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SCIENTIFIC INVESTIGATIONS

Evaluation of Home Polysomnography Findings, Quality of Sleep, and Fatigue in Inflammatory Bowel Disease: A Case Series

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Study Objectives: The pathogenesis of inflammatory bowel disease (IBD) is not well understood, and sleep disorders may be potential triggers for IBD. Thus, an evaluation of the sleep characteristics, fatigue symptoms, and cytokine levels was performed in patients with IBD during periods of active disease and remission.

Methods: A total of 20 participants presenting with Crohn's disease or ulcerative colitis, with active disease (n = 7) or in remission (n = 13), underwent home polysomnography (H-PSG). Pittsburgh Sleep Quality Index (PSQI) and Modified Fatigue Impact Scale (MFIS) were applied, in addition to the evaluation of interleukin (IL)-6, IL-10, and tumor necrosis factor alpha (TNF-α) serum levels. Exploratory analysis, *t* test and Mann-Whitney *U* test were used.

Results: The mean sleep latency in patients with active disease was 133.07 minutes and 106.79 minutes in those in remission. The sleep efficiency and sleep fragmentation in patients with active disease and those in remission were 80.90% and 84.20% (median), and 76.36/min and 69.82/min (mean), respectively, although the H-PSG parameters did not differ between the groups. The PSQI scores indicated poor sleep quality (global score above 5) in all participants with IBD, and the participants with active disease presented more symptoms of fatigue ($P = .032$). IL-6 and TNF-α average levels were higher in the participants with disease remission, although with a larger dispersion of the data.

Conclusions: No significant difference in the H-PSG characteristics was observed between the patients with IBD with active disease and those in remission; however, the perception of the participants with IBD showed significant effect on the sleep quality and fatigue symptoms.

Keywords: fatigue, inflammatory bowel disease, interleukins, polysomnography, sleep disorders

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disorders may be potential triggers for inflammatory bowel disease as the pathogenesis of the disease is not well understood. In an attempt to gain deeper understanding, we evaluated the sleep characteristics, fatigue symptoms, and cytokine levels in patients with inflammatory bowel disease during periods of active disease and remission.

Study Impact: While we found no significant difference in the home polysomnography characteristics between the patients with active disease and those in remission, the perception of the participants with inflammatory bowel disease showed significant effect on sleep quality and fatigue symptoms.

INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a disorder primarily involving the gastrointestinal tract.[1] IBD usually presents with frequent relapses and severe clinical manifestations. The symptoms of both CD and UC include intestinal manifestations such as abdominal pain, chronic diarrhea with or without rectal blood, and presence of mucus in feces.[2]

CD usually affects young people, whereas UC is bimodal. These diseases affect people from different socioeconomic levels, age, sex, nationality, and origin.[3] In Brazil, some studies have shown an increase in the incidence of these diseases.[4–6]

The pathogenesis is not well understood, but genetic, immunological, and environmental factors have been linked to IBD. It has been reported that environmental factors play an important role in modifying the development and activity of IBD. Moreover, the environmental stimulus may alter the microbiome leading to a defective response of both innate and adaptive immune system, with the recruitment of lymphocytes and macrophages followed by the release of soluble cytokines and other inflammatory mediators.[7–9] An effect of sleep disorders on the course of these diseases was reported in previous studies.[10–15]

Sleep is a complex and vitally important phenomenon for maintaining health and quality of life. Human sleep is

classified into two stages: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep.[16–18] A shorter or longer sleep period has great influence on health. The ideal duration of sleep may differ among individuals, but many studies have recommended 7 to 8 hours of sleep per night for adults as the optimal duration.[19] Alterations in normal sleep pattern are thought to be a significant contributor to an array of illnesses including depression, cancer, metabolic syndrome, inflammation, and gastrointestinal diseases.[20,21]

Interruption of sleep due to nocturnal symptoms of diarrhea and abdominal pain has been consistently reported by patients with IBD.[22,23] This is probably why fatigue is a common symptom observed in these patients; also, previous studies have shown an association between increased interleukin (IL)-6 levels and sleep disorders.[9,24]

