HHS Public Access

Author manuscript

Ann Gastroenterol Dig Disord. Author manuscript; available in PMC 2019 May 20.

Published in final edited form as:

Ann Gastroenterol Dig Disord. 2018 ; 1(1): 9–25.

The Relationship between Sleep Disturbance, Quality of Life and Psychosocial Functioning in Pediatric Patients with Inflammatory Bowel Disease

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Abstract

Background: Pediatric patients with inflammatory bowel disease (IBD) are at risk for psychiatric symptoms that impact quality of life (QoL) and psychosocial functioning. Sleep disturbance has been reported to impose adverse effects on host defense mechanisms by affecting the magnitude and characteristics of the inflammatory response. The current study sought to assess the relationships among sleep disturbance, QoL, and psychosocial functioning in children with IBD.

Methods: Pediatric IBD patients completed multiple measures of sleep and daytime functioning as well as measures of QoL and psychosocial functioning. The parents completed complementary

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Contributor's Statement

Chaowapong Jarasvaraparn: Dr. Jarasvaraparn was a principal investigator, conceptualized, searched literature, designed the study, recruited participants, collected data, carried out initial analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Kimberly Zlomke: Dr. Zlomke conceptualized and interpreted all questionnaires, designed the study, critically reviewed and approved the final manuscript as submitted.

Noelle C. Vann: Noelle Vann recruited participants, conceptualized and interpreted all questionnaires, designed the control group, designed the study, and approved the final manuscript as submitted.

Bin Wang: Dr. Wang designed and carried out statistical analyses, drafted the initial method part of manuscript, and approved the final manuscript as submitted.

Karen D. Crissinger: Dr. Crissinger designed the study, critically reviewed, revised the manuscript, and approved the final manuscript as submitted.

David A. Gremse: Dr. Gremse conceptualized, designed the study, critically reviewed, revised the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Financial Disclosure

No financial relationships relevant to this article to disclose.

Conflict of Interest

The authors have no conflicts of interest to disclose.

measures of sleep, QoL, and psychosocial functioning. The HRQOL results for subjects with IBD were compared to a healthy control group.

Results: Fifty-three children with pediatric IBD and their parents were enrolled in the study. QoL was positively associated with sleep quality, based on significant negative correlations between QoL and both sleep quality and daytime sleepiness scales ($r = -0.62, -0.57$; p value <0.001, respectively). Patients with CD reported significantly better QoL and psychosocial functioning than patients with UC. The QoL was similar between IBD patients and healthy controls.

Conclusions: The present study suggests that a positive association exists between sleep functioning and QoL in pediatric patients with IBD. Patients with pediatric IBD should be screened for sleep disturbance, QoL and psychosocial functioning. Prevention and intervention strategies of sleep disturbance aimed at improving QoL and psychosocial functioning in children with IBD should be developed and evaluated.

Keywords

Sleep disturbance; Inflammatory bowel disease; Quality of life; Psychosocial functioning and children

Introduction

Inflammatory bowel disease (IBD) is characterized by chronic inflammation in the gastrointestinal tract. Pediatric IBD, Crohn's Disease (CD) and Ulcerative Colitis (UC) affect 43 and 28 children per 100,000 persons, respectively [1]. Approximately 20 to 30% of individuals with IBD are diagnosed during childhood [2]. The incidence of childhood-onset IBD has emerged globally as an important pediatric chronic disease that can significantly affect a child's quality of life (QoL). Moreover, pediatricians and other health providers are increasingly encountering very young children with IBD. These children are living long lives with chronic disease; therefore, knowledge of factors affecting long-term outcomes is becoming increasingly important for optimum management of IBD in children. Developing a better understanding family/patient dynamics is one factor that may influence treatment outcomes for pediatric IBD.

IBD is an immune-mediated chronic inflammatory disease of the intestinal tract with intermittent disease activity characterized by symptomatic periods (flare-ups) alternating with asymptomatic periods (remissions). During flare-ups, patients may experience frequent diarrhea, bloody diarrhea, abdominal pain, weight loss, growth delay, fever, arthralgia/arthritis and/or fatigue. The specific etiology and trigger(s) for flare-ups of IBD are undefined and there is no current cure for IBD. Therefore, the primary goal is to improve QoL and psychosocial functioning by treating flare-ups and maintaining remission.

Sleep plays an important role in the regulation of many physiological processes and also is vital in promoting growth, maturation and the overall health of children and adolescents. Sleep disturbance has been reported to decrease the magnitude of the inflammatory response, adversely affecting host defense mechanisms and one's ability to overcome infection [3]. In a retrospective study of 12,014 German workers, those who worked long or irregular hours had an increased prevalence of IBD compared to those who worked regular

hours [4]. In animal models of dextran sodium sulfate-induced colitis, introduction of acute or chronic sleep disturbance exacerbated colonic inflammation [5]. Sleep is associated with immune system activity. Inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin-1 (IL-1) and IL-6 have directly been shown to act as mediators on the effects from sleep [6]. Irwin et al. [7] first reported evidence of an alternation in a functional cellular innate immune response following sleep loss. Pediatric studies describe relationships between sleep disturbance and chronic diseases such as juvenile rheumatoid arthritis [8], chronic kidney disease [9], migraines [10] and type I diabetes mellitus [11]. Sleep disturbance, therefore, might be an important factor that affects the course of chronic inflammatory disorders.

