Sleep-Wake Cycles of Individuals with Inflammatory Bowel Disease

Linda Yoo

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Reading Committee:

Margaret Heitkemper, Chair

Kendra Kamp

Sarah Iribarren

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Abstract

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Linda Yoo

Chair of the Supervisory Committee:

Margaret Heitkemper

School of Nursing

Background: Individuals with inflammatory bowel disease (IBD), a chronic illness of the gastrointestinal (GI) system, report high rates of poor sleep quality and sleep disturbances. Among those with IBD, sleep problems are more prevalent during active disease, a period marked by inflammation and severe GI symptoms. Animal models have demonstrated that altered sleep-wake cycles and disruptions in the circadian rhythm can cause increased susceptibility to inflammation and intestinal dysbiosis. IBD studies report the association between increased GI symptoms and inflammation with less consistent daily rhythms. Limited studies have examined the social and societal factors that impact the sleep-wake cycles of those with IBD. The overall purpose of this dissertation is to explore different aspects of the sleep-wake cycles of individuals with IBD through the social-ecological model of sleep (SEM).

Methods: In this prospective cohort study, 50 participants were recruited from an IBD clinic in Seattle, WA. Individuals collected wrist actigraphy for 10 days, a stool sample, baseline surveys, and daily electronic diaries. 24 of the 50 participants completed semi-

structured interviews. The aim of manuscript one was to examine the relationship between sleep and fatigue outcomes (i.e., PROMIS sleep disturbance and fatigue, Pittsburgh Sleep Quality Index), GI symptoms (i.e., abdominal pain, bloating, diarrhea, constipation, nausea), and fecal calprotectin with rest-activity rhythm (RAR) characteristics and social jetlag (SJL). RAR characteristics and SJL were analyzed from wrist actigraphy. Fecal calprotectin, a biomarker of gut inflammation, was measured using ELISA assays from the stool samples. Survey data used were sleep and fatigue outcomes and GI symptoms from daily diaries. In manuscript two, generalized estimating equations (GEE) was used to test if sleep fragmentation from wrist actigraphy and self-reported sleep quality from daily diaries predicted next-day GI symptoms (i.e., abdominal pain, bloating, diarrhea, constipation, nausea). For manuscript three, a hybrid thematic analysis was used to explore factors across the individual, social, and societal levels that impact sleep-wake cycles of those with IBD, and describe the strategies used to improve sleep health.

Results: There were no significant relationships between RAR characteristics and SJL with sleep, fatigue, GI symptoms, and fecal calprotectin. The midline estimating statistic of rhythm (MESOR) and relative amplitude were higher in those in remission than those with clinically active disease. Sleep fragmentation and self-reported sleep quality were non-statistically significant predictors of next-day GI symptoms. Among the participants, wake after sleep onset was higher, and sleep efficiency was lower than the recommendations from the National Sleep Foundation. The factors and strategies that impact sleep-wake cycles were three individual-level themes (7 subthemes) and three social-level themes (4 subthemes). The individual-level themes were lifestyle and

behaviors (daytime behaviors and habits, nighttime influences, diet, and technology use), physical health (IBD and GI symptoms; non-GI pain, fatigue and other health conditions; medications and supplements), and mental health. The social-level themes were sleep environment, interpersonal relationships (partner, children, pets, friends) and work. Participants provided strategies that both directly and indirectly positively impacted sleep health.

Conclusion: In this study, participants in clinical remission had more robust rest-activity rhythms than those in active disease. There is an opportunity for improvements in nighttime sleep (e.g., sleep efficiency, wake after sleep onset) despite the sample's average total sleep time and sleep onset latency meeting recommendations by the National Sleep Foundation. Future multilevel sleep interventions in the IBD population should accommodate not only individual-level factors but also social-level factors that impact sleep-wake cycles. Although the social-level factors identified in the study might not be modifiable in the lives of those with IBD, it is important to account for these factors when creating tailored interventions. Future studies should examine different aspects of the circadian rhythm (e.g., chronotype, dim light melatonin onset) and the peripheral intestinal clock alongside individual-level IBD health outcomes, such as inflammation and GI symptoms, and social-level factors.

Dedication

I dedicate this work to the inflammatory bowel disease (IBD) community. I am incredibly grateful to the participants of IBD studies who have graciously shared their information, time, and efforts.

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Table of Contents

CHAPTER I

Introduction to the Dissertation

1.1 Content of the Dissertation

Inflammatory bowel disease (IBD), a lifelong gastrointestinal (GI) disease, impacts an estimated 2.39 million Americans and 6.8 million individuals globally.[1,2] Those with IBD can face severe GI (e.g., diarrhea, nausea, abdominal pain) and extra-intestinal symptoms (e.g., fatigue, joint pain) during times of active disease. In general, those with IBD have poorer sleep than the average population, and active disease is related to having worse sleep than remission.[3,4] Approximately thirty-eight percent of individuals with IBD report sleeping less than 7 hours, and 63.5% report fatigue.[5] Sleep disturbances are noted as a risk factor for relapse into active disease leading to GI symptoms, such as nocturnal abdominal pain and bowel movements.[6,7] IBD sleep research has revealed the bidirectional relationship between sleep and inflammation. However currently, there is a limited description of the sleep-wake cycle (e.g., sleep timing and the overall daily rest-activity rhythm (RAR)), and its relationship to IBD characteristics.

This dissertation is composed of five chapters. Chapter one provides an overview and introduction of the dissertation. Chapter two (Manuscript 1: Rest-Activity Rhythms and Social Jetlag in Adults with IBD) examines the relationships between RAR characteristics and social jet lag (SJL) with measures of GI symptoms, fatigue, sleep, and fecal calprotectin. Chapter three (Manuscript 2: Sleep Fragmentation and Next-Day Symptoms Across and Within Individuals in IBD) focuses on nighttime sleep outcomes and tests if sleep fragmentation and subjective sleep quality predict next-day GI symptoms. Chapters two and three (Manuscript 1 and 2) utilize actigraphy data collected over 10 days. Chapter four (Manuscript 3: Factors Impacting Sleep-Wake Cycles in IBD: A Qualitative Study) aims to describe factors related to sleep-wake cycles across the individual, social, and societal levels founded on the social-ecological model of sleep. Each manuscript focuses on unique attributes of sleep-wake cycles of individuals with IBD through quantitative (Manuscript 1 and 2) and qualitative (Manuscript 3) methods. Chapter five concludes this dissertation by providing information on the implications and next steps for future research studies.

This introduction will provide an overview of IBD, fecal calprotectin, wrist actigraphy, and the social-ecological model of sleep.

1.2 Inflammatory Bowel Disease (IBD)

There are two main types of IBD: Crohn's disease and ulcerative colitis. Ulcerative colitis is limited to the large intestine, whereas Crohn's disease can appear in any part of the GI tract. The peak incidence of IBD is in the third decade of life.[8] Although less commonly diagnosed in minority populations, the incidence rate of IBD in minority populations is increasing (134%) more than that in White Americans.[1,9] The cause of IBD has yet to be uncovered. However, risk factors for developing IBD include: family history of IBD, antibiotic use, and smoking.[10,11] There have been significant advances in treatment for IBD through the development of new pharmaceutical agents, such as

biologic therapies inhibiting tumor necrosis factor (e.g., infliximab, adalimumab), interleukin (e.g., Ustekinumab), and Janus Kinase (e.g., Upadacitinib).[12] However, treatments are costly, as the annual direct costs for IBD healthcare are estimated at $22,987.[13] Those with IBD experience times of active inflammation with severe symptoms (e.g., diarrhea, tenesmus, abdominal pain) and remission, inactive disease. Active disease is associated with high levels of depression, lower quality of life, lower odds of being employed, and increased absenteeism from school and work.[14-17] Severe active disease might warrant surgical interventions, such as a colectomy, and lead to complications, such as intestinal strictures.[18,19] The goal of IBD treatment is to quickly induce individuals into remission, a state with no presence of mucosal inflammation, and maintain remission for as long as possible to reduce complications and morbidity.

1.3 Fecal calprotectin

The gold standard to diagnose IBD and measure IBD disease activity is through an endoscopy (upper endoscopy and/or colonoscopy). Patients with IBD often find completing an endoscopy to be difficult and burdensome. Colonoscopy preparation is required to cleanse the bowels of any fecal material; this is reported to be the most burdensome part of a colonoscopy procedure for those with IBD.[20] Additionally, colonoscopies are often performed on weekdays and require a separate person to drive the patient home after the procedure; this results in a need to plan and potentially leave work and/or school to complete disease surveillance. For these reasons, fecal calprotectin, an inflammatory biomarker specific to the GI system, can be used for IBD disease activity measurement and as a potential replacement for endoscopic disease surveillance. Stool samples can be easily collected at home and transported to the laboratory. Enzyme-linked immunosorbent assays (ELISA) are typically used to measure fecal calprotectin and can produce test results in a short amount of time.[21] This dissertation project collected stool samples from participants to measure fecal calprotectin as a proxy for gut inflammation. Fecal calprotectin is used in Manuscript 1.

1.4 Wrist Actigraphy

Wrist actigraphy presents an objective method to measure nighttime sleep and RARs. A wrist actigraph contains an accelerometer that records activity data through changes in motion. The gold standard for objective sleep measures is polysomnography (PSG). Wrist actigraphy is found to be acceptable and produces similar sleep measures to PSG, such as wake after sleep onset and total sleep time.[22,23] The wrist actigraph used in Manuscripts 1 and 2 is the Phillips Actiwatch Spectrum Plus (Phillips Respironics, Bend, OR). When collecting the data, the researchers worked to minimize potential errors with the Actiwatch. They ensured that the Actiwatches were charged fully; the battery life for an Actiwatch is estimated to be 60 days. Additionally, servicing by the manufacturer was completed on the Actiwatches before use. The Actiwatch does not allow for simultaneous data collection and upload into the researcher's software. In the study, participants and researchers worked together to determine the schedule for data collection, and researchers first programmed the watch to begin data collection on the desired date. Then, participants were mailed the watch and instructed to wear the watch continuously on their nondominant wrist for 10 days. Additional instructions were printed for participants, such as information on battery warnings and pressing the marker button

to indicate sleep and wake times. In 2023, Phillips Respironics discontinued support for the Actiwatch and Actiware software.

While wearing the Actiwatch, participants completed daily electronic morning diaries. This diary asked questions about their previous night's sleep, including the time when they got out of bed, when they woke up, when they went to bed, and when they slept. Participants also had the opportunity to leave comments about their sleep in the electronic diaries. After data collection was complete, participants returned the watches in a pre-paid mailing package, or the researcher met the participant to collect the watch in-person. The researcher imported the actigraphy data from the Actiwatch into the Actiware Software 6.3.

