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Characterization of Relationships Between Sleep, Inflammation, and Psychiatric Dysfunction in Depressed Youth with Crohn's Disease

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Abstract

Objectives—Recent reports demonstrate a link between Inflammatory Bowel Disease (IBD) and sleep disturbance. Increased psychiatric dysfunction is consistently reported in patients with IBD. Our objective is to examine relationships among sleep disturbance, inflammation, and psychiatric dysfunction in a pediatric population with Crohn's disease (CD) and depression.

Methods—Pediatric CD patients with depression (n = 96) and healthy controls (n = 19) completed measures of sleep (Pittsburgh Sleep Quality Index [PSQI]), depression, anxiety, and abdominal pain, and provided blood for inflammatory markers. CD activity was determined by Pediatric Crohn's Disease Activity Index (PCDAI). Factor analysis was performed on subscales of the PSQI in order to derive measures of sleep disturbance. Univariate and multivariate regression analyses assessed relationships between sleep disturbance, psychosocial, and biological measures of CD and psychiatric dysfunction.

Results—Sleep disturbance in depressed youth with CD was significantly greater than healthy controls, and was significantly related to measures of abdominal pain, depression, and anxiety, but not biomarkers of inflammation. Factor analysis of the PSQI demonstrated a two-factor solution. The first factor, termed 'Qualitative,' included Subjective Sleep Quality, Daytime Dysfunction, Sleep Disturbance, and Sleep Latency, whereas the second, 'Quantitative,' factor consisted of Habitual Sleep Efficiency and Sleep Duration. This factor showed a significant relationship with inflammatory markers. Multivariate modeling suggested Qualitative sleep disturbance was

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predicted by disease activity, pain, and anxiety whereas Quantitative sleep disturbance was predicted by disease activity.

Conclusions—These results indicate that sleep disturbance in depressed CD sufferers differs depending upon illness activity. Patients may require different interventions depending upon the sleep disturbance exhibited.

Keywords

Crohn's disease; sleep disturbance; depression; inflammation; pediatric inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD) is comprised of Crohn's disease (CD) and ulcerative colitis (UC), afflicts approximately 1.4 million Americans, and is becoming more prevalent both in the United States and throughout the world.¹ Although CD and UC are often linked together due to their similar symptom profiles, these are two histologically distinct illnesses and appear to have different pathways to inflammation. Many studies will combine CD and UC, but because they have different underlying pathophysiology, this paper focuses only on CD. Commonly diagnosed in children and adolescents, CD is incurable and often accompanied by severe morbidity in both adults and children. In addition to recurrent bouts of spasmodic abdominal pain and bloody diarrhea, CD is often accompanied by extra-intestinal manifestations including severe fatigue, skin lesions, iritis, uveitis, mouth ulcers, and joint pains/arthritis.^{2–3} These immunologic conditions underscore the dysregulation of cytokine-mediated inflammatory responses in CD. In addition to the physical manifestations of illness, neuropsychiatric difficulties are very common in CD, with increased levels of depression and anxiety in adults and children.^{2–3} Medical and psychiatric well-being are interrelated in this multifactorial disorder, and certain symptoms seem to impact, as well as be affected by, both medical and psychiatric factors.

One such symptom is sleep disturbance. Sleep is a complex phenomenon that is critical to the general well-being of individuals, and when disrupted, poor sleep has deleterious effects on physical health. Both acute and chronic sleep disturbance have been linked to multiple medical conditions that are at least partly inflammatory in etiology, ranging from diabetes to cardiovascular disease to rheumatoid arthritis.⁴ Insulin resistance and autonomic dysregulation have both been suggested as potential mechanisms by which sleep disturbance can lead to inflammation.⁵ The majority of the studies linking sleep disturbance and chronic physical illness have been performed in adults, however there are pediatric studies revealing a similar relationship. Studies of children with rheumatoid arthritis,^{6–7} chronic kidney disease,^{8–10} and migraine¹¹ find subjective reports of poorer sleep quality. There are fewer studies that objectively measure sleep in medically ill pediatric patients, however some demonstrate alterations in sleep architecture that occurs in patients with juvenile idiopathic arthritis^{12–13} and type I diabetes mellitus.¹⁴

Recent reports have illustrated that poor sleep is a prominent feature in adult patients with IBD and has been linked to both inflammatory and non-inflammatory factors.^{15–16} Poor sleep is thought to exert cytokine-mediated effects on the immune system, and sleep deprivation has been shown to cause reactivation of colitis in a rodent model.¹⁷ Thus, it is possible that symptoms related to inflammation (*e.g.*, nocturnal diarrhea) and non-inflammatory factors (*e.g.*, chronic abdominal pain) may be implicated in the etiology of sleep disturbance in this population. Sleep disruption has also been associated with more severe pain in several rheumatologic conditions,¹⁸ as well as anxiety and depression, all of which are prevalent symptoms in adults and children with IBD.^{2–3, 19}