This combination alters sleep, and sleep disorders affect immune function. The 24-hour sleep-wake cycle is involved in the regulation of the diurnal changes in immune cell number and levels of cytokines, which may serve as chemical messengers to regulate immune cell behavior and response in the blood.[25,26] Therefore, sleep disorders may result in significantly increased levels of circulating innate immune cells such as granulocytes and monocytes and impaired immunocyte function. A number of cytokines and chemokines, including IL-1, IL-6, and tumor necrosis factor alpha (TNF-α), have been related to insomnia.[26,27]

There is a lack information in the literature on the association of gastrointestinal disorders and sleep disorders, and studies are necessary to evaluate the sleep quality in patients with IBD and, thus, to understand the influence of sleep alterations that may trigger or impair the inflammatory process in these patients. Therefore, this study aimed to evaluate the sleep characteristics, fatigue symptoms, and inflammatory cytokine levels in patients with IBD during periods of active disease and remission.

METHODS

Collection of Patients' Data

A convenience sample of 20 participants was included, of which 11 had UC and 9 had CD; of these, 7 participants had active disease, and 13 were in remission, according to the Crohn's disease activity index (CDAI). All were receiving treatment at the São Paulo Hospital (School of Medicine, Universidade Federal de São Paulo, Brazil). The exclusion criteria were patients with a primary sleep disorder, those taking sleep-inducing drugs, those receiving psychiatric treatment, and those with other chronic diseases. The study was carried out from January to August 2016.

Ethical Considerations

This is a cross-sectional study that was approved by the Ethics Committee of Universidade Federal de Sao Paulo, UNIFESP (0742/2015). The study was conducted in accordance with the statement regarding ethical principles for medical research involving human participants of the Declaration of Helsinki.

Home Polysomnography

Home polysomnography (H-PSG) was performed in the presence of a trained sleep technician overnight using Lamarck SC810 Polysomnography Device (Series-LK105; Meditron Eletromedicina LTDA, Thessaloniki, Greece). The test included electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG), electromyogram (EMG), airflow measurements using both oronasal-thermal sensors and nasal air pressure transducers, transtracheal sounds via microphone, rib cage and abdominal movement by inductance plethysmography using thoracoabdominal belts, and continuous pulse oximetry, in accordance with the American Academy of Sleep Medicine (AASM) standards.

The following parameters were assessed: total sleep time (TST), sleep efficiency (%), sleep latency (minutes), stage N1 sleep (% TST), stage N2 sleep (% TST), stage N3 sleep (% TST), stage R sleep (% TST), wake after sleep onset (WASO) (minutes), arousal index (events/h), basal saturation, time of saturation, periodic leg movement index (events/h) and apnea-hypopnea index (events/h).

It is important to emphasize that the sensors were quite fixed and the wires were long enough to avoid restricting the participants' movements.

Pittsburgh Sleep Quality Index Questionnaire

Sleep quality was assessed using the Portuguese version of the Pittsburgh Sleep Quality Index (PSQI), previously validated for the Brazilian Portuguese language by Bertolazi et al.[28] This instrument was used to evaluate the sleep quality over 1 month. It consists of 19 items for self-reporting and an additional 5 questions that have to be answered by roommates; the latter information was used for clinical purposes.

The PSQI questionnaire was administered on the same day of polysomnography. The 19 self-rated questions yield 7 component scores: self-reported sleep quality (C1), sleep latency (C2), sleep duration (C3), efficiency of habitual sleep (C4), sleep disturbances (C5), use of sleep medication (C6), and diurnal dysfunction (C7), all of which are summed to a single global score that ranges from 0 to 21, with a higher score indicating poorer sleep quality. A PSQI global score above 5 indicates poor sleep quality.

Modified Fatigue Impact Scale Questionnaire

The Portuguese version of Modified Fatigue Impact Scale (MFIS) questionnaire was also administered on the same day of polysomnography. The instrument was previously translated and validated for the Brazilian Portuguese language by Pavan et al.[29] It consists of 21 questions in three domains: cognitive fatigue (range = 0 to 40), physical fatigue (range = 0 to 36), and psychosocial fatigue (range = 0 to 8).[29,30] Values below 38 denotes the absence of fatigue and, above this value, the higher the score, the greater the degree of fatigue.