Actigraphy scoring was completed on the Actiware Software 6.3. Manual scoring was first conducted by one researcher using the University of Washington Center for Innovation in Sleep Self-Management actigraphy scoring manual. To score actigraphy, the researcher used the light data from the watch, actogram, morning electronic diary data, and markers manually set by participants. The scoring manual provides a step-by-step protocol for using these different sources of data to accurately score the actigraphy. Then, a second researcher reviewed the scoring and identified actograms that needed to be reviewed or revised. The justifications for the actigraphy scoring were noted throughout the process. A third researcher with expertise in actigraphy met with both researchers to review the discrepancies. Together, the researchers reached a consensus on the actigraphy scoring. The Actiware Software 6.3 can calculate and export total sleep time, sleep and wake times, sleep efficiency, sleep fragmentation, and other sleep variables. Additionally, 60-second epoch data were exported for RAR analysis.

1.5 Social-ecological model of sleep

Daily rhythms and nighttime sleep can be driven by social and societal-level factors. The context in which people live, learn, work, and age, the social determinants of health, can impact sleep health.[24] This dissertation used the social-ecological model (SEM) of sleep health by Grandner.[25] The model illustrates three distinct yet interconnected levels- individual, social, and societal- that are nested within each other. Sleep health and daily rhythms are not merely impacted by individual choices and behaviors but rather shaped by external social and societal-level factors.[25] Most IBD sleep studies have focused on individual-level factors (e.g., inflammation, symptoms, medication use), and have not examined or described the social (e.g., work, school) and societal-level factors (e.g., public policy, economics) impacting sleep health.[26] Thus, this study aimed to look at these different factors for a holistic understanding of sleep-wake cycles.

Manuscript 1 focuses on the individual and social level by measuring SJL, which is dependent on the sleep time of work and free days. Manuscript 2 focuses on the individual level by examining sleep fragmentation from wrist actigraphy and sleep quality from daily diaries. Manuscript 3 explores factors at all three levels that impact sleep-wake cycles through qualitative data obtained in phone interviews with participants. A comprehensive understanding of the relationships between the sleep-

wake cycles of those with IBD and factors across the individual, social, and societal levels will allow for the development of multilevel interventions to improve sleep and, consequently, other IBD health outcomes.

CHAPTER II

MANUSCRIPT 1: Rest-Activity Rhythms and Social Jetlag in Adults with Inflammatory Bowel Disease

2.1 Introduction

An estimated 2.39 million Americans have Inflammatory bowel disease (IBD), a chronic disease of the gastrointestinal (GI) system.[1] IBD is primarily composed of Crohn's disease and ulcerative colitis. IBD has a varying disease trajectory with periods of active disease marked by severe GI symptoms (e.g., diarrhea, nausea, bloating) with inflammation, as well as periods of remission or inactive disease. In a meta-analysis, 56% of adults with IBD reported poor sleep, with poor sleep being associated with increased objective disease activity (i.e., C-reactive protein, fecal calprotectin, endoscopic findings, histology).[3] Although the length of nighttime sleep and restful sleep are vital for health, sleep timing and consistency are also crucial to regulating the complex cycles and processes in the body, such as the digestive and immune systems.[27]

The human body's circadian rhythm is regulated by the suprachiasmatic nucleus (SCN), the central clock, which is primarily entrained by light.[28] Chrono-disruption and irregularity of the sleep-wake cycle of humans impact physical and mental health.[29,30] Additionally, key areas of the GI system, such as gut motility, intestinal barrier integrity, and the gut microbiome can be negatively affected by circadian rhythm disruptions.[30,31] Animal models have pointed to the adverse impacts of chrono-disruptions. Animals induced with colitis using dextran sulfate sodium (DSS) and exposed to shifting light-dark cycles and chrono-disruption have increased susceptibility to inflammation, microbiota dysbiosis, and intestinal permeability.[32-35] Circadian clock genes (e.g., CLOCK, Bmal1, Cry1, Cry2, Per1) are responsible for creating feedback loops that allow for a consistent and predictable daily cycle for the human body. There is evidence that those with IBD have different expressions of certain clock genes (BMAL1, PER1, PER3, TIMELESS, and NPAS2) when compared to non-IBD or healthy individuals and decreased mRNA levels of circadian clock genes (Bmal1, Cry1, Cry2, and Rev-erbα) in inflamed tissues.[36,37] Alteration of circadian clock gene expression levels could indicate a dysregulated internal circadian rhythm in those with IBD. IBD researchers have proposed targeting the circadian rhythm for future interventions to improve disease activity by altering environmental signals (e.g., light, meal timing, timing of medication administration) that regulate and cue the body’s circadian rhythm.[38]

There is preliminary evidence that daily rhythms are associated with IBD health outcomes. Rest-activity rhythms (RAR) can be measured using wrist actigraphy. A study with IBD participants found that decreased RAR fragmentation across days (inter-daily stability [IS]) is associated with decreased gas/bloating and heartburn symptoms.[39] Additionally, increased RAR fragmentation within a day (intra-daily variability [IV]) was associated with increased gut permeability and higher inflammation measured by serum tumor necrosis factor alpha levels in those with IBD.[40] Social jetlag (SJL) is an example of a circadian disruption occurring due to differences in sleep timing on free days (typically weekends) and workdays.[41] Sleep times to calculate SJL can be obtained via

self-reported measures or wrist actigraphy. Rather than following their predisposed innate circadian rhythms, individuals might alter their daily rhythms to social obligations, such as waking up earlier on workdays. One IBD study found that SJL is higher in those with IBD than in healthy individuals.[42] Additionally, those with IBD with an SJL greater than 2 hours were more likely to have a more severe phenotype of Crohn's disease (i.e., fistulizing or stricturing disease types).[43] To obtain a comprehensive view of the circadian rhythm and IBD outcomes, this study will examine both GI symptoms and gut inflammation through fecal calprotectin in relation to RAR characteristics and SJL.

To date, IBD sleep research has focused on nighttime sleep outcomes, such as sleep quality and quantity. There is a lack of IBD research on the impact of sleep timing and consistency of sleep-wake cycles. This information is necessary to tailor IBD sleep interventions that can include information on daily rhythms to target IBD-specific health outcomes, such as abdominal pain, gut inflammation, and fatigue. Additionally, through examining RARs, researchers can consider the impacts of daytime activities (e.g., daytime rest) and nighttime sleep that, in combination, create daily rhythms. Nighttime sleep variables fail to account for daytime napping, exercise, and other activities during the day which can impact overall health. The aims of this study are to 1) describe the SJL and RAR characteristics as representative of sleep-wake cycle of those with IBD; 2) examine the relationship between RAR characteristics and SJL with measures of GI symptoms, fatigue, sleep, and fecal calprotectin. This study hypothesizes that more inconsistent rhythms within and across days and greater SJL are related to increased inflammation and symptoms, worse nighttime sleep outcomes, and increased fatigue.

2.2 Materials and Methods

Ethical considerations

The University of Washington Institutional Review Board (IRB) approved this study (STUDY00016807).

Study population and participants

In this cohort study, participants were recruited from an adult IBD clinic in Seattle, WA, USA between 2019-2021 and 2023-2024. Data from a previous IBD sleep study (2019-2021) was included with the prospectively collected data.[44] The same recruitment approach was used for both datasets. Participants were identified through the electronic medical record (EMR) and clinic staff; then, participants were prescreened using the EMR. If eligible, then individuals were contacted via email or phone call. If interested, a phone screening was completed. Individuals ages 18-55 were eligible for the study if they had a diagnosis of ulcerative colitis or Crohn's disease and were able to read and write English. They were excluded if they were currently breastfeeding or pregnant, traveling across 3 time zones during the study, or working shiftwork. Participants were provided information about the study, and consent forms were completed electronically. For the study, participants wore a wrist actigraph, completed baseline surveys and daily electronic diaries, and collected one stool sample. All electronic data was collected using the Research Electronic Data Capture system (REDCap), a secure database for data collection.[45,46]

Measures

Demographic and Clinical Data

Demographics included age, race, sex, education, and employment. Clinical data included the type of medications and clinical disease activity measured using the Simple Clinical Colitis Activity Index (SCCAI) for Crohn's disease and the Harvey Bradshaw Index (HBI) for ulcerative colitis. A SCCAI score greater than 3 and a HBI score greater than 5 are indicative of active disease.[47,48]

Wrist Actigraphy for Rest-Activity Rhythm Analysis and Social Jetlag (SJL)

Participants wore an Actiwatch Spectrum Plus continuously for 10 days (Phillips Respironics, Bend, OR) on their nondominant wrist and were provided instructions to use the marker when going to bed and when waking up. Activity counts were recorded in 60-second epochs. Actiwatches were able to detect and capture the times that participants were not wearing the watch. Participants were informed of potential errors that could appear on the Actiwatch screen and when to notify researchers. No known errors occurred during data collection.

Electronic Diaries (GI symptoms, SJL)

During the 10-day period, electronic diaries were sent to the participant twice a day (morning and night). The night-time diaries were focused on symptom severity. Participants indicated if the symptom was not present (0), mild (1), moderate (2), severe (3), and very severe (4) in the last 24 hours. The average was calculated across days of the following symptoms: abdominal pain, bloating, constipation, diarrhea, and nausea. Additionally, in the night diaries, the participants indicated if they attended school or work for the day; this information was later used to calculate SJL. The morning diaries asked participants about the time they were in bed, fell asleep, woke up, and left the bed. These morning diaries were used to score the wrist actigraphy and obtain the sleep times for SJL calculation.

Pittsburgh Sleep Quality Index, PROMIS sleep disturbance, and PROMIS fatigue

The Pittsburgh Sleep Quality Index (PSQI) has 7 domains and 19 items that are based on the participant's sleep in the past month.[49] A global PSQI score greater than 5 indicates a poor sleeper. The Patient-Reported Outcomes Measurement Information System (PROMIS) short form sleep disturbance asks about the participant's sleep in the past 7 days, and PROMIS fatigue asks about the participant's fatigue in the past 7 days. PROMIS T scores will be used. A standard T score of 50 is representative of the general US population.[50] PROMIS questionnaires are reliable.[51,52]

Fecal calprotectin

Calprotectin, a protein found in neutrophils, is an inflammatory biomarker found in stool.[53-55] Fecal calprotectin can be used to measure gut inflammation and quantify the severity of disease activity in those with IBD.[21,56-62] Clinically, a fecal calprotectin greater than 50ug/g can indicate that an individual is experiencing gut inflammation, not specific to IBD.[63]

Fecal calprotectin is a clinical biomarker for IBD care because it allows for convenient disease monitoring through stool samples without an endoscopy or other invasive monitoring techniques. In this study, participants collected a stool sample at their home and immediately placed it in their home freezers (estimated -20 degrees C). Participants had the option to bring their sample to their appointment or arrange a pickup at their residence; the sample was on ice during transportation. When the sample was received, it was placed in -80°C freezers. The samples were thawed and placed in aliquots using a protease inhibitor, then frozen at -80°C. Enzyme-linked immunosorbent assays (ELISA) were used to measure fecal calprotectin (Hycult Biotech, Uden, Netherlands; catalog number HK382). For the samples collected in 2023-2024, a separate assay was completed in triplicates for the samples that were below 16 ug/g or with a coefficient of variation greater than 15%.

