Relationships among Sleep, Circadian Rhythms, Social Timing and Symptoms in Adults Living with a Health Condition

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ABSTRACT

Relationships among Sleep, Circadian Rhythms, Social Timing and Symptoms in Adults Living with a Health Condition

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The overall purpose of this dissertation was to examine the relationships among sleep, circadian rhythms, social timing and symptoms in adults living with a health condition and in particular adults with acute respiratory failure (ARF) and irritable bowel syndrome (IBS). Manuscript one examined diary and actigraphic sleep variables as well as actigraphic rest-activity circadian rhythms in ARF survivors three months after hospital discharge, and to compared them with a community-dwelling population. Sleep diary, actigraphy data, and insomnia symptoms were collected in a pilot study of 14 ARF survivors. Rest-activity circadian rhythms were assessed

with wrist actigraphy and sleep diary for nine days, and were analyzed by cosinor and nonparametric circadian rhythm analysis. The results showed that all ARF participants had remarkable actigraphic sleep fragmentation, 71.5% had subclinical or clinical insomnia symptoms. Compared to community-dwelling adults, this cohort had less stable rest-activity circadian rhythms ($p<0.001$), and weaker circadian strength ($p<0.001$). The pilot study showed insomnia and circadian disruption were common in ARF survivors. As such, sleep improvement and circadian rhythm regularity may be a promising approach to improve quality of life and daytime function after ARF.

Manuscript two examined potential indirect effects of sleep on abdominal pain symptoms simultaneously through psychological distress and daytime dysfunction in adults with IBS. Daily symptoms of nighttime sleep complaints (poor sleep quality and unrefreshed sleep), psychological distress, daytime dysfunction (fatigue, sleepiness, and hard to concentrate) and abdominal pain were collected in baseline assessments from two randomized controlled trials of 332 adults (mean age 42 years and 85 % female) with IBS. Structural equation modeling (SEM) was used to examine the global relationships among nighttime sleep complaints, psychological distress, daytime dysfunction and abdominal pain. SEM analyses suggest that the primary impact of nighttime sleep complaints on abdominal pain is indirect. The indirect effect appears primarily through daytime dysfunction. Such understanding provides a potential avenue to optimize personalized and hybrid behavioral interventions for adults with IBS through addressing daytime dysfunction and sleep behaviors. Additional study integrating symptoms with biological markers is warranted to explore the underlying mechanisms accounting for these symptoms.

Manuscript three explored associations among chronotype, social jetlag (SJL) and weekday sleep outcomes (sleep quality, sleep need met and restorative sleep) in women with IBS through

multiple linear regression analyses. This sample included 62 women with IBS (IBS predominant constipation [IBS-C] =29, IBS with predominant diarrhea [IBS-D] =33) and 58 healthy control (HC) women who completed 28-day daily diary from two study cohorts. Chronotype was estimated from daily diary data with the average mid-sleep time on weekends (MSW^{we}). SJL was calculated by subtracting the average mid-sleep time on weekdays from MSW^{we}. Sleep outcomes included diary-reported ratings of sleep quality, sleep need met and restorative sleep during weekdays. In HCs, later chronotype was predictive of lower sleep quality ($\beta = -0.19$, $p < 0.01$), a perception of sleep need not met ($\beta = -0.17$, $p < 0.001$) and a less restorative sleep during weekdays ($\beta = -0.15$, $p = 0.073$), whereas SJL was not associated with sleep outcomes. Similar to HCs, earlier chronotypes in women with IBS-C reported better sleep quality and more sufficient sleep need met and restorative sleep during weekdays than later chronotypes (all $p > 0.05$). Compared to HCs, the relationships of chronotype with weekday sleep outcomes in women with IBS-D were in the opposite directions (all $p < 0.05$). The data from this exploratory study suggest that chronotype may be an important contributor to sleep outcomes in women with and without IBS, particularly sleep quality and sleep need met.

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CHAFPTER 1: INTRODUCTION

Background

Sleep deficiency**,** including inadequate amount of sleep and poor quality, is a public health concern and contributes to potential comorbidity (1). Adequate sleep duration recommended by the National Sleep Foundation is 7-9 hours a night for adults to promote optimal physical health, mental health and overall well-being (2). A meta-analysis of prospective cohort studies found that approximately 7 hours of sleep per day was associated with the lowest risk of all-cause mortality and cardiovascular diseases (3). However, the Centers for Disease Control and Prevention reported that 10.1% of the U.S. adult population perceived they got insufficient sleep or rest every day in the past month (4), and nearly 35% reported sleep less than 7 hours per 24-hour period (5). Left untreated sleep deficiency has been associated with a broad range of adverse health consequences including cardiovascular disease, metabolic syndrome, chronic pain, daytime dysfunction (e.g., fatigue, sleepiness, difficulty concentrating) and psychological distress (e.g., depressive mood, anxiety) (6-8). Since sleep deficiency is treatable, sleep is considered as a valuable target to design effective symptom management for adults living with a health condition (9-14).

Circadian rhythms are endogenous physiological and behavioral cyclic processes that are entrained to the 24-h external environment to enable individuals to anticipate and adapt to periodic environmental changes (15). Inter-individual differences in circadian entrainment can be attributed to intrinsic (e.g. circadian genes, age, gender, health conditions, gut microbiome) and extrinsic factors (e.g., light exposure, eating behaviors, social timing) (15-18), leading to different circadian phenotypes, known as chronotypes (19). Chronotype is in part determined by an individual's phase of circadian entrainment relative to the external 24-h environment (19). Early chronotypes, "larks", prefer waking up and going to bed early while late chronotypes,

"owls", prefer waking up and going to bed late. Optimal circadian entrainment is necessary for the optimization of physical and behavioral functions and overall human health (20-23). For example, investigators have found that chronotype is an important determinant of sleep quality and quantity in multiple populations including students and employees with regular daytime work/school schedules. Specifically, late chronotypes are more likely to report poor sleep quality (24-26), less restorative sleep (27), shorter sleep duration (28), insomnia (29, 30) and daytime dysfunction symptoms (24) compared to early chronotypes. Even though emerging evidence has linked circadian misalignment and/or chronotype with chronic diseases or health outcomes in multiple populations, it remains to be explored in adults living with specific health conditions.

Sleep behaviors such as habitual sleep bedtimes and risetimes are influenced by social factors such as work/school schedules and other social commitments. These social factors lead to a variance in bedtime and risetime timing between weekdays and weekends creating a circadian misalignment known as "social jetlag" (SJL) (31, 32). For example, after a weekend, on Monday individuals experience symptoms consistent with jet lag associated with travelling across time zones (32). SJL is used as an estimate of the time discrepancy between endogenous circadian phase, which an individual will naturally follow during the weekend, and imposed social timing, and it is considered the most common circadian misalignment in modern society (33). Adults with greater SJL are more likely to report poor sleep quality (34, 35) and sleep less on weekdays (36) as compared to those with less SJL. It remains to be determined whether individuals living with specific health conditions experience more SJL and whether SJL influences weekday sleep outcomes.

Content of the dissertation

The overall purpose of the dissertation was to gain new knowledge regarding the relationships among sleep, circadian rhythms, social timing (i.e., weekdays vs. weekend) and symptoms in adults living with a health condition. The second chapter selected the survivors of acute respiratory failure (ARF) as the example of adults living with a health condition. It examined diary and actigraphic sleep variables as well as actigraphic rest-activity circadian rhythms in ARF survivors three months after hospital discharge, and compared them with a community-dwelling population. The third and fourth chapters selected adults with irritable bowel syndrome (IBS) as another example of adults living with a health condition. The third paper used structural equation modeling to examine potential indirect effects of sleep (poor sleep quality and unrefreshed sleep) on abdominal pain symptoms simultaneously through psychological distress and daytime dysfunction (fatigue, sleepiness, and difficulty concentrating). The fourth chapter examined the associations between chronotype, SJL and weekday sleep outcomes (sleep quality, sleep need met and restorative sleep) in women with IBS. Each of the three chapters form related but independent manuscripts, with separate introduction, methods, results, and discussion sections. The formatting varied based on the style of journal or target journal, respectively.

Conceptual framework

The dissertation was based on the model of the circadian clock and disease developed by Roenneberg and Merrow (22). This model was used to conceptualize the relationships among sleep, circadian rhythms, social timing and symptoms in adults living with a health condition. In this model, circadian rhythm-sleep-behavior network and environmental factors (environmental Zeitgebers, social timing) are critical to maintain human health. Twenty-four-hour environmental Zeitgebers (e.g., light, food, exercise) can synchronize circadian clocks to adjust the phase of

endogenous circadian rhythms to the phase of environmental Zeitgebers, termed as the phase of the circadian entrainment or chronotypes. An inappropriate phase of circadian entrainment has adverse impacts on sleep, behaviors and health. Also, the deficits in sleep, behavioral outcomes and human health can influence the circadian system. As for social timing, social timing/schedules (i.e., work/school schedules) primarily influence human behaviors (i.e., sleep-related behaviors, eating behaviors), in turn, to impact circadian rhythms and sleep. The discrepancies between social and biological clocks imposed by social timing, termed as SJL, can result in the deleterious consequences of circadian disruption and/or sleep deficiency on human health. The model of the circadian clock and disease provides the framework to explore the relationships among circadian rhythm variables (rest-activity circadian rhythms, chronotypes, SJL), sleep (sleep-wake patterns, perceptions of sleep quality and quantity), social timing (weekday versus weekends), health-related outcomes (abdominal pain, psychological distress and daytime dysfunction symptoms) in adults living with health conditions, specifically adults with ARF or IBS (**Figure 1**).

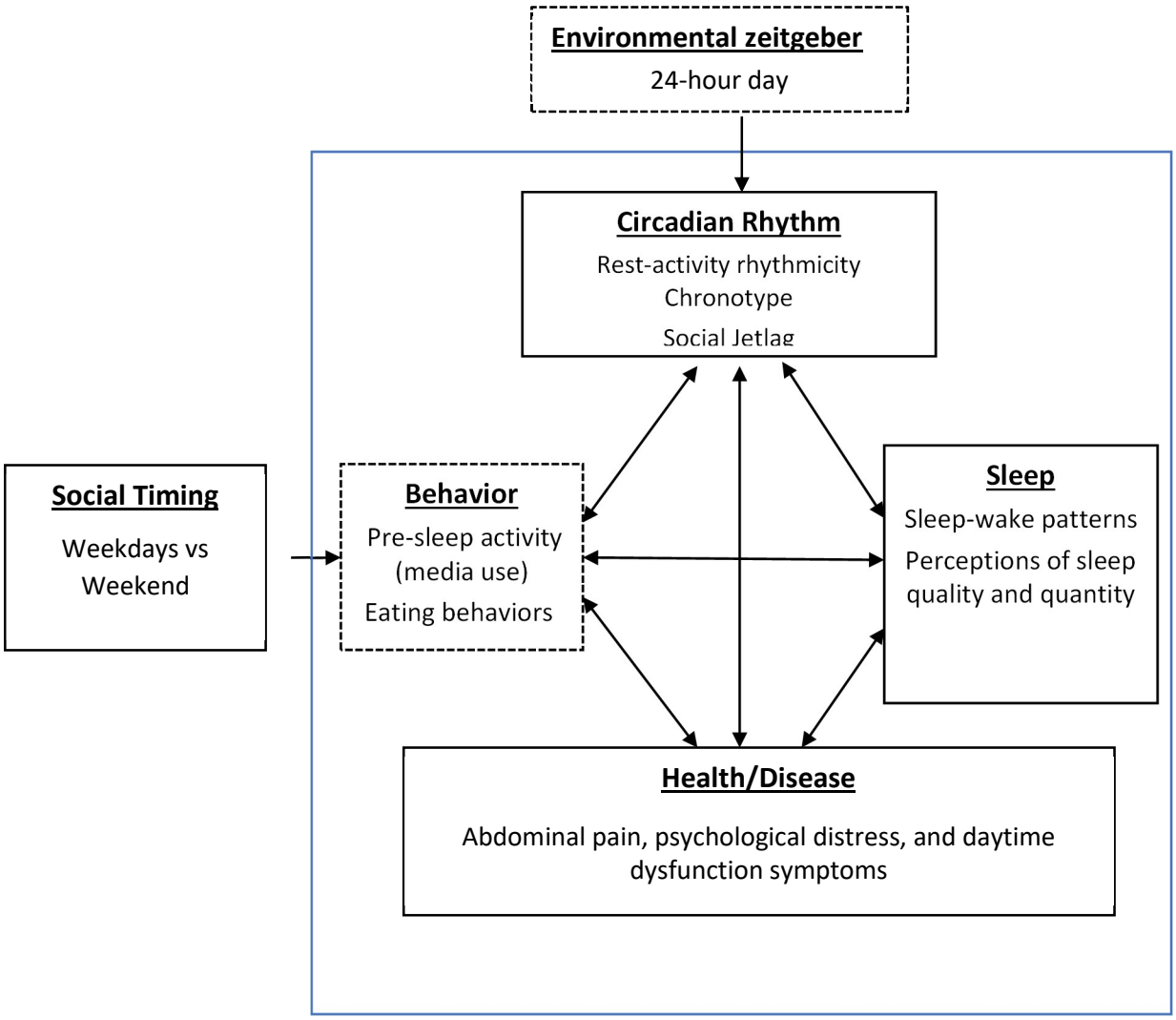

Figure 1: Conceptual Framework for Study of Circadian Rhythms, Sleep, Social Timing and Symptoms in Adults living with a health condition. Adapted from "The Circadian Clock and Human Health." by Roenneberg, T., & Merrow, M., Curr Biol. 2016;26(10):R432-R443. doi:10.1016/j.cub.2016.04.011 Note: Data in the boxes with dotted lines is not available in this dissertation.

References

1. Buysse DJ. Sleep health: can we define it? Does it matter? Sleep. 2014;37(1):9-17 DOI: 10.5665/sleep.3298.
2. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep health. 2015;1(4):233-43 DOI: https://doi.org/10.1016/j.sleh.2015.10.004.
3. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, et al. Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. Journal of the American Heart Association. 2017;6(9):e005947 DOI: 10.1161/JAHA.117.005947.
4. Centers for Disease Control Prevention. Effect of short sleep duration on daily activities--United States, 2005-2008. MMWR Morbidity and mortality weekly report. 2011;60(8):239.
5. Centers for Disease Control Prevention. Short Sleep Duration Among US Adults: National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health; 2017 [Available from: https://www.cdc.gov/sleep/data_statistics.html.
6. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. Prog Cardiovasc Dis. 2009;51(4):294-302 DOI: 10.1016/j.pcad.2008.10.003.
7. Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT. Duration of sleep contributes to next-day pain report in the general population. Pain. 2008;137(1):202-7 DOI: 10.1016/j.pain.2008.01.025.

8. Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annual review of psychology. 2015;66:143-72 DOI: 10.1146/annurev-psych-010213-115205.
9. Palma J-A, Urrestarazu E, Iriarte J. Sleep loss as risk factor for neurologic disorders: A review. Sleep Medicine. 2013;14(3):229-36 DOI: https://doi.org/10.1016/j.sleep.2012.11.019.
10. Buchanan DT, Cain K, Heitkemper M, Burr R, Vitiello MV, Zia J, et al. Sleep measures predict next-day symptoms in women with irritable bowel syndrome. J Clin Sleep Med. 2014;10(9):1003-9 DOI: 10.5664/jcsm.4038.
11. Patel A, Hasak S, Cassell B, Ciorba MA, Vivio EE, Kumar M, et al. Effects of disturbed sleep on gastrointestinal and somatic pain symptoms in irritable bowel syndrome. Aliment Pharmacol Ther. 2016;44(3):246-58 DOI: 10.1111/apt.13677.
12. Tang H-Y, McCurry SM, Pike KC, Von Korff M, Vitiello MV. Differential predictors of nighttime and daytime sleep complaints in older adults with comorbid insomnia and osteoarthritis pain. J Psychosom Res. 2017;100:22-8 DOI: https://doi.org/10.1016/j.jpsychores.2017.06.020.
13. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain. 2013;14(12):1539-52 DOI: 10.1016/j.jpain.2013.08.007.
14. Parsons EC, Hough CL, Vitiello MV, Zatzick D, Davydow DS. Insomnia is associated with quality of life impairment in medical-surgical intensive care unit survivors. Heart & Lung: The Journal of Acute and Critical Care. 2015;44(2):89-94 DOI: https://doi.org/10.1016/j.hrtlng.2014.11.002.

15. Parkar SG, Kalsbeek A, Cheeseman JF. Potential Role for the Gut Microbiota in Modulating Host Circadian Rhythms and Metabolic Health. Microorganisms. 2019;7(2):41 DOI: 10.3390/microorganisms7020041.
16. Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, et al. Epidemiology of the human circadian clock. Sleep Med Rev. 2007;11(6):429-38 DOI: 10.1016/j.smrv.2007.07.005.
17. Fischer D, Lombardi DA, Marucci-Wellman H, Roenneberg T. Chronotypes in the US – Influence of age and sex. PLoS One. 2017;12(6):e0178782 DOI: 10.1371/journal.pone.0178782.
18. Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, Malaisse WJ, et al. Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A. 2014;111(47):16647-53 DOI: 10.1073/pnas.1413965111.
19. Roenneberg T. Having trouble typing? what on earth is chronotype? J Biol Rhythms. 2015;30(6):487-91 DOI: 10.1177/0748730415603835.
20. Oosterman JE, Kalsbeek A, la Fleur SE, Belsham DD. Impact of nutrients on circadian rhythmicity. Am J Physiol Regul Integr Comp Physiol. 2015;308(5):R337-50 DOI: 10.1152/ajpregu.00322.2014.
21. Baron KG, Reid KJ. Circadian misalignment and health. Int Rev Psychiatry. 2014;26(2):139-54 DOI: 10.3109/09540261.2014.911149.
22. Roenneberg T, Merrow M. The Circadian Clock and Human Health. Curr Biol. 2016;26(10):R432-R43 DOI: https://doi.org/10.1016/j.cub.2016.04.011.

23. Honma S. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm. J Physiol Sci. 2018;68(3):207-19 DOI: 10.1007/s12576-018-0597-5.

24. Chrobak AA, Nowakowski J, Zwolinska-Wcislo M, Cibor D, Przybylska-Felus M, Ochyra K, et al. Associations between chronotype, sleep disturbances and seasonality with fatigue and inflammatory bowel disease symptoms. Chronobiol Int. 2018;35(8):1142-52 DOI: 10.1080/07420528.2018.1463236.

25. Orr WC, Elsenbruch S, Harnish MJ. Autonomic regulation of cardiac function during sleep in patients with irritable bowel syndrome. Am J Gastroenterol. 2000;95(10):2865-71 DOI: https://doi.org/10.1016/S0002-9270(00)01110-2.

26. Yun JA, Ahn YS, Jeong KS, Joo EJ, Choi KS. The relationship between chronotype and sleep quality in Korean firefighters. Clin Psychopharmacol Neurosci. 2015;13(2):201-8 DOI: 10.9758/cpn.2015.13.2.201.

27. Tutek J, Molzof HE, Lichstein KL. Multilevel modeling of chronotype and weekdays versus weekends to predict nonrestorative sleep. Chronobiol Int. 2017;34(10):1401-12 DOI: 10.1080/07420528.2017.1373118.

28. Soehner AM, Kennedy KS, Monk TH. Circadian preference and sleep-wake regularity: associations with self-report sleep parameters in daytime-working adults. Chronobiol Int. 2011;28(9):802-9.

29. Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Lahti T, Partonen T. Relation of chronotype to sleep complaints in the general Finnish population. Chronobiol Int. 2012;29(3):311-7 DOI: 10.3109/07420528.2012.655870.

30. Ong JC, Huang JS, Kuo TF, Manber R. Characteristics of insomniacs with self-reported morning and evening chronotypes. J Clin Sleep Med. 2007;3(3):289-94.
31. Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. Chronobiol Int. 2006;23(1-2):497-509 DOI: 10.1080/07420520500545979.
32. Roenneberg T, Pilz LK, Zerbini G, Winnebeck EC. Chronotype and Social Jetlag: A (Self-) Critical Review. Biology (Basel). 2019;8(3) DOI: 10.3390/biology8030054.
33. Beauvalet JC, Quiles CL, de Oliveira MAB, Ilgenfritz CAV, Hidalgo MPL, Tonon AC. Social jetlag in health and behavioral research: a systematic review. ChronoPhysiology and Therapy. 2017;7:19-31.
34. Sűdy ÁR, Ella K, Bódizs R, Káldi K. Association of Social Jetlag With Sleep Quality and Autonomic Cardiac Control During Sleep in Young Healthy Men. Front Neurosci. 2019;13:950- DOI: 10.3389/fnins.2019.00950.
35. Islam Z, Hu H, Akter S, Kuwahara K, Kochi T, Eguchi M, et al. Social jetlag is associated with an increased likelihood of having depressive symptoms among the Japanese working population: the Furukawa Nutrition and Health Study. Sleep. 2019;43(1) DOI: 10.1093/sleep/zsz204.
36. Rutters F, Lemmens SG, Adam TC, Bremmer MA, Elders PJ, Nijpels G, et al. Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? J Biol Rhythms. 2014;29(5):377-83 DOI: 10.1177/0748730414550199.

CHAPTER 2: Sleep and Circadian Rhythms in Survivors of Acute Respiratory Failure

Manuscript One

This manuscript has been published. The authors are **Pei-Lin Yang**, PhD (c), MSN, RN, doctoral candidate, Department of Biobehavioral Nursing and Health Informatics, School of Nursing, University of Washington, Seattle, **Teresa M. Ward**, PhD, RN, FAAN, Professor, Chairperson, Department of Child, Family, and Population Health Nursing, School of Nursing, University of Washington, Seattle, **Robert L. Burr**, PhD, Research Professor, Department of Biobehavioral Nursing and Health Informatics, School of Nursing, University of Washington, Seattle, **Vishesh K. Kapur**, MD, MPH, Professor, Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, **Susan M. McCurry**, PhD, Research Professor, Department of Child, Family, and Population Health Nursing, School of Nursing, University of Washington, Seattle, **Michael V. Vitiello**, PhD, Professor, Department of Psychiatry & Behavioral Sciences, University of Washington, Harborview Medical Center, Seattle, **Catherine L. Hough**, MD, Associate Professor, Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, and **Elizabeth C. Parsons**, MD, MS, Associate Professor, Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle. The

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Abstract

Background: Little is known about sleep and circadian rhythms in survivors of acute respiratory failure (ARF) after hospital discharge.

Objectives: To examine sleep and rest-activity circadian rhythms in ARF survivors three months after hospital discharge, and to compare them with a community-dwelling population.

Methods: Sleep diary, actigraphy data, and insomnia symptoms were collected in a pilot study of 14 ARF survivors. Rest-activity circadian rhythms were assessed with wrist actigraphy and sleep diary for nine days, and were analyzed by cosinor and nonparametric circadian rhythm analysis.

Results: All participants had remarkable actigraphic sleep fragmentation, 71.5% had subclinical or clinical insomnia symptoms. Compared to community-dwelling adults, this cohort had less stable rest-activity circadian rhythms ($p<0.001$), and weaker circadian strength ($p<0.001$).

Conclusion: Insomnia and circadian disruption were common in ARF survivors. Sleep improvement and circadian rhythm regularity may be a promising approach to improve quality of life and daytime function after ARF.

Keywords: Acute respiratory distress syndrome, critical illness, sleep, circadian rhythm, actigraphy

INTRODUCTION

Survivors of Acute Respiratory Distress Syndrome (ARDS) experience impairments in physical, psychological, and cognitive functioning, as well as quality of life (1-4). Sleep disorders may play an important role in post-intensive care unit (ICU) syndrome, defined as a constellation of cognitive, psychological and physical impairment lasting months to years after discharge (5). A systematic literature review found that sleep disturbances affected an estimated 67% of ARDS survivors at one-month post hospitalization and 39% beyond one-month post hospitalization (6). The majority of these studies use self-report measures that focus on sleepiness or insomnia (6, 7). Few studies have incorporated objective sleep measures that could identify circadian rhythm (also known as sleep-wake) disorders for which ARDS survivors are at risk (7).

Many biobehavioral processes in humans, including sleep-wake behavior, follow a diurnal pattern, often called a circadian rhythm. Circadian rhythms are endogenous rhythmic patterns in multiple physiological and behavioral processes such as sleep-wake patterns, rest-activity patterns, mood, cognitive function, body temperature, heart rate, and hormone secretions that are entrained to a 24-hour day to enable individuals to anticipate and adapt to periodic environmental changes (8-10). Optimal circadian entrainment, exhibiting a 24-hour period with an appropriate amplitude (strength) and phase (timing), is essential for the optimization of physical, psychological, and behavioral functions and overall human health (9, 10). Abnormalities in the circadian rhythm have been identified in the acute ICU period, including a dampened circadian amplitude, and/or a delayed phase of physiological circadian biomarkers (i.e., melatonin, cortisol, cytokines) (11-13). Left untreated, circadian disruption may contribute to persistent sleep complaints including insomnia (9, 10) and/or influence mood and cognition (14, 15).

However, to date, it is not known whether circadian rhythms are disrupted after hospital discharge among ARDS survivors.

Wrist actigraphy is a noninvasive, objective measure of sleep-wake patterns and circadian rest-activity rhythms recordable for extended periods of time in a natural environment. Estimates of sleep parameters (i.e., sleep onset and offset, total sleep time, sleep efficiency) and rest-activity circadian rhythms with actigraphy in conjunction with sleep diaries have been validated by polysomnography (PSG) and other circadian biomarkers such as melatonin and core body temperature (16-20). Wrist actigraphy has been accepted as a reliable surrogate measure of sleep and entrained endogenous circadian rhythms in both clinical and research settings (16-18, 21). To our knowledge, there are no published studies using actigraphy in conjunction with sleep diary to identify circadian disruption among ARDS survivors.

The purpose of this pilot study was to: 1) examine sleep duration, sleep quality, and rest-activity circadian rhythms as measured by sleep diary and actigraphy in ARDS survivors three months after hospital discharge; and 2) compare sleep and circadian rest-activity rhythms of ARDS survivors to community dwelling adults in the U.S. A better understanding of sleep and circadian rest-activity rhythms in ARDS survivors after hospital discharge may provide new knowledge for the development of interventions to improve sleep and daytime function on the ARDS population.

MATERIALS AND METHODS

Participants and Procedures

This study is a subset analysis from a prospective observational cohort pilot study named **S**leep **A**nd **R**ecovery after **A**cute Respiratory Failure (**SARA study**). SARA recruited 21 patients with acute respiratory failure admitted to an urban medical center in the Pacific Northwest, a tertiary care hospital from December 2012 to August 2013. Patients in the medical and surgical ICU

were screened consecutively for eligibility in this prospective observational cohort study. Eligible patients (or their healthcare proxies) were approached before or shortly after hospital discharge (within 1 week of discharge) and invited to participate in the study. Enrolled patients included both medical and surgical ICU patients with a variety of primary diagnoses and varying lengths of stay. Inclusion criteria included 1) ≥18 years, 2) admitted to the ICU, and 3) required ≥ 48 hours of mechanical ventilation. Participants were excluded if they had 1) chronic mechanical ventilation, 2) primary neurological injury or diagnosis, or pregnancy, or 3) inability to obtain patient or surrogate consent. The SARA study was reviewed and and approved by the University Human Subjects Institutional Review Board (No. 43516). Informed consent was obtained from all participants prior to data collection. Patients enrolled in the study were evaluated prospectively using sleep questionnaires, actigraphy and sleep diary. At three months post discharge, study evaluation included a survey of sleep and quality of life symptoms, and nine days of actigraphy and sleep diary. Of 21 patients enrolled in the SARA study, this subset analysis included the 14 patients with sleep diary and actigraphy data (the participant rate: 66.7%, two patients were lost to follow-up, 1 withdrew from the study, 4 refused actigraphy).

Measures

Sleep Characteristics

Sleep characteristics were evaluated objectively by actigraphy and subjectively by sleep diary for nine consecutive days at home.

Objective Sleep Estimates. Participants were asked to wear a wrist actigraphy (Actiwatch2, Phillips-Respironics) on the non-dominant wrist to record raw activity counts in one minute epochs. Actigraphy data were scored as sleep or wake with medium (40 activity count threshold) wake sensitivity settings under Actiware software (Mini-Mitter Philips Respironics, Inc.) (6, 19, 20, 22). The onset and offset of the rest intervals were determined by the sleep diaries and was

based on the American Academy of Sleep Medicine (AASM) scoring actigraphy standard criteria (19, 20, 23). Five actigraphy sleep parameters were included in this study: 1) sleep onset, defined as the time of the first period of 10 or more consecutive minutes of immobility; 2) sleep offset, defined as the time of the last period of 10 or more consecutive minutes of immobility; 3) total sleep time (TSTA), defined as the total amount of nocturnal sleep duration in hours during the nighttime rest period scored as sleep; 4) actigraphy sleep efficiency (SEA), defined as the ratio of TST to the nighttime rest period [multiplied by 100 to yield a percentage]; and 5) amount of wake, defined as the wake time after sleep onset (WASO) in minutes.

Subjective Sleep Estimates. Three sleep parameters derived from sleep diary included 1) total sleep time (TST_D), defined as the time participants reported in the item as "the total amount of time they slept at night;" 2) diary-derived SE (SE_D), defined as the ratio of TST_D to total time in bed (multiplied by 100 to yield a percentage); and 3) self-reported sleep quality, assessed by how participant rated the item "when I woke up for the day, I felt" on the level of refreshed, somewhat refreshed, or fatigued.

Insomnia Symptoms. Participants were administered the Insomnia Severity Index (ISI) to measure their perception of insomnia symptoms over the past two weeks. The ISI is a self-reported seven-item questionnaire designed to assess the severity of sleep problems (e.g., sleep-onset, difficulties in maintenance), satisfaction with current sleep patterns, interference with daily functioning, the impairment of quality of life and distress about sleep problems (24). Each item is rated with a five-point Likert scale ("not at all" to "extremely") and total score ranges from 0 to 28 with higher scores indicating greater severity of insomnia symptom. An ISI value between 8 and 14 was used to identify subclinical insomnia; a cut-off value of ≥15 was used to

identify clinically significant insomnia (24). The ISI has established reliability and validity for survivors of critical illness (25, 26).