Quantitative Levels of TNF-α, IL-10, and IL-6 by Colorimetric Enzyme-Linked Immunosorbent Assay

Blood samples were collected to assess TNF-α, IL-1, and IL-6 serum levels. The samples were centrifuged immediately after

Table 1—Clinical characteristics of the participants.

Groups	Sex (female/male)	Age, years mean (SD)	Weight, kg mean (SD)	Height, m mean (SD)	BMI, kg/m² mean (SD)	Clinical Condition (active disease/remission)
Crohn's disease (n = 9)	5/4	30.89 (11.35) *	68.44 (16.82)	1.65 (0.10)	24.87 (5.03)	5/4
Ulcerative colitis (n = 11)	8/3	46.36 (13.92) *	72.05 (15.73)	1.60 (0.06)	28.29 (6.24)	2/9

* P = .0152 (two-tailed t test). BMI = body mass index, SD = standard deviation.

collection (1,100 g; 10 minutes; 4°C), and the serum samples were stored at −80°C until the day of analysis.

Serum TNF-α, IL-1, and IL-6 measurements were performed using human interleukins colorimetric enzyme-linked immunosorbent assay with commercial kits (Human IL-6 2649681, Human IL-10 2673186, and Human TNF-α 2603416, Merck Millipore, Darmstadt, Germany); the analysis was performed following the good clinical laboratory practice and the manufacturer's instructions by using a microplate reader at 450 nm (Stat Fax 2100, Awareness Tech. Inc., Palm City, Florida, United States).

Statistical Analysis

Statistical analysis was performed using SigmaPlot 11.0 (Systat Software, Germany) and BioEstat 5.3 softwares (Mamirauá, Belém, PA, Brazil).

The exploratory analysis consisted of means, standard deviation (SD), medians, and quartiles. Normality was tested by the Shapiro-Wilk test, and the data dispersion was analyzed by box plot. Nonparametric tests were used when the data did not present normal distribution.

The frequencies of males and females between groups were tested using Fisher exact test; t test for independent samples or Mann-Whitney U test was used to compare the subgroups with UC and CD and those with active disease and in remission.

RESULTS

Characteristics of the Participants

The sociodemographic characteristics of the 20 participants according to the groups (CD and UC) and clinical condition (active disease or remission) are summarized in **Table 1**. The average age of the participants was 39.4 years (range 17–62 years; median = 33 years); 7 men and 13 women.

There was no difference between the groups regarding sex (P = .6242; Fisher exact test) and body mass index (t = 1.33; P = .201). However, the age of the UC participants was significantly higher than that of the CD participants (t = 2.68; P = .0152; power = 0.86).

Home Polysomnography Findings

The mean REM sleep latency in the participants with active disease was 133.07 minutes, whereas in those presenting with remission, it was 106.79 minutes. The median TST was 318 minutes in those with active disease and 329 minutes in those in remission, although it did not differ between the disease groups. The participants with active disease showed 80.9% (median) of sleep efficiency and those in remission 84.20%, whereas the mean WASO was 76.36 minutes and 69.82 minutes, respectively.

The medians found for stage N2 sleep were 46.2% in participants with active disease and 37.4% in participants with disease remission. Also, the mean frequency of REM sleep was 17.26% in those with active disease and 17.71% in those in remission. However, no significant difference was found on comparing the H-PSG parameters between the participants with active disease and those in remission.

The mean basal saturation observed was 97% in participants with active disease and 96% in those in remission. In addition, the periodic leg movement was absent in participants with IBD. Apnea-hypopnea index showed a large variability in the remission group (mean = 5.90; SD = 13.80 events/h). These results are summarized in **Table 2**.

Perception About Sleep Quality

The assessment of the participants' perception about their sleep quality in the past 30 days showed poor sleep in 5 of the 7 participants with active disease and 4 of the 13 participants in remission. Most participants (6 of the 7 with active disease and 10 of the 13 in remission) reported having a total sleep latency of more than 15 minutes. On analyzing the sleep difficulties, most of the participants in remission reported having difficulties sleeping on weekdays; however, most of the participants reported more than 6 hours of sleep per night.