Data Analysis

Rest-activity rhythm (RAR) characteristics
SPSS and R software were used to conduct RAR analysis on the actigraphy data. Two analyses were conducted: cosinor and non-parametric circadian rhythm analysis (NPCRA). A logarithmic transformation was conducted on raw activity counts from wrist actigraphy.

The cosinor analysis is a regression method that fits a single harmonic cosine curve to the data.[64] From the cosinor analysis, the following RAR characteristics were calculated: 1) Midline estimating statistic of rhythm (MESOR): the mean activity of the 24-hour rhythm; 2) Acrophase: clock time of highest activity in 24 hours; 3) Circadian quotient (CQ): the ratio of the amplitude to the MESOR, which indicates the strength of the rhythm. From the NPCRA, the following characteristics were calculated: 1) Intra-daily variability (IV): fragmentation of the rhythm over 24 hours impacted by daytime napping and/or nighttime sleep disturbances. A value closer to 0 indicates less fragmentation; 2) Inter-daily stability (IS): the consistency of RARs between 24 hours. A value closer to 1 shows greater consistency across days; 3) Relative amplitude (RA): the value from dividing the difference of the value of the most active 10 hours (M10) from the value of the least active 5 hours (L5) with the sum of the M10 and L5.

Social Jetlag (SJL)
The wrist actigraphy data was scored, and then reviewed with an actigraphy expert using the University of Washington Center for Innovation in Sleep Self-Management actigraphy scoring manual. Scoring the actigraphy consisted of using the actigraphy data, light data from the actigraph, and electronic diaries using Actiware software 6.3 (Phillips Respironics, Bend, OR). SJL was calculated by subtracting the average mid-sleep of free days (MSF) from the average mid-sleep point on workdays (MSW). R software with the MCTQ package version 0.3.2 was used.[65] Free days were determined based on whether the participant attended school or work that day as indicated in their night diaries; if the participant did not attend school or work, their free days nights were noted as Friday and Saturday nights. If the participant reported working all days, then their SJL was not calculated (N= 3).

Demographic and clinical data were presented using means, standard deviations (SD), medians, interquartile ranges (IQR), and frequencies, as appropriate. T-tests were used to compare outcomes between the clinically active and inactive disease groups. Pearson correlations were used to test the relationships between sleep, fatigue, and GI symptoms with RAR characteristics and SJL.

2.3 Results

There was a total sample of 50 participants. There were 10 individuals with ulcerative colitis and 40 with Crohn's disease, with a mean age of 35.8 (SD: 8.7) years. The sample consisted of 30 females and 20 males. A majority of participants (98%) identified as White for race and had a bachelor's degree or a higher level of education (78%). Based on clinical disease activity, 34 were in remission, and 15 were in active disease. For IBD treatment, a majority (56%) were taking a biologic medication. Fecal calprotectin was available for 45 participants; the median fecal calprotectin was 21.77 ug/g (IQR: 2.78-106.26). Additional demographic and clinical information are provided in Table 1. The average SJL for the sample was less than 1 hour (Mean: 2650.64 seconds, SD: 2088.71 seconds). Two out of 47 participants had a SJL greater than 7200 seconds (2 hours). The values for SJL and RAR characteristics are shown in Table 2.

Table 1: Demographic and Clinical Characteristics

	Total Sample (N=50)
Age M (SD)	35.81 (8.65)
Female N (%)	30 (60%)
Race, White N (%)	49 (98%)
Employment status, working N	
Employed or keeping house	38
Looking for work (unemployed) or temporarily laid off, sick leave, or maternity leave	5
Retired or disabled (permanently or temporarily)	4
Other	2
Highest level of education N	
Vocational School or 12th grade, graduated high school, or GED	3
Associate's degree/some college	7
Bachelor's degree	23
Master's or doctorate degree	16
Current Medications N (%)	
Mesalamine	7 (14%)
Biologic	22 (44%)
Biologic and Immunomodulator	6 (12%)

JAK Inhibitor	3 (6%)
Fecal calprotectin µg/g median (IQR)	21.77 (2.78-106.26)

Table 2: Social jetlag and rest-activity rhythm characteristics

	Mean	SD
Social Jetlag (seconds)	2650.64	2088.71
Rest-activity rhythm characteristic		
Midline estimating statistic of rhythm	3.20	0.36
Acrophase*	15:27	1.42*
Circadian quotient	0.71	0.09
Intra-daily variability	0.38	0.09
Inter-daily stability	0.49	0.08
Relative amplitude	0.76	0.07

*= Acrophase indicates a clock time; the SD needs to be interpreted based on clock time

Sleep and fatigue with SJL and RAR characteristics

The average PROMIS sleep disturbance score was 52.97 (SD: 6.74); the average PROMIS fatigue was 54.89 (SD: 6.45). Sixty-eight percent of participants (N=34) were poor sleepers (PSQI >5). Table 3 shows the relationships between SJL and RAR characteristics with PROMIS sleep disturbance, PROMIS fatigue, and PSQI; none were significant.

Table 3: Sleep and fatigue with social jetlag and rest-activity rhythm characteristics

	PROMIS sleep disturbance	PROMIS fatigue	PSQI
Social jetlag	-0.23	-0.24	-0.04
Rest-activity rhythm characteristic			
Midline estimating statistic of rhythm	-0.08	-0.16	-0.05
Acrophase	0.07	0.05	-0.03
Circadian quotient	0.08	0.23	0.15
Intra-daily variability	0.15	0.10	-0.05
Inter-daily stability	-0.03	0.09	-0.01
Relative amplitude	0.05	0.09	0.06

Note: Pittsburgh sleep quality index (PSQI), patient-reported outcomes measurement information system (PROMIS)

Fecal calprotectin and GI Symptoms with SJL and RAR characteristics

Forty-two percent of participants (N=19) had a fecal calprotectin level higher than 50 ug/g, indicative of active inflammation. Fecal calprotectin had a statistically non-significant relationships with SJL and RAR characteristics. Based on clinical disease activity those in remission had a greater MESOR (p=0.02) and relative amplitude (p=0.01) than those in active disease. There were no statistically significant

relationships between SJL and RAR characteristics with GI symptoms of abdominal pain, bloating, constipation, diarrhea, or nausea (view Table 4).

Table 4: Gastrointestinal symptoms with social jetlag and rest-activity rhythm characteristics

	Abdominal pain	Bloating	Constipation	Diarrhea	Nausea
Social jetlag	-0.19	-0.03	-0.05	-0.10	-0.17
Rest-activity rhythm characteristic					
Midline estimating statistic of rhythm	-0.22	-0.14	-0.18	-0.14	-0.16
Acrophase	0.18	0.11	0.11	-0.06	0.17
Circadian quotient	0.09	0.21	0.07	0.14	0.08
Intra-daily variability	0.13	0.09	0.26	-0.14	-0.004
Inter-daily stability	-0.25	-0.06	-0.26	0.03	-0.14
Relative amplitude	0.01	0.08	-0.02	0.04	0.04

2.4 Discussion

This study of adults with IBD was designed to describe daily rhythms and to determine relationships between symptoms, inflammation, sleep, and fatigue with SJL and RAR characteristics. In addition, comparisons were made between those with clinically active disease and remission. Although two-thirds of the sample were self-reported poor sleepers and had an average sleep disturbance score greater than that of the general population, there were no significant relationships between RAR characteristics and SJL with symptoms, fatigue, sleep, and gut inflammation. Only two participants experienced significant SJL as determined by wrist actigraphy. Those in active disease had a statistically significantly lower MESOR and relative amplitude than those in remission, which supports the notion that individuals with active disease, as compared to those in remission, have less robust RAR.

The lack of significant relationships between RAR characteristics and health indicators differs from the findings of recent reports using similar RAR methodology. A study by Swanson and colleagues (2022) with 42 IBD participants in remission found that fragmentation of the rhythm within a day (intra-daily variability [IV]) was positively correlated with inflammation measured by serum tumor necrosis factor alpha (TNF-α).[40] Participants with Crohn's disease and low inter-daily stability (IS) had an increased relative abundance of pathobionts in their microbiome (e.g., *Streptococcus lutetiensis, S. coeruleorubidus, and Clostridium polysaccharolyticum*). In terms of symptoms, Conley and colleagues (2021) with 37 adults with IBD found that decreased IS was associated with increased gas/bloating and heartburn/reflex, and increased IV was correlated with increased heartburn/reflux. Both these research studies suggested that the RAR characteristics and stability of the rhythm across and within days are associated with IBD health outcomes, such as the gut microbiome, symptoms, and inflammation.

In our study, participants in remission had greater MESOR and relative amplitude compared to those with active disease. Conley and colleagues found that those in active disease had an earlier acrophase when compared to those in remission.[39] Swanson and colleagues studied a sample of participants in remission; those with a more aggressive IBD course (i.e., history of steroid dependence, use of biologic or immunomodulator, perianal disease) had decreased stability in the rhythm across and within days (IS and IV) when compared to non-aggressive disease types. For this study and the other two studies, disease activity was measured using subjective disease measures (HBI, SCCAI, physician global assessment (PGA)). Subjective self-reported disease measures are limited in that underlying inflammation in the gut mucosa can present in patients without symptoms, and symptoms can be present in remission due to other co-morbid conditions, such as irritable bowel syndrome. Thus, the difference in findings across studies could be attributed to the different disease activity measures in IBD, as there is a lack of information on endoscopic disease activity.

This study has several limitations. The outcomes of this study might differ from previous IBD studies on RAR and SJL due to data collected during and post-COVID-19 pandemic (2020-2023) when adults' work lives were changed with work-from-home options being more available. For Americans, the pandemic resulted in divergent sleep results. The National Sleep Foundation (NSF) found that SJL decreased by 9 minutes to less than 1 hour in Americans, and found increased sleep duration with weeknights due to later wake times; however sleep quality in general worsened.[66] The NSF conjects that work and school from home could be the cause of the increased sleep duration. The mean SJL in this study (44.18 minutes) is lower than a previous IBD study in 2018 with 115 IBD subjects with an SJL of 79.2 minutes which was greater than that of a small healthy control group (63 minutes).[42] There is a potential that the pandemic impacted the outcomes of SJL and RAR characteristics in this study due to the changes in daily life and work/school obligations. This study sample was recruited from a tertiary care hospital, but the eligibility criteria might have limited the target population. There are potentially missed insights on daily rhythms as the sample lacks diversity in race, employment, and educational attainment.