Understanding the long-term impacts of pediatric-onset IBD on mental and psychological well-being is limited by the quality of studies published in this area. Children with IBD are at risk for more difficulties in psychosocial functioning than healthy children, including anxiety, depression and social difficulties [12]. IBD presents many potential challenges to psychological adjustment. For example, children with IBD may be reluctant to talk about their symptoms since bathroom embarrassment is common among children and adolescents. The disease activity fluctuates and can be embarrassing or limit social activities. It can also obstruct treatment. Pediatric IBD clearly has the potential to impact psychosocial functioning and QoL and may impact disease activity, such as more frequent IBD flare-ups, higher hospitalization rates, and lower compliance with chronic treatment. Most studies have concluded that, in pediatric patients with IBD, the disease activity is the main predictor of QoL; however, it is not yet defined how sleep disturbance affects QoL in youth with IBD.

The primary aim of this study was to assess how sleep disturbance is correlated with QoL and psychosocial functioning. The two secondary aims of the study were: 1) to examine the relationships between QoL and psychosocial functioning to IBD disease activity and inflammatory markers and 2) to compare reports of QoL and psychosocial functioning in order to characterize the subscales of QoL between CD and UC.

Materials and Methods

This study was cross-sectional and included surveys to evaluate sleep disturbance, QoL and psychosocial functioning in pediatric patients with IBD from December 2015 to July 2017 (19 months). With the approval of the hospital's Institutional Review Board (IRB), this study was conducted at the University of South Alabama Pediatric Gastroenterology Clinic.

Participant characteristics

Participants aged less than 18 years and diagnosed with IBD were recruited. The exclusion criteria included 1) non-English speaking participants; 2) patients who were diagnosed with any chronic medical conditions other than IBD. A total of 53 IBD patients (38 CD, 12 UC and 3 indeterminate colitis) and their parents enrolled in the study. An additional 32 healthy controls, without any chronic medical illnesses or diagnoses of any psychological disorders, were recruited. Only patients older than ten years filled out questionnaires by themselves and parents reported on all youth, regardless of age. Parents and adolescents were instructed

to complete their questionnaires independently and each participant was given $10 for their participation in the study.

Procedures

Participants were recruited in the clinic setting by investigators (C.J., N.V.). After obtaining written informed consent from parents and assent from subjects older than 10 years, the QoL and psychosocial functioning questionnaires were distributed to parents/ patients for completion. At the time of evaluation, a number of parameters were recorded: demographics, IBD classification, current treatment, hospitalization during the previous two years and a physical examination. All subjects were evaluated by pediatric gastroenterologists. A chart review was conducted to obtain additional IBD-related information (e.g., duration, laboratory test results, medication history, etc.).

Measures

1. The Child Sleep Habits Questionnaire (CSHQ) is a screening instrument used to identify both behaviorally-based and medically-based sleep problems in children [13]. This sleep instrument utilizes parent responses to a validated questionnaire designed for school-aged children. The CSHQ is a 45-item questionnaire with eight subscales including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnia, sleep disordered breathing and daytime sleepiness. Parents reported all observed sleep behaviors based on recall of the previous week. Items were rated on a 3-point scale: “usually” if the sleep behavior occurred 5 to 7 times/ week; “sometimes” for 2 to 4 times/week; and “rarely” for 0 to one time/week. A cut-off total CSHQ score of 41 yielded a sensitivity of 80% and specificity of 72% to identify both behaviorally-based and medically-based sleep problems in school-aged children [13]. Parents completed the CSHQ for all youth participants.

2. The Pittsburgh Sleep Quality Index (PSQI) is used to measure the quality and patterns of sleep in adolescents/adults [14]. It differentiates “poor” from “good” sleep quality by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications and daytime dysfunction over the last month. Items are rated on a 4-point scale: not during the past month (0), less than once a week (1), once or twice a week (2) and three or more times a week (3), yielding a potential score ranging from 0–21. A total component score of 5 or greater is indicative of poor sleep quality with a diagnostic sensitivity of 89.6% and specificity of 86.5% [14]. Only participants over the age of 10 years completed the PSQI.

3. The Pediatric Daytime Sleepiness Scale (PDSS) [15] includes 32 items related to daily sleep patterns, school achievement, mood, sleepiness, QoL and extracurricular activities in a Likert-scale format (eg, never = 0, seldom = 1, sometimes = 2, frequently = 3, always = 4). Higher scores indicate greater levels of sleepiness [15]. Only participants over the age of 10 years completed the PDSS.

4. The Adolescent Sleep Wake Scale (ASWS) is a 28-item self-report instrument that assesses sleep quality in 12- to 18-years-old adolescents [16]. ASWS uses a 6-point scale (“always,” “frequently-if not always,” “quite often,” “sometimes,” “once in a while” and “never”), which is measured along five behavioral dimensions: going to bed, falling asleep, maintaining sleep, reinitiating sleep and returning to wakefulness. The higher scores indicate better sleep quality [16]. This questionnaire was utilized with adolescent patients (older than ten years).

5. The KINDL^{R} Questionnaire for Children and Adolescents is a short, methodologically suitable and flexible set of instruments, which can be completed by either children/adolescents or their parents. This was available for different age groups and stages of development, which is validated not only for healthy but also ill children [17]. It consists of 24 Likert-scaled items (1 = never, 2 = sometimes, 3 = very often) associated with six dimensions: physical well-being, emotional well-being, self-esteem, family, friends and everyday functioning (school or nursery school/kindergarten). Moreover, KINDLR also has another dimension to assess chronic illness, which assesses prolonged illness or hospitalization of children. This dimension was used in patients with IBD- but not healthy controls. A higher score corresponds to a higher QoL. Parents and adolescents independently completed the KINDL-R for both IBD patients and healthy controls.