In adolescents, patients with severe IBD reported problems with sleep disruption and feeling overtired, whereas patients with mild IBD reported sleep problems at the same rate as healthy controls.²⁰ Although these findings are compelling, this study did not examine the role of psychological comorbidities such as anxiety and depression which have been reported in pediatric IBD at rates higher than either the general population or compared to youth with other chronic illnesses.^{21–22}

Depression and sleep disturbance commonly coexist in children and adolescents, and there are reports that sleep disturbance predicts depression²³ and vice versa,²⁴ suggestive of a bidirectional relationship linking depression and sleep disturbance.²⁵ Youth with depression frequently report subjective complaints of poor sleep,^{26–27} however objective measures of sleep such as polysomnography in this population indicate minimal alteration in sleep architecture compared to healthy controls.^{26, 28} Conversely, youth with anxiety disorders have decreased slow-wave sleep and increased numbers of awakenings.²⁸ It has been hypothesized that both sleep disruption²⁹ and psychiatric dysfunction³⁰ may be impacted by dysregulation of the immune system, thus providing a potential manner in which IBD may exacerbate both processes. This could result in a complex tripartite interaction, in which the effects of sleep disturbance, psychiatric illness, and disruption of the immune system (as in IBD) may worsen each other.

To date, the relationship between sleep, inflammation, and neuropsychiatric dysfunction has not been explored in a pediatric population. Furthermore, the specific types of sleep disturbances found in either CD or UC (*e.g.*, hypersomnia, insomnia, nighttime awakenings, or daytime sleepiness) have yet to be elucidated in either children or adults. By understanding these sleep disturbances and their interactions with medical and psychiatric factors in this population, it may be possible to design specific treatments to target these sleep problems.

This study has three aims: 1) To determine the degree of sleep disturbance in children and adolescents with depression and CD; 2) To characterize the type of sleep disturbances experienced; and 3) To examine the relationship between sleep, neuropsychiatric dysfunction, and inflammatory illness. Specifically, the relationships between sleep and CD activity, measures of anxiety, depression, pain, and inflammation are assessed.

Materials and Methods

Participants

Participants ages 9–17 ($n = 96$) with CD diagnosed by standard criteria³¹ were part of a multi-site study for treatment of depression at the Children's Hospital of Pittsburgh and Children's Hospital Boston, and they were recruited over a three-year period. Assessments included in this study were performed at baseline, before treatment of depression commenced. All procedures were approved by the Institutional Review Boards at the University of Pittsburgh and Children's Hospital Boston with assent from patients and consent from parent/guardian to participate in the study.

Study Eligibility

To determine study eligibility, consecutive participants seen in gastroenterology clinics were screened for depression using the child and parent versions of the Children's Depression Inventory (CDI), a pair of validated 27-item questionnaires that probe symptoms of depression over the past two weeks.³² CDI was completed by parents and children independently of one another. Both CDI measures assess similar symptoms of depression from either the child's or the parent's perspective. For the purposes of this study, a score of 10 reported by either the child or the parent was the cut-off for further assessment. In total,

495 subjects with CD completed the CDI, and 187 subjects scored ≥ 10 on either the parent or child component of the CDI, making them eligible for the second phase of the screening. Sixty-six subjects opted not to continue, thus 121 participated in the second phase of screening.

The second phase of screening involved administration of the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL). This is a semi-structured diagnostic interview designed to assess for the presence of psychiatric disorders based on DSM-IV criteria that has been validated in children and adolescents.^{33–34} The K-SADS-PL was administered by clinicians skilled in its usage in order to confirm the presence of depressive symptoms and assess any comorbid psychiatric disorders. To be eligible, subjects had to have at least 2 symptoms of depression, one of which had to be sadness, irritability, or anhedonia. Twenty-two subjects were excluded from the study due to not meeting depressive symptom criteria on the K-SADS-PL, and 3 subjects were deemed too ill to continue, resulting in a sample size of $n = 96$.

For comparison, healthy adolescent controls with neither depression nor IBD ($n = 19$) completed similar measures. IRB-approved recruitment ads were placed in hospital employee newsletters and at community pediatric practices (Pittsburgh site only). Parents of interested participants contacted research assistants and completed telephone screens to ensure the potential subjects had no medical or cognitive issues that would preclude them from serving as healthy controls. Subsequently, those potential subjects then completed the two-part screening for study inclusion in person as described above. The data from these patients were used as comparisons for the main depressed CD cohort evaluated in this study. In all instances, assessors were blinded to disease activity measures and laboratory values.