There is a continued need to examine the daily rhythms and circadian preferences of those with IBD. One method to explore the impact of SJL is to examine individuals who experience large amounts of SJL and whose work and life schedules are variable, such as nightshift workers (e.g., healthcare workers, firefighters, police officers). One of the first evidence of the impact of disturbed sleep-wake cycles in IBD was in 1990. A German study found that occupations with irregular shifts (i.e., electricians, technical assistants, bakers, female hairdressers) had greater odds of Crohn's disease or ulcerative colitis.[67] However, the extent to which these individuals in the study experience SJL is not reported. Additionally, chronotype, a measure of an individual's innate circadian type correlated with dim light melatonin onset (DMLO), could provide insight into the innate circadian preferences of individuals. There is evidence that later chronotypes, those who prefer to sleep and wake up later in the day, have worse IBD quality of life.[42] Additionally in those with irritable bowel syndrome, chronotype was a predictor of subjective sleep quality.[68] It is possible that IBD could be the driver for

changes in daily rhythms; there needs to be further investigation into the directionality of the relationship between circadian rhythm disruptions and IBD. Other aspects of daily timing should also be explored, such as meal timing. Animal models demonstrate that the timing of eating can impact gut inflammation in mice with dextran sulfate sodium (DSS) induced colitis.[69] Thus, future research should examine the relationship between the consistency of daily rhythms, not limited to sleep-wake patterns, and IBD health outcomes as well as optimize IBD health outcomes by leveraging the body's circadian rhythm.

2.5 Conclusion

In conclusion, adults with IBD in active disease appear to have less robust daily rhythms than those in remission. A majority of participants in this study did not experience significant SJL. No significant relationships were found between RAR characteristics and SJL with symptoms, fatigue, sleep, and fecal calprotectin; however, poor sleep was reported in most participants. Future research is needed to identify key features of the daily rhythm, such as food timing, that could improve nighttime sleep and IBD health outcomes.

CHAPTER III.

MANUSCRIPT 2: Sleep Fragmentation and Next Day Symptoms Across and Within individuals in Inflammatory Bowel Disease

3.1 Introduction

Individuals with inflammatory bowel disease (IBD), a chronic illness, report high rates of poor sleep.[3] Those with IBD experience two disease states: 1) active disease, the presence of inflammation, and consequently severe gastrointestinal (GI) symptoms; 2) remission, a period without inflammation. Poor sleep quality has been linked to an increased risk of relapse into active disease from remission and decreased quality of life.[70] Bowel movements at night and IBD-specific pain are noted as top problems that impact sleep.[71] Individuals with IBD who are in active disease have poorer sleep quality than those in remission.[3] Additionally, 49% of those with IBD report that sleep problems can affect their disease, and 27% thought active disease could result from chronic poor sleep.[72] The bidirectional relationship between disease activity and sleep is well noted, as increased inflammation drives poor sleep, and poor sleep, in turn, increases inflammation.[73] However, only a few IBD sleep studies have worked to unravel the relationship between sleep and IBD-related GI symptoms (e.g., abdominal pain, diarrhea).

The collection of self-reported sleep quality and actigraphy measured sleep outcomes allows a multidimensional perspective on sleep. This study focused on sleep fragmentation and self-reported sleep quality. Sleep fragmentation is measured based on the frequency rather than the length of awakenings, unlike other sleep variables based on length of time, such as wake after sleep onset (WASO) and sleep efficiency. A previous study found that perceived sleep quality is closely aligned with the number of awakenings, which is reflected in sleep fragmentation.[74] In those with IBD, sleep fragmentation has been associated with abdominal pain and heartburn/reflux.[39] Thus, the use of both sleep fragmentation and sleep quality can provide a comprehensive view of the subjective and objective sleep of those with IBD.

Two IBD studies examined the directionality between symptoms and sleep outcomes. One study found a bidirectional relationship between self-reported sleep quality and abdominal pain using general estimating equations (GEE).[75] Another study using cross-lagged path analysis collected data over 14 days through actigraphy and daily sleep diaries found that self-reported nightly awakenings and abdominal pain had a bidirectional relationship. However, actigraphy measured WASO, sleep efficiency, and total sleep time did not significantly predict next-day pain.[76] These studies point to the importance of considering both the perceived sleep of participants alongside objective sleep measures as they can yield different temporal relationships with self-reported symptoms.

Not only is it important to consider the participants' responses and sleep over time as a whole, but it is also important to consider the within-person changes and fluctuations longitudinally in the relationship between sleep and symptoms. Two previous studies on

irritable bowel syndrome and sleep present differing significance in relationships between sleep outcomes (e.g., sleep efficiency, sleep disturbances) and symptoms (e.g., abdominal pain, bloating, constipation, diarrhea, intestinal gas) when examining across-subject and within-subject effects.[77,78] Thus, there is a need to examine not only the directionality between sleep and symptoms across the sample as a whole, but also the impact of within-subject variability. The aims of this manuscript are to 1) describe the nighttime sleep outcomes of those with IBD; 2) test if sleep fragmentation from wrist actigraphy and self-reported sleep quality from daily diaries predicts next-day GI symptoms (i.e., abdominal pain, bloating, constipation, diarrhea, nausea) across and within adults with IBD.

3.2 Methods

Study Design

This study utilized an observational prospective cohort design.

Ethical considerations

The University of Washington Institutional Review Board (IRB) approved this study (STUDY00016807).

Study population and participants

Participants were recruited from an adult IBD clinic located in a University hospital in the Pacific Northwest. Data for this study were collected at two times: 1) 2019-2021 in a previous IBD sleep study[44]; 2) 2023-2024 (collected for this dissertation). The eligibility criteria for the study were a diagnosis of ulcerative colitis or Crohn's disease, ages between 18 to 55, and able to read and write English. The exclusion criteria were breastfeeding or pregnant or having a child 1-year-old or younger, having a diagnosed sleep apnea or narcolepsy, traveling across 3 time zones during the study, or working shiftwork. Individuals were also screened for restless legs syndrome and obstructive sleep apnea.

Participants collected data for 10 days. They first completed a baseline questionnaire. Then they wore a wrist actigraph from Phillips Respironics for 10 days while completing daily electronic diaries. All questionnaires were completed through the Research Electronic Data Capture system (REDCap).[45,46]

Measures

Demographic Data

Demographic information related to age, sex, marital status, household size, and number of pets.

Sleep Fragmentation & Sleep Outcomes

Wrist actigraphy data was collected over 10 days using the Actiwatch (Phillips Respironics, Bend, OR). Wrist actigraphs contain accelerometers that measure movement, are easily worn, and are found to be feasible to use in the IBD population.[79] Participants who had a menstrual cycle began their data collection on the first day of menstruation. The participants were instructed to mark the beginning and end of nighttime sleep by pressing a button on the side of the watch. Sleep diaries were

electronically completed by participants in the morning in which they reported the time they went to bed, fell asleep, woke up, and got out of bed.

Self-reported Symptom Severity & Sleep Quality
While wearing the watch, participants were sent a daily email in the evening through REDCap, which asked them to rate the following symptoms: abdominal pain, bloating, constipation, diarrhea, and nausea. The participants reported their symptom severity at night which was based on the last 24 hours as not present (0), mild (1), moderate (2), severe (3), and very severe (4). Every morning, participants were asked to rate their sleep quality for the last night as extremely poor sleep (0) to extremely good sleep (10).

Data Analysis
The wrist actigraphy data was scored by two researchers using the actigraphy data, light data, and sleep diaries. Actigraphy data was collected in 60 second epochs. The actigraphy data was analyzed using the Actiware software 6.3 (Phillips Respironics, Bend, OR). The sleep fragmentation index was calculated by the software as the sum of percentage of minutes mobile (number of mobile epochs/total number of epochs) and percentage of immobile bouts < 60 seconds in length divided by the total number of immobile bouts. A higher sleep fragmentation index is associated with more sleep disruptions or more restless sleep. Other sleep outcomes from actigraphy, such as total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency, are reported.

Demographic information and GI symptoms were described through means and standard deviations, and counts and percentages, as applicable. Pearson correlations were used to describe the relationship between sleep fragmentation and subjective sleep quality. Generalized estimating equations (GEE) with an autoregressive correlation structure were used to test the sleep fragmentation and sleep quality with next-day GI symptoms. The GI symptom scores were led by 1 day in the models to associate the symptom on the next day with the correct night's sleep fragmentation. The GI symptom scores did not need to be led for self-reported sleep quality (for example: day 2 morning diary with information on the previous night's sleep was tested with day 2 symptom diary). The within-subject measure was calculated by subtracting the daily value from the mean value across days (e.g., sleep fragmentation (day 1) - sleep fragmentation (average across days 1-10)). The across and within-subject measures did not have a linear relationship and were checked for collinearity. From the GEE analysis, beta estimates, robust standard errors, and p-values were reported. R software and geepack version 1.3.12 package were used in data analysis.

3.3 Results

A total of 50 adults with IBD were included in this study. Thirty individuals identified as female, and the mean age for the sample was 35.81 years (SD: 8.65). Most were married or in an unmarried partner relationship (60%), and the average household size was 2.90 (SD: 1.21), with a majority (64%) having 1 or more pets. The mean scores for the GI symptoms- abdominal pain, diarrhea, bloating, constipation, nausea- were less

than mild with a score less than 1. The top symptoms based on mean scores were abdominal pain (0.65) and diarrhea (0.65).

The average total sleep time measured by wrist actigraphy for the sample was 424.40 minutes (7 hours and 4 minutes). The mean sleep onset latency, the time to fall asleep, was 17 minutes. The average time awake after falling asleep measured by WASO was 53 minutes. The mean sleep efficiency, the time spent asleep by the total time in bed, was 83%. The mean sleep fragmentation was 31.43. For self-reported sleep, the mean sleep quality score from the electronic diaries was 6.35 (10 being extremely good sleep). GI symptoms, subjective sleep, and sleep variables measured by wrist actigraphy are presented in Table 1.

Table 1: Gastrointestinal symptoms and sleep outcomes

Daily Diaries	
GI symptoms (0-4)	Mean (SD)
Abdominal pain	0.65 (0.88)
Bloating	0.58 (0.79)
Constipation	0.32 (0.69)
Diarrhea	0.65 (0.90)
Nausea	0.27 (0.69)
Sleep Quality (0-10)	Mean (SD)
Sleep Quality	6.35 (1.90)
Actigraphy	
Nighttime sleep outcomes	Mean (SD)
Total nighttime sleep (min)	424.40 (57.02)
WASO (min)	53.33 (22.15)
Sleep latency (min)	16.57 (13.96)
Sleep efficiency (%)	83.10 (5.76)
Sleep fragmentation (%)	31.43 (10.12)

Note: gastrointestinal (GI), wake after sleep onset (WASO)

Sleep fragmentation measured by actigraphy was inversely correlated with subjective sleep quality ($r=-0.26$, $p<0.05$). Sleep fragmentation measured by wrist actigraphy was not significantly associated with next-day GI symptoms (Table 2). The across-subject beta value for nausea and sleep fragmentation can be interpreted as the following: the estimated mean difference of next-day self-reported nausea (on a scale of 0-4) is 0.009 between two groups that differ by one unit of sleep fragmentation and have the same difference of sleep fragmentation from their average across nights. The across-subject beta value for nausea and sleep quality can be interpreted as the following: the estimated mean difference of next-day self-reported nausea is -0.096 between the two groups that differ by one unit of sleep quality (on a scale of 0-10) and have the same difference in sleep quality from their average across nights. Daily self-reported sleep quality was not associated with next-day GI symptoms (View Table 3).

