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

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Abstract

Background & Aims—Impairment of sleep quality is common in patients with inflammatory bowel diseases (IBD; Crohn's disease [CD], 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 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 gender, 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 2-fold increase in risk of active disease at 6 months (adjusted odds ratio [OR], 2.00; 95% confidence interval [CI], 1.45–2.76); no effect was observed in patients with UC (OR 1.14; 95% CI 0.75 – 1.74). These findings persisted in a number of sensitivity analyses.

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Conflicts of Interest: None

Conclusion—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

INTRODUCTION

Inflammatory bowel diseases (IBD; Crohn's disease (CD), 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 could also be modifiable and reduce the risk of active disease.

Sleep disturbances are common in the population and 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 support the biological plausibility that disturbed sleep may be a modifiable behavioral risk factor for disease relapse in IBD patients[12–17]. Patients with IBD, even during period 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-α (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) affect sleep[17]. In human studies of juvenile idiopathic arthritis, administration of anti-TNF biologic therapy improves sleep quality in addition to the achieving disease remission[19]. There have been no prior studies 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: (1) to identify predictors of sleep quality among patients with CD and UC; and (2) to examine if sleep quality during remission is associated with 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 (IC) who were older than age 18 years were invited to participate in the study through the CCFA email 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 were then invited to complete a follow-up questionnaire at 6 months after enrollment,

ascertaining 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 were then held among those with sleep disorders and normal sleepers, and the question bank 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 which demonstrated excellent measurement properties. The short form of the PROMIS questionnaire has comparable performance to 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 four questions that examined sleep quality. Respondents were asked if over the past 7 days, (1) their sleep quality was good, (ii) their sleep was refreshing, (iii) they had a problem with their sleep, or (iv) 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 mean of 50 and a standard deviation (SD) of 10 (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 > 50 were considered as having disturbed sleep while T-scores < 50 were considered normal. In sensitivity analyses, we defined disturbed sleep as requiring a T-score > 60, and as a continuous variable. To validate our use of the PROMIS questions, a subset of patients were also administered the PSQI. Correlation between the two questionnaires was examined using the Pearson correlation co-efficient.

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 hospitalization or surgery, as well as medications for treatment of IBD including 5-aminosalicylates (oral), corticosteroids (oral), immunomodulators, and biologic 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]. A SCDAI < 150 or an SCCAI ≤ 2 indicated clinical remission for CD and UC respectively with values above this threshold indicating active disease[21]. Baseline depressive symptoms were ascertained using a PROMIS depression T-score scored similar to the sleep T-score. Medication adherence was assessed using the Morisky Medication Adherence Scale (MMAS)[29]. Smoking status was stratified as never, past, and current smoking at the time of baseline questionnaire with very few (< 10 patients) describing a change in their smoking status at 6 months.

Outcomes

Our primary outcome was presence of active disease at 6 months. This was defined as SCDAI > 150 for CD or SCCAI > 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 above the threshold above, or initiation of a new IBD medication, 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 > 150 and a 100-point increase in SCDAI from baseline for CD and an SCCAI > 5 for UC.

Statistical Analysis

All analysis was performed using Stata 11.0 (StataCorp, College Station, TX). Continuous variables were summarized using means and standard deviations and compared using the t-test. Categorical 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 3,173 patients. Next, among participants who were in clinical remission at baseline (n=1,798), we evaluated the association between sleep disturbance during remission and risk of disease flare. Variables significant in the univariate analyses at p-value < 0.10 were included in the final multivariable regression models where a p-value < 0.05 indicated independent statistical significance. The study was approved by the Institutional Review Board (IRB) of Massachusetts General Hospital. The CCFA Partners cohort study was approved by the IRB of University of North Carolina, Chapel Hill.

RESULTS

Study Cohort

A total of 4,366 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 (IQR) 6.5 – 7.8 months). After excluding patients with a stoma or pouch (as 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 3,173 patients (Figure 1). A total of 1,798 patients (507 UC, 1291 CD) were in clinical remission at baseline. Patients excluded from the study were similar to the final cohort in age and gender, were slightly more likely to have UC, and had a lower frequency of prior hospitalization or surgery.

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 T. Overall, there was a strong correlation between the two scores (correlation co-efficient 0.80, p < 0.0001). 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 was 4 and 9 respectively (p < 0.0001). Four-fifths (82%) of patients with sleep-T scores above the median and 98% of those with sleep-T scores above 60 had a PSQI > 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 < 0.05 for

all) (Table 1). They were also more likely to be currently using systemic corticosteroids, narcotics, or anti-TNF biologic therapies, and were more likely to have ever required an IBD-related hospitalization or surgery. Over half the patients with sleep disturbance had active disease (55%) compared to a quarter of those with no sleep disturbance (26%) ($p < 0.001$). Conversely, 48% of those in remission at baseline had sleep T-scores > 50 compared to 76% of those with active disease ($p < 0.001$). 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), while female gender, 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 risk of sleep disturbance.