Psychosocial Measures

Demographic information and portions of certain reports (CDI and Children's Depression Rating Scale-Revised [CDRS-R]) were completed by the parents. The remainder of information was provided by child report.

Pittsburgh Sleep Quality Index—The Pittsburgh Sleep Quality Index (PSQI) is an 18 question self-report questionnaire designed to measure sleep quality during the previous month. It consists of seven subscales (Sleep Duration, Sleep Disturbance, Sleep Latency, Daytime Dysfunction, Habitual Sleep Efficiency, Subjective Sleep Quality, and Usage of Sleep Medications). The procedure for calculation of each subscale has been defined previously by Buysse *et al.*³⁵ The PSQI is one of the most widely used measures of sleep quality, and it includes several items that are scored on a Likert scale to determine some of the subscales (Sleep Disturbance, Daytime Dysfunction, Subjective Sleep Quality, and Usage of Sleep Medications). The PSQI also contains numerical questions that require the subject to estimate their bedtime, wake time, time to fall asleep, and number of hours slept, and these are necessary to determine the other subscale scores (Sleep Duration, Sleep Latency, Habitual Sleep Efficiency). Each subscale is scored from 0–3, with higher values being indicative of poorer sleep, and the sum of all 7 subscales comprises the total PSQI score, meaning scores range from 0–21. Scores > 5 suggest clinically significant sleep disturbance. The PSQI is a reliable measure that is validated compared to polysomnography, considered to be the gold standard for measurement of sleep. The PSQI provides an overall estimate of sleep disturbance, and though it has not been formally validated for use in children, several studies have reported data collected from children using the PSQI.^{36–39}

Children's Depression Rating Scale-Revised—The Children's Depression Rating Scale-Revised (CDRS-R) is a validated, clinician-rated measure of depressive symptoms

incorporating input from both child and parent that provides information on several different subscales of depression.⁴⁰ It contains information on 17 domains of functioning, and scores

30 are suggestive of clinically significant depressive symptomatology. The CDRS-R differs from the CDI in that it is a semi-structured interview and responses are scored on a 7-point Likert scale, thus providing a bit more resolution than the 3-point Likert scale of the CDI. Though both measures assess similar content, the CDI was used as a screening tool in the larger study, whereas the CDRS-R was one of the primary outcomes measured.

Abdominal Pain Index—The Abdominal Pain Index (API) is a validated 5-item assessment designed to characterize the self-reported duration, severity, and frequency of pain suffered by the patient over the past two weeks.⁴¹ Scores > 15 are indicative of clinically significant pain.

Screen for Child Anxiety Related Disorders—Self-reported anxiety was measured with the Screen for Child Anxiety Related Disorders (SCARED). The SCARED assessment is a validated measure of anxiety that encompasses symptoms experienced during the past two weeks.⁴² The measure consists of 41 items that are scored on a 0–2 range (0 being no anxiety, 2 being severe symptoms). Scores ≥ 25 are considered to be suggestive of clinically significant anxiety.

Assessment of Disease Type and Activity

The diagnosis of CD was made by pediatric gastroenterologists at Children's Hospital of Pittsburgh or Children's Hospital Boston. Activity of illness was estimated by gastroenterologists using the Pediatric Crohn's Disease Activity Index, (PCDAI).⁴³ The PCDAI is an aggregate total of historical reports by patients, laboratory values, and physical examination findings. Patients were defined to have inactive, mild, or severe disease based upon their PCDAI (0–14 = inactive, 15–30 = mild, 31+ = severe) score. Blood samples were obtained at the time of initial screening and recruitment, and erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) were measured as markers of generalized inflammation. CD was also categorized based upon the Paris pediatric modification of the Montréal criteria.⁴⁴

Statistical Methods

Descriptive statistics were computed for all clinical measures to address Aim 1. To characterize sleep (Aim 2), factor analysis was performed on the components of the PSQI. Factor analysis was chosen, because previous reports have suggested that this technique may detect sleep impairment limited to certain subscales of the PSQI that may not be noted by using the total PSQI score.⁴⁵ Principal Axis Factoring method with Direct Oblimin rotation and the Kaiser normalization was used. The Kaiser-Meyer-Olkin value and the Bartlett's Test of Sphericity were performed to assess the adequacy of these data for use with factor analysis. Initially all seven subscales of the PSQI were included in the factor analysis, however less than 10% of all children indicated any use of sleeping medications, thus this subscale was excluded. An oblique rotation solution rather than an orthogonal rotation solution was used as the emergent factors were highly correlated with one another ($r = 0.77$). The number of factors was based upon extraction of variables with Eigenvalues greater than 1 as well as examination of a scree plot. Factor scores using factor weights were generated for each factor that emerged. These scores were subsequently used in further regression analyses.