Table 2: Sleep fragmentation as a predictor of next-day gastrointestinal symptoms

	Across-subjects				Within-subjects		
	Beta	SE	*p*		Beta	SE	*p*
Abdominal pain	0.0002	0.004	0.96		-0.0002	0.004	0.97
Bloating	-0.002	0.004	0.60		0.005	0.004	0.29
Constipation	-0.001	0.004	0.76		0.003	0.004	0.47
Diarrhea	-0.009	0.005	0.09		0.007	0.005	0.12
Nausea	0.009	0.005	0.07		-0.004	0.005	0.39

Table 3: Self-reported sleep quality as a predictor of next-day gastrointestinal symptoms

	Across-subjects				Within-subjects		
	Beta	SE	*p*		Beta	SE	*p*
Abdominal pain	-0.069	0.064	0.28		0.051	0.073	0.49
Bloating	-0.024	0.061	0.70		-0.002	0.067	0.10
Constipation	0.010	0.041	0.82		-0.010	0.042	0.83
Diarrhea	-0.018	0.068	0.79		0.021	0.079	0.79
Nausea	-0.096	0.055	0.08		0.098	0.061	0.11

3.4 Discussion

This study collected data over the course of 10 days using electronic diaries and wrist actigraphy to describe the nighttime sleep outcomes and test the directionality of sleep fragmentation and sleep quality with common IBD GI symptoms. The sample, on average, had a total sleep time of about 7 hours and short sleep latency, minutes to fall asleep, which were within the National Sleep Foundation's (NSF) guidance on good sleep quality.[80] The average WASO for the sample, 53 minutes, was greater than the NSF's recommendation of less than 41 minutes, indicating that this sample had a greater WASO than recommended for good sleep quality.[81] Additionally, the average sleep efficiency (SE), a measure of sleep quality, of the sample was marginally lower than the minimum 85% SE recommendation by NSF.[81] Daily measured sleep fragmentation and self-reported sleep quality were not significant predictors of next-day GI symptoms across and within subjects.

Both self-reported and actigraphy measured sleep outcomes are valuable for IBD sleep research. The mean sleep fragmentation in this sample was higher than that of healthy controls and people with primary insomnia.[82,83] In this study, a higher sleep fragmentation index was significantly associated with poorer sleep quality (a lower sleep quality score on the electronic diary). Other IBD sleep studies have found relationships between sleep and next-day symptoms. An IBD sleep study composed of 26 participants reported a bidirectional relationship between self-reported nightly awakenings and abdominal pain. Additionally, self-reported SE and sleep quality predicted next-day pain. However objective wrist actigraphy-measured sleep variables (e.g., WASO, total sleep time, SE) did not predict next-day symptoms. Additionally, the within-subject directionality was not examined. Although our study did not find sleep

fragmentation or self-reported sleep quality to be associated with next-day GI symptoms, there is a potential that there is a need to further investigate discrepancies in objective sleep outcomes and self-reported sleep in those with IBD.

Overall, our sample recruited from a university medical center had a low symptom burden, with the average GI symptom scores for 10 days being less than mild. Rather than solely utilizing self-reported symptoms, there is a need to understand the combined impact of symptoms and inflammation on sleep outcomes. Although individuals with IBD typically have GI symptoms in active disease, the presenting symptoms are heterogeneous, including both intestinal and extraintestinal symptoms. The use of objective disease measures is rare in IBD sleep studies. A meta-analysis on IBD sleep found only 8 studies that used an objective disease activity measure (e.g., C-reactive protein, fecal calprotectin, endoscopic and histologic findings). Combining symptom data with objective inflammatory biomarkers, such as C-reactive protein and fecal calprotectin, could provide information on certain phenotypes that are related to poor sleep in IBD. Additionally, serial collection of inflammatory biomarkers and symptom diaries alongside wrist actigraphy collected over time could allow for the examination of the combined impact of symptoms and inflammation with sleep outcomes.

There are study limitations to consider while interpreting results. There is recall bias with self-reported symptom severity and sleep. Recalling information about sleep can be especially difficult for participants as they might not remember the exact timing of their bedtime and wake time in the morning. Additionally, there might not be sufficient wrist actigraphy to substantially test the relationship between symptoms and sleep. It is unclear on the length of time wrist actigraphy data should be collected to test the directionality between symptoms and sleep, as multiple factors, such as the menstrual cycle, work schedules, and other obligations, can impact sleep. There is a potential that undiagnosed sleep disorders impacted this study. Sleep disorders are highly prevalent in IBD. One study found that 67% of IBD participants with poor sleep met the criteria for insomnia, and about a third met the criteria for at least 2 sleep disorders.[71] This is especially important as our sample had a higher sleep fragmentation than that found in primary insomniacs.[78] Thus, future work should screen IBD participants for insomnia and account for undiagnosed sleep disorders in the population.

Mental health and sleep are closely linked. Studies have found that improving sleep quality can also improve mental health.[84] A meta-analysis found that the prevalence of anxiety symptoms in individuals living with IBD is 32.1% based on 58 studies, and depression is 25.2% based on 75 studies.[16] Additionally, depression is significantly associated with poor sleep in those with IBD.[3] Past research on irritable bowel syndrome finds that within subjects, self-reported sleep quality was a predictor of next-day anxiety among participants.[77] Additionally, across-subjects, sleep efficiency from wrist actigraphy was a significant predictor of next-day depressed mood for those with irritable bowel syndrome. Thus, future work should consider mental health outcomes when examining sleep in those with IBD.

3.5 Conclusion

Our findings suggest the potential need to improvement WASO and SE in those with IBD despite meeting the healthy sleep guidelines for total sleep duration and sleep onset latency. Additionally, the study sample reported less than mild GI symptoms (i.e., abdominal pain, bloating, constipation, diarrhea, and nausea). Sleep quality and sleep fragmentation were not significant predictors of next-day GI symptoms. Future research focused on examining the directionality of the relationship between sleep and symptoms with a sample with greater symptom burden and considering the impact of mental health.

CHAPTER IV

MANUSCRIPT 3: Factors Impacting Sleep-Wake Cycles in Inflammatory Bowel Disease: A Qualitative Study

4.1 Introduction

Adults with inflammatory bowel disease (IBD) experiencing poor sleep and sleep disturbances have decreased quality of life and increased pain, fatigue, and inflammation.[85] Poor sleep quality in those with IBD has been associated with future adverse health outcomes (e.g., surgery, hospitalization, drug escalation).[86] When an individual experiences active IBD, also referred to as a flare-up, they can endure excruciating gastrointestinal (e.g., diarrhea, nausea, urgency) and extraintestinal (e.g., fatigue, oral ulcers) symptoms. Despite the growing evidence of biological and behavioral factors impacting the sleep of those with IBD, there is limited knowledge on the influence of social determinants of health and the context in which sleep occurs (e.g., education level, marital status, area of residence).[26]

Improving sleep in those with IBD requires attention beyond individual factors, such as age and sex. Sleep health is a multidimensional concept and factors, such as work schedule and family life, have a significant influence on sleep schedules, sleep outcomes, and overall daily patterns. The social-ecological model of sleep (SEM) provides a useful framework to begin exploring the impact of external social and societal-level factors.[25] In the SEM, the individual, social, and societal levels are nested within each other and together, these levels produce sleep outcomes. Past research on sleep health using the SEM and other social-ecological models have found that the neighborhood, social support, gender, and relationships can influence sleep.[87-89] Utilizing the SEM in IBD sleep research is critical, as current IBD sleep interventions, such as cognitive behavioral therapy for insomnia, fail to address factors outside of the individual-level factors, such as sleep behaviors and attitudes toward sleep.

Few IBD sleep studies have used qualitative methods to understand the perspectives and experiences related to sleep of those with IBD.[90-92] Of the three IBD qualitative studies on sleep, two describe the intertwined relationship between fatigue, daytime napping, sleep, and painful flare-ups, and the interconnection between sleep, mental health, and IBD.[90,91] Another identified factors using content analysis across the SEM (individual, social, and societal) impacting the sleep of those with IBD.[92] All three studies were limited by their use of data from free text responses from surveys. Thus, the use of semi-structured interviews in this study provides richer insights into the lived experiences of those with IBD, which is especially important when exploring factors across the SEM. This study aims to identify factors that influence sleep-wake cycles in adults with IBD and strategies they use to improve sleep quality.

4.2 Materials and Methods

Design

A qualitative descriptive research design with a postpositivist research lens was used to understand the factors that impact sleep-wake cycles of adults with IBD through semi-structured individual interviews. A hybrid thematic analysis, which included both

inductive and deductive reasoning, was used to understand the perspectives of IBD participants on the multilevel factors that impact their sleep-wake cycles.[93] The interview guide and analysis were informed by the social-ecological model of sleep.[25] Results are reported using the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines.[94]

Sample/participants

Participants were recruited from the University of Washington Digestive Health Center from May 2023-June 2024 for a study on sleep-wake cycles (described in Manuscripts 1 and 2). All participants were diagnosed with IBD and between the ages of 18-55 years. Those who had a known sleep disorder or worked shiftwork were excluded from the study. Before the phone interview, participants wore a wrist actigraph for 10 days, collected a stool sample, and filled out electronic surveys.

The sample consisted of 24 individuals with IBD (20 Crohn's disease and 4 ulcerative colitis). 15 were female and 9 were male. The ages ranged from 21-53 years. For race, all participants reported as identifying as White. Most participants (92%) did not live alone, and the average household size was close to 3 people. A majority (87.5%) reported low to moderate influence of the sleep environment on their nighttime sleep quality based on their assessment of sleep environment scores (ASE). Additionally, this sample had a mean sleep hygiene score index (SHI) score of 18.5 which is indicative of good sleep hygiene. When asked about the relationship between IBD and sleep, 14 participants (54%) stated there was a relationship; 6 participants stated there was not a relationship; 4 were unsure or did not know of a relationship. Table 1 presents demographic information and data from the ASE and SHI.[95,96]

Table 1: Demographics, sleep hygiene, and sleep environment among adults with inflammatory bowel disease

Characteristic (N=24)	
Age M (SD)	38.2 (9.2)
Living arrangement N (%)	
Live alone	2 (8%)
With spouse/partner/significant other	18 (75%)
With relative(s)	3 (12.5%)
With roommate (non-relative)	1 (4%)
Total number in household M (SD)	2.9 (1.3)
Number of pets N (%)	
1	8 (33.3%)
2	7 (29.2%)
2+	2 (8.3%)
Marital Status N (%)	
Married	14 (58.3%)
Divorced	2 (8.3%)
Never married	4 (16.7%)
A member of an unmarried couple	4 (16.7%)

Employment N (%)	
Working now or keeping house	18 (75%)
Looking for work, unemployed	1 (4%)
Disabled, permanently or temporarily	3 (12.5%)
Other	2 (8.3%)
Student N (%)	3 (12.5%)
Sleep hygiene index M (SD)	18.5 (7.4)
Assessment of sleep environment N (%)	
Low	14 (58.3%)
Moderate	7 (29.2%)
High	3 (12.5%)

Note: A total assessment of sleep environment score between 0-9 is low; 10-19 is moderate; above 20 is a high influence of the sleep environment on difficulty sleeping. A higher sleep hygiene index indicates poorer sleep hygiene; this score ranges from 0 to 52.