Sleep disturbance and risk of disease flare in Crohn's disease

Half of the 1,291 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 to 12% of those without disturbed sleep (OR 1.96, 95% CI 1.45 – 2.65). On multivariable analysis, presence of sleep disturbance was associated with twofold increase in risk of disease flare at 6 months (OR 2.00, 95% CI 1.45 – 2.76) (Table 4). 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 a SCDAI > 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 below our remission threshold influencing sleep status and likelihood of flare, in a sensitivity analysis we defined remission as SCDAI ≤ 200, and active disease on follow-up as values above this threshold. The association with sleep impairment and subsequent active disease was further strengthened on 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 and follow-up surveys were significantly more likely to have active disease at the follow-up (OR 2.37, 95%I 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 MMAS (data available on 832 patients) (OR 1.63, 95% CI 1.10 – 2.42) or depressive symptoms (data available on 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 to those with T-scores of 50 or less (Table 5). We did not find a statistically significant interaction by age, gender, disease phenotype, depressive symptoms, or medication adherence in susceptibility to the effect of sleep disturbance ($p > 0.05$ 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]. Biologic mechanisms support a potential role for sleep impairment in disease relapse in IBD[15–17]; nevertheless there are no published studies examining this hypothesis. Using a large IBD cohort, we demonstrate 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.* 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 to healthy controls[15]. Sleep quality was associated with lower health-related quality of life (HRQoL)[15]. However the assessment of sleep quality and HRQoL was cross-sectional (i.e. at the same time point). A larger study of 318 patients with CD and UC demonstrated that 77% of those with active and 49% of those with inactive disease experienced poor sleep measured using the PSQI[33]. This is nearly identical to our proportion of 76% and 48% of those with active disease or in remission using the PROMIS sleep questions.

Impairment of sleep in patients with IBD is likely 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 co-morbidities 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 (REM) sleep and alters sleep patterns[39]. Administration of IL-6 increases non-rapid eye movement sleep (NREM) and reduces slow wave sleep during the first half of the sleep cycle[40]. Thus, elevated circulating cytokines in patients in clinical remission could contribute to the sleep disturbances.

A key and novel finding of our study is that CD patients who had disturbed sleep even while in clinical remission had nearly two-fold increase in likelihood of disease flare at 6 months compared to those with unimpaired sleep. Considerable laboratory evidence supports the biologic plausibility of such an association. Sleep deprivation in humans is associated with an increase in IL-6 and TNF soluble receptors[16, 17, 37]. In an elegant study, Tang *et al.* examined the effect of sleep deprivation on susceptibility to DSS-induced colitis[18]. Three groups of twelve mice each were subjected to acute sleep deprivation (24 hours), chronic intermittent sleep deprivation (10 days), and no deprivation. Both the acute and chronically sleep deprived mice displayed increased susceptibility to DSS colitis and exacerbation of colon inflammation[18]. Additionally, 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 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 ulcerative colitis. While 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 demonstrating differential effect 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 yet undefined. Identifying such divergence in

effects provides strong impetus to understanding the mechanisms how the environment may influence different components of the immune system, and may help further our understanding of the pathogenesis of these diseases.

There are 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 could potentially yield a modifiable risk factor to reduce the likelihood of subsequent disease relapse. There is 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. As well, identification of an association between depressive symptoms and sleep quality suggests the need to also continue to incorporate routine screening for psychiatric co-morbidity 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 is 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 due to this is unlikely to be differential by sleep impairment. The use of symptom-based disease activity scores is also subject to limitations including influence by superimposed irritable bowel syndrome. However, we attempted to increase the robustness of our results by demonstrating consistency of effect using an alternate definition that relied not just on symptom-based indices but also 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 is also likely to bias towards the null, making our results a conservative estimate. Both sleep quality and disease activity was assessed for the 1 week period prior to completion of the questionnaire, allowing for these to be more representative measures that 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 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 may ultimately impact patient outcomes.