Rest-Activity Circadian Rhythm

Rest-activity circadian rhythms derived from actigraphy recordings in this study were analyzed by two different methods to account for both normal and non-normal distributions of data, using traditional parametric cosinor analysis and nonparametric circadian rhythm analysis (NPCRA) (16, 27, 28). Analysis of circadian rhythms requires specialized statistical analyses to account for the periodicity of the data, the distribution of the data, and temporal changes over time. Cosinor analysis is a traditional approach to characterize rest-activity circadian rhythms, in which a cosinor curve with a period of 24 hours is fit to a multiple-day time series of measurements of raw activity counts by using least-squares methods (27-31). Three cosinor parameters were included in this study:1) mesor, defined as mean activity count of the fitted 24-hour circadian rhythm pattern; 2) magnitude, defined as mesor-to-peak difference, indicating half estimated extent of the variation within the cycle; and 3) acrophase, defined as highest activity timing in the cycle expressed in decimal hours (Figure 1) (28, 29). These three parameters were used to characterize the circadian phase (timing) and circadian strength. Clinically, acrophase is the measure of circadian phase; mesor and magnitude reflect the robustness of rest-activity circadian rhythms.

As the assumed temporal distribution of cosinor analysis may not always fit the real-world rest-activity patterns well, we also performed a nonparametric analysis (NPCRA) to make our data analysis more robust (32). Six NPCRA variables were included in this study: 1) interdaily stability (IS) provides an estimate of stability of rest-activity rhythms across days, ranging from 0 to 1, and a higher IS value indicates a better synchronization to 24-hour environmental cues; 2) intradaily variability (IV) provides the estimate of fragmentation of the 24-hour rest-activity

rhythms, ranging from 0 to 2, and a higher IV value is found in individuals who have worse sleep efficiency or greater fragmented circadian rhythm patterns; 3) M10 midpoint is determined by the midpoint of the 10 most active consecutive hours, indicating the time of highest activity; 4) L5 midpoint is determined by the midpoint of the 5 least active consecutive hours, indicating the time of lowest activity; 5) amplitude is determined by difference between M10 and L5 levels, indicating the difference in activity level of highest and lowest activity periods; and 6) relative amplitude (RA) is determined by the amplitude divided by the sum of L5 and M10 levels, ranging from 0 to 1, and a higher RA indicates stronger circadian rhythm strength (27, 29, 33).

Demographic and Clinical Characteristics

Trained research personnel extracted demographic (i.e., age and gender) and clinical characteristics including pre-existing comorbidities [heart disease, sleep apnea, hypertension, diabetes, and depression], body mass index (BMI), diagnosis at ICU admission [trauma or medical], length of hospital stay and ICU stay, duration of medical ventilation, PaO2/FiO2 ratio, and illness severity at ICU admission based on Acute Physiology And Chronic Health Evaluation II classification system (APACHE II) (34) from electronic medical record. Participants were asked about living situation and employment status as well as if they needed any assistance with any of eight instrumental activities of daily living (IADLs) including using the telephone, walking, shopping for groceries, preparing meals, doing housework or handyman work, doing laundry, taking medication, and managing money (35) on a scale of 0 (unable to do at all), 1 (need some help), and 2 (need no help). The summed individual IADL scores were used to create a global IADL score, indicative of patient functional status; global IADL scores could range from 0 (low function, dependent) to 16 (high function, independent).

Statistical Analysis

Descriptive statistics were used to describe the demographic and clinical characteristics of the participants. As only actigraphy sleep data with matching sleep diary data were included in the analyses, participants had between 6 and 9 days of concurrent actigraphy sleep data (median=9 days, five participants had less than 9 days of concurrent data). Actigraphy-measured sleep onset and offset, TST_A, SE_A, and WASO plus self-reported TST_D and SE_D from the sleep diary were averaged over consecutive study days for each participant. The sleep characteristics were skewed; consequently, medians and interquartile ranges (IQR) were reported for the actigraphy and self-report sleep measures.

Actigraphy circadian outcomes were analyzed by cosinor analysis and NPCRA analysis to quantify 24-hour rest-activity circadian rhythms for each participant. Actigraphy raw activity data were transformed using natural log (ln) function followed by fitting a 24-hour cosine curve through regression analysis. Given the activity count data were highly skewed, natural log transformation was able to make the activity count data at each time point more uniform and balanced over a 24-hour period, especially important for the low-activity nighttime period (36). Circadian outcomes were presented as means ± standard deviation (SD) to depict rest-activity circadian rhythms.

Given the nature of this pilot study with the lack of comparison group, each of the mean actigraphy circadian parameters, TST_A, and SE_A used Hedges' G effect sizes to compare with those from a sample of 578 community-dwelling U.S. adults, which have been described in detail elsewhere (37). Data analyses were performed using SPSS (v 25).

RESULTS

Participant Demographic and Clinical Characteristics

Table 1 shows the demographic and clinical characteristics of the study sample. The mean age of the sample was 49±15.9 years; 72% were male and lived independently. 57% were trauma

patients and 79% met the criteria for moderate and severe ARDS (PaO2/FiO2 ratio ≤ 200) (38). The mean premorbid IADL score was 12.8 ± 2.5, indicating mild functional limitations, yet only 14% (*n*=2) were full-time employed.

Sleep Characteristics in ARDS Survivors

Table 2 summarizes the actigraphy and sleep diary data and insomnia symptom scores. The median TST_A was 7.8 hours (IQR: 6.2-8.3 hours), the median WASO was 59.8 minutes (IQR: 45.0-92.8 minutes) and the median SE_A was 81.9% (IQR: 78.9-86.0%). Based on sleep diary data, the median TST_D was 6.8 hours (IQR: 5.3-6.9 hours), with a median SE_D of 70.0% (IQR: 62.2-86.0%). The median ISS score was 12.0 (IQR: 6.8-15.0). 42.9% of participants had subclinical insomnia (8≤ ISS score ≤14), and 28.6% had clinically significant insomnia (ISI score ≥15).

Rest-Activity Circadian Rhythm

Table 3 summarizes circadian rest-activity measures, as well as TST_A and SE_A and compares them with a community-dwelling sample of US adults (37). Additionally, comparisons of age and BMI between the two samples were performed to examine the potential effects of age and BMI on rest-activity circadian rhythms (37, 39). No significant differences in age and BMI between two samples were found, indicating the sample of community-dwelling US adults was comparable to our sample on these important rest-activity measures.

24-hour Rhythm Stability/Variability. ARDS survivors had a mean IS of 0.32 (±0.10) compared to a typical value of 0.6 in healthy adults (27), suggesting ARDS survivors had a less stable rest-activity rhythm across the days. ARDS survivors had a mean IV of 0.55 (±0.18) which was congruent to the typical value of <1 for healthy adults (27). This suggests that ARDS survivors have a fairly regular rest-activity rhythm within a single day. ARDS survivors had significantly less stable rest-activity circadian rhythms across days (Hedges' G effect size, $E.S._{(G)}$

for IS=-1.42, p<0.001), and less fragmented rest-activity circadian rhythms within a single day (E.S.$_{(G)}$ for IV=-1.29, p<0.001) compared with the sample of community-dwelling US adults. Less stability of rest-activity circadian rhythms across days in ARDS survivors could represent the suboptimal entrainment of endogenous circadian rhythms to environmental and social cues (37).

24-hour Rhythm Phase. ARDS survivors exhibited later timing for peak activity (E.S.$_{(G)}$ for acrophase=0.61, E.S.$_{(G)}$ for M10 midpoint=0.65) and rest periods (E.S.$_{(G)}$ for L5 midpoint=0.55), and it might indicate a delayed circadian phase (also known as circadian phenotype) in ARDS survivors (40); however, the mean acrophase, L5, and M10 midpoint values were not significantly different in the two samples. ARDS survivors exhibited greater variances in peak activity (SD for acrophase=2.05 vs. 1.3, SD for M10 midpoint=2.64 vs. 1.6, respectively) and rest periods (SD for L5 midpoint=3.44 vs. 1.3, respectively) compared with the sample of community-dwelling US adults, indicating higher heterogeneity of circadian phase in ARDS survivors.

Activity Strength and 24-h Rhythm Strength. A large effect size in mesor (E.S.$_{(G)}$=-2.6, p<0.001), magnitude (E.S.$_{(G)}$=-1.6, p<0.001), amplitude (E.S.$_{(G)}$=-12.03, p<0.001), and RA (E.S.$_{(G)}$=-1.18, p<0.001) were found in ARDS survivors of the sample compared with the sample of community-dwelling US adults. These results indicate that ARDS survivors were less active and had weaker rest-activity circadian rhythms compared to community-dwelling adults.

Sleep Quantity and Efficiency. Both TST_A (E.S.$_{(G)}$=0.51, p=0.15) and SE_A (E.S.$_{(G)}$=-0.57, p=0.01) produced moderate effect sizes, but only SE_A was statistically significant, indicating that ARDS survivors had a longer objective total nighttime sleep time but lower sleep efficiency at three months after hospital discharge relative to the comparison sample.

DISCUSSION

This study provides preliminary data regarding rest-activity circadian rhythms and sleep quality after discharge among acute respiratory failure survivors. At three months post discharge, our cohort of ARDS survivors exhibited subclinical and clinical insomnia symptoms, supported by findings from actigraphy (sleep fragmentation) and sleep diaries (reduced sleep time and quality). Survivors' rest-activity circadian rhythms displayed less stability and lower amplitude compared to that of a published U.S. community-dwelling population. To the best of our knowledge, this is the first study to identify persistent circadian rhythm disruption in ARDS survivors after hospital discharge.

Sleep Disruption in ARDS Survivors

Resolving the literature on sleep disruption after critical illness can be challenging due to the heterogeneity of ICU populations across studies. ICU survivors are a heterogenous group of patients with a variety of diagnoses, pre-existing comorbidities, severity of illness, and long-term outcomes. ARDS survivors are a useful population to examine the link between sleep and/or disruption and functional impairment, because this population shares a common pathophysiology (respiratory failure) and has a high prevalence of long-term functional impairment (4). Our goal in this study was to identify sleep and/or circadian disruptions that could reasonably contribute to the functional impairment of post ICU syndrome.

Our cohort of ARDS survivors reported moderately impaired sleep time and sleep efficiency on their sleep diaries, but these findings were less notable in the actigraphy data. Subjective sleep disturbance was more pronounced, similar to prior questionnaire studies in ICU survivors (7). The prevalence of ISI-defined clinical insomnia at 3-months post discharge was 28.6%, similar to the prevalence at 12-months post discharge in our previous work of ICU survivors (26).

Objective total sleep time is slightly better in our cohort compared than found among 1-month ICU survivors by Solverson and colleagues (TST_A: 7.8 vs 6.2 hours, respectively); sleep efficiency estimates are quite similar (SE_A: 81.9 vs 78 %, respectively) (41). The improved sleep time in our cohort compared to Solverson's may reflect methodological differences and/or the population studied (6, 7). We performed an average of 9 nights of actigraphy (Solverson and colleagues performed 3 nights). Given the potential for night-to-night variability, particularly among ICU survivors with insomnia (7, 42), a longer assessment period would be expected to generate more reliable sleep estimates. Factors that might explain slightly worse sleep in Solverson's cohort include the earlier assessment period (1 month post ICU vs. 3 months after hospital discharge) and longer duration of mechanical ventilation (240 vs. 175 hours, respectively). Solverson's study also included mostly medical ICU patients, who tend to be older and exhibit more pre-existing comorbidities than trauma ICU patients (57% of our cohort). Interestingly, our ARDS cohort exhibited higher severity of illness (APACHE II score: 24.5 vs. 20, respectively) and longer hospital length of stay (21 vs.15 days, respectively) than those in Solverson's cohort. The relative importance of pre-existing comorbidity and ICU factors in predicting post-ICU sleep disruption is a question that bears further investigation.

Most survivors in our cohort reported insomnia symptoms and subjective deficits in sleep quantity and quality, while standard actigraphy measures of sleep (total sleep time and sleep efficiency) were fairly normal. There are several possible reasons for these findings. First, sleep diary may align better with subjective sleep impairment than standard actigraphy measures, and sleep diary tends to underestimate sleep time and efficiency compared to actigraphy (22, 43, 44). Second, identifying circadian abnormalities requires specialized analyses that take into account the timing of the sleep period, which is not reflected in standard actigraphy parameters.

Untreated circadian disruption may contribute to insomnia (45), and effective treatment must take account both sleep and circadian components. While limited in size and scope, this pilot study provides an intriguing potential insight into a circadian contribution to the subjective sleep complaints commonly described among survivors of critical illness (6, 42, 46).

Rest-Activity Circadian Disruption in ARDS Survivors

Our cohort exhibited multiple circadian abnormalities including a less stable rest-activity circadian rhythm, later timings for their peak activity and rest periods, a greater variance in circadian phase, and less active and weaker rest-activity circadian strength compared to the community-dwelling US adult sample with similar age and BMI distribution. To our knowledge, the present study is the first using actigraphy to examine rest-activity circadian rhythms after critical illness.

Possible contributors to circadian disruption after hospitalization among ARDS survivors include inflammation, delirium, side effects of ICU treatments (i.e., sedative medications, mechanical ventilation), and post-ICU depression, anxiety, and post-traumatic stress disorder (3, 11-13, 47-49). Our cohort exhibited weaker rest-activity circadian rhythms compared to community-dwelling adults reflected in the lower values of cosinor magnitude as well as NPCRA amplitude and RA. A recent population-based study showed that lower relative amplitude of rest-activity rhythms was related to depressed mood, mood instability, and poor subjective wellbeing (i.e., happiness, health satisfaction) (50). A lack of regular daily routine may be another possible explanation for post-ICU circadian disruption, supported by findings in our cohort including the low IS value, large variance in sleep offset times, and high percentage of unemployed participants. Regular daytime routines (i.e., work or social schedules; exposure to light, exercise, and food cues) are essential to strengthen the regularity of the circadian system

(9, 10, 51, 52). Further work is needed to identify post-ICU mental health and behavioral factors that may be associated with circadian disruption and serve as appropriate targets for intervention.

Left untreated, rest-activity circadian disruption may exacerbate cognitive and psychological comorbidities in ARDS survivors. Participants in our study were able to live independently and had mild functional limitations in activities of daily living, but IADLs only reflect some domains of cognitive function. ARDS survivors often experience persistent impairments in physical activity and social functioning (3, 4, 53), both of which have been found to be associated with low physical activity and weak circadian strength (54, 55). Impairments in memory, executive functioning, attention, visual-spatial construction, and language have been described in ARDS survivors but were not measured in this study (56, 57). In other populations rather than ICU survivors, cognitive impairment has been associated with disrupted rest-activity circadian rhythms (i.e., less stability, more fragmentation or lower rest-activity amplitude) (39, 55, 58-60). A prospective study with 1,282 healthy older community-dwelling women reported that a less stable, lower rest-activity amplitude, and delayed peak activity timing of rest-activity circadian rhythms predicted the development of either mild cognitive impairment or dementia 4.9 years later, independently of SE and TST (58). Future studies are needed to identify if rest-activity circadian disruption may be a contributor to long-term cognitive deficits among ARDS survivors.

Circadian re-entrainment may be a valuable treatment for sleep and quality of life improvement after critical illness (13, 36, 47). Re-entrainment generally includes a combination of chronotherapy (light and/or melatonin exposure) and behavioral interventions (e.g., set wake time). The timing of these therapies differs by the patient's underlying circadian phenotype. Delayed circadian phase ("night owl" phenotype) is treated with morning light and evening

melatonin, while advanced circadian phase ("morning lark" phenotype) is treated with evening light. In our cohort, we discovered large variances in circadian phase markers of acrophase, M10, and L5 midpoints. Some subjects displayed delayed circadian phase ("night owl" phenotype) while others displayed advanced circadian phase ("morning lark" phenotype) (61). In the ICU, morning light and/or evening melatonin have been prescribed to improve nighttime sleep, circadian rhythms, and decrease delirium (13, 47). This timing of therapy is likely beneficial in patients with delayed circadian phase (e.g., "night owl" phenotype). However, it could worsen advanced circadian phase (e.g., "morning lark" phenotype) and may yield minimal benefit among those with normal circadian phase. Larger studies are needed, but our findings suggest that sleep interventions in ICU survivors may need to account for multiple circadian phenotypes.

