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SLEEP DISTURBANCE AND DISEASE ACTIVITY IN ADULT PATIENTS WITH INFLAMMATORY BOWEL DISEASES

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The aim of the study was to identify whether poor quality of sleep is connected to inflammatory bowel disease (IBD) and if so, whether sleep disturbances are related to disease activity. Prospective, observational cohort study was performed. In all enrolled adult patients, the disease activity was assessed by using Crohn's Disease Activity Index (CDAI) for Crohn's disease (CD) and Partial Mayo Score for ulcerative colitis (UC), respectively. All patients were also asked to respond to a questionnaire to define Pittsburgh Quality Sleep Index (PSQI). Sixty-five patients were enrolled in our study: n = 30 with CD and n = 35 with UC. The poor sleep was noted in 78% (40/51) patients with clinically exacerbation and in 35% (5/14) patients in remission (P = 0.002; OR 6.5, 95% confidence interval, 1.8 – 23.6). A global PSQI score of 5 points yielded a sensitivity of 84%, a specificity of 39%, and a positive predictive value of 89% for discriminating participants with exacerbation of IBD from those in clinical remission; PSQI higher than 6 indicates the exacerbation of IBD with 77% sensitivity and 62% specificity. The poorest sleep quality was reported in IBD patients with severe exacerbations (9.1 ± 2.9). Sleep disturbance was confirmed in adult IBD patients, both in CD and UC. Confirmation of the relationship between sleep abnormalities and IBD may show the new pathway in pathophysiology, course and treatment of IBD.

Key words: *sleep disturbances, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, C-reactive protein*

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) belong to inflammatory bowel disease (IBD), a group of chronic, immune system-mediated inflammatory diseases of the gastrointestinal (GI) tract (1). The pathogenesis of IBD is not well recognized: however, a similar cytokine activation pattern is also observed in rheumatoid arthritis, psoriasis, and systemic lupus erythematosus, which are all associated with generalized immune imbalance (2-4). Environmental and infectious factors, together with genetic predisposition lead to elevated levels of proinflammatory cytokines and specific (abnormal) tissue responses during the course of IBD (5, 6).

Nowadays sleep is known as vital to health and quality of sleep is an important aspect in human life (7). Recent studies showed that individuals with sleep disturbance are exposed to serious adverse health and economic consequences (8). Sleep and its disturbance are rather subjective. In order to standardize and objectify sleep disturbances, in 1989 Buysse *et al*. introduced Pittsburgh Quality Sleep Index (PSQI) (9). Recent studies suggested that sleep disturbances may play crucial role in the course of diseases like asthma, systemic lupus erythematosus and rheumatoid arthritis (10-11). Currently, the relationship between IBD and sleep disturbance is still unclear. The aim of our study was to identify whether poor quality of sleep is connected to IBD in adult patients and if so, whether sleep disturbances are related to disease activity. In this study we formulated the hypothesis that among adults with IBD there is a relationship between poor subjective sleep and disease exacerbation and higher inflammatory markers.

MATERIALS AND METHODS

A prospective, observational cohort study was conducted to assess the relationship of the sleep disturbances and disease activity in IBD patients. Adult patients with IBD of Caucasian origin admitted to the gastroenterology department were enrolled to the study. Data on demographics, medical history, and lifestyle habits have been collected by self-administered questionnaires. In all enrolled patients the disease activity was assessed by using validated scales including Crohn's Disease Activity Index (CDAI) for CD and Partial Mayo Score for UC, respectively.

According to European Crohn's and Colitis Organization (ECCO). The second European evidence-based consensus on the diagnosis and management of Crohn's disease, for CD, CDAI < 150 was defined as remission; CDAI 150-220 with no features of obstruction, fever, dehydration, abdominal mass, or tenderness was defined as mild CD; CDAI 220-450 or intermittent vomiting, or weight loss > 10% or treatment for mild disease ineffective, or tender mass with no overt obstruction was defined as moderate CD; CDAI > 450 or

cachexia (BMI < 18 kg/m^2), or evidence of obstruction or abscess or persistent symptoms despite intensive treatment was defined as severe CD. For UC, clinical remission was defined as a Partial Mayo Score of 0; mild UC was defined as Partial Mayo Score of 1; moderate UC was defined as Partial Mayo Score of 2; severe UC was defined as Partial Mayo Score of 3.

