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High C - reactive protein is Associated with Poor Sleep Quality Independent of Nocturnal Symptoms in Patients with Inflammatory Bowel Disease

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Abstract

Background—Sleep disruption is common in inflammatory bowel diseases (IBD). However, studies demonstrating a similar prevalence in irritable bowel syndrome (IBS) suggest that nighttime disruption due to diarrhea and abdominal pain may be key drivers of poor sleep quality. Whether inflammation is associated with poor sleep independently has not been examined previously.

Methods—This single center study included subjects with IBD recruited to an ongoing prospective registry who completed a questionnaire assessing sleep quality and mood. Inflammatory marker levels (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)) and clinical disease activity including nighttime disruption on the day of enrollment was obtained from the medical record. Logistic regression models were used to identify predictors of sleep quality.

Results—The study included 131 subjects (72 women) with a median age of IBD diagnosis of 25 years. Twenty-three subjects (19%) had a high C-reactive protein level (≥ 8 mg/dL). Poor sleep was more common in those with high CRP levels than with normal values (70% vs. 39%, $p=0.009$). This association remained significant on multivariate analysis (Odds ratio (OR) 4.12, 95% confidence interval (CI) 1.38 – 12.29). Adjusting for the presence of nighttime disruption did not significantly alter this association (OR 3.16, 95% CI 1.01 – 9.90). High CRP correlated with poor sleep even in patients not experiencing nocturnal symptoms ($n=101$, OR 4.89, 95% CI 1.24 – 19.36).

Conclusion—High CRP is associated with poor sleep quality in IBD independent of the presence of nighttime disruptions, suggesting a relationship exists between circulating inflammatory markers and sleep.

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Keywords

sleep; inflammatory bowel disease; c-reactive protein; inflammation

INTRODUCTION

The inflammatory bowel diseases (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), are chronic intestinal disorders that affect an estimated 1.5 million people in the United States¹. IBD incurs a significant physical and financial burden on patients with many requiring hospitalization or surgery at some point during the course of their disease². In addition, IBD also has more subtle effects on wellbeing that impairs quality of life and work productivity^{3, 4}. Though several genetic and immunologic factors that contribute to an individual's likelihood of contracting IBD have been uncovered, its cause remains elusive^{1, 5}. The role of the external environment in influencing risk of disease and natural history is being increasingly recognized and several factors that increase risk of disease or influence behavior have been described from observational studies⁶⁻⁸. Two such risk factors that appear to have a bidirectional association with IBD, both by modifying risk and natural history of disease, but at the same time being influenced in their occurrence by inflammation and active disease, are sleep impairment and depression⁹⁻¹⁴.

Sleep problems are remarkably common in society and have been linked to a number of diseases and stressors including acute and chronic illness, physical and psychiatric disorders^{10, 15-20}. In the context of IBD, recent work has suggested both depression and sleep impairment to be common, increase risk of relapses, and even precede a diagnosis of IBD⁹⁻¹⁴. One possible explanation for the link between depression, impaired sleep quality, and IBD would be that the former two are symptoms of exacerbations of the latter. Several studies have reported a similar prevalence of sleep disturbance in those with IBD as irritable bowel syndrome with such impairment in sleep being strongly influenced by the presence of nocturnal symptoms of diarrhea and abdominal pain in both diseases^{21, 22}. However, impaired sleep quality may be common even in periods of clinical remission^{10, 21, 23}. The mechanism behind such an effect is unclear but may be related to the direct effect of circulating pro-inflammatory cytokines on the central nervous system²³⁻²⁹. Prior studies examining impairment of sleep quality in IBD have not examined the effect of inflammation independent of disruption by nocturnal symptoms. Furthermore, they have relied mainly on use of clinical symptoms to define active disease which is open to confounding posed by the overlay of functional symptoms in such patients.

Consequently, we performed the following study in a well phenotyped IBD cohort with structured assessment of sleep and depression to examine if circulating inflammatory markers correlate with impaired sleep and mood independent of symptoms. We hypothesized that a higher inflammatory burden would result in impaired sleep independent of the presence of nocturnal symptoms.