Limitations

Limitations of the current study include our small sample size and restriction of the sample to ARDS survivors. Our findings need replication in larger and more diverse samples of ICU survivors. Data analysis only included data from the ARDS survivors who completed actigraphy and sleep diary for nine consecutive days. Participant bias may potentially limit our results to generalize a general population of ARDS survivors. Data on sleep prior to critical illness were not available, and therefore we cannot identify a causal role for critical illness in the circadian abnormalities found in our cohort. Our study suggests that actigraphy is a feasible method to identify circadian disruption in ARDS survivors. While actigraphy is a widely accepted method for estimating sleep and entrained circadian rhythms in other populations, its use has not formally been validated against PSG (the gold standard) in ARDS survivors. Additional study is warranted to examine the validity of actigraphy concurrently with PSG. Larger studies are needed to capture a more comprehensive picture of circadian rhythms after ARDS, potentially

incorporating biological markers (i.e., melatonin) and measures of behavioral and environmental contributors (i.e., light exposure) that perpetuate circadian disruption.

CONCLUSIONS

Findings from this pilot study show that sleep and rest-activity circadian disruption is common among survivors of acute respiratory failure three months after hospital discharge. Sleep and circadian disruption are potentially treatable through chronotherapy (i.e., light, melatonin) as well as behavioral strategies. Sleep improvement and circadian rhythm regularity may be a promising approach to improve quality of life and daytime function in ARDS survivors. Future research is warranted in larger samples to validate these findings, their association with quality of life, and to target specific chronotypes with effective circadian interventions.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

EP contributed to design, patient enrollment, data collection/management, analysis and interpretation. VK, SM, MV and CH contributed to the design and implementation of the research. PLY, TW, and RB performed data analysis and interpretation. PLY, TW, RB and EP took the lead in writing manuscript. All authors provided critical feedback to this manuscript and approved the final manuscript for publication.

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REFERENCES

1. Dodoo-Schittko F, Brandstetter S, Blecha S, Thomann-Hackner K, Brandl M, Knüttel H, et al. Determinants of Quality of Life and Return to Work Following Acute Respiratory Distress Syndrome: A Systematic Review. Dtsch Arztebl Int. 2017;114(7):103.
2. Rubenfeld GD, Herridge MS. Epidemiology and outcomes of acute lung injury. Chest. 2007;131(2):554-62. doi: 10.1378/chest.06-1976.
3. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med. 2016;42(5):725-38. doi: 10.1007/s00134-016-4321-8.
4. Bein T, Weber-Carstens S, Apfelbacher C. Long-term outcome after the acute respiratory distress syndrome: different from general critical illness? Curr Opin Crit Care. 2018;24(1):35-40. doi: 10.1097/mcc.0000000000000476.
5. Rawal G, Yadav S, Kumar R. Post-intensive Care Syndrome: an Overview. J Transl Int Med. 2017;5(2):90-2. doi: 10.1515/jtim-2016-0016.
6. Dhooria S, Sehgal I, Agrawal A, Agarwal R, Aggarwal A, Behera D. Sleep after critical illness: Study of survivors of acute respiratory distress syndrome and systematic review of literature. Indian J Crit Care Med. 2016;20(6):323-31. doi: 10.4103/0972-5229.183908.

7. Altman MT, Knauert MP, Pisani MA. Sleep Disturbance after Hospitalization and Critical Illness: A Systematic Review. Ann Am Thorac Soc. 2017;14(9):1457-68. doi: 10.1513/AnnalsATS.201702-148SR.
8. Foster RG, Kreitzman L. The rhythms of life: what your body clock means to you! Exp Physiol. 2014;99(4):599-606. doi: 10.1113/expphysiol.2012.071118.
9. Roenneberg T, Merrow M. The Circadian Clock and Human Health. Curr Biol. 2016;26(10):R432-R43. doi: https://doi.org/10.1016/j.cub.2016.04.011.
10. Baron KG, Reid KJ. Circadian misalignment and health. Int Rev Psychiatry. 2014;26(2):139-54. doi: 10.3109/09540261.2014.911149.
11. Knauert MP, Haspel JA, Pisani MA. Sleep Loss and Circadian Rhythm Disruption in the Intensive Care Unit. Clin Chest Med. 2015;36(3):419-29. doi: https://doi.org/10.1016/j.ccm.2015.05.008.
12. Telias I, Wilcox ME. Sleep and Circadian Rhythm in Critical Illness. Crit Care. 2019;23.
13. Oldham MA, Lee HB, Desan PH. Circadian Rhythm Disruption in the Critically Ill: An Opportunity for Improving Outcomes. Crit Care Med. 2016;44(1):207-17. doi: 10.1097/ccm.0000000000001282.
14. Vadnie CA, McClung CA. Circadian Rhythm Disturbances in Mood Disorders: Insights into the Role of the Suprachiasmatic Nucleus. Neural Plast. 2017;2017:1504507-. doi: 10.1155/2017/1504507.
15. Videnovic A, Lazar AS, Barker RA, Overeem S. 'The clocks that time us'--circadian rhythms in neurodegenerative disorders. Nat Rev Neurol. 2014;10(12):683-93. doi: 10.1038/nrneurol.2014.206.

16. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep. 2003;26(3):342-92.
17. Wirz-Justice A. How to measure circadian rhythms in humans. Medicographia. 2007;29(1):84-90.
18. Hofstra WA, de Weerd AW. How to assess circadian rhythm in humans: A review of literature. Epilepsy Behav. 2008;13(3):438-44. doi: https://doi.org/10.1016/j.yebeh.2008.06.002.
19. Taibi DM, Landis CA, Vitiello MV. Concordance of polysomnographic and actigraphic measurement of sleep and wake in older women with insomnia. J Clin Sleep Med. 2013;9(3):217-25. doi: 10.5664/jcsm.2482.
20. Ward TM, Lentz M, Kieckhefer GM, Landis CA. Polysomnography and actigraphy concordance in juvenile idiopathic arthritis, asthma and healthy children. J Sleep Res. 2012;21(1):113-21. doi: 10.1111/j.1365-2869.2011.00923.x.
21. Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, et al. Practice Parameters for the Use of Actigraphy in the Assessment of Sleep and Sleep Disorders: An Update for 2007. Sleep. 2007;30(4):519-29. doi: 10.1093/sleep/30.4.519.
22. Schwab KE, Ronish B, Needham DM, To AQ, Martin JL, Kamdar BB. Actigraphy to Evaluate Sleep in the Intensive Care Unit. A Systematic Review. Ann Am Thorac Soc. 2018;15(9):1075-82. doi: 10.1513/AnnalsATS.201801-004OC.
23. Iber C, American Academy of Sleep M. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine 2007.

24. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2(4):297-307. doi: https://doi.org/10.1016/S1389-9457(00)00065-4.

25. McKinley S, Fien M, Elliott R, Elliott D. Sleep and psychological health during early recovery from critical illness: An observational study. J Psychosom Res. 2013;75(6):539-45. doi: https://doi.org/10.1016/j.jpsychores.2013.09.007.

26. Parsons EC, Hough CL, Vitiello MV, Zatzick D, Davydow DS. Insomnia is associated with quality of life impairment in medical-surgical intensive care unit survivors. Heart Lung. 2015;44(2):89-94. doi: https://doi.org/10.1016/j.hrtlng.2014.11.002.

27. Calogiuri G, Weydahl A, Carandente F. Methodological Issues for Studying the Rest–Activity Cycle and Sleep Disturbances:A Chronobiological Approach Using Actigraphy Data. Biol Res Nurs. 2013;15(1):5-12. doi: 10.1177/1099800411416224.

28. Cornelissen G. Cosinor-based rhythmometry. Theor Biol Med Model. 2014;11(1):16. doi: 10.1186/1742-4682-11-16.

29. Thomas KA, Burr RL, Spieker S. Maternal and infant activity: Analytic approaches for the study of circadian rhythm. Infant Behav Dev. 2015;41:80-7. doi: https://doi.org/10.1016/j.infbeh.2015.08.002.

30. Lentz MJ. Time-series analysis--cosinor analysis: a special case. West J Nurs Res. 1990;12(3):408-12. doi: 10.1177/019394599001200313.

31. Refinetti R, Lissen GC, Halberg F. Procedures for numerical analysis of circadian rhythms. Biol Rhythm Res. 2007;38(4):275-325. doi: 10.1080/09291010600903692.

32. Swaab DF, Colenda CC, Cohen W, McCall WV, Rosenquist PB. Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by

application of nonparametric methods. Chronobiol Int. 1999;16(4):505-18. doi: 10.3109/07420529908998724.

33. Thomas KA, Burr RL, Spieker S, Lee J, Chen J. Mother–infant circadian rhythm: Development of individual patterns and dyadic synchrony. Early Hum Dev. 2014;90(12):885-90. doi: https://doi.org/10.1016/j.earlhumdev.2014.09.005.
34. Knaus WAM, Draper EAM, Wagner DPP, Zimmerman JEM. APACHE II: A severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
35. Hopkins RO, Suchyta MR, Kamdar BB, Darowski E, Jackson JC, Needham DM. Instrumental Activities of Daily Living after Critical Illness: A Systematic Review. Ann Am Thorac Soc. 2017;14(8):1332-43. doi: 10.1513/AnnalsATS.201701-059SR.
36. Dowling GA, Burr RL, Van Someren EJ, Hubbard EM, Luxenberg JS, Mastick J, et al. Melatonin and bright-light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. J Am Geriatr Soc. 2008;56(2):239-46. doi: 10.1111/j.1532-5415.2007.01543.x.
37. Cespedes Feliciano EM, Quante M, Weng J, Mitchell JA, James P, Marinac CR, et al. Actigraphy-Derived Daily Rest-Activity Patterns and Body Mass Index in Community-Dwelling Adults. Sleep. 2017;40(12). doi: 10.1093/sleep/zsx168.
38. Umbrello M, Formenti P, Bolgiaghi L, Chiumello D. Current Concepts of ARDS: A Narrative Review. Int J Mol Sci. 2016;18(1):64. doi: 10.3390/ijms18010064.
39. Luik AI, Zuurbier LA, Hofman A, Van Someren EJW, Tiemeier H. Stability and Fragmentation of the Activity Rhythm Across the Sleep-Wake Cycle: The Importance of Age, Lifestyle, and Mental Health. Chronobiol Int. 2013;30(10):1223-30. doi: 10.3109/07420528.2013.813528.

40. Roveda E, Vitale J, Montaruli A, Galasso L, Carandente F, Caumo A. Predicting the actigraphy-based acrophase using the Morningness-Eveningness Questionnaire (MEQ) in college students of North Italy. Chronobiol Int. 2017;34(5):551-62. doi: 10.1080/07420528.2016.1276928.
41. Solverson KJ, Easton PA, Doig CJ. Assessment of sleep quality post-hospital discharge in survivors of critical illness. Respiratory Medicine. 2016;114:97-102. doi: https://doi.org/10.1016/j.rmed.2016.03.009.
42. Lee CM, Herridge MS, Gabor JY, Tansey CM, Matte A, Hanly PJ. Chronic sleep disorders in survivors of the acute respiratory distress syndrome. Intensive Care Med. 2009;35(2):314-20. doi: 10.1007/s00134-008-1277-3.
43. Harvey AG, Tang NK. (Mis)perception of sleep in insomnia: a puzzle and a resolution. Psychol Bull. 2012;138(1):77-101. doi: 10.1037/a0025730.
44. Hartmann JA, Carney CE, Lachowski A, Edinger JD. Exploring the construct of subjective sleep quality in patients with insomnia. J Clin Psychiatry. 2015;76(6):e768-73. doi: 10.4088/JCP.14m09066.
45. Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. J Sleep Res. 2016;25(2):131-43. doi: 10.1111/jsr.12371.
46. Parsons EC, Kross EK, Caldwell ES, Kapur VK, McCurry SM, Vitiello MV, et al. Post-discharge insomnia symptoms are associated with quality of life impairment among survivors of acute lung injury. Sleep Med. 2012;13(8):1106-9. doi: 10.1016/j.sleep.2012.05.010.
47. McKenna HT, Reiss IK, Martin DS. The significance of circadian rhythms and dysrhythmias in critical illness. J Intensive Care Soc. 2017;18(2):121-9. doi: 10.1177/1751143717692603.

48. Huang M, Parker AM, Bienvenu OJ, Dinglas VD, Colantuoni E, Hopkins RO, et al. Psychiatric Symptoms in Acute Respiratory Distress Syndrome Survivors: A 1-Year National Multicenter Study. Crit Care Med. 2016;44(5):954-65. doi: 10.1097/CCM.0000000000001621.
49. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF, Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171(4):340-7. doi: 10.1164/rccm.200406-763OC.
50. Lyall LM, Wyse CA, Graham N, Ferguson A, Lyall DM, Cullen B, et al. Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. Lancet Psychiatry. 2018;5(6):507-14. doi: 10.1016/s2215-0366(18)30139-1.
51. Oosterman JE, Kalsbeek A, la Fleur SE, Belsham DD. Impact of nutrients on circadian rhythmicity. Am J Physiol Regul Integr Comp Physiol. 2015;308(5):R337-50. doi: 10.1152/ajpregu.00322.2014.
52. Honma S. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm. J Physiol Sci. 2018;68(3):207-19. doi: 10.1007/s12576-018-0597-5.
53. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293-304. doi: 10.1056/NEJMoa1011802.
54. Innominato PF, Komarzynski S, Palesh OG, Dallmann R, Bjarnason GA, Giacchetti S, et al. Circadian rest-activity rhythm as an objective biomarker of patient-reported outcomes in patients with advanced cancer. Cancer Med. 2018;7(9):4396-405. doi: 10.1002/cam4.1711.

55. Carvalho-Bos SS, Riemersma-van der Lek RF, Waterhouse J, Reilly T, Van Someren EJ. Strong association of the rest-activity rhythm with well-being in demented elderly women. Am J Geriatr Psychiatry. 2007;15(2):92-100. doi: 10.1097/01.JGP.0000236584.03432.dc.
56. Hopkins RO, Weaver LK, Chan KJ, Orme JF, Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. J Int Neuropsychol Soc. 2004;10(7):1005-17.
57. Jackson JC, Mitchell N, Hopkins RO. Cognitive functioning, mental health, and quality of life in ICU survivors: an overview. Crit Care Clin. 2009;25(3):615-28, x. doi: 10.1016/j.ccc.2009.04.005.
58. Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann Neurol. 2011;70(5):722-32. doi: 10.1002/ana.22468.
59. Journal of neurogastroenterology and motilityWu JQ, Li P, Stavitsky Gilbert K, Hu K, Cronin-Golomb A. Circadian Rest-Activity Rhythms Predict Cognitive Function in Early Parkinson's Disease Independently of Sleep. Mov Disord Clin Pract. 2018;5(6):614-9. doi: 10.1002/mdc3.12692.
60. Cochrane A, Robertson IH, Coogan AN. Association between circadian rhythms, sleep and cognitive impairment in healthy older adults: an actigraphic study. J Neural Transm (Vienna). 2012;119(10):1233-9. doi: 10.1007/s00702-012-0802-2.
61. Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A Phase Response Curve to Single Bright Light Pulses in Human Subjects. J Physiol. 2003;549(3):945-52. doi: 10.1113/jphysiol.2003.040477.