Regarding the reported sleep efficiency, most participants in remission reported lower efficiency when compared with the participants with active disease. Sleep disorders were found in 2 participants with active disease and 7 in remission, and daytime dysfunction was observed in all participants with active disease and 12 of the 13 in remission. The total score of PSQI was ≥ 5 for all participants, denoting poor sleep quality in this studied sample, although there was no difference between the groups (P = .93) (**Figure 1**).

Fatigue Symptoms

Significant differences in the MFIS scores was found between the clinical groups (t = 1.975; P = .032, one-tailed t test; power = 60%); also, 9 of the 13 participants in remission had a score below 38, denoting the absence of fatigue. However, because of the small sample size and low power of the test (below 80%), this result should be interpreted with caution (**Figure 2**).

IL-6, IL-10, and TNF-α Serum Levels

Because of sample losses and the small number of participants who provided blood samples for serum cytokine quantification,

Table 2—Results of home polysomnography findings according to the clinical condition of the participants.

Parameters	Active Disease (n = 7)	Remission (n = 13)	Test	95% CI	*P*
REM sleep latency, minutes, mean (SD)	133.07 (58.76)	106.79 (48.17)	*t* test	−24.88 to 77.43	.29
TST, minutes, median (ID)	318.00 (120.25)	329.00 (67.50)	Mann-Whitney	–	.94
Sleep efficiency, %, median (ID)	80.90 (12.45)	84.20 (9.10)	Mann-Whitney	–	.38
Stage N1 sleep, % TST, mean (SD)	14.57 (10.43)	13.67 (10.37)	*t* test	−9.33 to 11.13	.86
Stage N2 sleep, % TST, mean (SD)	42.93 (12.02)	41.82 (9.99)	*t* test	−9.43 to 11.66	.83
Stage N3 sleep, % TST, mean (SD)	22.54 (8.02)	26.82 (11.28)	*t* test	−14.44 to 5.88	.39
Stage R sleep, % TST, mean (SD)	17.26 (9.19)	17.71 (7.08)	*t* test	−8.18 to 7.28	.90
WASO, minutes, mean (SD)	76.36 (35.34)	69.82 (49.73)	*t* test	−38.22 to 51.30	.76
Arousal index, median (ID)	12.60 (13.25)	22.30 (15.20)	Mann-Whitney	–	.36
Basal saturation, %, mean (SD)	97.00 (0.82)	96.08 (1.32)	*t* test	−0.24 to 2.08	.11
Time of saturation < 90%, median (ID)	0.00 (0.25)	0.50 (1.60)	Mann-Whitney	–	.11
PLM index, events/h, median (ID)	0.00 (000)	0.00 (0.00)	Mann-Whitney	–	.61
Apnea-hypopnea index, events/h, median (ID)	0.90 (1.95)	5.90 (13.80)	Mann-Whitney	–	.06

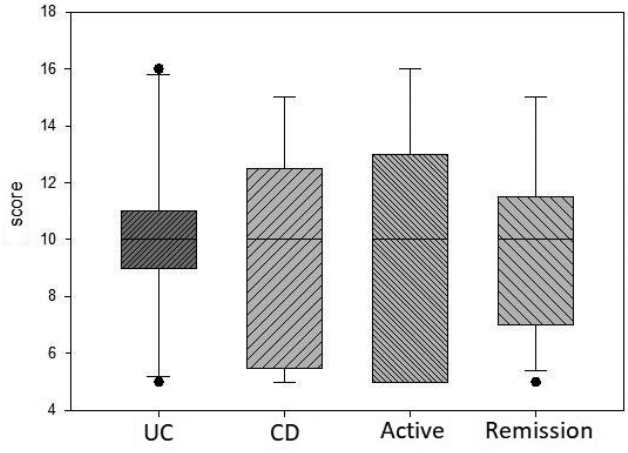
CI = confidence interval, ID = interquartile deviation, NREM = non-rapid eye movement, PLM = periodic leg movement, REM = rapid eye movement, SD = standard deviation, TST = total sleep time, WASO = wake after sleep onset.

Table 3—Description of serum cytokine levels (pg/mL) of the participants (n = 15).