6. The Pediatric Symptom Checklist (PSC) is a 35-items screening measure of psychosocial functioning [18]. Parents and patients rate each of the items as occurring “often”, “sometimes” or “never” with numeric values of 2, 1 and 0, respectively. A score of 28 or higher within a range of 0–70 for children aged 6–16 years-old indicates a level of psychosocial difficulties that may benefit from further assessment by a mental health provider. The PSC has shown high rates of sensitivity (77% to 95%) and specificity (68% to 100%) [18].

Disease activity

Participants were diagnosed with IBD by a pediatric gastroenterologist, who determined disease activity based on the Pediatric Crohn’s disease activity index (PCDAI) [19] in the CD group. This is a weighted score based on symptoms reported by patients, laboratory values and physical examination findings. Patients were defined to have either inactive, mild, or moderate/severe disease based on their PCDAI score (range from 0–100; 0–10 = inactive, 11–30 = mild, ≥31 = moderate/severe). Disease activity in UC patients was determined by the Pediatric Ulcerative Colitis Activity Index (PUCAI) [20], which is based on patient-reported symptoms. The PUCAI was used as a primary outcome measure to reflect disease activity in pediatric UC. Total sum scores of PUCAI (range from 0–85) were divided into groups of remission (< 10), mild disease (10–29), moderate (30–64) and severe (≥ 65). Additionally, we reviewed routine laboratory tests collected as part of the clinic visit, which included Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). Patients with indeterminate IBD were assessed using the PUCAI score.

Statistical analysis

Statistical analysis was performed by a medical biostatistician (B.W.). Summary statistics for continuous variables were analyzed by t-test when comparing mean values of two samples when both sample sizes were 30 or larger. For sample sizes that were less than 30, normality was assessed from the Shapiro test. If the normality test failed, the Mann-Whitney U test (Wilcox test) was used for statistical analysis. Additionally, results were validated from a permutation test. For numeric variables, we compared the mean values from an unpaired t-test. For categorical variables, we compared the distribution of different levels from a Fisher's exact test. Spearman's correlation coefficients (r) were used to evaluate for correlation between two quantitative variables. A significance level of 0.05 was used to determine the significance of results.

Results

Patients characteristics

A total of 53 IBD patients (38 CD, 12 UC and 3 indeterminate colitis), 32 parent controls and 29 adolescent controls were enrolled in our study. There were 45 adolescent IBD subjects (32 with CD, 10 with UC and 3 with indeterminate IBD), who were older than or equal to ten years, who filled out the questionnaires independently.

Health related quality of life

Within the parental section of the KINDL^R, there was a significant inverse relationship between the age at the time of diagnosis of IBD and the KINDL^R score, ($r = -0.31$, $p = 0.02$), meaning that as the age of diagnosis of IBD decreased, the QoL significantly improved. Analysis of IBD symptoms including nocturnal abdominal pain, nocturnal bowel movement(s) and feeling too cold/hot significantly correlated with KINDL^R scores ($p = 0.001$, 0.003 and 0.015, respectively). There were no significant correlations between the parental section of the KINDL^R and disease activity based on PCDAI or PUCAI scores (Table 2). However, the UC remission group (mean KINDL^R = 72.50) had a significantly better KINDL^R score than the UC active group (mean = 55.52) by parental report ($p = 0.05$), meaning that remission patients with UC had significantly better QoL than active disease patients with UC.

Analysis of parental KINDL^R subscales for physical and school functioning found significantly lower scores for pediatric IBD patients compared to healthy controls ($p = 0.001$ and 0.02, respectively; Figure 1). However, KINDL^R scores were similar between IBD patients and healthy controls for other subscales and total score (Figure 1). Moreover, parental KINDL^R was inversely correlated with white blood cell (WBC) significantly within the UC group ($p = 0.05$, Table 3) but not the total IBD or CD group, meaning that UC patients with higher WBC had significantly worse QoL. As for Table 4, there were significant correlations between PCDAI and physical well being, self esteem, family and friends, meaning that CD patients with more severe disease activity performed significantly worse within these subscales of QoL.

Within the adolescent section of the KINDL^R, there was a significant inverse correlation between the age at the time of diagnosis of IBD and the KINDL^R score ($r = -0.47$, $p = 0.001$). There was also a significant relationship between the white blood cell (WBC) count and the KINDL^R score ($p = 0.04$) but there were no significant correlations between the KINDL^R score and other characteristics or laboratory tests, meaning that IBD patients with higher WBC had significantly worse QoL. Nocturnal abdominal pain and nocturnal bowel movement(s) were significantly correlated with KINDL^R (p values = 0.008 and 0.001, respectively). There were no significant correlations between the KINDL^R, PCDAI or PUCAI scores. However, those in remission in the UC group (mean KINDL^R = 68.75) had a significantly better KINDL^R score than the UC active group (mean = 46.22) by adolescent report ($p = 0.02$), meaning that remission patients with UC had significantly better QoL than active disease patients with UC. Furthermore, there were no significant differences in the QoL score between IBD patients and healthy controls reported by adolescents.

Analysis of KINDL^R subscales in adolescent reporting revealed that physical functioning was inversely correlated with PCDAI and PUCAI, which reached the level of statistical significance (Table 4), meaning that IBD with more severe disease activity had significantly worse physical functioning in both groups (CD and UC). Moreover, as for the UC group, the emotional well-being, self-esteem and friends subscales were also inversely correlated with PUCAI (Table 4). Additionally, there was no significant difference in the KINDL^R scores reported by parents (mean KINDL^R = 67.07) and adolescents (mean KINDL^R = 64.07, $p = 0.42$; see Figure 1).