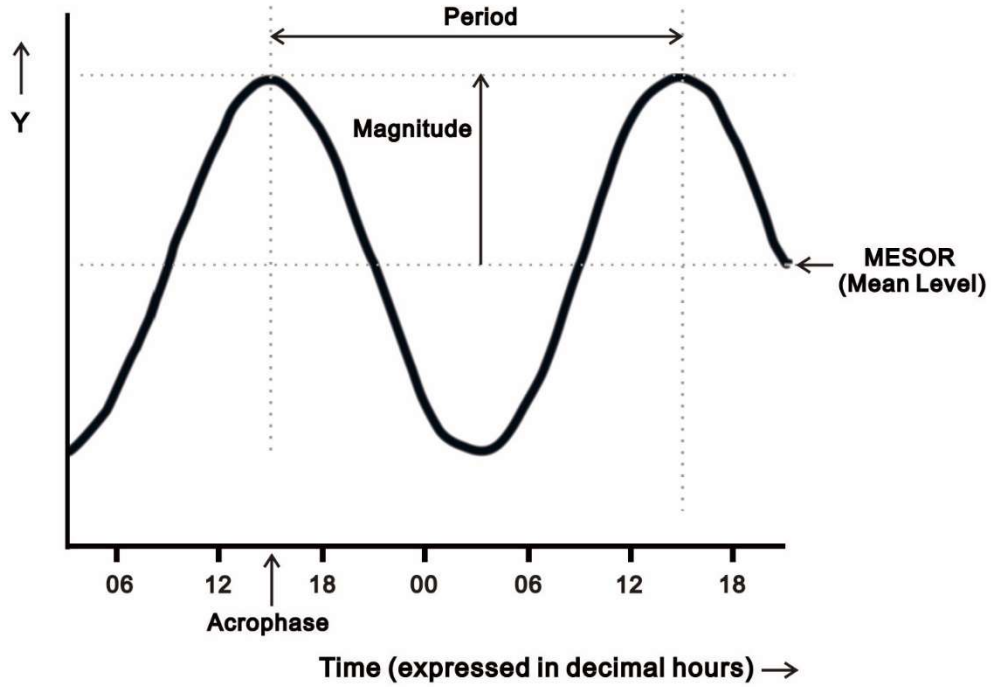

Figure 1: Diagram illustrating four parameters of the oscillation from cosinor analysis: mesor (the estimated mean activity count of the fitted 24-hour pattern), period (the duration of a full cycle), magnitude (mesor-to-peak difference, indicating robustness/strength of rhythm), and acrophase (the time of peak activity). Adapted from "Cosinor-based rhythmometry" by Cornelissen, G. Theor Biol Med Model. 2014;11(1):16. https://doi.org/10.1186/1742-4682-11-16.

Table 1. Demographic and clinical characteristics of ARDS survivors (*n*=14)

Variables [a]	Total sample
Demographics	
Age, years	49.1 ± 15.9
Male, *n* (%)	10 (71)
Body mass index, kg/m^2	27.4 ± 3.5
Living situation	
House/apartment (independent)	10 (71)
Rehabilitation facility	2 (14)
Others	2 (14)
IADL scores (0-16)	12.8 ± 2.5
Full time employment, *n* (%)	2 (14)
Pre-existing comorbidities, *n* (%)	
Heart disease	5 (36)
Sleep apnea	2 (14)
Hypertension	5 (36)
Diabetes	4 (29)
Depression	1 (7)
ICU characteristics	
Diagnosis at ICU admission, *n* (%)	
Trauma	8 (57)
Medical	6 (43)
Disease severity, APACHE II score	24.5 ± 4.9
PaO2/FiO2 ratio	163.8 ± 90.0
PaO2/FiO2 ratio ≤ 200, *n* (%)	11(79)
Length of hospital stay, days	21 ± 17.5
Length of ICU stay, days	11 ± 8.8
Duration of mechanical ventilation, hours	175.8 ± 135.0

Abbreviation: ARDS, acute respiratory distress syndrome; IADL, instrumental activities of daily living; ICU, intensive care unit; APACHE II, acute physiology and chronic health evaluation II (APACHE II) classification system.[a] Reported as mean ± standard deviation unless specified.

Table 2. Sleep characteristics measured by actigraphy, sleep diary, and symptom survey (n=14)

Variables	Median (IQR)
Actigraphy	
Sleep onset [a]	23:29 (22:11-00:30)
Sleep offset [a]	7:24 (6:11-09:19)
TST_A, hours	7.8 (6.2-8.3)
TST_A < 7 hours, *n* (%)	5 (35)
SE_A, %	81.9 (78.9-86.0)
SE_A <85%, *n* (%)	9 (64.3)
WASO, minutes	59.8 (45.0-92.8)
WASO >30 minutes, *n* (%)	14 (100)
Sleep diary	
TST_D, hours	6.6 (5.3-6.9)
TST_D < 7 hours, *n* (%)	11 (79)
SE_D, %	70.0 (62.2-80.6)
SE_D <85%, *n* (%)	11 (79)
Self-reported sleep quality [b]	
Refreshing sleep > 3 nights, *n* (%)	2 (14.3)
Somewhat refreshing night > 3 nights, *n* (%)	9 (64.3)
Fatigued sleep> 3 nights, *n* (%)	4 (28.6)
Insomnia symptoms, ISI score	12.0 (6.8-15.0)
Clinical insomnia (ISI ≥15), *n* (%)	4 (28.6)
Subthreshold (8≤ ISI ≤14), *n* (%)	6 (42.9)
No clinically significant insomnia (ISS<8), *n* (%)	4 (28.6)

Abbreviation: IQR, interquartile range; TST_A, total sleep time estimated by actigraphy; SE_A, sleep efficiency estimated by actigraphy; WASO, wake after sleep onset; TST_D, total sleep time estimated by sleep diary; SE_D, sleep efficiency estimated by sleep diary; ISS, insomnia severity index.
[a] Sleep onset, sleep offset times are presented in 24-hour clock format.
[b] Due to missing data (18 number of days), 96 number of days were included to examine self-reported sleep quality.

Table 3. Comparisons of the results from actigraphy rest-activity circadian rhythm and sleep data with those from a sample of community-dwelling US adults[a]

Parameters	ARDS survivors (*n*=14)	Community-dwelling US adults (*n*=578)	$E.S._{(G)}$	*p*
Age, years	49.1 (15.9)	51.9 (14.9)	-0.19	0.489
Body mass index, kg/m^2	27.4 (3.5)	27.5 (6.0)	-0.02	0.951
24-h rhythm stability /variability				
NPCRA IS	0.32 (0.10)	0.49 (0.12)	-1.42	**<0.001**
NPCRA IV	0.55 (0.18)	0.86 (0.24)	-1.29	**<0.001**
Activity strength				
Cosinor Mesor, ln counts	2.9 (0.43)	3.9 (0.5)	-2.00	**<0.001**
24-h rhythm strength				
Cosinor Magnitude, ln counts	1.8 (0.39)	2.6 (0.5)	-1.60	**<0.001**
NPCRA Amplitude, ln counts	3.23 (0.68)	7.0 (0.3)	-12.03	**<0.001**
NPCRA Relative Amplitude (RA)	0.64 (0.11)	0.77 (0.11)	-1.18	**<0.001**
24-h rhythm phase				
Cosinor Acrophase, decimal hours	15.40 (2.05)	14.6 (1.3)	0.61	0.261
NPCRA L5 midpoint, decimal hours	3.44 (2.49)	2.7 (1.3)	0.55	0.288
NPCRA M10 midpoint, decimal hours	15.26 (2.64)	14.2 (1.6)	0.65	0.158
Actigraphy sleep parameters				
Total sleep time, hours	7.4 (1.2)	6.90 (0.97)	0.51	0.146
Sleep efficiency, %	81.7 (4.8)	85.6 (7.10)	-0.57	**0.010**

Abbreviation: ARDS, acute respiratory distress syndrome; NPCRA, nonparametric circadian rhythm analysis; Ln, natural log; IS, interdaily stability; IV, intradaily variability; $E.S._{(G)}$, Hedges' G effect sizes.
[a] Data reported by Cespedes Feliciano and colleagues. Sleep. 2017;40(12). doi: 10.1093/sleep/zsx168.

CHAPTER 3: Indirect Effect of Sleep on Abdominal Pain through Daytime Dysfunction in Adults with Irritable Bowel Syndrome

Manuscript Two

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ABSTRACT

Study Objectives: Sleep deficiency, psychological distress, daytime dysfunction and abdominal pain are common in adults with irritable bowel syndrome (IBS). Prior research on individuals with chronic pain has identified the indirect effect of sleep on pain through psychological distress or daytime dysfunction; however, it is less clear in IBS. The purpose of this study was to examine potential indirect effects of sleep on abdominal pain symptoms simultaneously through psychological distress and daytime dysfunction in adults with IBS.

Methods: Daily symptoms of nighttime sleep complaints (sleep quality and refreshment), psychological distress, daytime dysfunction (fatigue, sleepiness, and hard to concentrate) and abdominal pain were collected in baseline assessments from two randomized controlled trials of 332 adults (mean age 42 years and 85 % female) with IBS. Structural equation modeling (SEM) was used to examine the global relationships among nighttime sleep complaints, psychological distress, daytime dysfunction and abdominal pain.

Results: SEM analyses found a strong indirect effect of poor sleep on abdominal pain via daytime dysfunction, but not psychological distress. More than 95% of the total effect of nighttime sleep complaints on abdominal pain is indirect.

Conclusions: These findings suggest that the primary impact of nighttime sleep complaints on abdominal pain is indirect. The indirect effect appears primarily through daytime dysfunction. Such understanding provides a potential avenue to optimize personalized and hybrid behavioral interventions for adults with IBS through addressing daytime dysfunction and sleep behaviors. Additional study integrating symptoms with biological markers is warranted to explore the underlying mechanisms accounting for these symptoms.

Keywords: Irritable bowel syndrome, sleep, pain, daytime dysfunction, psychological distress.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Prior research on multiple populations with chronic pain has identified an indirect effect of sleep on pain through psychological distress or daytime dysfunction (i.e., fatigue, sleepiness). However, these indirect effects in the sleep-pain relationship in adults with irritable bowel syndrome (IBS) are less clear.

Study Impact: This study supports a strong indirect effect of poor sleep on abdominal pain via daytime dysfunction, but not psychological distress, in adults with IBS. Such understanding provides a new window to develop effective and hybrid interventions for adults with IBS through addressing sleep behaviors and daytime functioning.

INTRODUCTION

Irritable bowel syndrome (IBS) is a prevalent chronic functional bowel disorder worldwide, characterized by chronic, recurrent abdominal pain/discomfort related to defecation or a change in bowel habits (constipation and/or diarrhea).[1,2] Adults with IBS often experience gastrointestinal (GI) symptoms (i.e., abdominal pain, constipation and/or diarrhea, abdominal bloating and distension), as well as non-GI symptoms (e.g., sleep deficiency, psychological distress, daytime dysfunction).[1,3] IBS adversely impacts health-related quality of life and work productivity.[4-8] In the U.S., the estimated direct medical costs of IBS (i.e., outpatient care, primary and specialist physician visits) is between $1.7-$10 billion/year and indirect cost (i.e., productivity loss, work productivity, quality of life) is $20 billion. There is an urgent need to identify modifiable risk factors in order to design effective treatments for adults with IBS.[8]

Sleep deficiency is a well-documented health concern in adults living with IBS, affecting an estimated 37.6 % of this population.[9,10] Sleep deficiency is a broad concept encompassing both sleep deprivation and poor sleep quality.[11] Researchers, using both self-reported and objective measures, have shown that poor sleep quality is a significant predictor of next-day IBS symptoms (i.e., abdominal pain/discomfort), psychological distress (i.e., depression, anxiety), and daytime dysfunction (i.e., fatigue and sleepiness).[12-16] Poor sleep quality is a modifiable risk factor for IBS symptom flare-ups, particularly for abdominal pain, which is the most bothersome of IBS symptoms.[17-19]

Systematic reviews of the sleep-pain relationship reveal that an indirect effect of sleep on pain through psychological distress or daytime dysfunction in individuals with chronic pain-related conditions such as fibromyalgia, rheumatoid arthritis, abdominal pain or headache.[20,21] However, less is known about the roles of psychological distress and daytime dysfunction in the sleep-pain relationship in adults with IBS. Limited evidence in IBS suggests an indirect effect of

sleep on pain through psychological distress. One study in 24 adults with IBS found the effect of poor sleep quality (indicated by waking episodes measured by a wrist-worn actigraph) on self-reported abdominal pain symptoms was partially mediated by psychological distress.[13]

There is even less known about the indirect effect of sleep on pain through daytime dysfunction in persons with IBS. In a study of 918 female adolescents, Bonvanie and colleagues found that self-reported poor sleep quality indirectly affected abdominal pain through fatigue (one component of daytime dysfunction); however, the investigators did not adjust for potential confounding effect of psychological distress.[22] Taken together, prior studies have not simultaneously evaluated the potential indirect effects of sleep on pain through both psychological distress and daytime dysfunction.

Sleep deficiency, abdominal pain, daytime dysfunction and psychological distress are common in individuals with IBS,[3,12,23] and therefore clarifying the roles of varied factors in the sleep-pain pathway in persons with IBS could have significant clinical implications for management of symptom clusters. The purpose of this study was to examine the potential indirect effects of sleep on pain through psychological distress and/or daytime dysfunction among adults with IBS by using a structural equation modeling (SEM) approach. SEM allows for the inclusion of multiple indicators to measure the multifaceted symptom constructs of sleep deficiency, psychological distress, daytime dysfunction and abdominal discomfort/pain,[3,20,21] and further to reduce measurement error of these four multifaceted symptoms of interest.[24] Also, SEM is able to include analyses of multiple relationships simultaneously (i.e., direct and indirect effects) to build a more sophisticated statistical model rather than doing several individual regressions.[24,25] Utilizing SEM may provide a unique window into the understanding of how

sleep deficiency, abdominal discomfort/pain, daytime dysfunction and psychological distress interact to optimize symptom management in IBS populations.

METHODS

Participants

This study is a secondary data analysis using baseline symptom diary data recorded over 28 consecutive days from two randomized controlled trials (RCTs) among adults with IBS. This study includes a total sample of 332 adults with IBS (RCT-1 = 224, RCT-2 = 108), both previously described in detail elsewhere and registered in ClinicalTrials.gov. of the U.S. National Institutes of Health (Clinicaltrials.gov identifier: NCT00167635 for RCT 1; NCT00907790 for RCT 2).[26,27] Participants were recruited through community advertisements. Both RCTs applied similar eligibility criteria: 1) a medical diagnosis of IBS and experiencing symptoms compatible with Rome II (for RCT-1) or III (for RCT-2) criteria for IBS, and 2) 18-70 year-old adults; 3) no significant co-morbidity based on the guiding principle of whether the morbidity could affect symptom measures or compromise a participant's ability to complete the study (i.e., symptoms of cognitive impairments, untreated sleep disorder, severe depression, and a moderate to severe pain disorders), and 4) not taking medications that could affect outcome measures (i.e., antidepressants, calcium-channel blockers, anticholinergics, cholestyramine, narcotics, colchicine, iron supplements, or laxatives).