Research Team & Reflexivity

LY is a female PhD student in Nursing Science who has conducted interviews in the past for an IBD sleep study. She is part of the IBD community and has volunteer experience with the IBD community. The participants were familiar with the researcher, as LY recruited and collected data from participants before the interview. EF is a female PhD student in Nursing Science and worked together with LY on data analysis. EF's research focuses on individuals with atrial fibrillation and she has experience with qualitative research. SI is a female professor at the School of Nursing and reviewed the themes and subthemes after coding was completed. SI is a member of LY's dissertation committee and has expertise in qualitative and mixed methods research.

Data collection

Participants conducted a semi-structured interview with LY via phone call after collecting 10 days of sleep data collection. The phone interviews were recorded and notes were made after the interviews by LY. Participants were compensated with $25 gift cards twice during the study (i.e., after wrist actigraphy data collection, after the phone interview). The mean interview length was 27 minutes (ranging from 15- 41 minutes). The interview guide is included in supplemental table 1. The interviewer asked additional questions to further gain insight from participants. Transcripts were not returned to participants and participants did not provide feedback on findings.

Ethical considerations

This study (STUDY00016807) was approved by the University of Washington Institutional Review Board (IRB). Participants' consents were obtained before beginning the audio recording of the interview. Additionally, participants were verbally reminded that they were able to stop the interview at any time, and/or take breaks as needed.

Data analysis

Audio recordings were transcribed using Rev Software. Hybrid thematic analysis was conducted.[93] Data management and analysis was augmented using Atlas.ti software

(Atlas.ti, Berlin, Germany). Two researchers (LY, EF) began data analysis by reading the transcripts and writing memos. These memos were compared and discussed. Then the researchers independently coded transcripts and discussed, revised, and compared codes to create the initial codebook. Additional independent coding was conducted, and then, through an iterative process, the final codebook was created. Later, the codes were organized, and themes and subthemes were identified. Themes were added, removed, or changed to ensure that the themes were clear and distinct. The SEM was used to organize the themes within each level (individual, social, and societal) as defined by Grandner.[97] The two researchers communicated throughout the process of data analysis, and an audit trail was kept. An additional researcher, SI, audited and reviewed the themes, and subthemes. All three researchers provided feedback and communicated any necessary changes to the themes and subthemes.

4.3 Results

Across the individual and social levels, six themes and 11 subthemes are reported (view Table 2). No societal-level themes were reported.

Table 2: Individual and social level impacts on sleep-wake cycles with definitions: Themes & subthemes

Level	Theme	Subtheme	Definitions
Individual	Lifestyle and behaviors	Daytime behaviors	Behaviors that occur during the daytime impacting sleep-wake cycles
		Nighttime influences	Behaviors, events, happenings at night impacting sleep-wake cycles
		Diet	The timing or type of foods eaten affecting sleep-wake cycles
		Technology use	The timing or type of technology impacting sleep-wake cycles
	Physical health	IBD and GI symptoms	IBD disease activity and GI symptoms influencing sleep-wake cycles
		Non-GI pain, fatigue & other health conditions	Pain, fatigue, and other comorbidities impacting sleep-wake cycles
		Medications and supplements	The schedule and intake of certain medication and supplements impacting sleep-wake cycles
	Mental health		Feelings and emotions impacting sleep-wake cycles
Social	Sleep environment		Happenings and items inside in the bedroom and immediately around the bedroom influencing sleep-wake cycles

	Interpersonal relationships	Partner	Partner's, schedules, habits, or behaviors impacting sleep-wake cycles
		Child	Children's schedules, habits, or actions that impacting sleep-wake cycles
		Pets	Pet's schedule and behaviors impacting sleep-wake cycles
		Friends	Socialization and time with friends influencing sleep-wake cycles
	Work		Work schedules and workload impacting sleep-wake cycles

Throughout the themes, participants stated strategies they used to indirectly or directly improve their sleep health. These strategies are listed in Table 3.

Table 3: Strategies used by participants that directly and indirectly impact sleep health

	Strategies
Directly related to sleep	• Reading before sleep • Avoid certain foods • Minimize caffeine • Stop using technology at night before bed • No napping too close to bedtime • Awareness of liquid intake close to bed • Earplugs, music, audiobooks, podcasts, noise machines • Facemask, blackout blinds

Indirectly related to sleep	• Self management techniques
	  ○ Distraction
	  ○ Deep breathing
	  ○ Changing sleep positions
	  ○ Warm bath
	  ○ Heating pad

Individual-Level

1) Lifestyle and behaviors

Four subthemes arose from the theme of lifestyle and behaviors which were daytime behaviors, nighttime influences, diet, and technology use. Many lifestyles and behaviors were based on personal choices and beliefs, and some of these behaviors were specific to a participant's IBD journey or life circumstances.

1.1 Daytime behaviors

The thoughts and beliefs on exercise and activity on nighttime sleep were mixed. The intensity and timing of exercise were noted to either positively or negatively impact sleep, such as exercising close to bedtime negatively impacting sleep. Participants reported varied experiences of the impact of daytime napping. Some stated that they felt worse or not refreshed after napping, while others stated they were helpful and improved their productivity. One participant stated they used napping to compensate for nighttime sleep loss. Most noted that they worked on minimizing daytime rest close to bedtime to prevent any issues with falling asleep.

> "I think if I nap during the day, it's harder for me to go to sleep at night." (Male, 39 years old)

1.2 Nighttime influences

Nightmares, vivid dreams, and nighttime urination were frequently discussed by participants as causes of waking up at night. Liquid intake was mentioned by some as influencing bathroom use at night. One participant even stated that they prevented frequent bathroom use at night by minimizing their hydration during the day. Others mentioned drinking water in the evening to catch up on their hydration for the day.

> "For me it's not always having a bowel movement at night… I'm not drinking sometimes as much water as I need to during the day at work. So I try to overcompensate at home when I get home from work and then I drink too much water and then will end up using the restroom." (Female, 45 years old)

Additionally, reading was routinely stated as a part of a bedtime routine by participants.

> "I usually just read until I physically fall asleep. I'll wake up with my Kindle in my hand, and it's rare for me to actually just put it down and be like, "It's time to sleep." (Female, 41 years old)

1.3 Diet

The types of foods eaten before sleep were recognized as influencing nighttime IBD symptoms, and consequently, nighttime sleep. A participant noted that poor diet, in combination with other factors, such as work stress, could lead to a flare-up with IBD symptoms and in turn, impact their sleep. Symptoms associated with foods were heartburn, bloating, abdominal pain, increased intestinal activity, nocturnal defecation, and urgency.

> "I try to never eat ice cream. I don't know. It just messes with me. It just messes with my stomach. That's the only thing that I've known over the years that has... I love ice cream, too, but I just can't. Especially at night. If I have it in the middle of the day, or earlier in the evening, then it won't affect me as much. But if I get a couple scoops of ice cream and watch a movie at night, and we all eat popcorn and hanging out, I'll wake up in the middle of the night for sure with a stomachache." (Male, 47 years old)

It was also noted that diet could cause worry which can impact sleep.

> "Even being in remission now, as I mentioned, just the sort of thought of there being an issue because I ate something I wasn't supposed to eat, that, just the thought of that, could potentially be keeping me from getting as good sleep as I could." (Male, 45 years old)

To prevent issues with food, participants avoided certain foods or ingredients, such as dairy, excess sugar, fried foods, raw vegetables, and caffeine. Participants discussed leaving time between their last meal and bedtime. Hunger and the amount of food eaten before bed were also noted as influencing nighttime sleep.

> "I mentioned eating too close to bed, or if it's something that typically doesn't sit well with me, having that for either lunch or dinner." (Female, 34 years old)

The timing of caffeine intake was considered to minimize disruptions to sleep and drinking alcohol was stated to increase nighttime awakenings, being more restless, negatively impacting sleep quality, and making it harder to fall asleep.

> "I think alcohol can make it a worse sleep as well. I know for some people it helps them fall asleep. But when I do go out and have a couple drinks, yeah, I don't think it's as good of a sleep." (Female, 52 years old)

1.4 Technology use

Participants discussed their use of phones, TVs, and computers near bedtime, noting that their sleep could benefit from abstaining from technology use near bedtime. However, one participant stated that using technology can help them get "tired enough to go to sleep." Others described that a more relaxing and peaceful sleep environment would include not having a TV, and that TV watching can result in difficulty in falling asleep. A delay in bedtime was mentioned by those who used the TV or phone before bed; one participant stated that time passed quickly without them noticing, resulting in delayed bedtime. A few participants spoke about turning off their electronic devices to "slow things down mentally" before bed.

> "I think it would be better if I didn't use my phone in bed at all. I think that would be an improvement." (Female, 33 years old)

2) Physical health

Three subthemes comprised the physical health theme: IBD and GI symptoms, non-GI pain, fatigue and other health conditions, and medications and supplements. Participants described the impact of their health on sleep outcomes, such as nighttime awakenings, as well as strategies to cope with health problems.

2.1 IBD and GI symptoms

Several GI symptoms were described as causing nighttime awakenings, poor sleep quality, increased fatigue, and difficulty falling asleep. The GI symptoms noted by participants were abdominal pain, cramps, constipation, bowel urgency, increased bowel movements, flatulence, bloating, nausea, and vomiting. Abdominal pain was frequently mentioned in relation to poor sleep.

> "I guess to say one that has the most influence would probably be pain, just because it's really uncomfortable and so then you have a hard time falling asleep, and then if it happens in the middle of the night, then you might wake up and feel it and then have to try and go back to sleep versus if you're needing to go to the bathroom, usually you can just get up, go and then fall back asleep." (Female, 21 years old)

Waking up and using the bathroom was reported by participants when experiencing a flare-up. Flare-ups would increase nighttime awakenings, impede falling asleep, and

increase fatigue during the day. It is important to note that some participants reported no symptoms that impacted their sleep, symptoms not having an impact on sleep, no abdominal pain with urgency, or felt that they fell asleep sooner and had better sleep with active inflammation.