METHODS

Study Population

This was a single center study that included subjects recruited to the ongoing Prospective Registry for IBD Study at Massachusetts General Hospital (PRISM). Subjects include adults 18 years or older, with CD or UC diagnosed by their treating gastroenterologist according to accepted criteria. After providing informed consent, patients completed their enrollment by providing details regarding demographics, disease and treatment history. Disease diagnosis, location, and phenotype were confirmed by the treating gastroenterologist. Patient information on intake questionnaires was supplemented by review of the electronic medical records.

Assessment of sleep, depression, and inflammatory markers

A consecutive subset of patients who were enrolled in PRISM was invited to complete an 8-item questionnaire regarding their sleep quality and a 16-item questionnaire regarding their mood. These questions were derived from the National Institutes of Health (NIH) Patient-Reported Outcome Measurement Information System (PROMIS) bank of questions (www.nihpromis.org, Accessed 10 May 2014)^{30, 31}. Details about their derivation have been published previously. In brief, these questions are developed from an initial pool of items identified from candidate citations that were pilot tested in a national sample of participants. Items from the PROMIS question bank have demonstrated validity in the areas of content, construct, criterion, and responsiveness. For the purpose of this study, patients were asked questions regarding their sleep quality and mood, both encompassing the past seven days (Appendix 1). The questionnaires were scored per standard procedures recommended for scoring the PROMIS questions with higher values representing greater impairment of sleep quality or more depressed mood^{30, 31}. Values above the median for the cohort indicated poor sleep or depressed mood.

Objective assessment of inflammatory activity included the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Only subjects who had these values measured on the day they filled out the sleep and mood questionnaires were included in the study. ESR and CRP levels were defined as being elevated when they were above 20mm/hr and 8mg/dL respectively in accordance with normal values for our laboratory.

Covariates

Information on each subject's sex, age at diagnosis, duration of disease, and smoking status was assessed by medical records review, self-report, and enrollment interview by a trained research coordinator. Disease location and behavior in CD and disease extent in UC was classified according to the Montreal classification³². Use of medications including immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) and anti-tumor necrosis factor- α biologics (anti-TNF; infliximab, adalimumab, certolizumab pegol) was obtained. Disease activity was recorded based on their physician assessment of their symptoms on the day they completed the sleep and mood questionnaires. Patients were classified as having clinically active disease or in remission by the treating gastroenterologist, and the presence of nighttime symptoms in the week prior to the visit was noted.

Statistical Analysis

Continuous variables were summarized using means and standard deviations with use of medians and interquartile ranges (IQR) when skewed. Categorical variables were expressed as proportions. In our primary analysis, we performed univariate logistic regression models with poor sleep defined as values above the median as a dichotomous outcome. Variables that were found to have a statistically significant effect at $p < 0.2$ were included in our multivariate logistic regression model examining the association between elevated inflammatory markers and poor sleep adjusting for relevant confounders. To test the robustness of our findings, we repeated the analysis using a linear regression model with the sleep score as a continuous variable. Subgroup analyses were performed excluding those with nocturnal symptoms, and on including the presence of nocturnal symptoms in the multivariate model to see if the association between inflammation and sleep was mediated through nighttime sleep disruption. Data was analyzed using Stata 13.0 (StataCorp, College Station, TX). The Institutional Review Board of Partners Healthcare approved this study.

RESULTS

A total of 131 patients (78 CD; 53 UC) who had completed questionnaires on sleep and mood and had concurrent serum inflammatory markers available were included in this study (Table 1). The median age of diagnosis was 25 years (interquartile range (IQR) 18 – 37 years) and a slight majority (55%) of the cohort was female. Among those with CD, a third had inflammatory disease (37%) while 22% and 41% had stricturing or penetrating disease phenotype respectively. Two-thirds of those with UC had pancolitis (68%). Twenty-nine patients had at least one IBD-related surgery (22%) and seventy-three had current or past use of anti-TNF therapy (56%). None of the patients had obstructive sleep apnea or other diagnosed disorders of sleep. None were on prescription antidepressants or sleep aids.

The median CRP and ESR levels of patients were 2 mg/dL (IQR 0.8 – 6.2) and 8mm/hr (IQR 5 – 16) with good correlation between the two inflammatory markers (correlation coefficient $\rho=0.57$, $p < 0.001$). Twenty-three patients (19%) had an elevated CRP and 35 patients (26%) had an elevated ESR. The median sleep score in our cohort was 10 (IQR 5 – 16). Fifty-nine subjects (44%) who had sleep scores above the median were considered to have poor sleep. The median mood score was 5 (IQR 1 – 14). Fifty-five patients (42%) were clinically active and the remaining 58% were in clinical remission. The mean CRP level in those with clinical active disease was significantly greater than those in remission (12.3mg/dL vs. 2.9mg/dL, $p=0.0013$).