Psychosocial functioning

Eight out of 53 parents (18%) reported some level of psychosocial difficulties due to a PSC score of 28 or higher while 9 out of 45 adolescents (20%) reported some level of psychosocial difficulties. There was a significant relationship between ESR and PSC scores from parent responses ($r = 0.42$, $p = 0.001$, Table 2), meaning that the higher ESR was significantly correlated with lower/worse psychosocial functioning.

Regarding the laboratory tests, only ESR in the CD group and CRP in the UC group were significantly correlated with PSC reported by parents and adolescents ($p = 0.003$, 0.01 respectively, Table 3), meaning that patients with higher ESR and CRP had significantly worse psychosocial difficulties. There were no significant differences of PSC scores between active and remitted disease in CD or UC group.

A comparison between parental and adolescent responses to the PSC was shown in Figure 2. Adolescents with UC (mean PSC = 12.46) reported a significantly higher PSC score or worse psychosocial functioning than observed by parents (mean PSC = 6.46, $p = 0.01$), while the PSC in total IBD and CD groups were similar.

Differences between CD and UC

Patients with CD (mean KINDL^R = 67.80) had a significantly better QoL score than patients with UC (mean KINDL^R = 54.88, $p = 0.02$) by adolescent report (Table 5). PSC scores recorded by patients with UC (mean = 12.46) were significantly higher than those reported by patients with CD (mean = 8.09, $p = 0.02$, Table 5), meaning that patients with UC

reported significantly worse psychosocial difficulties than patients with CD. There were no significant differences in night-time symptoms between CD and UC patients including: night-time bowel movement(s), night-time abdominal pain or feeling too cold/ hot.

Analysis of KINDL^R subscales (the emotional well-being and school functioning) reported by parents show the CD group reported significantly better scores than the UC group (Table 5). As for adolescent subscales reports, the CD group also reported significantly better scores than the UC group in terms of physical well-being, self-esteem, family and prolong illness subscales (Table 5).

Comparison of correlations between all sleep questionnaires, QoL and psychosocial functioning

For youth with IBD, there were significant negative correlations between the PSQI and KINDL^R and between the PDSS and KINDL^R ($r = -0.62$, $p < 0.0001$; $r = -0.57$, $p < 0.0001$, respectively, Table 2). Also, the ASWS was significantly correlated with the KINDL^R ($r = 0.29$, $p = 0.04$), meaning that pediatric IBD patients with poorer sleep quality had significantly worse QoL. PSQI and PDSS scores were significantly correlated with the KINDL^R score not only for the total IBD group but also the separated CD and UC groups (Table 3). Furthermore, there was positive correlation between ASWS and KINDL^R in the total IBD and CD groups but not in the UC group (Table 2 and 3).

7) The PSQI and PDSS were significantly correlated with adolescent PSC (Table 2), meaning that pediatric IBD with more sleep disturbance had significantly worse psychosocial difficulties.

Discussion

To our knowledge, this is the first study to present the correlation among sleep disturbance, impact on QoL and psychosocial functioning in pediatric IBD. Children with IBD may experience an impaired QoL and an increased risk of psychosocial difficulties. The results of this present study indicate that sleep disturbance is a major factor related to low QoL and psychosocial difficulties in children with IBD.

Quality of life scores inversely correlated with quality of sleep based on the PSQI in adult inactive IBD subjects [21]. This was similar to the observations in the present pediatric study (PSQI, PDSS and ASWS). In an adult Japanese study, Uemura et al. [22] reported that QoL scores were significantly lower in patients with any sleep disturbance than in patients without sleep disturbance. Another study in adults showed that sleep disorders, which included longer sleep latency, shorter sleep duration and fatigue, are characteristic symptoms of restless legs syndrome in IBD patients, resulting in worse QoL [23]. This pediatric study showed that the adolescent sleep questionnaires significantly correlated with QoL and psychosocial functioning scores. This implies that patients with more sleep disturbance had poorer QoL and psychosocial difficulty outcomes.

Patients with IBD may have some sleep disturbance because of nocturnal abdominal pain or the presence of ostomies that require night-time care. This present study showed patients

who had abdominal pain and bowel movement(s) overnight had worse QoL than patients who did not have nocturnal symptoms. However, in this small sample of those having ostomies, this relationship was not observed. Use of medications such as corticosteroids [24] may also cause sleep disturbance or changes in mood and QoL. One pediatric study showed patients with CD who were treated with corticosteroids had significantly lower scores in bowel symptoms and systemic symptoms domains in the QoL score (IMPACT) compared to steroid-free CD patients (P=0.047 and 0.045 respectively) [25]. However, this present study did not show any correlation between corticosteroid use, sleep disturbance and QoL scores.

Previous studies investigating QoL in children with IBD reveal its negative effects on body image, self-esteem, mood and social functioning [26]. Results from studies concerning QoL indicate that thirty-one to fifty percent of children report that IBD restricts their social activities [12]. Moreover, children with IBD have been found to have fewer close friends and are less likely to participate in organized activities than healthy children [27]. Additionally, short stature and delayed puberty in children suffering from IBD may contribute to lower self-esteem and feeling different from friends. Significantly, more parents of children with IBD reported clinical problems in social competence (22%) than parents of healthy children (2%) [27]. Interestingly, Pirinen et al. [28] reported 157 adolescents with IBD reporting sleep problems had significantly more psychosocial symptoms than adolescents without sleep trouble.