All patients were asked to respond to a questionnaire to define Pittsburgh Quality Sleep Index (PSQI). PSQI was developed with several goals: to provide a reliable, valid and standardized measure of sleep disorders and to discriminate between "good" and "poor" sleepers. The PSQI survey is a 9-question, 19 item self-report instrument, designed to measure sleep quality and disturbance over a 1-month period. PSQI survey questions 1 – 4 request specific respondent information, such as customary bed time and length of time to fall asleep. PSQI survey questions 5 – 8 are answered on a 0 – 3 scale with 0 indicating no symptom presence and 3 representing symptom presence 3 or more times the past week. Question 9, concerning relationship with partner or roommate is answered on a 0 – 3 scale with 0 meaning "very good" and 3 representing "very bad". All scores are combined according to the scoring criteria included with the form to produce a Global PSQI Score. Scores above 5 indicate clinically significantly disturbed or poor sleep.

Questionnaire used in the study was a translated version of the original one (the applicant has obtained the consent from the authors of the original survey for use in the study). The original version, in English, has been translated into Polish and consulted with a professional psychologist and psychotherapist, who have permanent cooperation with IBD patients.

Additional laboratory tests including peripheral complete blood count and serum C-reactive protein (CRP) using automatic devices were also performed. In all groups the blood was taken at the time of admission.

Current smokers, obese patients (BMI > 25 kg/m^2), patients with a history of cardiovascular disease, pulmonary and kidney disease, allergy, diabetes, lichen planus, psoriasis, atopic dermatitis and other autoimmune skin lesions and those treated with anti-inflammatory drugs (except azathioprine and steroids), antioxidants, or statins, which can affect the inflammation process, anti-depressants, sedatives, hypnotics were excluded from the study.

The study was conducted in accordance with the ethical principles of the 1975 Declaration of Helsinki and the study protocol was approved by the Committee of Bioethics of Medical University of Lodz (RNN/621/14/KB). All participating subjects gave written, informed consent prior to enrollment.

Statistical analysis

The data were analyzed using the Prism 5.0 (GraphPad Software Inc., La Jolla, CA, United States). Continuous demographic and biochemical data are presented as means ± standard error of mean (SEM), demographic categorical data were described with absolute frequencies and percentages. An analysis of variance (one-way ANOVA or Kruskal-Wallis test) followed post-hoc tests (Bonferroni or Dunn's multiple comparisons test) were used to calculate differences. Shapiro-Wilk's W test was used to test the distribution of the variables. Comparisons between groups were performed using the Student's t-test (or nonparametric Mann-Whitney U-test) and $\chi 2$ test. A value of P values < 0.05 was considered statistically significant. Ct values obtained for reference gen were tested using Grubbs test for possible outliers.

RESULTS

Sixty-five patients who were hospitalized at the gastroenterology department were enrolled in the study: 30 with CD and 35 with UC. The detailed baseline characteristics data, laboratory findings and treatment history are demonstrated in *Table 1*. The analyzed groups were homogenous in terms of age, gender, and body mass index (BMI). There were no significant differences in disease type, gender, the presence of depression or CRP between the patients with clinical exacerbation and those in remission of disease.

In our study the poor sleep was noted in 69% (45/65) of IBD patients: in 78% (40/51) patients with clinically active and in 35% (5/14) patients with inactive disease (P = 0.002; OR 6.5, 95% confidence interval, 1.8 23.6). A global PSQI score of 5 points yielded a sensitivity of 84%, a specificity of 39%, and a positive predictive value of 89% for discriminating participants with exacerbation of IBD from those in clinical remission. ROC curves were constructed to assign optimal cutoff values associated with clinical exacerbation of disease. Area under curve was 0.75 for PSQI score. The analysis showed that PSQI higher than 6 indicates the exacerbation of IBD with 77% sensitivity and 62% specificity (*Fig. 1*).

Table 1. Baseline characteristics data, laboratory findings and treatment history for patients enrolled in the study.

