements as well as persistence of symptoms such as abdominal pain can result in sleep disturbance. Second, medications frequently used in the setting of active disease such as corticosteroids or narcotics may result in impaired sleep. Third, associated psychiatric comorbidities including depression and anxiety more common in IBD patients[38] also influence sleep quality. However, we found that nearly half the patients in clinical remission also had impaired sleep quality. One hypothesis for this occurrence is the presence of subclinical inflammation in such patients. Injection of IL-1 or TNF-α in animal models suppresses rapid-eye movement sleep and alters sleep patterns.[39] Administration of IL-6 increases non–rapid eye movement sleep and reduces slow-wave sleep during the first half of the sleep cycle.[40] Thus, increased circulating cytokines in patients in clinical remission could contribute to the sleep disturbances.

A key and novel finding of our study was that CD patients who had disturbed sleep even while in clinical remission had nearly a 2-fold increase in likelihood of disease flare at 6 months compared with those with unimpaired sleep. Considerable laboratory evidence supports the biological plausibility of such an association. Sleep deprivation in human beings is associated with an increase in IL-6 and TNF-soluble receptors.[16,17,37] In an elegant study, Tang et al[18] examined the effect of sleep deprivation on susceptibility to DSS-induced colitis. Three groups of 12 mice each were subjected to acute sleep deprivation (24 h), chronic intermittent sleep deprivation (10 d), and no sleep deprivation. Both the acute and chronically sleep-deprived mice

Table 4. Multivariable Analysis of Effect of Sleep Disturbance on Risk of Disease Flare in CD and UC

	CD		UC	
	OR	95% CI	OR	95% CI
Symptomatic flare				
Unadjusted model	1.96	1.45–2.65	1.15	0.76–1.73
Fully adjusted model	2.00[a]	1.45–2.76	1.14[b]	0.75–1.74
Expanded definition of disease flare[c]				
Unadjusted model	1.59	1.25–2.02	1.07	0.69–1.48
Fully adjusted model	1.64[a]	1.27–2.11	1.05[b]	0.70–1.56

NOTE. Disturbed sleep was defined as having a PROMIS sleep t-score greater than 50.
[a]CD multivariable model adjusted for age, sex, prior CD-related surgery and hospitalization, disease behavior and location, current use of steroids, narcotic use, and smoking status (never, past, current).
[b]UC model adjusted for age, sex, prior UC-related hospitalization, current use of steroids, narcotic use, and smoking status (never, past, current).
[c]Expanded definition of disease flare comprised symptomatic flare (SCDAI >150 or SCCAI >2) or new initiation of IBD therapy, new IBD hospitalization, or surgery.

Table 5. Sensitivity Analyses Examining Effect of Sleep Disturbance on Risk of Disease Flare in CD and UC

Model	CD Adjusted OR (95% CI)	UC Adjusted OR (95% CI)
Fully adjusted model[a] medication adherence	(n = 832) 1.63 (1.10–2.42)	(n = 414) 1.17 (0.75–1.84)
Fully adjusted model[a] depressive symptoms	(n = 1206) 1.77 (1.27–2.45)	(n = 481) 1.13 (0.74–1.75)
Alternate definitions for sleep disturbance		
PROMIS sleep t-score >60	1.64 (1.00–2.69)	1.33 (0.57–3.11)
Based on stratification of the PROMIS sleep t-score		
PROMIS sleep t-score <50	Reference	Reference
50 ≤ PROMIS sleep t-score < 60	1.68 (1.20–2.37)	1.10 (0.70–1.72)
PROMIS sleep t-score ≥60	2.21 (1.30–3.77)	1.39 (0.58–3.34)
PROMIS sleep t-score on a continuous scale		
For every 10-point (1 SD) increase	1.46 (1.19–1.79)	1.15 (0.86–1.52)

SD, standard deviation.
[a]CD multivariable model adjusted for age, sex, prior CD-related surgery and hospitalization, disease behavior and location, current use of steroids, narcotic use, and smoking status (never, past, current).