Another pediatric study compared children with IBD to an age-standardized healthy population and demonstrated that the QoL score was strongly correlated with disease activity (P<0.001) [29]. Chouliaras et al. [25] reported that disease activity assessed by either the PUCAI, PCDAI or Physician's Global Assessment was significantly associated with all sub-domains of the QoL scores (IMPACT). In contrast, this present study did not show any significant correlations between the QoL score and disease activity (PCDAI and PUCAI). However, Haapamäki's report [29] used a three-level scale based on symptom severity from patient's history to assess the disease activity, which differed from this present study that utilized, PCDAI and PUCAI in order to compare the disease activity.

This present study found that as the age of diagnosis of IBD decreased, the QoL significantly improved, which was similar to the largely prospective pediatric IBD assessment of QoL based on the IMPACT questionnaire during the first 12 months after diagnosis [30]. Haapamäki et al. [29] also reported that the oldest age group with IBD had significantly lower QoL scores than the age-standardized population and there was no gender difference in the QoL scores. Another study showed the QoL score (IMPACT) was positively related to disease duration (P=0.04) and the age at IMPACT completion (p=0.05) [25]. We hypothesized that children growing into adolescence would develop less vulnerability to psychosocial difficulties due to their chronic illness. Genders, hospitalization during the previous 2 years and current types of medications were not correlated to the KINDL^{R} QoL score in this present study.

One Swiss study demonstrated that parents of children with IBD reported a significantly lower overall QoL for their children with IBD, as well as lower subscales of mood, family life and friends [31]. Diederen et al. [32] recently reported significantly lower QoL scores

(total PedsQL) in pediatric IBD subjects compared to healthy children. The difference in the QoL scores in the present study from the report by Diederen et al. [32] may be explained by the use of different QoL questionnaires. However, the PedsQL subscale score from Diederen et al. [32] found significantly lower physical and school functioning in pediatric IBD than in healthy children, which was similar to the differences between KINDL^R scores in the present study.

Claar et al. [33] found that pediatric patients with CD reporting pain while in remission or a flare-up were significantly associated with a decreased QoL. In another recent study, gastrointestinal symptoms were significantly associated with a decreased QoL score including: stomach pain, food/drink limits, gas/bloating, constipation, bloody stools and diarrhea [34]. This present study also reported that night-time bowel movement(s), night-time abdominal pain and feeling too cold/hot were inversely correlated with the QoL. Interestingly, this present study also showed only patients with UC in remission had significantly better QoL than UC subjects with active disease but no significant difference was observed in CD subjects.

Previous studies have been inconsistent regarding comparisons of QoL between patients with CD and UC. Some studies suggested that there are no differences of QoL between CD and UC [35,36], whereas one study showed that adults with CD had worse scores than those with UC on measures of PROMIS global health (P=0.027), physical functioning (P=0.047) and pain interference (P=0.0009) [37]. Chouliaras et al. [25] reported in pediatrics, CD patients had better QoL than UC patients although they did not reach statistical significance. Another pediatric study reported there were no significant differences in the quality of life (PedsQL) scores between pediatric CD and UC [38]. In contrast, this present finding demonstrated patients with CD had a significantly better QoL than patients with UC in terms of the physical well-being, emotional well-being, school performance, self-esteem, family, prolong illness, and total QoL score (KINDL^R score). Although CD and UC are both chronic gastrointestinal diseases, there are some differences in symptoms, clinical response and immune response. We speculate that pediatric patients with UC had a worse QoL score than adult patients with UC because pediatric UC is more likely to progress to worse disease activity than adult UC. One study showed children with UC are more likely to require a colectomy compared to adults with UC [39]; however; we did not include the effects of colectomy in this study due to a small number of colectomy patients. Future studies are needed to investigate the disease activity between pediatric and adult IBD.

One pediatric IBD study showed an overall significant (P<0.05) inverse association between the QoL (IMPACT III), fecal calprotectin and ESR, whereas albumin, hemoglobin and vitamin-D were directly and significantly associated [40]. Another pediatric study showed laboratory results (hemoglobin, ESR, CRP, white blood cell and platelet) did not correlate with the QoL scores [29]. However, this present study did not include the fecal calprotectin and found only the inverse correlation between WBC and QoL to be significant, meaning that pediatric IBD with leukocytosis had a significantly lower QoL score. This present study also found a significantly positive correlation between psychosocial functioning scores and level of ESR, meaning that pediatric IBD with higher psychosocial difficulty had a significantly higher ESR level.

This present study has several limitations. First, the cross-sectional design of the study prevents the ability to determine causal relationships. We speculated a bi-directional relationship between sleep and QoL in IBD. Secondly, sleep characteristics were based on survey responses, instead of polysomnography, which is a more objective measure of sleep quality. Thirdly, sleep disturbance in IBD may be caused by other factors, such as psychological stress, pain, anxiety or depression, which were not analyzed in the present study.

In conclusion, sleep disturbance might affect QoL and psychosocial function. The direction of this relationship needs further investigation. Therefore, physicians treating IBD patients should be alert for sleep disturbance and recognize its impact on the QoL. Correct diagnosis and treatment of sleep disturbance in pediatric IBD can potentially increase one's QoL, and decrease psychosocial difficulty and disease activity. Future studies with larger sample sizes could attempt to understand more about the relationship between sleep disturbance, QoL and disease activity. Psychological counseling and referral to sleep specialists for children with IBD is advised in addition to standard treatment schedules.

Acknowledgement

We would like to thank the following doctors for helping our initiation at the beginning of this project: Dr. George J. Fuchs and Dr. Elizabeth M. McDonough

Funding Source

Statistical analysis in this project was supported by a grant from the Simons Foundation (# 422535, Bin Wang) and an award from the National Center for Advancing Translational Sciences of the National Institutes of Health (UL1TR001417).