Regression analyses were conducted to assess the relationship of sleep with measures of depression, anxiety, pain, disease activity, and inflammatory markers (Aim 3). First, univariate models were fit to assess the importance of each covariate to the prediction of

overall sleep. Given the set of important predictors, a multivariate model was fit using a backwards elimination strategy (and a liberal elimination p-value < 0.10). ESR and CRP are both non-specific markers of inflammation. Because CRP is a more specific measure of CD,⁴⁶ we only used CRP in the multivariate models. In addition to characterizing the relationships between overall sleep disturbance and other psychosocial and laboratory measures of illness, regression models utilizing the two factors of sleep were also fit in order to more specifically define the aspects of sleep disturbance that were affected in this population.

In addition, a disease severity variable was created by categorizing patients into inactive, mild, or severe CD activity, based upon their PCDAI scores at time of initial screening. This variable was comprised of two indicator variables representing the comparisons mild versus inactive and severe versus inactive and subsequently used in regression models to assess whether IBD disease severity also had an effect on sleep disturbance.

Results

Demographics

Ninety-six patients met study entry criteria and were included in this analysis. Demographic and clinical data are presented in Table 1. Our cohort was almost two-thirds female, and 87.5% of patients were Caucasian, 8.5% were African American, 3% were biracial, and 1% were Asian. Patients exhibited mild-to-moderate levels of depression, and only 3% were on antidepressant medications. Total PSQI scores were not associated with age, gender, duration since CD diagnosis, or ethnicity (data not shown). Despite the presence of active disease in 68% of this cohort, only 13% of the patients were taking corticosteroids, and daily steroid load was not associated with significant sleep disturbance in this study ($r = -.05$; $p = .78$). Furthermore, 12.5% of subjects had undergone previous surgical resection for their CD. Control group data (healthy subjects without depression or IBD [$n = 19$]) are shown in Table 1 as well. Socioeconomic status was defined as the ratio of household income to number of household dependents. The difference between the groups was borderline statistically significant ($p = .06$), with CD households having greater income/dependent ratio than healthy control subjects (data not shown).

Out of the 96 patients who completed the PSQI, 51 (53.0%) patients had total PSQI scores > 5, consistent with clinically significant sleep disturbance, with a mean global PSQI score of 6.2 ± 3.0 . Total PSQI scores were normally distributed, with some skewing towards sleep disruption (data not shown). This is significantly greater sleep disruption than in healthy controls, as shown in Table 1. Figure 1 illustrates the distribution of PSQI component scores from 0–3 (no disruption to severe disruption). As illustrated by Figure 2, distributions of Sleep Duration and Habitual Sleep Efficiency were similar to one another, as were Sleep Latency, Daytime Dysfunction, and Subjective Sleep Quality. Notably, only 7 of the 96 (7.3%) patients who completed the PSQI indicated any usage of medication to aid with sleep.

Characterization of Sleep

The Kaiser-Meyer-Olkin value was 0.7 (> 0.7 considered good for factor analysis⁴⁷) and the Bartlett's Test of Sphericity (which tests the null hypothesis that the variables are unrelated) was statistically significant ($p < .0001$), both of these indicating that these data were appropriate for factor analysis. Factor analysis revealed a 2-factor solution in which 6 out of 7 components of the total PSQI mapped onto one of two factors. Sleep Disturbance, Subjective Sleep Quality, Daytime Dysfunction, and Sleep Latency clustered onto Factor 1. Habitual Sleep Efficiency and Sleep Duration clustered on Factor 2. Use of Sleeping

Medications was minimal in this population, and it did not load onto either factor, therefore this subscale was excluded when Principal Axis Factoring was performed. Rotated factor loading values from the extracted pattern matrix are presented in Table 2. Because the bulk of the items in Factor 1 are Likert ratings, and the items in Factor 2 require the subject to put in specific numerical values, Factor 1 and Factor 2 have been termed 'Qualitative' and 'Quantitative,' respectively.