> "…depending upon the severity of the flare, you can be waking up in the middle of the night to have to go to the bathroom and that's not fun either…because of those symptoms that I would suffer from my IBD, it would make it harder to get more sleep, which then led to more exhaustion, led to more stress, led to poor diet choices." (Male, 31 years old)

Some participants pointed to having worse symptoms when they had poor sleep. A participant made an observation on the connection between the brain and gut.

> "I can't tell you how many times I've been told that the gut is the second brain. So if there's a reason for why you're so sleepless, maybe you're stressed out or something's on your mind that it would make sense that lack of sleep and then also stomach pain. I don't know. I think everything's connected." (Female, 32 years old)

Two participants shared their self-management techniques, such as distraction, deep breathing, and changing sleep positions to mitigate symptoms at night.

> "Because when I'm really experiencing pain and can't fall asleep, I really do need to kind of distract my mind from the pain. It's not ideal, but I do find that just watching a show kind of just takes my mind off of it, and then I can fall asleep when I get really tired." (Female, 33 years old)

2.2 Non-GI Pain, Fatigue other health conditions

Different locations of pain (joint, muscle, back, head) and cramping (muscle, menstrual) influenced sleep.

> "I have joint pain and that will impact my nighttime sleep. It's very secondary to the spondyloarthritis. I have had a harder time getting to sleep since going through menopause. I did notice a change with that." (Female, 53 years old)

Women's health topics were also discussed, such as menopause negatively impacting sleep through hot flashes, and menstrual cramp pain causing nighttime awakenings. Other conditions, such as having a cold, skin conditions (e.g., erythema nodosum), and sinus issues, had negative effects on sleep.

Multiple participants reported fatigue. In terms of factors impacting fatigue, participants stated the following items: malabsorption, anemia, increased frequency of bowel movements, medication, IBD, lack of exercise, and busy lifestyle.

> "I know that at my worst with IBD, I was tired all the time. And I don't know if it was being malnourished or if my body was busy doing other things, but I was exhausted constantly. So I would try to take a nap. It would throw off my nighttime schedule because I would be sleeping." (Male, 45 years old)

Participants shared specific management techniques for joint pain which included bathing in warm water and using a heating bad. Additionally, there were different ways to cope with fatigue, such as napping and sleeping more at night.

2.3 Medications and supplements

Participants discussed the side effects of their prescription medications, causing fatigue or needing more rest on the day of medication administration. This included IBD medications to induce remission, such as Adalimumab and Ustekinumab.

> "I think it's just dependent on how I feel, especially when I'm closer to when I take my dose of medication, I tend to be a little bit more tired and fatigued, and I feel like it can impact my sleep a little bit." (Male, 33 years old)

Some participants adjusted their sleep-wake schedules to their medical regimen, such as setting alarms to take medications in the morning. There were mixed responses on the impact of supplements and other medications, such as vitamin B, iron, and melatonin, on sleep.

3) Mental health

Mental health, including anxiety and stress, impacted the sleep of participants. Many participants described the negative relationships between anxiety, "thinking" before sleep, and rumination, as well as stress from life circumstances, such as extended family, school, and managing IBD, causing difficulty with sleep. There were a variety of nighttime sleep outcomes (e.g., more nighttime awakenings, more restlessness, earlier wake up time, difficulty falling back asleep) that were stated to be impacted by stress and anxiety.

> "but sometimes at night I get anxious and start making lists in my head of all the things I have to do but that's getting a lot better... I think I've had it my whole life, but it's definitely gotten much worse since the Crohn's diagnosis, and mainly just because I have a lack of control, and that's really difficult for me." (Female, 41 years old)

Daytime emotions could have an impact at night. These emotions did not necessarily have to be negative, such as anxiety or stress, to have an impact on sleep.

> "When I have the high emotion days, something awesome happened or something bad happened. It's replaying in my head on a loop, and that's where that starts to make it harder to fall asleep because my mind doesn't want to slow down and just relax." (Male, 37 years old)

<u>Social-Level</u>

4) Sleep environment

Participants provided insight into the different elements in their sleep environment, which included noise, lighting, temperature, and the condition of the bedroom. A few participants commented on the cleanliness of their room and the condition of their beds, which influenced their sleep. Participants also stated that an uncomfortable temperature in the room (too cold or too hot) would result in difficulty sleeping.

> "I would say, if it's too hot or too cold, that changes how I sleep, but that's just something that you don't know until you go to bed, so it's not a permanent change that can be made" (Female, 28 years old).

Noise in the external environment, such as traffic and neighbors, would result in sleep disturbances. Participants described listening to audiobooks, podcasts, or music, and using earplugs to control the sounds in their sleep environment. Several participants used white noise machines to assist with sleeping.

*"*I do sleep with a noise machine. I used to have various fans running, especially during the summer, until we put a unit in for AC. So I do sleep with a noise fan machine. That definitely helps as I sleep" (Male, 33 years old).

Light coming from the outside environment would result in awakenings at night or result in earlier than normal waking due to the light in the morning. There was a preference for a dark sleep environment; blackout blinds and face masks were used by participants to decrease external light.

5) Interpersonal relationships

Interpersonal relationships with a participant's partner, children, pets, and friends, were reported as impacting sleep schedule, nighttime sleep quality, and overall day-to-day life. Some participants provided insight into the interconnected nature of the various relationships in their lives.

5.1 Partner

Participants reported on the influence of their partner, who typically shares the bedroom with the participant. There are nighttime influences, such as snoring, noises (e.g., CPAP machine), technology use in bed, movements (e.g., "tosses and turns", use of the bathroom), and changes of temperature in bed due to their partners, can influence the time to fall asleep and stay asleep.

> "If he can't sleep, he tosses and turns, and he's on his phone and I can tell, and then I wake up, so that definitely impacts my sleep." (Female, 44 years old)

The use of early alarms and differences in schedules of partners also impacted the sleep and wake times of participants. Several participants mentioned that their partner's work schedule would negatively impact sleep, such as working an early shift, being on call, or traveling for work.

5.2 Child

Sleep was disrupted due to the needs of children at night which included comforting the child, responding to the child's call for help, and providing emotional support to pass night terrors. A participant described a domino effect where a child waking up the participant's partner will result in the participant also waking up. Several participants stated that their young child would come into their room at night which would wake them up.

> *"*Sometimes let's say I have to go and comfort them in the night and then I fall asleep in their room and that affects the sleep. I get good sleep, if I sleep in my bed and I don't get the best sleep if I have to share the bed with the kids because they tend to… make sounds and then wake me up." (Male, 33 years old)

Adult participants were highly reliant on the sleep-wake schedules of their children. The earliest that adults could go to sleep was dependent on their children's bedtime. However, other tasks after the children were asleep, such as work obligations and free time, would ultimately determine their sleep time.

> "Really, I mean, in a perfect day, I decide when I get into bed, but that hardly ever happens. It's more whenever I get my son to go to sleep." (Male, 38 years old)

Parents mentioned that fatigue would sometimes drive them to fall asleep in their children's bed. Additionally, a participant discussed the impact of their child's daytime napping on the child's bedtime and, consequently, the participant's bedtime as an adult. The participants reported that their children's school schedules and preparation for school superseded the impact of work on their wake times.

> "sometimes it's earlier because we get up and get the kids ready and out the door, regardless of whether I'm working from home or not." (Female, 41 years old)

5.3 Pets

Pets influenced the nighttime sleep of participants through their actions and sounds. Pets joining their family members in bed or making noise, such as barking, caused interrupted sleep.

> "…It's usually like 5:00 AM-ish, 6:00 AM…It's like when he gets hungry and then he'll come in and just kind of cuddle with one of us or walk on my head." (Female, 28 years old)

Many participants stated that their pet's schedule, such as feeding and bathroom use, would impact their sleep-wake schedules.

> "So I get up at the same time to feed them because I do a consistent dinner, breakfast schedule for the cats. And my one cat gets insulin. So that was a factor during the study. I would get up at a pretty consistent time to take care of the cats." (Female, 42 years old)

Several participants stated that their pets had particular needs that occurred at the same time every day, with some pets having minimal flexibility to change schedules.

5.4 Friends

Socialization and time with friends were a reason for delaying sleep times. Nighttime social events called for an exception to the usual bedtime.

> "Sometimes, I do play some games with my friends, and sometimes, that can get a little long before you realize the time that's passed, so I do that sometimes as well." (Female, 21 years old)

One participant stated that most social events occurred during the night and alluded to a change in the amount of socialization after the end of the Covid-19 pandemic.

6) Work

Participants reported that work influenced their sleep and wake times. For example, work stress would negatively impact their sleep quality and ability to fall asleep, as well as increase night awakenings. Bedtimes were especially impacted by whether the next day was a weekend without work or a workday.

Several participants stated that having to work late at night resulted in a delay in bedtime. Additionally, participants woke later than usual during the weekends for lost sleep from the weekday, or woke later on days without office commute.

> *"…*when I have a workday, I try to ideally just shoot for a bedtime that would enable me to get enough sleep. But I think sometimes that gets interrupted by my work schedule, I guess, and especially with my current job, just because I have a ton of work. So sometimes it's just based on when I can finish my work for the

day and just can get into bed. But I guess in an ideal world, it would be based on when I need to get up the next day so I would get about eight hours of sleep. But then that often gets interrupted by a very demanding job." (Female, 33 years old).

4.4 Discussion

Individuals with IBD reported individual and social-level factors influencing their sleep-wake cycles. Participants shared their current strategies to improve their sleep. At the individual level were lifestyle and behaviors (daytime behaviors and habits, nighttime influences, diet, and technology use), physical health (IBD and GI symptoms, non-GI pain and other health conditions, fatigue, and medications and supplements), and mental health were found to impact sleep. At the social-level, sleep environment, interpersonal relationships (partner, children, pets, and friends) and work were described as impacting sleep-wake cycles. No societal-level factors were stated by participants. Several of the factors, such as work schedule not in the control of participants, heavily impacted their sleep health. This study illuminates the importance of considering these factors when examining the sleep health of those with IBD and for future intervention development.

Participants reported individual-level factors related to lifestyle and behaviors, physical health, and mental health as influencing sleep-wake cycles. Participants reflected on the interconnected nature and combined impact of these individual-level factors. For example, one participant described that the worry related to diet could impact sleep. Similarly, prior studies have found that active disease and anxiety are factors associated with poor sleep in those with IBD.[73] It is important to note that individual-level factors are nested within social and societal-level factors which can make it difficult for participants to clearly parse out. For example, approximately 92% of households in the United States have a computer, and 84% have a smartphone.[98] Although the rise of technology in modern society, a societal-level factor, has impacted sleep health, it is also an individual-level choice to use this technology at nighttime. Thus, it is crucial to acknowledge the interconnectedness of the factors across and within levels in the SEM.