		Crohn's disease	**Ulcerative colitis**	**P-value**
Subjects n (%)		30	35	NA
Sex	women, n (%)	13 (43%)	15 (43%)	0.878
	men, n (%)	17 (57%)	20 (57%)	
Age (years)		38.7 ± 12.5	42.0 ± 17.8	0.619
BMI (kg/m^2)		21.1 ± 2.4	21.0 ± 1.7	0.918
Disease duration (years)		5.3 ± 4.0	6.3 ± 8.2	0.773
Hemoglobin (g/dl)		12.7 ± 2.2	11.7 ± 2.8	0.151
White blood cell count (× 10^3/μl)		8.6 ± 3.6	9.6 ± 3.3	0.153
CRP (mg/l)		37.9 ± 64.5	29.7 ± 56.5	0.457
PSQI > 5, (n)		15	30	0.340

Data are presented as mean ± standard deviation (SD) or median (percentage) as appropriate. Comparisons between groups were performed using the Student's t-test (or nonparametric Mann-Whitney U-test) and $\chi 2$ test. *Abbreviations*: BMI, body mass index; CRP, C-reactive protein; PSQI, Pittsburgh Quality Sleep Index, NA, not applicable.

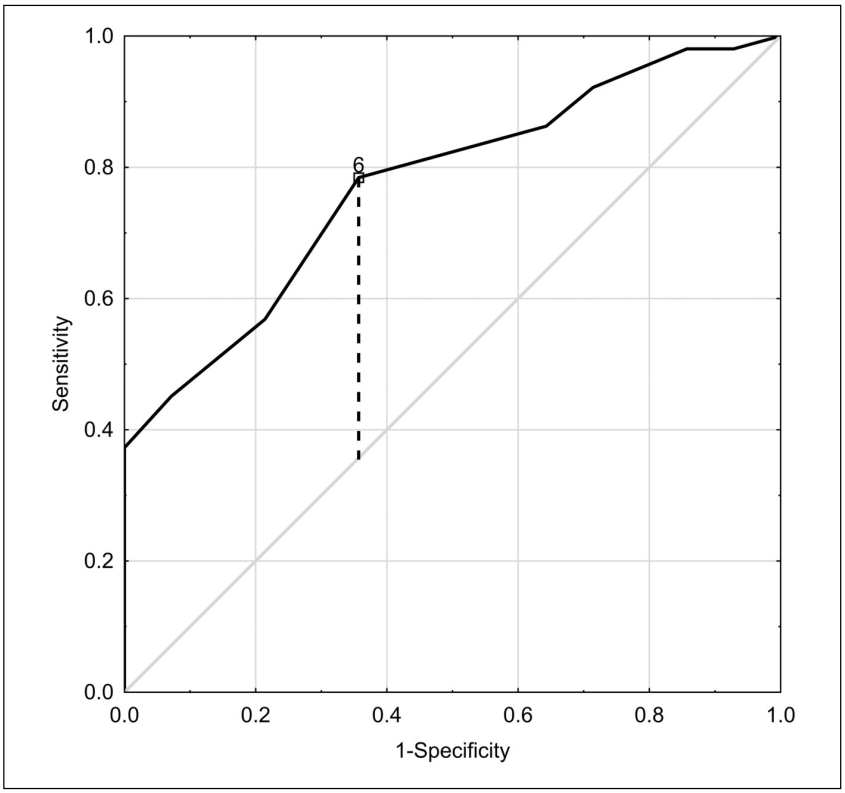

Fig. 1. Receiver operating characteristic (ROC) curves for PSQI score and the clinical exacerbation of disease in Crohn's disease and ulcerative colitis patients (AUC: 0.75; 77% sensitivity and 62% specificity).