Regression Analyses

Univariate regression analyses of total PSQI scores as well as the Qualitative and Quantitative factors that resulted from the factor analysis were carried out with psychosocial and biological measures (Table 3). Psychosocial measures were statistically significantly related with the Qualitative and Quantitative factors, including depression (CDRS-R) and child-reported abdominal pain (API). The measure of anxiety (SCARED) was only related to the Qualitative factor. Though both factors were associated with psychosocial measures, these measures were more strongly related to the Qualitative factor of the PSQI. Conversely, ESR was significantly related to the Quantitative factor but not the Qualitative factor.

Multivariate regression analysis was performed using the Qualitative and Quantitative factors of sleep in order to determine which covariates predicted each factor of sleep disturbance (Table 4). Disease activity was a significant predictor of both factors of sleep disturbance. Pain and anxiety were predictors of Qualitative sleep disturbance only.

To quantify the effect of disease activity in predicting the two factors of sleep disturbance, patients were categorized into inactive ($n = 31$), mild ($n = 37$), or severe CD activity ($n = 28$), based upon their PCDAI scores at time of initial screening. Mean total PSQI scores for the inactive (4.9 ± 2.3), mild (6.0 ± 2.8), and severe (8.1 ± 3.2) groups indicated that sleep difficulties increased with worsening CD disease status, however even the patients with inactive CD were nearing a score of 5, the cut-off for clinically significant sleep disturbance. Comparisons of these means showed that the activity difference in PSQI scores was significant when patients with active disease were compared to patients with either inactive disease ($t = 4.41$; $p < 0.0001$) or mild disease ($t = 2.97$; $p = 0.004$). This difference was not statistically significant when comparing mild and inactive disease groups ($t = 1.67$; $p = 0.099$), however the data did exhibit statistically significant trends (trend test $p < 0.0001$), illustrating that total PSQI scores and disease activity were related.

Discussion

The data presented here are one of the first detailed reports of sleep problems in depressed children with Crohn's disease, and one of the first to relate sleep disturbances with psychiatric and medical symptoms in this population. As with adults, clinically significant sleep disturbance is very prominent in depressed youth with CD, and it is significantly greater than sleep disturbance in healthy controls. This is not surprising given the number of potential reasons for these patients to have sleep disturbance. Although causes of sleep disturbance may be characterized in any number of ways, one possibility is to classify them as either related to psychosocial or physical illness factors. Psychosocial reasons for impaired sleep may include depression, anxiety, and familial stress. Medical reasons for sleep disturbance may include IBD medications, need for night-time bowel movements, the presence of ostomies that require night-time care, and the inflammatory process itself. Of the medications that are commonly prescribed for CD, corticosteroids are known to disrupt sleep,⁴⁸ however in our small sample taking steroids, this was not observed. Our findings also demonstrated an association between sleep disruption and disease severity, similar to results reported in adults with CD.¹⁶ We hypothesize that circulating cytokines may mediate this relationship, based upon animal models and human studies of sleep disruption.⁴⁹

Previous studies have suggested that sleep disturbance is a persistent problem for many adult patients, even when their IBD is inactive.¹⁶ Our findings indicate that clinically significant disturbance was present in pediatric patients with depression and inactive disease, although sleep quality was worse in individuals with moderate/severe disease activity (mean global PSQI score 8.1) as compared to patients with inactive disease (mean global PSQI score 4.9). This is consistent with findings previously reported in adults,⁵⁰ however the sleep-related symptoms reported by the patients differ a great deal, depending upon the activity of their CD. In patients with disease in remission, psychosocial dysfunction (*i.e.*, depression, pain, anxiety) was more related with sleep disturbance, especially 'Qualitative' measures (Factor 1). This relationship declined as CD activity increased. Conversely, the 'Quantitative' measures (Factor 2) of sleep disturbance were more closely linked to the biological measure of illness (CRP) when CD was flaring, a relationship that was not seen in inactive disease.

There is a fair amount of controversy surrounding the performance of factor analysis, and particularly the number of subjects necessary for optimal results. Some researchers suggest that the total number of subjects is less important than the ratio of subjects to variables that are consolidated.⁵¹ Although the numbers are small for a factor analysis, the data share similarities with a much larger factor analysis using the PSQI performed by Cole *et al.*⁴⁵ Their study, performed in older adults with and without depression, found a 3-factor solution, rather than the 2-factor model we present here. Because the study cohorts are different, it is entirely possible that the factor structures would be somewhat different. However, there are similarities to the current study as well. In the Cole *et al.* paper, they reported one factor consisting of Subjective Sleep Quality, Sleep Latency, and Use of Sleeping Medications, and a second factor consisting of Sleep Disturbances and Daytime Dysfunction. In the current study, the 2-factor model that combines all of those components into the 'Qualitative' factor yielded a better fit. In that study, Sleep Duration and Habitual Sleep Efficiency clustered together, identical to findings reported here. Further, Use of Sleeping Medications had the poorest loading statistics in that study similar to what was observed here. The current analysis was conducted in a pediatric population, and it seems logical that children would have less access and opportunity to take sleeping medications. Indeed, less than 10% of patients in this study reported the usage of any sleep medications, and the majority of these patients reported only infrequent usage of medications to aid with sleep.