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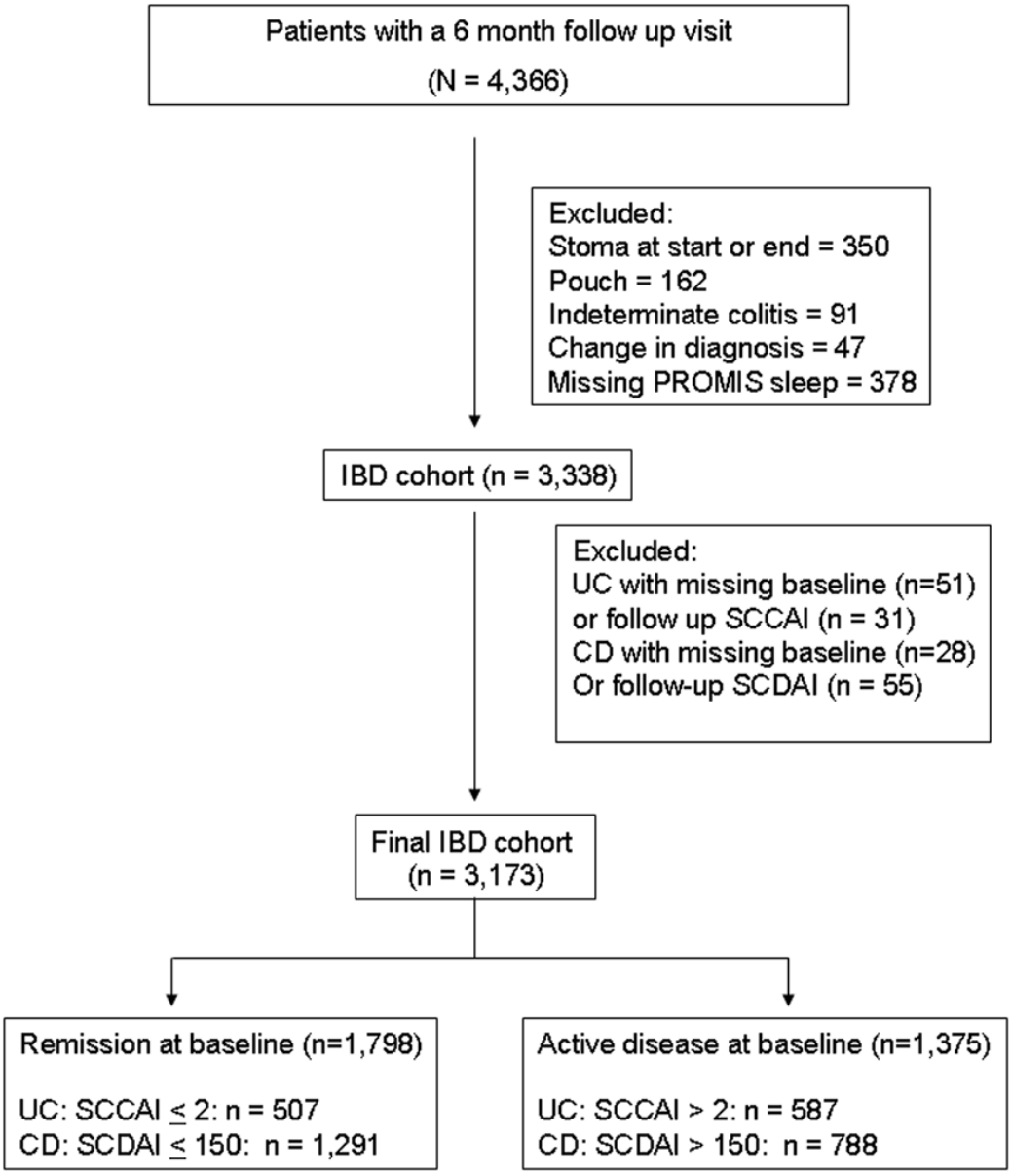

Figure 1. Flow chart establishing study cohort
PROMIS – NIH Patient Reported Outcomes Measurement Information Systems
IBD – Inflammatory bowel disease
SCDAI – short Crohn's disease activity index, SCCAI – simple clinical colitis activity index

Table 1

Baseline characteristics of the study cohort

	No sleep disturbance (n = 1,267) %	Disturbed sleep (n = 1,906) %	p-value
Median age in years (IQR)	43 (31 – 57)	45 (32 – 56)	0.90
Median age at diagnosis (IQR)	26 (20 – 39)	27 (20 – 39)	0.94
Female	70	75	0.005
IBD type			0.003
Crohn's disease	62	68	
Ulcerative colitis	38	32	
Smoking status			< 0.001
Never	68	61	
Past	28	32	
Current	4	7	
Family history of IBD	24	22	0.06
Depressive symptoms[‡]	33	63	< 0.001
Current medication use			
Steroids	10	17	< 0.001
5-aminosalicylates	52	49	0.10
Immunomodulators	32	30	0.41
Anti-TNF biologics	31	34	0.04
Narcotics	4	11	< 0.001
Prior IBD surgery	30	35	0.005
Prior hospitalization	59	63	0.01
Crohn's Phenotype			0.05
Inflammatory	42	37	
Stricturing	38	39	
Penetrating	19	23	
Crohn's Location			0.004
Ileal	34	30	
Colonic	17	13	
Ileocolonic	47	56	
Upper GI only	2	1	
Perianal Crohn's	26	30	0.09
UC Extent			0.65
Proctitis	5	5	
Left-sided colitis	43	42	
Pancolitis	37	40	
Unavailable	15	13	
Active disease[†]	26	55	< 0.001