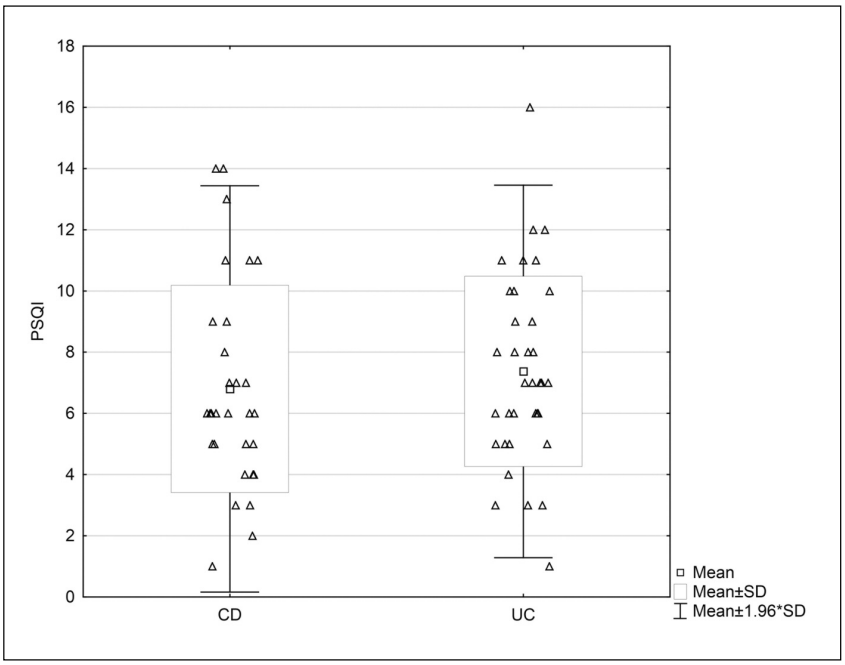

Fig. 2. The difference in PSQI score between Crohn's disease and ulcerative colitis patients (6.8 ± 3.4 versus 7.4 ± 3.1; P = 0.481).

There was no difference in quality of sleep between CD and UC patients (6.8 ± 3.4 versus 7.4 ± 3.1; P = 0.481) (*Fig. 2*). However, we observed statistically significant differences in quality of sleep related to clinical state of IBD patients (remission: 4.78 ± 0.69; mild: 5.55 ± 0.58; moderate: 9.78 ± 0.63; sever: 9.14 ± 0.69; P < 0.001) and the poorest sleep quality was reported in IBD patients with moderate and severe exacerbations (9.78 ± 0.63; 9.14 ± 2.9; respectively) (*Fig. 3*).

Finally, there was no linear correlation between CRP level and quality of sleep (r = –0.0724; P > 0.05) (*Fig. 4*). Furthermore, there was no statistically significant relationship between disease duration and sleep quality (r = 0.219; P > 0.05).

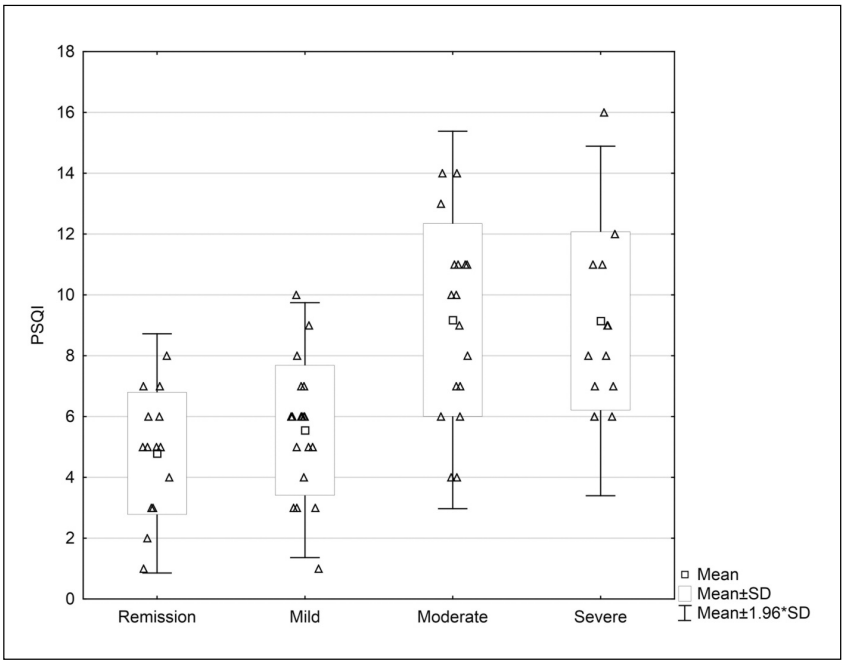

Fig. 3. The relationships between PSQI score and clinical status of disease in Crohn's disease and ulcerative colitis patients.