	Valid n/Total	IL-6 mean (SD)	IL-10 mean (SD)	TNF-α mean (SD)
Active disease	3/7	13.80 (14.37)	3.27 (0.81)	32.03 (7.98)
Remission	12/13	33.83 (33.86)	8.84 (7.95)	35.90 (21.27)

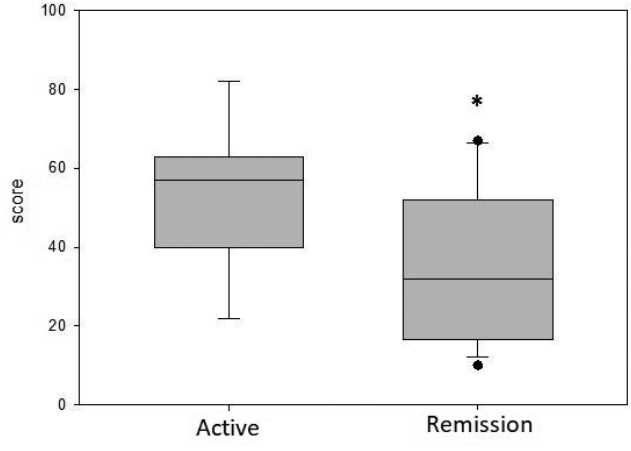
IL = interleukin, SD = standard deviation, TNF-α = tumor necrosis factor alpha.

Figure 1—Results of the PSQI.



Total score of PSQI according to the groups and clinical condition (*P* > .05). CD = Crohn's disease, PSQI = Pittsburgh Sleep Quality Index, UC = ulcerative colitis.

Figure 2—Results of the MFIS.



Total score of MFIS questionnaire according to the clinical condition (* *t* = 1.975; *P* = .032, one-tailed *t* test; power = 60%). MFIS = Modified Fatigue Impact Scale.

we performed an exploratory critical analysis of the results. The findings are shown in **Table 3**.

The mean IL-6 concentration in the participants with active disease was 13.80 pg/mL (n = 3) and in those in remission was 33.83 pg/mL (n = 12). The mean serum levels of IL-10 were 3.27 pg/mL and 8.84 pg/mL in participants with active disease and those in remission, respectively.

The mean TNF-α serum level in participants with active disease was 32.03 pg/mL and in those in remission was 35.90 pg/mL. All serum cytokines quantified showed higher average levels among participants with disease remission, although with a larger dispersion of the data.

DISCUSSION

The findings of this study suggest the presence of some differences in the sleep characteristics in patients with IBD

when compared with published normative values gathered from a healthy population.[18] However, this aspect was more evident when analyzing the participants' perception about their quality of sleep and fatigue symptoms, as discussed in the next paragraphs.

According to previous findings in a healthy population,[18] sleep efficiency should be above 85% (median), but it decreases with age; in the current study, the sleep efficiency was 80.90% (median) in participants with active disease and 84.20% among those with disease remission, which is comparable to the findings in the healthy population in the age groups of 31–40 years (median = 87.1%) and 41–50 years (median = 83.8%). However, the patients with IBD in the current study showed TST medians quite below the normative values, comparable to those found in older adults.[18] TST also decreases with age and was found to vary from 274 to 458 minutes (median = 420 minutes) in the age group of 31–40 years and from 294 to 450 minutes (median = 402 minutes) in the age group of 41–50 years.[18]

Stage N2 sleep, also referred to as the "true sleep" phase, represents about 45% (median) of total sleep in the healthy population[16–18] and does not vary across the age decades.[18] This phase is characterized by decreased ocular movements, relaxation of skeletal muscles, and passage of thoughts and fragmented images through the mind, and, in the current study, the median found in the participants with disease remission was 37.4%.

The awakening rate is associated with sleepiness and a decrease in daytime performance on the following day that varies according to age. An arousal index of 10 to 12 events/h up to 20 years and 20 to 22 events/h in those aged 50 to 60 years[31] or a median of 13 in the age range of 31 to 50 years[18] has been reported as normal. Thus, these findings may be considered comparable to those reported in the literature.[18,31]

Another important parameter examined was WASO. WASO time reflects sleep fragmentation, usually considered altered when it occurs more than 10 times per hour.[28] The current results showed a mean of 76.4 minutes for an entire night in the participants with active disease and 69.8 minutes in those in remission, which is also comparable with the previous findings in healthy adults.[18] Finally, in the healthy population, the ideal saturation has been reported to be around 90% to 94% in ambient air[18]; in patients with IBD, the median time of saturation < 90% was very low (close to zero).