The structure of the PSQI is notable in that it consists of several Likert-scored items as well as certain items that require the subject to enter numerical values. Interestingly, the components that loaded onto Factor 2 (*i.e.*, Habitual Sleep Efficiency and Sleep Duration) are both numerical values that are estimated by the subject or calculated by the administrator. In the case of Habitual Sleep Efficiency, determining the score requires calculation of a ratio of time spent asleep to total time spent in bed. On the other hand, Factor 1 consisted largely of Likert-scored items (*i.e.*, Sleep Disturbance, Subjective Sleep Quality, and Daytime Dysfunction). Although Sleep Latency requires a numerical value to be inserted by the subject, this is the component of the PSQI that was most poorly correlated with Factor 1.

When filling out the PSQI, it may be argued that patients with depression may be prone to overestimating their sleep symptoms, particularly in Likert-scored items, which constitute the majority of the Qualitative factor we have identified. This affective bias may diminish when patients are asked to pick out a specific number of hours or a ratio must be calculated by the scorer, as in the items comprising the Quantitative factor. The components of the PSQI that comprise the Qualitative factor were related with the more 'qualitative' psychosocial measures of our patients, namely depression, anxiety, quality of life, and pain.

This implies that psychosocial factors may be more influential on patient report of the Qualitative component of sleep when they are completing the PSQI.

Conversely, the measures of the PSQI comprising the Quantitative factor were more related with measures of inflammation, both CRP and ESR. Interestingly, ESR seems to have a stronger relationship with the Quantitative factor of sleep disturbance, whereas CRP is a better predictor of this factor of sleep disturbance in the multivariate models. This is difficult to interpret, though it is worth noting that CRP is a more sensitive marker than ESR in terms of detecting CD.⁴⁶ In addition, CRP has a relatively short half-life (19 hours), whereas ESR may remain elevated for several days after an inflammatory insult. One option for future studies is to measure fecal calprotectin, as this is a much more gut-directed marker of inflammation and may provide a more accurate measure of inflammation at the time of assessment.⁵²

Disease activity (as measured by PCDAI) was related to the total PSQI as well as both factors of the PSQI, however it was more strongly related to the Qualitative factor than the Quantitative factor of sleep. As the PCDAI is an aggregate of patient-reported measures and laboratory values, it seems logical that the PCDAI would correlate with both factors. The differences in scores for all measures of sleep were statistically significant for patients with severe disease compared to patients with either inactive disease or mild disease but not for those patients with mild disease compared to those with inactive disease. This implies that different components of sleep disturbance are affected differentially in different populations of CD patients. Therefore, patients may respond to different interventions to treat sleep, depending upon the severity of their disease. For instance, based upon results presented here, it may be argued that patients with inactive or mild CD and poor sleep might benefit from interventions targeting the 'qualitative' or psychosocial measures of illness.

There are multiple caveats to this study, perhaps the most important of which is the small sample size for a factor analysis. Though many studies will combine CD and UC patients to increase their numbers, these illnesses are histologically and immunologically distinct entities. In an adult population, Graff *et al*, found limited differences between CD and UC in their study of fatigue and sleep problems,⁵⁰ thus it is possible that sleep findings in CD will be applicable to populations with UC. A second limitation is that the PSQI has not been validated in children and adolescents, although there are several reports of its usage in pediatric settings. The PSQI is only one of several ways to measure sleep disturbance, and it is certainly possible that other measures such as polysomnography, actigraphy, sleep diaries, or different assessment tools could provide further or complementary information. For instance, fatigue is a common complaint in this population,⁵³ however the PSQI does not measure hypersomnia, and it is possible that patients with increased sleep requirements were missed in this analysis.

The control group used as a comparison in this study (healthy youth without depression or CD) is small, and this is a limitation of the study, however it was felt that using this small cohort would be preferable to having no control group at all. Another limitation is the lack of a control group with CD but without depression, as this would be the ideal way to differentiate the effect of depression on sleep disturbance from that of CD inflammatory activity on sleep disturbance. Data presented here suggest that severity of sleep disturbance is largely related to disease activity. In addition, depression and anxiety are also significant contributors to sleep disturbance although they appear to be responsible for a smaller percentage of the variance. In secondary analyses of this cohort, subjects were stratified by anxiety (SCARED ≥ 25 ; <25) or depressive severity (CDRS-R ≥ 40 ; <40), and reanalyzed, and the predictive relationships remained quite similar (data not shown). That is, CD activity continued to be the major predictor of sleep disturbance, and depression and anxiety were

notable secondary factors in this subgroup analysis. These findings underscore the importance of using a biopsychosocial model when examining youth with CD.