displayed increased susceptibility to DSS colitis and exacerbation of colon inflammation.[18] In addition, TNF-α can influence expression of clock genes, which are involved in regulating intestinal permeability.[17,41] Finally, sleep disturbance is associated with activation of natural killer cells and monocytes.[17,37,41] There is less direct evidence for why we observed an effect on CD but not UC. This is unlikely to be related to statistical power given the similar number of patients with CD or UC in our study, similar rates of active disease, and widely used measures of disease activity. Thus, it is possible that sleep quality as an environmental variable truly does not impact the course of UC. Although the vast number of genetic risk loci for CD and UC are shared, distinct dominant pathways exist in the pathogenesis of each disease.[7] Our findings add to the literature, showing differential effects of various environmental factors on CD and UC—classically smoking and appendectomy. The mechanisms for this divergence in effect for any of the parameters described remained as yet undefined. Identifying such divergence in effects provides a strong impetus to understanding the mechanisms of how the environment may influence different components of the immune system and may help further our understanding of the pathogenesis of these diseases.

There were several implications to our findings. The association between sleep impairment and disease relapse suggests a need to incorporate assessment of sleep quality more routinely in our care of patients with IBD. Identification of sleep disturbances potentially could yield a modifiable risk factor to reduce the likelihood of subsequent disease relapse. There is a need for research on the effectiveness of interventions to improve sleep quality. Also, given the identified association between corticosteroid and narcotic use and sleep quality, it is important for the treating physician to recognize these iatrogenic causes of sleep impairment, potentially modify treatment regimens, or institute interventions to address these treatment-related adverse effects. In addition, the identification of an association between depressive symptoms and sleep quality suggests the need to also continue to incorporate routine screening for psychiatric comorbidity in the management of patients with IBD.

We acknowledge several limitations to our study. First, the CCFA Partners cohort is a volunteer sample of patients. It is possible that the IBD patients enrolled in CCFA Partners may differ from a population-based IBD cohort. Nevertheless, the prevalence of sleep disturbance stratified by disease activity at baseline in our cohort was similar to that identified in the Manitoba population-based IBD cohort, suggesting our results may be generalizable to the larger IBD population. Second, diagnosis of IBD was by self-report. However, according to preliminary results from a validation study in which the treating physicians of randomly selected members of the cohort were mailed a 10-item questionnaire to confirm IBD type and diagnosis, IBD status was confirmed in 96% of the cohort, with matching IBD type confirmed 94% of the time (data not shown).

Third, information on disease phenotype, treatment, and disease activity was by self-report. The bias introduced because of this is unlikely to be differential by sleep impairment. The use of symptom-based disease activity scores also was subject to limitations including influence by superimposed irritable bowel syndrome. However, we attempted to increase the robustness of our results by showing consistency of effect using an alternate definition that relied not just on symptom-based indexes but also relied on more objective measures including initiation of new IBD treatments, surgery, or hospitalizations. We also did not have information on whether patients were on sleep aids at the time of assessment. However, this misclassification also was likely to bias toward the null, making our results a conservative estimate. Both sleep quality and disease activity was assessed for the 1-week period before completion of the questionnaire, allowing for these to be more representative measures than 24-hour recall. As in all observational studies, the possibility of unmeasured confounders exists. We attempted to adjust for most of the known important environmental factors, but were not able to fully capture all possibilities including use of over-the-counter medications. Finally, we examined outcomes up to 6 months after assessment of sleep quality. It is important to continue studies of environmental, behavioral, and lifestyle factors beyond this time frame to identify the long-term impact of such variables.

In conclusion, we identified sleep impairment during remission to be a risk factor for disease flares in CD in a large IBD cohort. Continued research is needed to further understand the mechanisms behind such an association. Furthermore, our findings suggest that sleep quality could be a modifiable factor in reducing risk of disease relapses in IBD. There is a need for further research on the potential benefits of routine assessment of sleep quality as well as intervention-based studies to improve sleep quality in patients with CD, which ultimately may impact patient outcomes.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

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