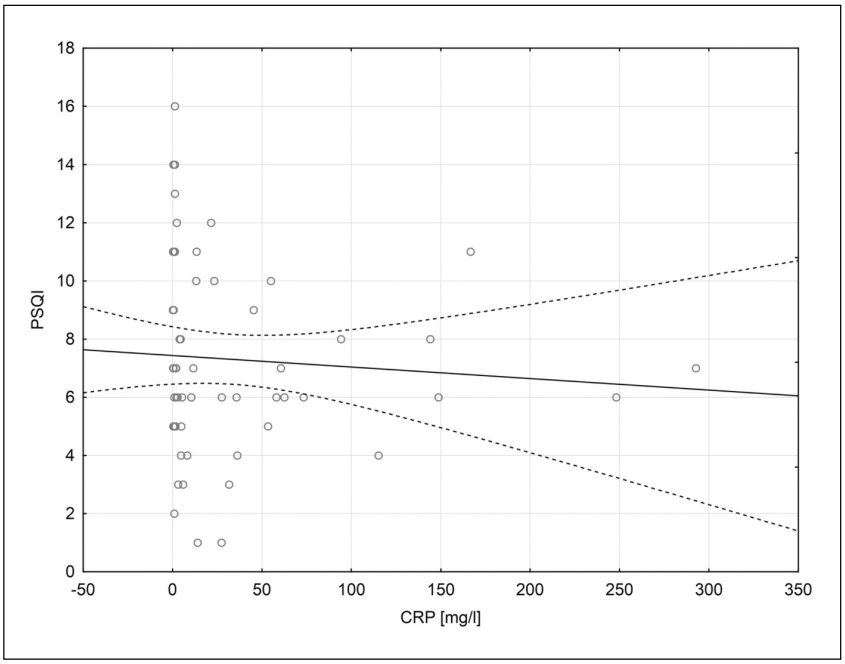

Fig. 4. The correlation between C-reactive protein (CRP) level and PSQI score ($r = –0.0724$; $P > 0.05$).

DISCUSSION

In our study, we identified a relationship between IBD and sleep disturbance. Specifically, we have proven that disease activity is associated with poor sleep quality and that there is a significant correlation between disease activity and PSQI score in both CD and UC, particularly in clinical exacerbation. Of note, of all patients with clinically active disease included in the study, 78% had poorer sleep quality.

Sleep is a naturally recurring state characterized by altered, relatively inhibited sensory activity. The mechanisms of sleep are only partially understood and have been the subject of a substantial, ongoing research. Sleep may help conserve energy, though this theory is not fully adequate as it only decreases metabolism by about 5 – 10% (12).

The role of sleep disturbances in IBD patients remained relatively unknown, with a small number of studies. In 2014 Ananthakrishnan *et al*. conducted a prospective study in women, enrolled in the Nurses' Health Study (NHS) I since 1976 and NHS II since 1989 and who were followed through detailed biennial questionnaires with > 90% follow-up (15). The results showed that less than 6 hours of sleep/day and more

than 9 hours of sleep/day are each associated with an increased risk of UC, but not CD (15). In recent papers by Maehlmann *et al*., it was reported that in children and adolescents with an active IBD, objective sleep was impaired and overall sleep quality and inflammation indices were associated in a complex manner. It seems thus advisable to include assessment of subjective sleep quality in the care of pediatric IBD patients as an additional indicator for objective sleep disturbances and inflammation (16, 17). Of note, Mahlmann *et al*., suggested that among children and adolescent patients with IBD an aerobic exercise training has the potential to improve exercise capacity, self-reported fitness, daily physical activity, and aspects of objective sleep (17).

Several studies reported that sleep quality may be strongly deteriorated by the presence of nocturnal symptoms of diarrhea and abdominal pain in IBD (18, 19). Sleep problems are also side-effects of medicine used in the treatment of IBD exacerbation such as steroids, mesalazine or aminosalicylic acid. However, overall there are too few reports to confirm that sleep disturbances are a risk factor of IBD.

In our study, we observed a relationship between IBD and the sleep quality. Poorer sleep quality was observed in 69% of IBD patients. This is in line with a recent study conducted by Keefer *et al*., reporting that IBD patients have subjective (PSQI score) and objective (using polysomnography) sleep disturbances compared to control group (18). In 2007 Ranjbaran *et al*. confirmed that IBD patients experience significant sleep disturbances (19). In the same study, it was noticed that the sleep disturbance in IBD subjects were similar to IBS subjects, but poorer sleep quality compered to healthy control.