Predictors of impaired sleep

Poor sleep was more common in those with high CRP levels than with normal values (70% vs. 39%, Odds ratio (OR) 3.52, 95% CI 1.33 – 9.33, $p=0.009$). Similarly, presence of clinically active disease (OR 3.96, 95% CI 1.89 – 8.27) was associated with poor sleep. However, we did not find an association between an elevated ESR and poor sleep (OR 1.72, 95% CI 0.79 – 3.75) (Table 2). Type of IBD, age at diagnosis, gender, disease phenotype, prior surgery, and need for anti-TNF therapy were also not associated with poor sleep. Each 1-point increase in the depression score was associated with increased likelihood of poor

sleep (OR 1.10, 95% CI 1.05 – 1.15). There was no difference in BMI between those with poor sleep (25.6kg/m²) compared to those with normal sleep (26.3kg/m², p=0.57). Since neither IBD type nor phenotype was found to have a significant effect on sleep, further analyses pooled together all subjects.

In a multivariate logistic regression model, only high CRP (4.12, 95% CI 1.38 – 12.29) and increasing depression score (OR 1.10, 95% CI 1.05 – 1.15) were independently associated with poor sleep quality. As there was a high degree of co-linearity between clinically active disease and elevated CRP (81% of those with clinically active disease also had a high CRP, $\rho=0.36$, $p < 0.001$), we were not able to include them in the same multivariate model. Examining the sleep score as a continuous variable, elevated CRP was associated with a 3 point higher sleep score when adjusting for potential confounders (+3.2 points, 95% CI +0.31 to + 6.13).

To examine if the association with elevated CRP was mediated through the presence of nighttime symptoms and sleep disruption, we repeated the multivariate analysis in those who reported no nocturnal symptoms (n=101). High CRP remained independently associated with poor sleep quality in this cohort (OR 4.89, 95% CI 1.24 – 19.36) when adjusting for depression and smoking status. The association between elevated CRP and poor sleep also remained independent of nocturnal symptoms when adjusting for it in the multivariate model (OR 3.16, 95% CI 1.01 – 9.90).

DISCUSSION

Sleep impacts chronic inflammation^{15, 17, 23, 26, 28, 29, 33, 34}. In relevance to IBD, impaired sleep quality is common and is associated with disease activity^{10, 13, 21, 22, 25, 35, 36}. However, to what extent impairment in sleep quality is due to frequent nocturnal disruptions from symptoms compared to an effect of a systemic pro-inflammatory state is unclear. In this study, we demonstrate that elevated C-reactive protein, a circulating marker of systemic inflammation, is independently associated with impaired sleep quality even in the absence of nocturnal symptoms, supporting a role for inflammation in disrupting sleep in IBD.

The role of sleep in patients with IBD is an area receiving increasing attention^{10, 25, 36–39}. In comparison to healthy controls, patients with IBD report significantly greater sleep impairment^{21, 22}. However in several studies, the impairment of sleep quality in IBD is similar to those with IBS, a chronic gastrointestinal disorder without overt systemic inflammation^{21, 22} questioning the relative contribution of symptoms and inflammation. Ranjbaran *et al.* administered the Pittsburgh Sleep Quality Index (PSQI), a validated measure of sleep quality, to 205 subjects including 80 with inactive IBD and 24 with IBS. Both subjects with IBD and IBS reported increased sleep latency and greater frequency of sleep interruption (IBD 70%, IBS 88%)²². In addition, the most common reason for poor sleep quality due to frequent awakening at night was the need to use the bathroom (81% in IBD and 87% of IBS) and abdominal pain (44% of IBD and 71% of IBS). This is consistent with other studies where symptomatic disease activity in IBD was the strongest predictor of impairment of sleep¹⁰.