Abbreviations:

IBD	Inflammatory Bowel Disease
CD	Crohn's Disease
UC	Ulcerative Colitis
PSC	Pediatric Symptom Checklist
CSHQ	Child Sleep Habits Questionnaire
PSQI	Pittsburgh Sleep Quality Index
PDSS	Pediatric Daytime Sleepiness Scale
ASWS	Adolescent Sleep Wake Scale
QoL	Quality of Life

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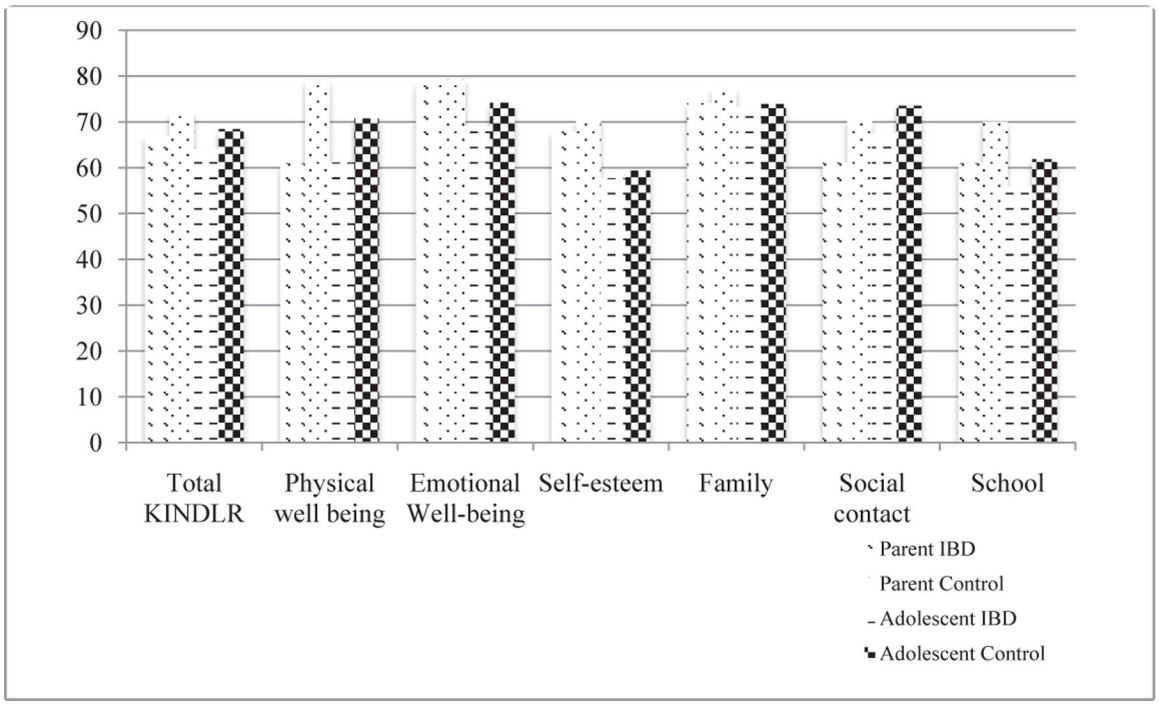

Figure 1:
Comparison of KINDLR scores between IBD subjects and controls.

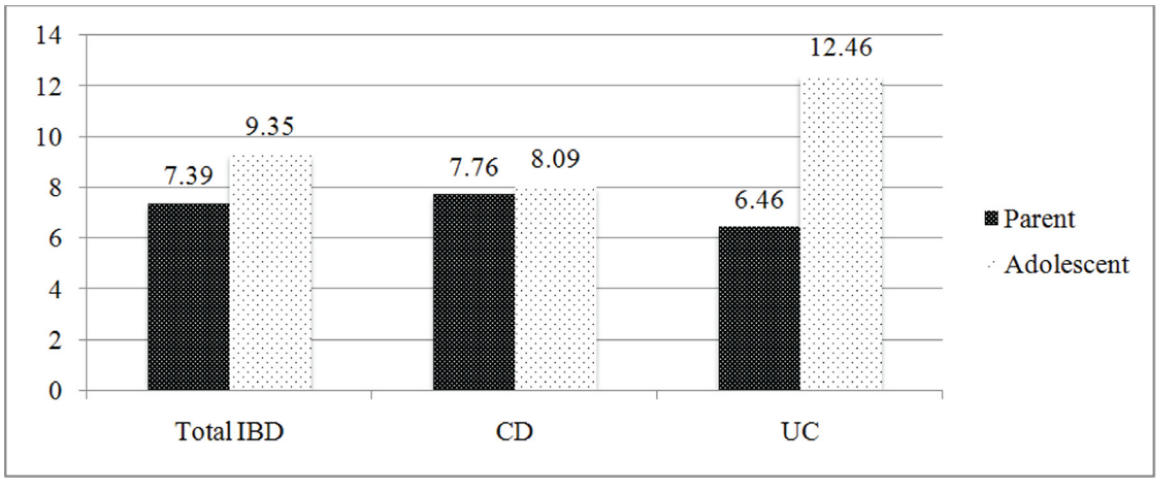

Figure 2:
Comparison of the Pediatric Symptom Checklist (PSC) in IBD.

Ann Gastroenterol Dig Disord. Author manuscript; available in PMC 2019 May 20.

Table 1:

Characteristics of IBD patients.