Interpersonal relationships were recognized as an important social-level factor identified to impact nighttime sleep and daily sleep-wake cycles. In our study, participants mentioned that a partner's snoring and use of technology negatively influenced their sleep. A study examining 48 heterosexual couples found that higher support and positive interactions within a couple have been associated with increased sleep-wake concordance, the percentage of time that both members of the couple were asleep and woke up at the same time, and consequently, sleep coregulation.[99] Thus, examining the quality of a relationship and viewing sleep at the level of the dyad is important for future sleep studies. Additionally, parents of children spoke about sleep disturbances and reliance on the sleep and wake times of their children. A longitudinal study collecting data over the course of 19 years found that a parent of a child between the ages of 2 to 5 had 70% increased odds of sleeping 6 hours or less per night when compared to those without children.[100] Studies have found that improvements in a young child's sleep can significantly improve maternal sleep quality.[101] Work was also mentioned as a social-level factor influencing sleep-wake cycles. Increased work stress has been associated with poor sleep quality.[102] A study observing pre and post- COVID-19

pandemic sleep and working conditions found that the proportion of days working in-office was associated with earlier sleep and wake times when compared to working from home.[103] Work schedules and family influences are necessary factors to consider in sleep research, even if it is not modifiable factors for participants.

Throughout each of the themes, participants provided strategies to improve their sleep health both directly and indirectly by managing their health condition. A majority of the study participants recognized a relationship between IBD and sleep, and the participants had overall good sleep hygiene and low influence of the environment on their sleep, which could be attributed to the current strategies that were described. Many of the strategies described by participants to improve sleep are similar to those provided in cognitive behavioral therapy for insomnia (CBT-I) which has been preliminarily found to improve sleep onset latency, sleep efficiency, and wake after sleep onset in those with IBD.[104] But these strategies were limited, and social-level strategies related to interpersonal relationships and work to improve sleep were not mentioned.

Few IBD sleep studies have used qualitative methods to describe the factors impacting sleep in those with IBD. A qualitative IBD study utilizing the SEM examined the open-ended responses on sleep and the factors that impacted sleep.[92] In this study, the most common subtheme for each level was mental health (individual level), family (social level), and natural environment and geography (societal level). From the 163 responses, the societal-level factors stated by participants included the natural environment and geography, technology, 24/7 society, and economics. The study was limited in its use of content analysis, which focuses on the frequency of codes, and did not seek in-depth contextual information from participants. The findings of this study and ours reported mental health and family as key factors.

There are limitations to this study. Most participants were employed and all identified as White. Sleep research has pointed to poorer sleep in minority populations and lower-income communities.[105,106] Within the IBD population, minority status was related to increased odds of fragmented sleep and poor sleep efficiency.[107] Although there is a higher prevalence of IBD in White Americans for both CD and UC, there is an increasing rate of IBD in minority populations.[1] The lack of representation of minority groups in this sample is a missed opportunity to fully uncover the factors impacting sleep-wake cycles in those with IBD. Additionally, the lack of societal-level responses from this sample could be the result of interview questions not adequately eliciting responses from participants. More questions on neighborhood, climate/weather, and societal pressures could be added for future work.

4.5 Conclusion

This study identifies individual and social-level factors that influence sleep-wake cycles of those with IBD. Future multilevel sleep interventions need to consider interpersonal relationships as the schedules of others, especially dependents, can significantly impact nighttime sleep. Furthermore, daytime activities, such as exercise, meal timing, and daily routines, should be investigated in relation to sleep. Since several of the factors

reported by participants are not capable of alteration or resistant to change, future qualitative studies should explore the acceptability and feasibility of multilevel tailored sleep interventions for those with IBD.

Supplemental table 1: Interview Guide

-Introduction-
-Building rapport-
Do you have any questions before we begin?
Do I have your permission to audio record the interview?

Prepared questions
How do you decide your bedtime?
Does your bedtime depend on whether you work or not? If yes, how?
Do you make any efforts to go to sleep and wake up every day at the same time? If yes, how?

Describe your bedroom: Some examples are TV, pets
Does anyone share the bedroom with you? Lighting?
Describe your neighborhood at night.
Is there anything that would make your sleep environment more relaxing/peaceful/easier to sleep?

What impacts your nighttime sleep? How does x impact your nighttime sleep?

Do you wake up at night? If yes, what things wake you up?
What makes your sleep worse?
How much control do you have over when you go to sleep?
How much control do you have over when you wake up?
How much control do you have over how much you sleep?
How much control do you have over how well you sleep?

-Add statement about any napping reported by participant during data collection-
Describe your napping schedule.
If you don't have a schedule, how and when do you determine when you should nap?
Some examples are how often you nap/where you nap/how long you nap

Do you think there is a relationship between your IBD and sleep? If yes, describe the relationship.
What symptoms influence your sleep the most?

-Added questions specific to open ended responses in surveys about nighttime sleep-

CHAPTER V

Conclusion to Dissertation

5.1 Summary of Findings

Grounded in the social-ecological model of sleep, this dissertation utilized quantitative (manuscripts 1 and 2) and qualitative (manuscript 3) methods to examine the sleep-wake cycles of individuals with inflammatory bowel disease. The results from manuscript one were that rest-activity rhythm (RAR) characteristics and social jetlag do not have significant relationships with fecal calprotectin, gastrointestinal symptoms, fatigue, and nighttime sleep outcomes. Additionally, those in clinical remission could have more robust rhythms, as per a greater average midline estimating statistic of rhythm and relative amplitude than those in active disease. The results from manuscript two were that daily sleep fragmentation and subjective sleep quality do not predict next-day gastrointestinal symptoms. Although total sleep time and sleep onset latency were aligned with recommendations from the National Sleep Foundation, the average wake after sleep onset and sleep efficiency did not meet recommendations. Manuscript three used hybrid thematic analysis to analyze qualitative data from phone interviews. There were six themes and 11 subthemes across the individual and social levels as impacting sleep-wake cycles. The individual-level themes (7 subthemes) were lifestyle and behaviors (daytime behaviors and habits, nighttime influences, diet, and technology use), physical health (inflammatory bowel disease and gastrointestinal symptoms; non-gastrointestinal pain, fatigue and other health conditions; medications and supplements), and mental health. The social-level themes (4 subthemes) were sleep environment, interpersonal relationships (partner, children, pets, friends) and work.

5.2 Limitations

The wrist actigraphy used in manuscripts one and two was collected across seasons. Mattlingly and colleagues examined 216 individuals across the United States and report changes in sleep duration, bedtime, and wake time across seasons, with spring being associated with shorter sleep duration, later bedtime, and earlier wake times.[108] An additional limitation is that although wrist actigraphy is viewed as an objective measure of sleep and determining sleep times, there are instances in which wrist actigraphy might not accurately reflect the activity or light experienced by the participant. For example, the stillness of the participant might lead to researchers overestimating sleep times, and watches covered with clothing or bedding might lead to inaccurate light data, especially during the winter season.

Another limitation is the lack of diversity in the sample in all three manuscripts. The sample of participants for this study does not represent the IBD population in the United States.[1] The incidence of IBD in minority communities is rising in the US.[109] Black/Indigenous/People of Color/Hispanic (BIPOC/H) individuals with IBD have poorer symptom control, lower quality of life, and more difficulties accessing IBD care.[110] Qazi and colleagues identified that minorities had more fragmented sleep and poor sleep efficiency measured by wrist actigraphy than non-minorities with IBD.[107] There is also a

cultural component to nighttime sleep.[111] The lack of participants of diverse backgrounds limits the understanding of social and societal-level influences on sleep-wake cycles in this study. Future IBD research should make concerted efforts to recruit from diverse populations.

5.3 Future Research

Previous IBD studies have mostly examined individual-level factors, such as age and disease activity, which limits the understanding of sleep in those with IBD.[26] The bidirectional relationship between inflammation and sleep has been well-studied using cross-sectional designs in IBD sleep research. However, longitudinal studies are scarce, and the combined effect of multiple factors influencing sleep across the SEM with inflammation and GI symptoms has yet to be explored. By leveraging a serial collection of inflammatory biomarkers (e.g., fecal calprotectin), symptom diaries, and wrist actigraphy while collecting data on family dynamics, work, neighborhood characteristics, and the social determinants of health, researchers can examine the combined effects of individual, social, and societal-level factors on the sleep and RAR of those with IBD over time. Longitudinal research projects would provide the basis for investigating sleep, RAR characteristics,and IBD health outcomes while looking at moderators that can affect this relationship.

In order to effectively develop sleep interventions that address social-level factors, IBD researchers must work collaboratively with the IBD community to create research projects that are accessible and meaningful to participants of different backgrounds and life circumstances. Patient advisory groups (PAGs) are an outlet for those with IBD to collaborate in research with academic researchers. Jointly with researchers, PAGs create new ways to collect data to improve study retention and satisfaction and develop solutions to problems that arise in study participation. Researchers can advance recruitment strategies with PAGs to improve participation in subpopulations in IBD and increase diversity in IBD studies.[112] Studies that aim to collect objective disease activity measures (e.g., fecal calprotectin, endoscopies) and objective sleep measures over time (e.g., wrist actigraphy) can be burdensome to participants. Thus, PAGs could help design longitudinal studies that are feasible and acceptable to the IBD community.

This dissertation focused on the sleep-wake cycle, however there are many peripheral clocks and cycles within the human body. Although the sleep-wake cycle can profoundly impact the GI system, the GI system is also regulated by food timing. Time-specific intake of foods could play a major role in the microbiome, intestinal motility, and GI symptoms of those with IBD. Thus, close examination of food timing and even timing of medication intake, could provide more insight into the impact of the circadian rhythm on IBD health outcomes.

5.4 Implications and Conclusion

By utilizing the SEM, this dissertation provides a holistic understanding of nighttime sleep as well as overall daily rhythms. This information is important for future multilevel intervention development. Current IBD sleep interventions, morning light treatment and

cognitive behavioral therapy for insomnia (CBT-I), are limited and focus on improving sleep through modifying individual-level factors.[113,114] Light therapy intervention utilizes a device that emits light to encourage consistency in the circadian rhythm and shift the IBD participant's circadian timing earlier, if needed. Cognitive behavioral therapy aims to improve sleep by working on the following 5 components: sleep restriction, stimulus control, sleep hygiene, cognitive therapy, and relaxation techniques. Neither of these interventions addresses family dynamics and work directly and does not provide individuals with IBD the skills or resources to navigate social and societal level issues that might impact sleep.

This dissertation reports that individuals with IBD in clinical remission have more robust rest-activity rhythms than those in active disease, opportunities for improvement in nighttime sleep outcomes (i.e., wake after sleep onset, sleep efficiency), and individual and social-level factors impacting sleep-wake cycles. Further investigation is needed on factors influencing poor sleep quality (self-reported and objective) outside of individual-level factors and an in-depth understanding of ways to account for social and societal-level factors that influence sleep and daily rhythms. Future IBD research that explores multiple levels of the social-ecological model of sleep would greatly benefit from collaborations with the IBD community. This dissertation provides the basis to continue holistically examining sleep and daily rhythms to develop sleep interventions that can be sustainable, meaningful, and applicable to the everyday lives of IBD participants.

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