Intriguing epidemiology and laboratory data support a bidirectional association between sleep and disease activity and an impact of circulating inflammatory markers on sleep quality. In a large prospective cohort study including 151,871 women followed over 24 years, we demonstrated that both short and long duration of sleep was independently associated with increased risk of incident UC³⁵. In a different cohort, while disease related symptoms was a key determinant of impaired sleep quality, poor sleep even during remission was associated with an increased risk of symptomatic disease flares at 6 months¹⁰. Experimentally, interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor (TNF) directly induces fatigue and sleep^{22–24, 38–40}. Intravenous or intra-cerebroventricular injections of recombinant TNF suppresses rapid-eye-movement (REM sleep)³⁴. In contrast, antibodies against TNF- α improve sleep quality when administered to patients with juvenile idiopathic arthritis⁴¹. In our present study, we were not able to examine the association between CRP and sleep quality independent of clinical disease activity as most patients with an elevated CRP also had clinically active disease. Sleep fragmentation has been associated with increased inflammatory cytokines in mouse models and human studies^{42–44}. In this study, we were able to demonstrate that the sleep disruption in IBD is not solely due to nighttime disruptions symptoms as noted in previous studies²² since the association between elevated CRP and poor sleep persisted in the group with no reported nocturnal symptoms.

Another significant association in our study is the relationship between sleep and depression. Large studies have found that symptoms of depression are most likely to be experienced by individuals who sleep either too little or too much, and decreased sleep quality is directly associated with depressive symptoms^{27, 45–47}. In a cohort study including 3,173 patients in the Crohn's and Colitis Foundation of America's (CCFA) Partners cohort, co-existing depression was a strong predictor of impaired sleep quality¹⁰. Depression has been associated with increased risk of incident disease as well as disease relapses^{9, 12–14, 46}, acting independently through various mechanisms including elevation of circulating inflammatory markers, alteration of the function and number of CD4 and CD8 lymphocytes, and through its effect of the autonomic nervous system and hypothalamus-pituitary-adrenal axis^{23, 29, 36–38}. Despite the co-existence of the two, the association between sleep and CRP persists after adjustment for mood suggesting that these two related factors potentially exert independent effects.

Our study has several strengths and implications. Use of validated sleep measures such as the NIH PROMIS question bank increases the face validity of our assessment of sleep quality and mood. The NIH PROMIS bank of questions have been carefully validated and are reliable for use either in the aggregate with the entire bank of questions, or with inclusion of specific question sets like the 8-item question bank used for the purpose of this study. While other sleep questionnaires like the Pittsburgh Sleep Quality Index (PSQI) may be more widely studied and validated, in a previous study, we demonstrated a strong correlation (co-efficient 0.80, $p < 0.0001$) between the two questionnaires¹⁰, despite differing time periods of study. Additionally, in a previous study, 82% of patients with a T-score above the median also had an abnormal score on the Pittsburgh Sleep Quality Index, validating this cut-off threshold¹⁰. For the purpose of this study, night time disruption was assessed without formal structured questionnaires during the clinical encounter. Future studies may need to develop more nuanced methods to identify nighttime disruption due to

active symptoms. Additionally, our focus on objective inflammatory markers provides greater certainty as to the presence of active disease in our subjects as opposed to symptom based disease activity scores. Reliance on symptoms may be open to confounding by co-existing functional symptoms. Additionally, objective inflammatory markers also allow us to potentially identify an effect of subclinical active disease as well. Few of the patients were on systemic steroids at the time of completion of this questionnaire. We did not have routine information on extraintestinal symptoms at the time of completion of this questionnaire. However, we do not believe either of these two variables to have differentially affected the association observed in our study. In conjunction with prior literature, our findings support an association between disease activity and sleep in IBD that is not solely due to nighttime awakenings and may be mediated by systemic inflammation. Further studies examining such an effect independent of clinical symptoms and in those with subclinical active disease are warranted. As well, our findings support the importance of routinely assessing sleep duration, quality, and disruption in patients with IBD. Whether this needs to be addressed through behavioral modification or requires pharmacologic therapy, and the impact of such interventions on longitudinal disease activity require further study. There is also an important unmet need to address the impact of nighttime disruption on next day cognitive and psychomotor functioning in patients with IBD.