Measures

Daily Symptom Measures of Abdominal Discomfort/Pain, Psychological Distress and Daytime Function. All participants completed a daily 26-item symptom diary every evening over 28 consecutive days (over one menstrual cycle).[26,27] The severity of each daily IBS symptom over the past 24 hours was rated on a scale of 0 (not present), 1 (mild), 2 (moderate), 3

(severe), or 4 (very severe). Items included in the present analyses were ratings of abdominal discomfort/pain (abdominal pain, abdominal pain after eating, abdominal distention, intestinal gas), psychological distress (depressive mood, anxiety, stress) and daytime dysfunction (fatigue, sleepiness during the day, hard to concentrate) were included in data analyses. Acceptable construct validity of the 26-item symptom diary has been confirmed by previous IBS studies.[3,28,29]

Daily Sleep Measures. Participants also daily assessed overall sleep quality and feelings of "refreshed sleep" at the same time when the daily symptom diary was completed. Participants evaluated overall sleep quality as "poor", "fair", "good", "very good" or "excellent", as well as rated the item "I felt refreshed by last night's sleep" on the level of "not at all refreshed", "somewhat", "moderately" or "very refreshed". The responses demonstrate appropriate validity when correlated with validated sleep measures.[30-32]

Statistical Analyses

All symptom measures were represented by the percentage of symptomatic days in the 28-day diary. For indicators of abdominal discomfort/pain, psychological distress, and daytime dysfunction, symptomatic days were indicated by ratings of 2 (moderate) to 4 (very severe) (100 % × number of days with of rating of ≥ 2 / 28 diary days).[3] For sleep quality, rating of "poor" or "fair" indicated nights with poor sleep, and for refreshing sleep, "not at all" or "somewhat" indicated night with unrefreshing sleep.[33] Using the percentage of symptomatic days over a 28-day diary data for each indicator was able not only to capture both the symptom severity and frequency, but also to minimize recall bias from self-report measures. All measures were collected at baseline and prior to any intervention.

Descriptive statistics were used to describe the demographic and clinical characteristics of the participants as well as all indicators of the latent variables of nighttime sleep complaints, abdominal discomfort/pain, daytime dysfunction and psychological distress (see **Table 1**).

The statistical analyses were performed in two phases.[24] In the first phase, the confirmatory factor analysis (CFA) was used to evaluate the validity of the hypothesized measurement model. Latent variables were free to co-vary without specifying structural relationships. Sequentially, the measurement invariance of the established measurement model was evaluated to examine moderating effects of the two parent studies (RCT-1 vs. RCT-2) and sex. Such tests of measurement invariance aimed to determine if combining the samples of two parent studies in the analyses was appropriate and the need for doing separate analyses based on sex. Therefore, we examined the measurement invariance of the final model across groups including the two parent studies and sex by comparing the model of configural invariance with the model of metric invariance.[34] Next, chi-square difference tests were used to determine whether the model of metric invariance would improve the goodness of fit index (GFI) of the measurement model.

In the second phase, SEM was used to examine the relationships among these four latent variables and to test hypotheses about the direct and indirect effects of sleep on pain through psychological distress and/or daytime dysfunction (**Figure 1**). In both phases, GFI including chi-square (χ^2), Comparative Fit Index (CFI), Standardized Root Mean-Square Residual (SRMR) and Root Mean-Square Error of Approximation (RMSEA) with 90% confidence interval (CI) were used to assess how well the models fit the dataset. The recommended cutoff of CFI is ≥ 0.90. SRMR above 0.10 indicates a poor fit and RMSEA less than 0.08 indicates an acceptable fit.[35] The statistical software package RStudio version 3.6.1 under "lavaan" statistical package was used for CFA and SEM with maximum likelihood estimation.

[Figure 1 here]

RESULTS

Descriptive Statistics and Correlations between Symptom Indicators

Of the 1,498 potential participants screened for two parent studies (RCT-1 = 771, RCT-2 = 727), [26,27] 1,166 persons (RCT-1 = 547, RCT-2 = 619) were excluded in this data analysis for various reason (i.e., not meeting inclusion criteria, declined to participate, did not respond to call). A total sample of 332 adults with IBS were included in this study. Demographic and clinical characteristics of the sample were previously described in detail elsewhere.[3] The mean age of the sample was 42.18 ± 14.61 years and 85% were females. Most of participants were racially self-identified as Caucasian (80.4%) and college-educated (84.3%) (data not shown). **Table 1** summarizes the descriptive statistics and correlations of the measures.

[Table 1 here]

Measurement Model

Table 2 presents the unstandardized and standardized factor loadings of the symptom indicators for the latent variables as well as GFI in our measurement model. Our measurement model yields an acceptable fit to the dataset (CFI = 0.95; RMSEA = 0.09 [90 % CI: 0.08-0.10], $P < 0.001$; SRMR = 0.05). Standardized factor loadings of symptom indicators within their latent variables were all statistically significant and greater than 0.6, suggesting the latent variables of nighttime sleep complaints, daytime dysfunction, psychological distress and abdominal discomfort/pain were measured adequately by their respective symptom indicators.

[Table 2 here]

Measurement Invariance

Table 3 presents the GFI of tests of measurement invariance by groups. The measurement model was invariant across 2 parent studies (RCT-1 vs RCT-2) and sex, indicating that the measurement model is valid for participants in both RCT-1 and RCT-2 studies and regardless of sex.

[Table 3 here]

SEM Model

Figure 2 illustrates the standardized estimates for structural relationships and factor loadings for each indicator of the initial SEM model. The GFI of the initial SEM model (CFI = 0.91; RMSEA = 0.12 [90 % CI: 0.11-1.14], $P < 0.001$; SRMR = 0.16) suggest inadequate model fit. Based on modification index values, a direct path between psychological distress and daytime dysfunction was added and it was also supported by empirical evidence.[23]

The final SEM model (**Figure 3**) yielded relatively good model fit to the data (CFI = 0.95; RMSEA = 0.09 [90 % CI: 0.08-0.10], $P < 0.001$; SRMR = 0.05). Nighttime sleep complaints was a significant predictor for psychological distress ($\beta = 0.26$, $P < 0.001$) and daytime dysfunction ($\beta = 0.31$, $P < 0.001$), but not for abdominal discomfort/pain ($\beta = 0.04$, $P = 0.621$). Similarly, psychological distress was a significant predictor for daytime dysfunction ($\beta = 0.59$, $P < 0.001$), but not for abdominal discomfort/pain ($\beta = 0.08$, $P < 0.301$). Daytime dysfunction was significantly predictive for abdominal discomfort/pain ($\beta = 0.48$, $P < 0.001$).

Table 4 summarizes the indirect and direct effects in the relationship from nighttime sleep complaints to abdominal discomfort/pain through psychological distress and daytime dysfunction in the initial and final SEM models. In both initial and final SEM models, there was a specific positive indirect relationship of nighttime sleep complaints with abdominal discomfort/pain significantly linked to daytime dysfunction (initial SEM model: $\beta = 0.23$, $P < 0.001$; the final model: $\beta = 0.74$, $P < 0.001$), but not significantly linked to psychological distress

(initial SEM model: $\beta = 0.03$, $P = 0.068$; the final model: $\beta = 0.02$, $P = 0.315$). The total effect of nighttime sleep complaints on abdominal discomfort/pain was significantly positive in both models (initial SEM model: $\beta = 0.30$, $P < 0.001$; the final model: $\beta = 0.80$, $P < 0.001$). Additionally, the direct effect of nighttime sleep complaints on abdominal discomfort/pain was not statistically significant (initial SEM model: $\beta = 0.04$, $P = 0.531$; final SEM model: $\beta = 0.04$, $P = 0.621$). Taken together, the path of nighttime sleep complaints to abdominal discomfort/pain was through daytime dysfunction, while not through psychological distress.

[Table 4 here]

DISCUSSION

To the best of our knowledge, this study is the first to examine the potentially indirect effects of sleep on abdominal pain through psychological distress and daytime dysfunction symptoms simultaneously in community-dwelling adults with IBS. The results of this study suggest that the primary impact of nighttime sleep complaints on abdominal discomfort/pain symptoms is indirect through daytime dysfunction. That is, a higher severity of nighttime sleep complaints appears to increase the severities of psychological distress and daytime dysfunction. Sequentially, a higher severity of daytime dysfunction appears to perpetuate the impact of nighttime sleep complaints on abdominal discomfort/pain symptoms in adults with IBS. As such the sleep-pain relationship in adults with IBS is significantly attenuated by an individual's perception of better daytime functioning.

The current evidence regarding the non-significant direct effect of poor sleep quality on abdominal discomfort/pain coincides with our previous findings in which actigraphic sleep efficiency was not predictive for next-day abdominal discomfort/pain across and within adult subjects.[12] Additionally, the indirect effect of sleep through daytime dysfunction may explain

previous findings in which effects of self-reported poor sleep quality on abdominal discomfort/pain symptoms only existed 'within' subjects but not 'across' subjects.[12] The indirect effect of sleep through daytime dysfunction could reflect inadequate coping strategies to daytime dysfunction symptoms[36] or an individual trait (i.e., catastrophizing)[37] toward globally reporting multiple symptoms with consistent severity ratings.[38] It may explain why comprehensive self-management including cognitive behavioral therapy is effective for alleviating abdominal discomfort/pain for adults with IBS.[26,27] However, there might also be a physiological pathway by which sleep dysfunction concurrently disrupts daytime function and also sensitizes the central nervous system to abdominal pain sensations.[39-41]

Daytime dysfunction symptoms are well-known consequences of sleep deficiency[42] and have also been previously linked with abdominal discomfort/pain symptoms. Two prospective population-based studies found that fatigue[43] or daytime tiredness[44] were significant predictors of the onset of abdominal pain. A population-based study in China found that persons with excessive daytime sleepiness were more likely to suffer functional gastrointestinal disorders on the basis of Rome II criteria.[45] Similarly, 'hard to concentrate' as a proxy of daytime dysfunction was also found to be associated with IBS-related discomfort and pain symptoms in persons with initiating and/or maintaining sleep.[46] Our current finding about the indirect effect of sleep on pain through daytime dysfunction reveals that the presence of daytime dysfunction symptoms provides a significant variance in the sleep-pain relationship in persons with IBS.

In contrast to the present findings, a prior study by Patel and colleagues identified the indirect effect of sleep on pain through psychological distress in 24 adults with IBS.[13] Such discrepancy might be attributed to the methodological differences and/or the sample characteristics between the studies. For example, Patel used multiple retrospective measures of psychological distress,

which may have been influenced by recall bias, and a prospective objective measure of sleep (actigraphy). The current study used prospective daily symptom diaries to assess both psychological distress and sleep.[38] It may be that the self-reported sleep measures in our study compared to actigraphic sleep measures in Patel's may capture different aspects of the sleep-pain relationship. The potential indirect effect of sleep on pain through psychological distress should be confirmed by a larger study that concurrently applies self-reported and physiological sleep measures in IBS.

The findings of this study have important implications for understanding and managing IBS symptoms. As nighttime sleep complaints directly predicted both daytime dysfunction and psychological distress, treating nighttime sleep complaints may alleviate both of these symptom clusters. However, an intervention only targeting sleep without taking account of daytime function (fatigue, tiredness, cognitive dysfunction) might be less effective for treating abdominal discomfort/pain. Addressing daytime dysfunction appears an even more critical target of IBS symptom management among adults with IBS who experience both nighttime sleep complaints and abdominal discomfort/pain (with and without psychological distress). Based on existing evidence in other populations with chronic diseases such as such cancer[47-49] and rheumatic diseases,[50] the underlying mechanisms of the sleep-pain relationship through daytime dysfunction remains unclear in IBS. Inflammation (i.e., interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α]), the hormones of the hypothalamic-pituitary-adrenal (HPA) axis system, and neurotransmitter dysregulation might be involved. For example, sleep dysfunction has been found to activate the immune system and significantly increase pro-inflammatory cytokine (IL-6, TNF-α) levels,[51] which could signal the central nervous system and lead to daytime dysfunction symptoms (i.e., fatigue) or other behavioral changes.[52] There is also evidence indicating that

inflammation has adverse effects on pain experience (i.e., visceral hyperalgesia) through the dysregulation of HPA and/or the autonomic nervous system, which may be due to the indirect effect of sleep dysfunction through fatigue.[49] Such proposed mechanisms are supported by a meta-analysis in which IL-6 levels are higher in individuals with IBS compared to healthy controls.[53] Whether there is a shared mechanism linking sleep with abdominal discomfort/pain through daytime dysfunction in adults with IBS is still a question that bears further research to integrate symptoms with biological markers.

Limitations

Despite our findings that add to the current knowledge regarding the relationship of nighttime sleep complaints and abdominal pain in adults with IBS, there are limitations in the current study. The study used a community sample of the adults with IBS and the majority were females. The relationships in the current SEM model might vary when different characteristics of the sample are analyzed. For example, a study in 871 adults with IBS found that the correlations between daytime dysfunction (indicated by driving lapses) and IBS-like pain symptoms only existed in females but not in males.[46] Therefore, replication in more diverse IBS samples including more men with IBS or those with additional comorbidities is warranted. Also, although the directional relationships among nighttime sleep complaints, psychological distress, daytime dysfunction and abdominal discomfort/pain in the hypothesized SEM model were supported by our prior sleep studies of women only with IBS,[12,15] this study utilized a cross-sectional SEM approach and thus temporal sequences among these latent variables in IBS cannot be established due to the current sample size limitations. There might be alternative models fitting the data equally well. For example, another alternative SEM model with the direct and indirect effect of sleep on daytime dysfunction through psychological distress and abdominal discomfort/pain symptoms could be considered as well. The directionality of these causal relationships in IBS

needs confirmation by experimental research or a cross-lagged panel analysis in a prospective study design with a large sample size. Thus, this study aimed to examine a hypothesized model that was supported by the data to test the global relationships among sleep, pain, psychological distress and daytime dysfunction among adults with IBS. Despite this limitation of temporal sequencing, this study has made a significant contribution by testing simultaneously multiple direct and indirect effects of sleep on pain through psychological distress and daytime dysfunction, and found a strong indirect effect only through daytime dysfunction, but not through psychological distress. This study also differs from previous studies in the utilization of multiple indicators and its account for measurement errors. Due to the lack of the information about the quantity of sleep obtained from the parent studies, our results may only support the direct and indirect effects of poor sleep quality on abdominal pain. It is suggested in future studies to add an indicator related to inadequate amount of sleep to capture a comprehensive picture of sleep deficiency among these symptom relationships of interest. Given the nature of this secondary analysis, symptom data were obtained from daily diary responses. Future researchers may consider adding other validated parallel indicators (i.e., the patient-reported outcomes information system [PROMIS] gastrointestinal symptom scales, Pittsburgh Sleep Quality Index)[54] to verify our SEM models. Symptom data in the current study relied on self-report measures rather than objective measures (i.e., actigraphy for sleep, provocation tests for abdominal pain). Even though this is considered a limitation, symptoms are subjective individual experiences; therefore, self-report might be appropriate measurement for symptoms. Our results are limited to understanding the relationships among self-perceived symptoms (i.e., sleep, pain, psychological and daytime functioning) in IBS.

CONCLUSIONS

Findings from our SEM analyses show a strong indirect effect of nighttime sleep complaints on abdominal pain through daytime dysfunction in the adults with IBS, suggesting daytime dysfunction is a critical target for IBS symptom management. Among adults with IBS, adequate daytime functioning essentially could reduce or remove poor sleep during the night as a risk factor for abdominal discomfort/pain symptoms even after adjusting for psychological distress. If adults with IBS experience poor sleep quality and/or psychological distress but they can maintain appropriate daytime functioning, the impact of poor sleep on abdominal discomfort/pain can be minimized. Our findings add to current knowledge in IBS population by linking nighttime sleep complaints to abdominal discomfort/pain through daytime dysfunction, and provides a potential avenue to optimize personalized and hybrid interventions through addressing daytime functioning and sleep behaviors for IBS populations. Additional work is warranted to address the issue of the causality and directionality as well as to understand a shared mechanism among these symptom constructs.