Characteristics	Total IBD	Crohn's Disease	Ulcerative Colitis/Indeterminate colitis	p-value
1. Number of IBD patients (%)	53	38 (71.7%)	12/3 (28.3%)	**0.01**
2. Sex (%)				
- Male	25	20 (80%)	5 (20%)	0.23
- Female	28	18 (64.3%)	10 (35.7%)	
3. Ethnicity				
- Caucasian	34	23 (67.6%)	11 (32.4%)	0.53*
- African American	18	14 (77.8%)	4 (22.2%)	
- Arabic	1	1 (100%)	0	
4. Age at enrollment (years, mean ± SD)	13.88 ± 3.43	13.88 ± 3.52	13.89 ± 3.34	0.99
5. Age at diagnosis of IBD (years, mean ± SD)	11.38 ± 3.59	11.04 ± 3.39	12.24 ± 4.05	0.32
6. Surgery (resection/colostomy)	10	10	0	**0.04**
7. Number of hospitalization within past 2 years (%)	28	17 (60.7%)	11 (39.3%)	0.07
8. Percentile of weight (kg, mean ± SD)	63.85 ± 31.11	57.96 ± 33.42	78.80 ± 17.52	**0.004**
9. Percentile of height (cm, mean ± SD)	42.34 ± 28.76	40.38 ± 28.35	47.33 ± 30.21	0.45
10. Percentile of BMI (kg^2/cm, mean ± SD)	70.79 ± 27.56	65.66 ± 29.32	83.77 ± 17.25	**0.05**
11. Current medication (%)				
- Mesalamine	36	23 (63.8%)	13 (36.2%)	0.10
- Steroid	23	16 (69.5%)	7 (30.5%)	0.77
- Azathioprine	18	14 (77.8%)	4 (22.2%)	0.54
- Infliximab	18	14 (77.8%)	4 (22.2%)	0.54
- Adalirumab	8	6 (75%)	2 (25%)	1.0
12. Laboratory tests				
- Hematocrit (%, mean ± SD)	37.10 ± 6.08	37.26 ± 5.36	36.68 ± 7.83	0.79
- Hemoglobin (g/dL, mean ± SD)	13.47 ± 5.67	13.21 ± 5.06	14.14 ± 7.15	0.65
- WBC ($x10^3/mm^3$, mean ± SD)	7.9 ± 2.6	7.8 ± 2.5	8.3 ± 2.8	0.55
- Platelet count ($x10^3/mm^3$, mean ± SD)	334 ± 85	333 ± 82	334 ± 96	0.97
- ESR (mm/hr, mean ± SD)	15.83 ± 16.20	16.89 ± 17.77	13.13 ± 11.38	0.36
- Serum albumin (g/dL, mean±SD)	4.09 ± 0.55	4.08 ± 0.57	4.11 ± 0.49	0.84

Characteristics	Total IBD	Crohn's Disease	Ulcerative Colitis/Indeterminate colitis	p-value
- CRP (mg/dL, mean ± SD)	2.76 ± 4.44	3.31 ± 5.02	1.54 ± 2.08	0.07
13. Severity of disease				
- Remission	32	27 (84.4%)	5 (15.6%)	**0.03**
- Mild disease	14	10 (71.4%)	4 (28.6%)	1.00
- Moderate/severe	7	1 (14.3%)	6 (85.7%)	**0.03**
14. Sleeping pill use (%)	6	5 (83.3%)	1 (16.7%)	0.66

SD: Standard Deviation; BMI: Body Mass Index; WBC: White Blood Cell; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein.

Table 2:

Correlations between sleep surveys, KINDLR, psychosocial functioning, laboratory tests and IBD severity score (p-value).

	Parent KINDL^R	Adolescent KINDL^R	Parent PSC	Adolescent PSC
CSHQ	−0.19 (0.17)	N/A	−0.11 (0.43)	N/A
PSQI	N/A	−0.62 (<**0.001**)	N/A	0.39 (**0.007**)
PDSS	N/A	−0.57 **(< 0.001)**	N/A	0.35 (**0.02**)
ASWS	N/A	0.29 (**0.04**)	N/A	−0.22 (0.15)
PCDAI	−0.09 (0.58)	−0.18 (0.31)	−0.25 (0.12)	0.04 (0.82)
PUCAI	−0.48 (0.06)	−0.39 (0.18)	0.25 (0.36)	0.13 (0.67)
Hct	−0.02 (0.90)	−0.09 (0.55)	0.04 (0.74)	0.18 (0.22)
Hb	−0.16 (0.26)	−0.05 (0.76)	0.16 (0.23)	−0.01 (0.99)
WBC	−0.05 (0.71)	−0.30 **(0.04)**	0.03 (0.78)	0.13 (0.38)
Platelet	0.03 (0.82)	0.03 (0.86)	0.02 (0.88)	0.01 (0.99)
ESR	0.03 (0.82)	0.01 (0.95)	0.42 (**0.001**)	−0.14 (0.35)
Albumin	0.16 (0.25)	0.14 (0.33)	0.20 (0.15)	0.14 (0.36)
CRP	0.18 (0.19)	0.04 (0.82)	−0.14 (0.29)	−0.14 (0.34)

Hct: Hematocrit; Hb:, Hemoglobin; WBC:White Blood Cell; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein

Table 3:

Correlations of sleep surveys, KINDL^R, psychosocial functioning and laboratory tests between the CD and UC groups separately (p-value).