We acknowledge several limitations to our study that strengthen the necessity for further research in this field. Our study was done at a single referral IBD center and consequently may be skewed towards more severe disease. Our sample size was small but remains one of the largest studies to examine correlation between sleep and C-reactive protein in IBD. As the vast majority of patients who had an elevated C-reactive protein also had clinical symptoms, we were not able to independently examine the effect of symptoms and CRP on sleep quality. Small prospective cohorts have suggested an association between histologic inflammation and sleep quality suggesting that clinically latent disease may have an impact on sleep quality²⁵. Larger studies are required to robustly demonstrate this finding. Nocturnal disruptions were noted through review of the medical records, and consequently may have resulted in misclassification. However, one would expect such misclassification to bias towards the null, supporting the robustness of our findings. We did not have information on use of sleep aids or other medications that may influence sleep quality.

In conclusion, we demonstrate that elevated C-reactive protein levels were associated with impaired sleep quality in patients with inflammatory bowel disease, and this association was independent of the presence of nocturnal symptoms. This suggests that nighttime disruption of sleep is not the sole mechanism for poor sleep quality in patients with IBD and further studies examining the bidirectional association between sleep and inflammation in IBD are warranted.

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REFERENCES

1. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med.* 2009; 361:2066–2078. [PubMed: 19923578]
2. Bernstein CN, Loftus EV Jr, Ng SC, et al. Hospitalisations and surgery in Crohn's disease. *Gut.* 2012; 61:622–629. [PubMed: 22267595]
3. Ghosh S, Mitchell R. Impact of inflammatory bowel disease on quality of life: Results of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) patient survey. *J Crohns Colitis.* 2007; 1:10–20. [PubMed: 21172179]
4. Ananthakrishnan AN, Weber LR, Knox JF, et al. Permanent work disability in Crohn's disease. *Am J Gastroenterol.* 2008; 103:154–161. [PubMed: 18076736]
5. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* 2012; 491:119–124. [PubMed: 23128233]
6. Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology.* 2011; 140:1785–1794. [PubMed: 21530745]
7. Danese S, Fiocchi C. Etiopathogenesis of inflammatory bowel diseases. *World J Gastroenterol.* 2006; 12:4807–4812. [PubMed: 16937461]
8. Ananthakrishnan AN. Environmental Risk Factors for Inflammatory Bowel Diseases: A Review. *Dig Dis Sci.* 2014
9. Ananthakrishnan AN, Khalili H, Pan A, et al. Association between depressive symptoms and incidence of Crohn's disease and ulcerative colitis: results from the Nurses' Health Study. *Clin Gastroenterol Hepatol.* 2013; 11:57–62. [PubMed: 22944733]
10. Ananthakrishnan AN, Long MD, Martin CF, et al. Sleep disturbance and risk of active disease in patients with Crohn's disease and ulcerative colitis. *Clin Gastroenterol Hepatol.* 2013; 11:965–971. [PubMed: 23376797]
11. Bernstein CN, Singh S, Graff LA, et al. A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol.* 2010; 105:1994–2002. [PubMed: 20372115]
12. Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut.* 2008; 57:1386–1392. [PubMed: 18390994]
13. Graff LA, Vincent N, Walker JR, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis.* 2011; 17:1882–1889. [PubMed: 21830266]
14. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? *Am J Gastroenterol.* 2009; 104:1298–1313. quiz 1314. [PubMed: 19337242]
15. Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. *Sleep Med Rev.* 2008; 12:211–228. [PubMed: 18486034]
16. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med.* 2003; 163:205–209. [PubMed: 12546611]
17. Brass SD, Duquette P, Proulx-Therrien J, et al. Sleep disorders in patients with multiple sclerosis. *Sleep Med Rev.* 2010; 14:121–129. [PubMed: 19879170]
18. Cappuccio FP, Cooper D, D'Elia L, et al. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J.* 2011; 32:1484–1492. [PubMed: 21300732]
19. Cappuccio FP, D'Elia L, Strazzullo P, et al. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep.* 2010; 33:585–592. [PubMed: 20469800]
20. Chandrasekhara PK, Jayachandran NV, Rajasekhar L, et al. The prevalence and associations of sleep disturbances in patients with systemic lupus erythematosus. *Mod Rheumatol.* 2009; 19:407–415. [PubMed: 19521744]
21. Keefer L, Stepanski EJ, Ranjbaran Z, et al. An initial report of sleep disturbance in inactive inflammatory bowel disease. *J Clin Sleep Med.* 2006; 2:409–416. [PubMed: 17557469]
22. Ranjbaran Z, Keefer L, Farhadi A, et al. Impact of sleep disturbances in inflammatory bowel disease. *J Gastroenterol Hepatol.* 2007; 22:1748–1753. [PubMed: 17914945]
23. Ranjbaran Z, Keefer L, Stepanski E, et al. The relevance of sleep abnormalities to chronic inflammatory conditions. *Inflamm Res.* 2007; 56:51–57. [PubMed: 17431741]