Finally, this was a cross-sectional study, thus it is not possible to determine causality between processes that were assessed at a single time-point. One may postulate a bidirectional relationship between sleep and inflammation in which sleep problems exacerbate inflammation and vice versa, leading to a positive feedback loop that increases CD severity. This relationship could be further modulated by the presence of neuropsychiatric symptoms such as anxiety and depression, leading to even further morbidity such that youth with CD who have a “double hit” of both CD-related inflammation and psychiatric dysfunction are likely to have especially disrupted sleep. Additionally, one may hypothesize a ‘tridirectional’ model in which sleep disruption, neuropsychiatric dysfunction, and inflammation all exacerbate one another. In this model, intervention at any corner would result in improvement in symptoms at the other corners (Figure 2).

This work is part of an emerging literature that shows that sleep disturbance is a serious concern in pediatric patients with IBD, both CD and UC. This study is the first to differentiate sleep disturbance into its individual domains in an effort to determine what parts of sleep are disrupted in young depressed patients with CD. Given the importance of sleep in daytime functioning, psychological health, and the ability to cope with stress, understanding sleep during childhood and adolescence, a time of ongoing brain development, is particularly important. While there are several medical and psychiatric treatments available for IBD and its comorbid illnesses, sleep disturbance is often neglected. The relationships between sleep disturbance, IBD-related inflammation and psychiatric illness are complex, and the relationships between each are likely to be bidirectional or multidirectional in nature.

Future studies should utilize more objective sleep measures such as polysomnography and actigraphy to further characterize the impact of CD (with and without depression) on sleep architecture. In addition, it will be important to understand the longitudinal relationships between sleep, IBD-related inflammation and depression course, as well as assessing sleep disturbance in non-depressed cohorts with IBD. Aggressive and personalized treatment of sleep disturbance based on the underlying etiology, may represent a new point at which to impact Crohn’s disease, in the hope that better sleep may exert positive effects on the illness itself and possibly even prevent future physical and mental manifestations of this life-long disease.

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Figure 1. PSQI Sleep Component Subscores by Frequency in Pediatric Patients with CD and Depression

The frequency of patients with disturbance in each of the 7 subscales of the PSQI is shown above (0 = no disturbance, 3 = severe disturbance). Note the proportional similarity in Sleep Duration and Habitual Sleep Efficiency, as these two subscales cluster together to form the basis of the Quantitative factor. As might be expected in a pediatric population, the Use of Sleeping Medications is minimal.

Figure 2. Putative Models of the Relationships Between Sleep, Inflammation, and Neuropsychiatric Dysfunction in CD

A. This figure illustrates a model whereby sleep disturbance contributes to inflammation and these two factors exert positive feedback upon one another, resulting in increasing CD severity. Sleep disturbance and psychiatric dysfunction have the capacity to worsen one another as well. **B.** In this panel, sleep disturbance, inflammation, and psychosocial dysfunction are separate entities, and each has the potential to impact one another directly. Thus, treatment of any one of these entities has the potential to improve the other two corners of the triangle. While treatment of the inflammatory and psychosocial components are the mainstay of managing CD, sleep disturbances are often neglected but may represent another means to effect improvement in this illness.

Table 1
Demographic Information for Pediatric Patients with Depression and Crohn's disease and Healthy Controls

Measure	Crohn's disease			Healthy Controls		
	n	Means (SD)	% Above Threshold [#]	n	Means (SD)	% Above Threshold [#]
Age	96	14.4 (2.3)	--	19	14.8 (2.0)	--
Gender	62.5% Female	--	--	63.2% Female	--	--
Months Since CD Diagnosis	78	23.2 (26.3)	--	--	--	--
CDI-Child [*]	95	13.6 (6.9)	75.8 (10)	18	2.5 (2.7)	0 (10)
CDI-Parent [*]	94	14.1 (6.4)	78.7 (10)	19	1.7 (2.1)	0 (10)
PSQI Total (Sleep) [*]	96	6.2 (3.0)	53.0 (>5)	19	3.0 (2.9)	15.8 (>5)
SCARED (Anxiety) [*]	92	24.2 (12.4)	41.3 (25)	18	7.5 (8.0)	5.6 (25)
CDRS-R (Depression) [*]	96	45.6 (11.9)	93.8% (30)	19	18.0 (2.4)	0 (30)
PCDAI (CD activity)	96	22.7 (16.3)	67.8 (15)	--	--	--
API (Abdominal Pain) [*]	90	20.6 (11.2)	76.7 (>15)	18	5.0 (6.7)	5.6 (>15)
ESR (mm/hr) [*]	90	24.4 (17.9)	73.3 (>10)	12	8.1 (4.0)	25.0 (>10)
CRP (mg/dL) [†]	81	1.6 (2.5)	53.1 (>0.5)	--	--	--
CD Classification [§]	88					
Ileal (L1)	14					
Colonic (L2)	11					
Ileocolonic (L3)	62					
Upper GI (L4)	1					
Inflammatory (B1)	78					
Strictureing (B2)	7					
Penetrating (B3)	3					