	Parent KINDL^R	Adolescent KINDL^R	Parent PSC	Adolescent PSC
CD				
1. CSHQ	0.20 (0.24)	N/A	−0.01 (0.94)	N/A
2. PSQI	N/A	−0.52 (**0.001**)	N/A	0.29 (0.10)
3. PDSS	N/A	−0.53 (**0.001**)	N/A	0.32 (0.07)
4. ASWS	N/A	0.37 (**0.03**)	N/A	0.04 (0.83)
5. Hct	−0.11 (0.53)	−0.02 (0.90)	0.15 (0.35)	0.17 (0.33)
6. Hb	−0.15 (0.38)	0.05 (0.78)	0.16 (0.34)	−0.01 (0.99)
7. WBC	0.14 (0.38)	−0.17 (0.34)	−0.03 (0.82)	0.16 (0.36)
8. Platelet	0.07 (0.65)	−0.03 (0.86)	0.02 (0.88)	0.14 (0.42)
9. ESR	0.10 (0.53)	−0.06 (0.75)	0.46 (**0.003**)	−0.11 (0.55)
10. Serum albumin	0.06 (0.69)	0.13 (0.48)	0.19 (0.24)	0.20 (0.26)
11. CRP	0.25 (0.13)	−0.18 (0.32)	−0.13 (0.44)	0.10 (0.55)
UC/Indeterminate IBD				
1. CSHQ	−0.41 (0.13)	N/A	−0.05 (0.84)	N/A
2. PSQI	N/A	−0.59 (**0.03**)	N/A	0.18 (0.54)
3. PDSS	N/A	−0.60 (**0.03**)	N/A	0.19 (0.52)
4. ASWS	N/A	0.15 (0.61)	N/A	0.01 (0.98)
5. Hct	0.21 (0.46)	−0.02 (0.95)	−0.11 (0.67)	0.23 (0.45)
6. Hb	−0.17 (0.54)	−0.02 (0.94)	0.12 (0.67)	−0.16 (0.60)
7. WBC	−0.50 (**0.05**)	−0.35 (0.24)	0.17 (0.54)	−0.27 (0.37)
8. Platelet	−0.06 (0.82)	0.21 (0.49)	0.05 (0.84)	−0.33 (0.27)
9. ESR	−0.13 (0.65)	0.04 (0.89)	−0.32 (0.24)	−0.14 (0.65)
10. Serum albumin	0.39 (0.15)	0.38 (0.19)	0.17 (0.54)	−0.34 (0.25)
11. CRP	0.02 (0.94)	0.34 (0.24)	0.07 (0.81)	0.71 (**0.01**)

Hct: Hematocrit; Hb: Hemoglobin; WBC: White Blood Cell; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein.

Table 4:

Correlation between subscales of quality of life scores and IBD severity score.

	PCDAI		PUCAI	
Parent Report	**Spearman's correlation coefficients**	**p-value**	**Spearman's correlation coefficients**	**p-value**
Total KINDL^R score	−0.09	0.58	−0.48	0.06
1. Physical well-being	0.51	**0.001**	−0.30	0.28
2. Emotional well-being	0.22	0.16	−0.25	0.37
3. Self-esteem	0.50	**0.001**	−0.45	0.09
4. Family	0.55	**0.001**	−0.34	0.21
5. Friends	0.36	**0.04**	−0.36	0.18
6. School	0.28	0.11	−0.51	**0.05**
7. Prolong illness	−0.07	0.66	0.18	0.51
Adolescent Report	**Spearman's correlation coefficients**	**p-value**	**Spearman's correlation coefficients**	**p-value**
Total KINDL^R score	−0.18	0.31	−0.40	0.17
1. Physical well-being	−0.41	**0.02**	−0.54	**0.05**
2. Emotional well-being	0.008	0.96	−0.67	**0.01**
3. Self-esteem	−0.08	0.96	−0.74	**0.003**
4. Family	−0.09	0.61	−0.20	0.51
5. Friends	−0.06	0.72	−0.62	**0.02**
6. School	−0.16	0.37	−0.06	0.85
7. Prolong illness	0.32	0.07	0.31	0.30

Table 5:

Characterization of total and subscales of quality of life scores within pediatric IBD patients.

	Total IBD		CD		UC		Difference between CD & UC
Parent Report	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Total KINDL^R score	67.08	15.65	69.41	15.16	61.18	15.84	0.09
1. Physical well-being	60.96	24.11	65.13	22.11	50.42	26.46	0.07
2. Emotional well-being	74.00	16.89	81.75	14.46	70.42	20.11	**0.04**
3. Self-esteem	64.25	18.87	65.71	18.55	64.58	20.27	0.87
4. Family	66.75	18.11	68.07	19.02	67.50	16.22	0.57
5. Friends	74.06	17.40	76.64	15.15	67.50	21.28	0.18
6. School	61.08	21.15	66.77	16.76	46.66	24.65	**0.003**
7. Prolong illness	37.73	19.20	37.50	19.15	38.33	19.99	0.72
Total PSC score	7.39	6.02	7.76	5.88	6.47	6.10	0.38
Adolescent Report	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Total KINDL^R score	64.07	18.61	67.80	18.90	54.88	14.76	**0.02**
1. Physical well-being	61.11	26.48	66.99	27.27	46.63	18.15	**0.02**
2. Emotional well-being	69.02	21.40	72.65	18.70	60.10	25.58	0.12
3. Self-esteem	57.64	21.36	60.74	22.85	50.00	15.31	**0.02**
4. Family	73.19	23.64	76.75	24.24	64.42	20.31	**0.04**
5. Friends	67.50	19.70	70.70	20.23	59.61	16.46	0.06
6. School	55.97	28.76	59.76	28.13	48.55	24.63	0.17
7. Prolong illness	33.19	24.42	27.5	25.08	48.07	14.96	**0.001**
Total PSC score	9.35	5.98	8.09	5.84	12.46	5.33	**0.02**