ABBREVIATIONS

IBS, irritable bowel syndrome

GI, gastrointestinal

SEM, structural equation modeling

RCT, randomized controlled trials,

CFA, confirmatory factor analysis

GFI, goodness of fit index

CFI, comparative fit index

SRMR, standardized root mean-square residual

RMSEA, mean-square error of approximation

CI, confidence interval

IL-6, interleukin-6

TNF-α, tumor necrosis factor-α

HPA, hypothalamic-pituitary-adrenal

PROMIS, patient-reported outcomes information system

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DISCLOSURE STATEMENT

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REFERENCES

1. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical Features, and Rome IV. *Gastroenterology.* 2016;150(6):1262-1279.e1262.
2. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol.* 2012;10(7):712-721. e714.
3. Han CJ, Pike K, Jarrett ME, Heitkemper MM. Symptom-based latent classes of persons with irritable bowel syndrome. *Res Nurs Health.* 2019;42(5):382-391.
4. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes.* 2017;15(1):35.
5. DiBonaventura M, Sun SX, Bolge SC, Wagner JS, Mody R. Health-related quality of life, work productivity and health care resource use associated with constipation predominant irritable bowel syndrome. *Curr Med Res Opin.* 2011;27(11):2213-2222.
6. Dean BB, Aguilar D, Barghout V, et al. Impairment in work productivity and health-related quality of life in patients with IBS. *Am J Manag Care.* 2005;11(1 Suppl):S17-26.
7. Pare P, Gray J, Lam S, et al. Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada), a naturalistic study. *Clin Ther.* 2006;28(10):1726-1735; discussion 1710-1721.
8. Hulisz D. The burden of illness of irritable bowel syndrome: current challenges and hope for the future. *J Manag Care Pharm.* 2004;10(4):299-309.
9. Tu Q, Heitkemper MM, Jarrett ME, Buchanan DT. Sleep disturbances in irritable bowel syndrome: a systematic review. *Neurogastroenterol Motil.* 2017;29(3).

10. Ben W, Ruqiao D, Liping D. Prevalence of sleep disorder in irritable bowel syndrome: A systematic review with meta-analysis. *Saudi J Gastroenterol.* 2018;24(3):141-150.
11. Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep.* 2014;37(1):9-17.
12. Buchanan DT, Cain K, Heitkemper M, et al. Sleep measures predict next-day symptoms in women with irritable bowel syndrome. *J Clin Sleep Med.* 2014;10(9):1003-1009.
13. Patel A, Hasak S, Cassell B, et al. Effects of disturbed sleep on gastrointestinal and somatic pain symptoms in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2016;44(3):246-258.
14. Goldsmith G, Levin JS. Effect of sleep quality on symptoms of irritable bowel syndrome. *Dig Dis Sci.* 1993;38(10):1809-1814.
15. Jarrett M, Heitkemper M, Cain KC, Burr RL, Hertig V. Sleep disturbance influences gastrointestinal symptoms in women with irritable bowel syndrome. *Dig Dis Sci.* 2000;45(5):952-959.
16. Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT. Duration of sleep contributes to next-day pain report in the general population. *Pain.* 2008;137(1):202-207.
17. Lackner JM, Gudleski GD, Dimuro J, Keefer L, Brenner DM. Psychosocial predictors of self-reported fatigue in patients with moderate to severe irritable bowel syndrome. *Behav Res Ther.* 2013;51(6):323-331.
18. Lacy BE, Chey WD, Lembo AJ. New and emerging treatment options for irritable bowel syndrome. *Gastroenterol Hepatol.* 2015;11(4 Suppl 2):1-19.
19. Cain KC, Headstrom P, Jarrett ME, et al. Abdominal pain impacts quality of life in women with irritable bowel syndrome. *Am J Gastroenterol.* 2006;101(1):124-132.
20. Whibley D, AlKandari N, Kristensen K, et al. Sleep and pain: a systematic review of studies of mediation. *Clin J Pain.* 2019;35(6):544-558.

21. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain.* 2013;14(12):1539-1552.
22. Bonvanie IJ, Oldehinkel AJ, Rosmalen JG, Janssens KA. Sleep problems and pain: a longitudinal cohort study in emerging adults. *Pain.* 2016;157(4):957-963.
23. Han CJ, Yang GS. Fatigue in irritable bowel syndrome: a systematic review and meta-analysis of pooled frequency and severity of fatigue. *Asian Nurs Res.* 2016;10(1):1-10.
24. Kline RB. *Principles and practice of structural equation modeling.* 4th ed: Guilford publications; 2016.
25. Naliboff BD, Kim SE, Bolus R, Bernstein CN, Mayer EA, Chang L. Gastrointestinal and psychological mediators of health-related quality of life in IBS and IBD: a structural equation modeling analysis. *Am J Gastroenterol.* 2012;107(3):451-459.
26. Jarrett ME, Cain KC, Barney PG, et al. Balance of Autonomic Nervous System Predicts Who Benefits from a Self-management Intervention Program for Irritable Bowel Syndrome. *J Neurogastroenterol Motil.* 2016;22(1):102-111.
27. Jarrett ME, Cain KC, Burr RL, Hertig VL, Rosen SN, Heitkemper MM. Comprehensive self-management for irritable bowel syndrome: randomized trial of in-person vs. combined in-person and telephone sessions. *Am J Gastroenterol.* 2009;104(12):3004-3014.
28. Hertig VL, Cain KC, Jarrett ME, Burr RL, Heitkemper MM. Daily stress and gastrointestinal symptoms in women with irritable bowel syndrome. *Nursing research.* 2007;56(6):399-406.
29. Han CJ, Jarrett ME, Heitkemper MM. Relationships between abdominal pain and fatigue with psychological distress as a mediator in women with irritable bowel syndrome. *Gastroenterol Nurs.* 2020;43(1):28-39.

30. Cappelleri JC, Bushmakin AG, McDermott AM, Sadosky AB, Petrie CD, Martin S. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. *Health Qual Life Outcomes.* 2009;7:54.
31. Snyder E, Cai B, DeMuro C, Morrison MF, Ball W. A new single-item sleep quality scale: results of psychometric evaluation in patients with chronic primary insomnia and depression. *J Clin Sleep Med.* 2018;14(11):1849-1857.
32. Libman E, Fichten C, Creti L, et al. Refreshing sleep and sleep continuity determine perceived sleep quality. *Sleep Disord.* 2016;2016:7170610.
33. Kamp KJ, Weaver KR, Sherwin LB, et al. Effects of a comprehensive self-management intervention on extraintestinal symptoms among patients with IBS. *J Psychosom Res.* 2019;126:109821.
34. Milfont TL, Fischer R. Testing measurement invariance across groups: Applications in cross-cultural research. *Int J Psychol Res.* 2010;3(1):111-121.
35. Pituch KA, Stevens JP. *Applied multivariate statistics for the social sciences: Analyses with SAS and IBM's SPSS.* 6th ed. New York, NY: Routledge; 2016.
36. Geenen R, Dures E. A biopsychosocial network model of fatigue in rheumatoid arthritis: a systematic review. *Rheumatology.* 2019;58(Supplement_5):v10-v21.
37. van Tilburg MAL, Palsson OS, Whitehead WE. Which psychological factors exacerbate irritable bowel syndrome? Development of a comprehensive model. *J Psychosom Res.* 2013;74(6):486-492.
38. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. *J Multidiscip Healthc.* 2016;9:211-217.

39. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev.* 2006;10(5):357-369.

40. Irwin MR, Olmstead R, Carrillo C, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. *Sleep.* 2012;35(4):537-543.

41. Staffe AT, Bech MW, Clemmensen SLK, Nielsen HT, Larsen DB, Petersen KK. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants. *PLoS One.* 2019;14(12):e0225849-e0225849.

42. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a Standard Research Assessment of Insomnia. *Sleep.* 2006;29(9):1155-1173.

43. Halder SL, McBeth J, Silman AJ, Thompson DG, Macfarlane GJ. Psychosocial risk factors for the onset of abdominal pain. Results from a large prospective population-based study. *Int J Epidemiol.* 2002;31(6):1219-1225.

44. El-Metwally A, Halder S, Thompson D, Macfarlane GJ, Jones GT. Predictors of abdominal pain in schoolchildren: a 4-year population-based prospective study. *Arch Dis Child.* 2007;92(12):1094-1098.

45. Wu S, Chen S, Zhao Y, Ma X, Wang R, He J. Association between excessive daytime sleepiness and functional gastrointestinal disorders: a population-based study in China. *J Neurogastroenterol Motil.* 2017;23(2):298-305.

46. Abdulahad S, Huls H, Balikji S, van de Loo AJAE, Roth T, Verster JC. Irritable bowel syndrome, immune fitness, and insomnia: results from an online survey among people reporting sleep complaints. *Sleep Vigil.* 2019;3(2):121-129.

47. Ji Y-B, Bo C-L, Xue X-J, et al. Association of inflammatory cytokines with the symptom cluster of pain, fatigue, depression, and sleep disturbance in chinese patients with cancer. *J Pain Symptom Manage.* 2017;54(6):843-852.
48. Kwekkeboom KL, Tostrud L, Costanzo E, et al. The role of inflammation in the pain, fatigue, and sleep disturbance symptom cluster in advanced cancer. *J Pain Symptom Manage.* 2018;55(5):1286-1295.
49. Bower JE. Cancer-related fatigue: mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol.* 2014;11(10):597-609.
50. Louati K, Berenbaum F. Fatigue in chronic inflammation - a link to pain pathways. *Arthritis Res Ther.* 2015;17(1):254.
51. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med.* 2006;166(16):1756-1762.
52. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol.* 2014;11(10):597-609.
53. Bashashati M, Moradi M, Sarosiek I. Interleukin-6 in irritable bowel syndrome: A systematic review and meta-analysis of IL-6 (-G174C) and circulating IL-6 levels. *Cytokine.* 2017;99:132-138.
54. Ballou S, Katon J, Rangan V, et al. Brief Behavioral Therapy for Insomnia in Patients with Irritable Bowel Syndrome: A Pilot Study. *Dig Dis Sci.* 2020.

Table 1. Descriptive statistics and zero-order correlations

Measure	Mean	(SD)	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
Age, years	42.18	(14.61)	--	--	--	--	--	--	--	--	--	--	--	--
Female (1=yes)	0.85	(0.36)	--	--	--	--	--	--	--	--	--	--	--	--
Outcomes														
Abdominal discomfort/pain														
1. Abdominal pain	37.08	(26.05)	--											
2. Abdominal pain after eating	29.64	(26.01)	.80	--										
3. Abdominal distention	31.01	(31.82)	.66	.68	--									
4. Intestinal gas	38.67	(30.05)	.57	.55	.62	--								
Predictors														
Nighttime sleep complaints														
5. Diminished sleep quality	40.65	(27.18)	.25	.25	.20	.22	--							
6. Unrefreshed sleep	48.61	(27.15)	.20	.22	.18	.21	.81	--						
Daytime dysfunction														
7. Fatigue	33.98	(27.25)	.45	.42	.40	.38	.39	.42	--					
8. Sleepiness during the day	26.43	(25.79)	.44	.43	.39	.35	.35	.36	.83	--				
9. Hard to concentrate	13.93	(20.77)	.35	.33	.32	.30	.27	.30	.62	.60	--			
Psychological distress														
10. Anxiety	18.76	(22.41)	.31	.25	.19	.30	.18	.18	.44	.43	.51	--		
11. Stress	25.64	(25.44)	.39	.35	.29	.28	.24	.25	.58	.58	.55	.75	--	
12. Depressive mood	9.64	(16.51)	.26	.25	.13	.20	.15	.17	.43	.43	.60	.70	.62	--

Note. N = 332 adults with irritable bowel syndrome; Pearson's r reported; Means (SDs) for abdominal discomfort/pain, daytime dysfunction and psychological distress indicators are the symptom severity for each indicator, defined as the percentage of days rated as "moderate" to "very severity" of each symptom severity over 28 days; Mean (SD) for diminished sleep quality indicator is defined as the percentage of days rated as "poor" to "fair" sleep quality over 28 days; Mean (SD) for unrefreshed sleep indicator is defined as the percentage of days rated as "not at all refreshed" or "somewhat refreshed" sleep over 28 days.
All correlation coefficients are significant at $P < .01$

Table 2. Summary of the measurement model from confirmatory factor analysis

Latent variable	Indicator	Unstandardized factor loading	Standardized factor loading	Standard error	Goodness-of-fit indexes	*P*[a]
Abdominal discomfort/pain	Abdominal pain	22.97	.88	1.16		
	Abdominal pain after eating	22.93	.88	1.16		
	Abdominal distention	24.73	.78	1.52		
	Intestinal gas	20.17	.67	1.52		
Nighttime sleep complaints	Diminished sleep quality	23.94	.88	1.49		
	Unrefreshed sleep	25.02	.92	1.48		
Daytime dysfunction	Fatigue	25.04	.92	1.18		
	Sleepiness during the day	23.09	.90	1.13		
	Hard to concentrate	14.37	.69	1.03		
Psychological distress	Anxiety	19.03	.86	1.04		
	Stress	22.13	.87	1.18		
	Depressive mood	12.47	.76	0.81		
Measurement model fit indexes						
χ^2(df)					174.09 (48)	< .001
CFI					0.95	
SRMR					0.05	
RMSEA					0.09	< .001
RMSEA 90% CI-lower					0.08	
RMSEA 90% CI-upper					0.10	

Note. N = 332 adults with irritable bowel syndrome. All loadings based on maximum likelihood estimates.
Abbreviation: df = degree of freedom; CFI = Comparative Fit Index; SRMR = Standardized Root Mean-Square Residual; RMSEA = Root Mean-Square Error of Approximation; CI = Confidence Interval.
All loadings are significant at $p < .001$; *P*[a] is for measurement model fit indexes of χ^2 and RMSEA.

Table 3. Fit statistics for tests of group invariance

Model	χ^2	df	CFI	RMSEA	SRMR	BIC	△ χ^2	△ df	P^a
RCT-1 (*n* = 224) vs. RCT-2 (*n* = 108)									
Configural invariance	248.64	96	0.942	0.098	0.055	34976			
Metric invariance with all loadings constrained equal	253.42	104	0.943	0.093	0.055	34934	4.778	8	0.781
Females (*n* = 283) vs. Males (*n* = 49)									
Configural invariance	233.57	96	0.947	0.093	0.052	34903			
Metric invariance with all loadings constrained equal	240.61	104	0.947	0.089	0.053	34864	7.039	8	0.53

Note. P^a is for chi-square difference tests.