In their recent studies Gamaldo *et al*., showed a correlation between the immune system and the quality of sleep. There is a hypothesis that adequate sleep strengthens immunological functions of the human body (13). On the other hand, sleep disorders have negative influence on the immune system. In line with this statement, Opp *et al*., recently showed that sleep deprivation can lead to immunological imbalance between pro- and anti-inflammatory cytokine levels (14). For example, experiments in relevant mouse models showed an increase in the level of proinflammatory proteins: interleukin (IL)-1β, IL-6 and tumor necrosis factor alpha (TNF-α), as well as CRP in patients with sleep disorders (14).

The relationship between sleep and the immunologic disturbances in IBD remains still unknown. In the study conducted by Uthgenannt *et al*., IL-1, IL-6, and TNF-α have been identified as major linking cytokines in sleep physiology and IBD development (20). It has been reported that production of TNF-α and IL-1 decreases during sleep, which promotes slow-wave sleep and nonrapid eye movement sleep. Moreover, inhibition of either IL-1 or TNF-α reduces spontaneous sleep. On the other hand, the hypothalamic-pituitary-adrenal (HPA) axis and circadian rhythm abnormalities play an important role in regulating and controlling immune responses and development of autoimmunological diseases.

Here we reported that sleep disturbances were significantly related to disease exacerbation, namely the sleep disturbance was observed in clinically active IBD patients, especially during severe exacerbation. Consequently, 35% of inactive IBD patients and 78% of clinically active were poor sleepers. Comparable results were reported by Gingold-Belfer *et al*., who showed that impaired sleep quality is associated only with active, but not inactive CD disease (21). Patients with active disease had a significantly higher mean global score on the PSQI than patients with inactive disease or control subjects, with no significant difference between the inactive disease and control groups. In line, in a study conducted by Ali *et al*., a strong association between clinically active IBD and poor sleep quality was reported (22). Abnormal PSQI was present in all clinically active patients and 72% of those with inactive disease. In contrast, Ranjbaran *et al*., showed that IBD patients experience significant sleep disturbances even when their disease is not active (19). Ali *et al*. also demonstrated that patients in clinical remission with sleep disturbances had a high chance of subclinical exacerbation of disease activity (22). In consequence, all patients with histologic sign of inflammation on recent colonoscopy examination also had abnormal PSQI scores, which were unrelated to the clinical disease activity status (22). Importantly, in the same study a significant correlation was observed between disease activity in UC and sleep disturbances expressed in PSQI score, however there were no such relationships in CD patients. This is in opposition to our observations - there was no difference in the quality of sleep between CD and UC patients. Whether this was the case for the inclusion criteria used in both projects may need further investigation.

The aforementioned data strongly supports the hypothesis that there is a bidirectional association between sleep disturbances and disease activity and that inflammatory parameters may have an impact on the quality of sleep (14). In line, in 2015 Wilson *et al*., showed that high CRP is associated with poor sleep quality in IBD independently of the presence of nighttime disruptions, further suggesting that a relationship exists between circulating inflammatory markers and sleep (23). However, in our study there was no correlation between CRP level and quality of sleep in IBD patients. Our observation does not exclude the existence of the above-mentioned association yet may require an in-depth analysis at the biomolecular levels of specific cytokines and other inflammation markers employed in this complex network. Whether other clinically useful biomarkers such as NGAL levels in the serum, recently showed to correspond to clinical and endoscopic activity of intestinal disorders in IBD and well correlated with serum concentration of CRP relate to sleep disturbances also needs further investigation (24).

Potential limitations of our study should be considered. First, our cohort included mostly Caucasian adults, and the results may not be generalizable to other ethnic groups. Second, our study included a small sample size, indicating that the reported effect sizes might still be underestimated. Finally, limitation of our study includes the lack of objective measurement of sleep such as polysomnography. We used only the clinical status of IBD patients, histopathological inflammation was not included. Evaluation of a complex relationships between sleep disturbances, immunoregulatory cytokines, and IBD should be thus performed. Currently a prospective follow-up of included patients is ongoing to provide long-term follow-up data on the patients within our original cohort.

In conclusion, our study shows a strong relationship between clinically active IBD and sleep disturbances. Nowadays the effectiveness of IBD treatment is still unsatisfactory, what hinders daily functioning of patients (25). Confirmation of the relationship between sleep abnormalities and IBD may show us a risk factor of exacerbation of IBD. This knowledge may allow the treatment of sleep disturbances (either pharmacological or psychological) become a new target in improvement of IBD therapy (26-28).

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