By using accelerometers, van Langenberg et al. evaluated participants with CD and observed more awakenings after the onset of sleep, especially among those in remission; but on comparing the patients with a control group, the participants with CD showed similar total sleep time.[32]

The self-reported analysis of the quality of sleep revealed that both groups of patients showed difficulties in sleeping, which was more frequent among patients with active disease and gastrointestinal disturbances. Ananthakrishnan et al. observed that almost half of the patients in clinical remission presented with impaired sleep quality, which may be explained by the presence of subclinical inflammation among these patients.[15] In the current study, half of the participants in the remission phase reported sleep disorders, and all participants achieved a global score above 5, indicating poor sleep quality in this sample.

Differences in fatigue symptoms were observed between the active disease and remission subgroups, and most of the participants in the remission subgroup were classified as showing absence of fatigue. According to Graff et al., fatigue is the perception of exhaustion, a common symptom in many chronic diseases, including inflammatory diseases mediated by the immune system, being related to increased levels of inflammatory cytokines.[33] Rampton suggested that psychological stress might increase inflammation and impair the course of the immune-mediated inflammatory disease.[34] As the perception of fatigue was more evident among participants with active disease, together with the findings of poor sleep quality in patients with IBD, we may infer that these observations are of importance because sleep quality may affect quality of life and, ultimately, their clinical condition.

It is known that the etiopathogenesis of IBD is directly related to immunomediation, with TNF-α being a very well-studied cytokine and a target for immunobiological drugs that aim to decrease its levels, thus inducing remission of the disease. Also, there are strong indications of the high levels of this cytokine in the feedback loop of sleep disorders.[35–37] By performing an exploratory IL-6, IL-10, and TNF-α measurement in the serum of participants with IBD, it was noted that all the serum cytokines quantified showed higher average levels in participants with disease remission, although with a larger dispersion of the data, probably because of the limited number and heterogeneity of the participants. Direct comparisons with the cytokine levels reported in the literature are limited because of the inherent differences between the populations, methodologies (equipment and assays), and laboratory practices.

Cytokines regulate/modulate sleep-wake behavior[26,27] and may mediate infection-/inflammation-induced alterations in sleep.[26] According to the literature, changes in IL-4 and IL-10 cytokine levels suppressed sleep in experimental studies *in vivo*,[26] and there is a possibility of ILs acting even in remission periods or their accumulation leading to a recurrence of intestinal inflammation. The literature shows that sleep disorders in patients with IBD are probably multifactorial, in which the presence of nocturnal bowel movements, abdominal pain, and use of drugs such as corticosteroids and narcotics during the disease activity may result in sleep impairment.[38–40]

As this study included a convenience sample and few participants, the findings may not be directly generalizable to the population. Also, the index applied to classify the clinical condition of the patients with CD (CDAI) is considered subjective by some researchers. However, this study highlights the important findings not yet described in patients with IBD, and included participants who were submitted to polysomnographic evaluation, known as the gold standard in the study of sleep.

In summary, there were no significant differences in the H-PSG sleep parameters between the patients with IBD with active disease and those in remission. However, the results suggest that some differences in the sleep characteristics may exist on comparing with the published normative values gathered from a healthy population. Also, the perception of the participants with IBD showed an important effect on their quality of sleep and fatigue symptoms.

It is necessary to monitor patients with IBD more intensely and longer in relation to fatigue and disturbances in sleep patterns. Studies with larger samples are required to help in understanding the factors that may trigger sleep and gastrointestinal disorders and to establish a cause and effect relationship.

ABBREVIATIONS

CD, Crohn's disease
CDAI, Crohn's disease activity index
ECG, electrocardiography
EEG, electroencephalography
EMG, surface electromyography
EOG, electrooculography
H-PSG, home polysomnography
IBD, inflammatory bowel disease
IL, interleukin
MFIS, Modified Fatigue Impact Scale
NREM, non-rapid eye movement
PLM, periodic leg movement
PSQI, Pittsburgh Sleep Quality Index
REM, rapid eye movement
TNF-α, tumor necrosis factor alpha
UC, ulcerative colitis
WASO, wake after sleep onset

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DISCLOSURE STATEMENT

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