IBD – Inflammatory bowel disease; CD – Crohn's disease; UC – ulcerative colitis; IQR – interquartile range

[‡] Depressive symptoms were defined as having a PROMIS depression T-score > 50

† Active disease was defined as SCCAI > 2 for patients with UC and a SCDAI > 150 for patients with CD

Table 2

Predictors of disturbed sleep[//] at baseline in the full cohort (n = 3,173)

Parameter	Odds Ratio	95% confidence interval
Sex		
Male	Reference	
Female	1.18	0.99 – 1.41
IBD type		
Crohn's disease	Reference	
Ulcerative colitis	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[†]		
No	Reference	
Yes	2.61	2.19 – 3.11
Depressive symptoms[‡]		
No	Reference	
Yes	2.75	2.34 – 3.23

[//] Disturbed sleep was defined as having a PROMIS sleep T-score > 50

[‡] Depressive symptoms were defined as having a PROMIS depression T-score > 50

[†] Active disease was defined as SCCAI > 2 for patients with UC and a SCDAI > 150 for patients with CD

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	45 (16)	45 (15)	0.67
Age at diagnosis	30 (14)	30 (13)	0.80
Female	69	74	0.04
IBD type			0.001
CD	68	75	
UC	32	25	
Smoking status			0.015
Never	70	64	
Past	26	31	
Current	4	5	
Family history of IBD	24	24	0.96
Depressive symptoms[‡]	27	50	< 0.001
Current medication use			
Steroids	7	9	0.10
5-aminosalicylates	51	49	0.59
Immunomodulators	32	30	0.27
Anti-TNF therapy	32	33	0.64
Narcotics	3	5	0.06
Prior IBD surgery	68	63	0.06
Prior hospitalization	40	38	0.34
Crohn's Phenotype			0.11
Inflammatory	42	41	
Stricturing	39	36	
Penetrating	19	24	
Crohn's Location			0.16
Ileal	36	34	
Colonic	17	13	
Ileocolonic	46	52	
Upper GI only	1.6	1.4	
Perianal Crohn's	26	28	0.61
UC Extent			0.33
Proctitis	5	4	
Left-sided colitis	38	45	
Pancolitis	40	38	
Unavailable	16	12	

IBD – Inflammatory bowel disease; CD – Crohn's disease; UC – ulcerative colitis; SD – standard deviation

[//]Disturbed sleep was defined as having a PROMIS sleep T-score > 50

[‡]Depressive symptoms were defined as having a PROMIS depression T-score > 50

Table 4

Multivariable analysis of effect of sleep disturbance[//] on risk of disease flare in Crohn's disease and Ulcerative colitis

	Crohn's disease		Ulcerative colitis	
	Odds ratio	**95% confidence interval**	**Odds ratio**	**95% confidence interval**
Symptomatic flare				
Unadjusted model	1.96	1.45 – 2.65	1.15	0.76 – 1.73
Fully adjusted model	2.00[+]	1.45 – 2.76	1.14[†]	0.75 – 1.74
Expanded definition of disease flare[‡]				
Unadjusted model	1.59	1.25 – 2.02	1.07	0.69 – 1.48
Fully adjusted model	1.64[+]	1.27 – 2.11	1.05[†]	0.70 – 1.56

[//] Disturbed sleep was defined as having a PROMIS sleep T-score > 50

[+] Crohn's disease multivariable model adjusted for age, gender, prior CD related surgery and hospitalization, disease behavior and location, current use of steroids, narcotic use, and smoking status (never, past, current)

[†] Ulcerative colitis model adjusted for age, gender, prior UC related hospitalization, current use of steroids, narcotic use, and smoking status (never, past, current)

[‡] 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 Crohn's disease and Ulcerative colitis

	Crohn's disease	**Ulcerative colitis**
Model	**Adjusted OR (95% confidence interval)**	**Adjusted OR (95% confidence interval)**
Fully adjusted model + medication adherence	(n = 832) 1.63 (1.10 – 2.42)	(n = 414) 1.17 (0.75 – 1.84)
Fully adjusted model + 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; OR – Odds ratio; PROMIS – Patient Reported Outcomes Measurement Information Systems

[+] Crohn's disease multivariable model adjusted for age, gender, prior CD related surgery and hospitalization, disease behavior and location, current use of steroids, narcotic use, and smoking status (never, past, current)

[†] Ulcerative colitis model adjusted for age, gender, prior UC related hospitalization, current use of steroids, narcotic use, and smoking status (never, past, current)