24. Abedelmalek S, Souissi N, Chtourou H, et al. Effects of partial sleep deprivation on proinflammatory cytokines, growth hormone, and steroid hormone concentrations during repeated brief sprint interval exercise. *Chronobiol Int.* 2013; 30:502–509. [PubMed: 23281720]
25. Ali T, Madhoun MF, Orr WC, et al. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. *Inflamm Bowel Dis.* 2013; 19:2440–2443. [PubMed: 23945186]
26. Axelsson J, Rehman JU, Akerstedt T, et al. Effects of sustained sleep restriction on mitogen-stimulated cytokines, chemokines and T helper 1/ T helper 2 balance in humans. *PLoS One.* 2013; 8:e82291. [PubMed: 24349251]
27. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med.* 2007; 3:519–528. [PubMed: 17803017]
28. Fragiadaki K, Tektonidou MG, Konsta M, et al. Sleep disturbances and interleukin 6 receptor inhibition in rheumatoid arthritis. *J Rheumatol.* 2012; 39:60–62. [PubMed: 22133618]
29. Rohleder N, Aringer M, Boentert M. Role of interleukin-6 in stress, sleep, and fatigue. *Ann N Y Acad Sci.* 2012; 1261:88–96. [PubMed: 22823398]
30. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep.* 2010; 33:781–792. [PubMed: 20550019]
31. Yu L, Buysse DJ, Germain A, et al. Development of short forms from the PROMIS sleep disturbance and Sleep-Related Impairment item banks. *Behav Sleep Med.* 2012; 10:6–24. [PubMed: 22250775]
32. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol.* 2005; 19(Suppl A):5–36.
33. Patel SR, Zhu X, Storfer-Isser A, et al. Sleep duration and biomarkers of inflammation. *Sleep.* 2009; 32:200–204. [PubMed: 19238807]
34. Shoham S, Davenne D, Cady AB, et al. Recombinant tumor necrosis factor and interleukin 1 enhance slow-wave sleep. *Am J Physiol.* 1987; 253:R142–R149. [PubMed: 3496800]
35. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. Sleep Duration Affects Risk for Ulcerative Colitis: A Prospective Cohort Study. *Clin Gastroenterol Hepatol.* 2014
36. Parekh PJ, Oldfield IV EC, Challapallisri V, et al. Sleep Disorders and Inflammatory Disease Activity: Chicken or the Egg? *Am J Gastroenterol.* 2014
37. Simpson N, Dinges DF. Sleep and inflammation. *Nutr Rev.* 2007; 65:S244–S252. [PubMed: 18240557]
38. Swanson GR, Burgess HJ, Keshavarzian A. Sleep disturbances and inflammatory bowel disease: a potential trigger for disease flare? *Expert Rev Clin Immunol.* 2011; 7:29–36. [PubMed: 21162647]
39. Tang Y, Preuss F, Turek FW, et al. Sleep deprivation worsens inflammation and delays recovery in a mouse model of colitis. *Sleep Med.* 2009; 10:597–603. [PubMed: 19403332]
40. Swanson G, Forsyth CB, Tang Y, et al. Role of intestinal circadian genes in alcohol-induced gut leakiness. *Alcohol Clin Exp Res.* 2012; 35:1305–1314. [PubMed: 21463335]
41. Ruperto N, Lovell DJ, Li T, et al. Abatacept improves health-related quality of life, pain, sleep quality, and daily participation in subjects with juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken).* 2010; 62:1542–1551. [PubMed: 20597110]
42. Ali T, Choe J, Awab A, et al. Sleep, immunity and inflammation in gastrointestinal disorders. *World J Gastroenterol.* 2013; 19:9231–9239. [PubMed: 24409051]
43. Tobaldini E, Cogliati C, Fiorelli EM, et al. One night on-call: sleep deprivation affects cardiac autonomic control and inflammation in physicians. *Eur J Intern Med.* 2013; 24:664–670. [PubMed: 23601527]
44. Trammell RA, Verhulst S, Toth LA. Effects of sleep fragmentation on sleep and markers of inflammation in mice. *Comp Med.* 2014; 64:13–24. [PubMed: 24512957]
45. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord.* 2011; 135:10–19. [PubMed: 21300408]

46. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflamm Bowel Dis.* 2009; 15:1105–1118. [PubMed: 19161177]
47. Sutton EL. Psychiatric disorders and sleep issues. *Med Clin North Am.* 2014; 98:1123–1143. [PubMed: 25134876]

Appendix 1: Assessment of sleep and mood using the NIH PROMIS questions

Sleep Habits

In the past 7 days...

		Very poor	Poor	Fair	Good	Very good
Sleep109 1	My sleep quality was	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
	In the past 7 days...					
		Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116 2	My sleep was refreshing.....	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
Sleep20 3	I had a problem with my sleep	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Sleep44 4	I had difficulty falling asleep	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Sleep106 5	My sleep was restless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Sleep72 6	I tried hard to get to sleep.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Sleep67 7	I worried about not being able to fall asleep	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Sleep115 8	I was satisfied with my sleep.....	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1

Mood

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
EDOEP04 1	I felt worthless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDOEP06 2	I felt helpless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDOEP29 3	I felt depressed	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDOEP41 4	I felt hopeless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDOEP22 5	I felt like a failure	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDOEP36 6	I felt unhappy	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDOEP05 7	I felt that I had nothing to look forward to	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDOEP09 8	I felt that nothing could cheer me up.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
EDANX01 1	I felt fearful.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX60 2	I found it hard to focus on anything other than my anxiety	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX41 3	My worries overwhelmed me	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX53 4	I felt uneasy	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX68 5	I felt nervous.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX07 6	I felt like I needed help for my anxiety	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX05 7	I felt anxious	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
EDANX54 8	I felt tense	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Table 1

Characteristics of the study population

Characteristic	N (%)
Age at Diagnosis (years) [Median(IQR)]	25 (18 – 37)
Type of IBD	
Crohn's Disease	78 (60)
Ulcerative Colitis	53 (40)
Sex	
Male	59 (45)
Female	72 (55)
Smoking History	
None	87 (67)
Former	36 (28)
Current	6 (5)
Prior Surgery	
None	102 (78)
Prior Surgery	29 (22)
Family History of IBD	
No	103 (79)
Yes	28 (21)
Anti-TNF Use	
None	58 (44)
Prior or Current	73 (56)
Sleep Score [Median(IQR)]	10 (5 – 16)
Depression Score [Median(IQR)]	5 (1 – 14)
ESR (mm/hr) [Median(IQR)]	8 (5 – 16)
C-reactive protein (mg/dL) [Median(IQR)]	2.1 (0.8 – 6.2)

IQR – interquartile range; Anti-TNF – monoclonal antibodies to tumor necrosis factor α (infliximab, adalimumab, certolizumab pegol); ESR – erythrocyte sedimentation rate; IBD – inflammatory bowel diseases

Sleep was assessed using an 8-item questionnaire and depression through a 16-item questionnaire from the NIH PROMIS question bank

Table 2

Univariate analysis of factors associated with poor sleep in patients with inflammatory bowel diseases

Characteristic	Odds ratio (95% confidence interval)
Age at Diagnosis	0.99 (0.96 – 1.01)
Type of IBD	
Crohn's Disease	1.0
Ulcerative Colitis	1.07 (0.53 – 2.16)
Sex	
Male	1.0
Female	1.15 (0.57 – 2.30)
Smoking History	
None	1.0
Ever	1.63 (0.78 – 3.43)
Prior Surgery	
None	1.0
Prior Surgery	1.23 (0.54 – 2.81)
Anti-TNF Usage	
None	1.0
Prior or Current	0.96 (0.48 – 1.92)
Depression Score	1.10 (1.05 – 1.15)
High C-reactive protein	3.52 (1.33 – 9.33)
High ESR	1.72 (0.79 – 3.75)
Clinically active disease	3.96 (1.89 – 8.27)