Measure	Crohn's disease			Healthy Controls		
	n	Means (SD)	% Above Threshold [#]	n	Means (SD)	% Above Threshold [#]
Perianal Disease Modifier (p)	9					
No Growth Delay (G ₀)	68					
Growth Delay (G ₁)	20					

^{*} Indicates that means are significantly different at p < 0.01 level when compared using Student's *t*-test.

[#] Threshold scores in parentheses.

[†] CRP was not obtained on the healthy controls.

[§] Location of disease based upon Paris pediatric classification schema.

Table 2

Principal Axis Factors Rotated Loadings of the Items of the PSQI

PSQI component	Factor 1-Qualitative	Factor 2-Quantitative
Sleep Duration	0.09	0.45
Sleep Disturbance	0.43	−0.02
Sleep Latency	0.53	−0.06
Daytime Dysfunction	0.52	0.06
Habitual Sleep Efficiency	−0.04	0.50
Subjective Sleep Quality	0.61	0.25

Boldfaced type signifies the factor onto which each component of sleep disruption loads. Use of Sleeping Medications is not included as there are less than 10% of patients endorsing any usage of medications, and this subscale did not load onto either of the two factors obtained (data not shown).

Table 3

Univariate Regressions between Total PSQI Scores, Factors 1 and 2, and Psychosocial and Biological Measures (n = 96)

Covariate	β -Coefficient	95% Confidence Interval	R ²	p-value
Total PSQI				
PCDAI (CD activity)	0.086	0.052, 0.120	21.6	p < 0.0001
CDRS-R (Depression)	0.075	0.025, 0.125	8.7	p = 0.004
SCARED (Anxiety)	0.071	0.022, 0.120	8.6	p = 0.005
API (Abdominal pain)	0.108	0.055, 0.162	15.7	p = 0.0001
ESR	0.016	-0.019, 0.051	0.9	p = 0.371
CRP	0.240	-0.018, 0.497	4.2	p = 0.067
Qualitative Factor (Factor 1)				
PCDAI (CD activity)	0.022	0.013, 0.031	19.2	p < 0.0001
CDRS-R (Depression)	0.019	0.006, 0.033	7.9	p = 0.006
SCARED (Anxiety)	0.022	0.009, 0.034	11.0	p = 0.001
API (Abdominal pain)	0.030	0.016, 0.044	17.0	p = 0.0001
ESR	0.003	-0.007, 0.012	0.4	p = 0.573
CRP	0.054	-0.015, 0.122	3.0	p = 0.125
Quantitative Factor (Factor 2)				
PCDAI (CD activity)	0.018	0.010, 0.026	18.3	p < 0.0001
CDRS-R (Depression)	0.012	0.0003, 0.024	4.3	p = 0.043
SCARED (Anxiety)	0.009	-0.003, 0.020	2.4	p = 0.144
API (Abdominal pain)	0.018	0.005, 0.030	7.9	p = 0.007
ESR	0.008	0.0001, 0.015	4.2	p = 0.052
CRP	0.086	0.030, 0.143	10.5	p = 0.003

Table 4

Multivariate Backwards Regression Analysis for Qualitative and Quantitative Factors of Sleep (n = 96)

Covariate	β-Coefficient	95% CI (p-value)	R ²	Model p-value
Qualitative Factor (Factor 1)				
PCDAI (CD Activity)	0.012	0.0004, 0.024 (p = 0.043)	22.6	p = 0.0003
API (Abdominal pain)	0.015	−0.002, 0.033 (p = 0.092)		
SCARED (Anxiety)	0.014	0.0004, 0.027 (p = 0.043)		
Quantitative Factor (Factor 2)				
PCDAI (CD Activity)	0.016	0.008, 0.025 (p < 0.001)	15.8	p = 0.0004