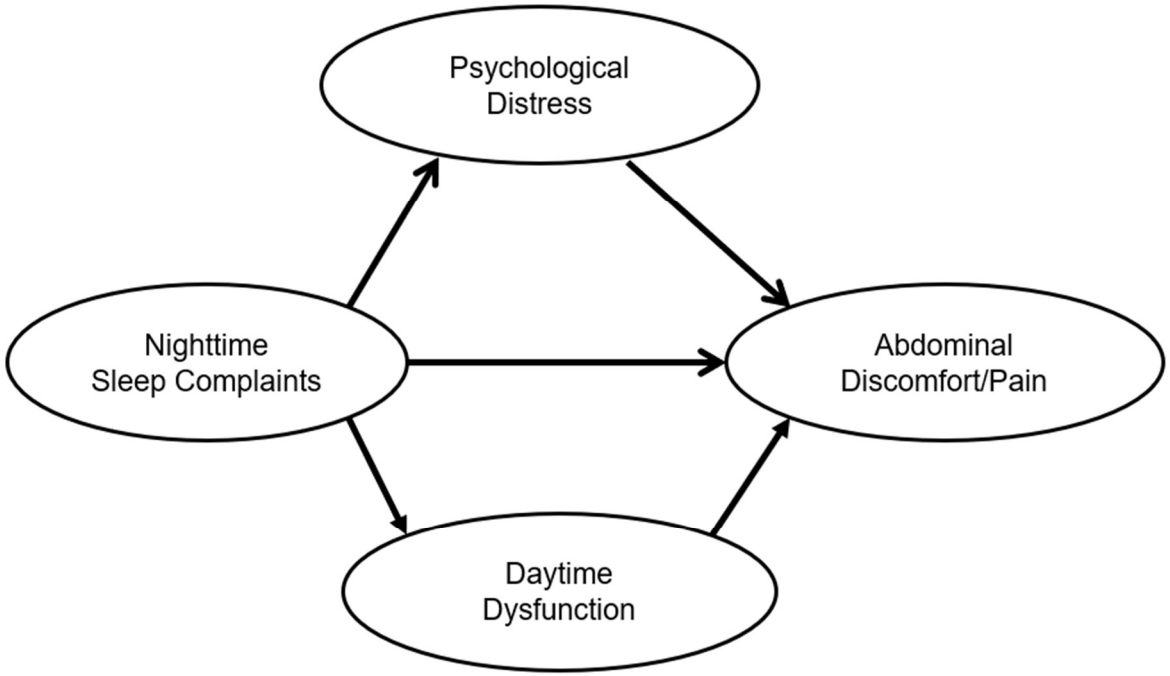
Abbreviation: RCT = randomized controlled trials; χ^2 = chi-square; df = degree of freedom; CFI = Comparative Fit Index; SRMR = Standardized Root Mean-Square Residual; RMSEA = Root Mean-Square Error of Approximation; BIC = Bayesian information criterion.

Table 4. Analysis of direct and indirect effects of sleep on pain

		Outcome variable Abdominal discomfort/pain			
Predictor variable	Mediator	Indirect effect	Total indirect effect	Direct effect	Total effect
Initial SEM model					
Nighttime sleep complaints	Psychological distress	0.03	0.26***	0.04	0.30***
	Daytime dysfunction	0.23***			
Final SEM model					
Nighttime sleep complaints	Psychological distress	0.02	0.76***	0.04	0.80***
	Daytime dysfunction	0.74***			

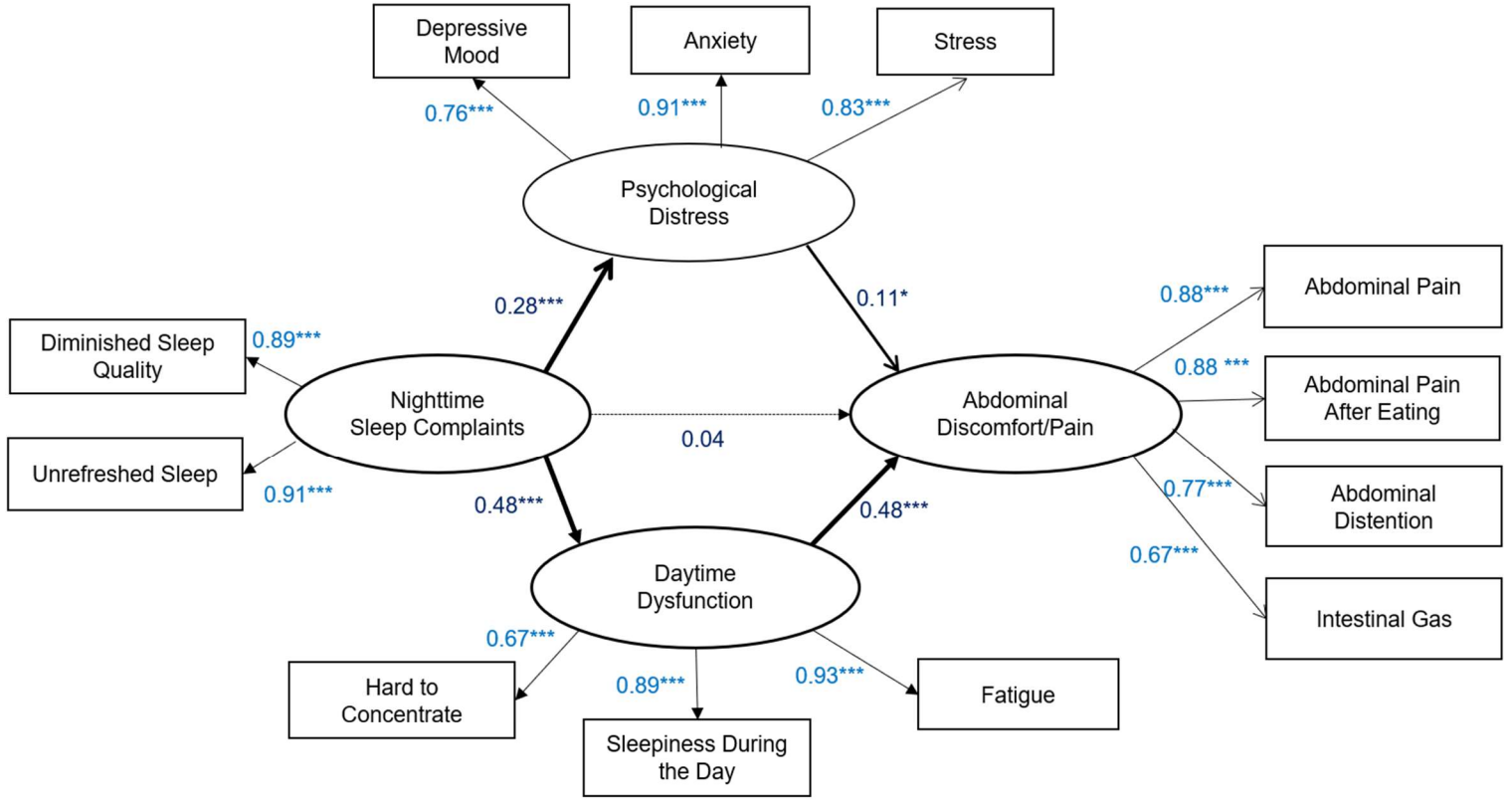
Abbreviation: SEM = structural equation modeling
*** $P < .001$.

Figure 1— Initial hypothesized structural model of direct and indirect effects of sleep on pain through psychological distress and daytime dysfunction.



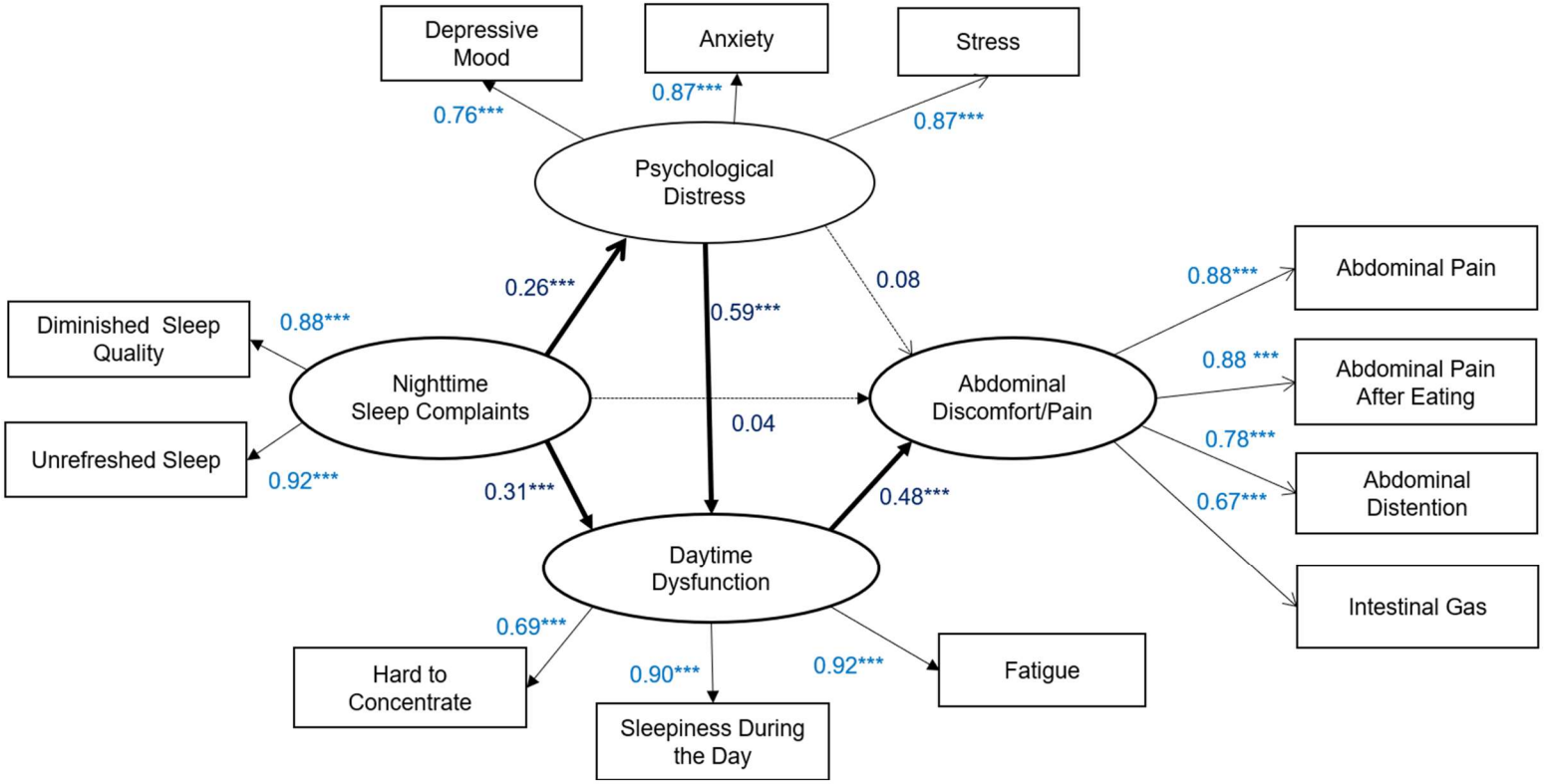
The variables represented in ovals were latent variables. This initial hypothesized structural model was set up to test the potential indirect effects of psychological distress and daytime dysfunction simultaneously in sleep-pain relationship in adults with irritable bowel syndrome.

Figure 2— Initial structural model of nighttime sleep complaints, psychological distress, daytime dysfunction and abdominal discomfort/pain symptoms in adults with irritable bowel syndrome



The latent variables were represented in ovals. The indicators of the latent variables were represented in rectangles. Standardized factor loadings (in light blue) of symptom indicators within their latent variables from confirmatory factor analyses were all statistically significant and greater than 0.6, suggesting the latent variables of nighttime sleep complaints, daytime dysfunction, psychological distress and abdominal discomfort/pain were measured adequately by their respective symptom indicators. The standardized estimates (in dark blue) were for structural pathway relationships between the latent variables from SEM analyses. However, this initial SEM model yielded inadequate model fit. Solid lines indicated significant paths; dashed lines indicated non-significant paths. SEM = structural equation modeling. * $P < .05$, ** $P < .01$, *** $P < .001$.

Figure 3— Final structural model of nighttime sleep complaints, psychological distress, daytime dysfunction and abdominal discomfort/pain symptoms in adults with irritable bowel syndrome



Given inadequate model fit of the initial SEM model, a direct path between psychological distress and daytime dysfunction was added to create this SEM model. This revised SEM model yielded relatively good model fit. Nighttime sleep complaint was a significant predictor for psychological distress (β = 0.26) and daytime dysfunction (β = 0.31), but not for abdominal discomfort/pain (β = 0.04). Psychological distress was a significant predictor for daytime dysfunction (β = 0.59), but not for abdominal discomfort/pain (β = 0.08). Daytime dysfunction was significantly predictive for abdominal discomfort/pain (β = 0.48). The latent variables were represented in ovals. The indicators of the latent variables were represented in rectangles. The standardized estimates (in dark blue) were for structural pathway relationships between the latent variables from structural equation modeling analyses. Solid lines indicated significant paths; dashed lines indicated non-significant paths. SEM = structural equation modeling. * $P < .05$, ** $P < .01$, *** $P < .001$.

Appendix

Permission from Jonathan Wendling, Communications Manager of American Academic Sleep Medicine to include in Pei-Lin Yang's PhD dissertation

From: Jon Wendling
Sent: Friday, June 26, 2020 8:57 AM
To: plinyang
Subject: re: JCSM MS # JC-20-00119R2 - [EMID:114942db5eaf74e4]

Hi Pei-Lin,

You have permission to use your paper "Indirect Effect of Sleep on Abdominal Pain through Daytime Dysfunction in Adults with Irritable Bowel Syndrome" in whole or in part in your PhD dissertation.

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CHAPTER 4: Associations between chronotype, social jetlag, and weekday sleep in women with irritable bowel syndrome

Manuscript Three

This manuscript has been submitted to Chronobiology International on Thursday, July 16, 2020. Instructions for authors can be found at the journal homepage: https://www.tandfonline.com/toc/icbi20/current. The authorship is as follows: **Pei-Lin Yang**, PhD (c), MSN, RN, doctoral Candidate, Department of Biobehavioral Nursing and Health Informatics, School of Nursing, University of Washington, Seattle, **Robert L. Burr**, PhD, Research Professor, Department of Biobehavioral Nursing and Health Informatics, School of Nursing, University of Washington, Seattle, **Horacio O. de la Iglesia**, PhD, Professor, Department of Biology, University of Washington, Seattle, **Diana T. Buchanan**, PhD, RN, Associate Professor, Department of Biobehavioral Nursing and Health Informatics, School of Nursing, University of Washington, Seattle, **Teresa M. Ward**, PhD, RN, FAAN, Professor, Chairperson, Department of Child, Family, and Population Health Nursing, School of Nursing, University of Washington, Seattle, **Carol A. Landis**, PhD, FAAN, Professor Emeritus, Department of Biobehavioral Nursing and Health Informatics, School of Nursing, University of Washington, Seattle, and **Margaret M. Heitkemper**, PhD, RN, FAAN, Professor, Chairperson, Department of Biobehavioral Nursing and Health Informatics, School of Nursing, University of Washington, Seattle.

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ABSTRACT

Sleep deficiency is well-documented in individuals with irritable bowel syndrome (IBS). Sleep deficiency includes poor sleep quality and an inadequate amount of sleep, and is a modifiable risk factor for IBS symptom exacerbations. Prior studies in other populations have identified chronotype and social jetlag (SJL) as important determinants of sleep outcomes. However, chronotype and SJL have not been examined in women with IBS. We used multiple linear regression analyses to determine whether chronotype and SJL are associated with sleep outcomes during weekdays among women with IBS predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D) and healthy control (HC) women. This sample included 62 women with IBS (IBS-C =29, IBS-D =33) and 58 HC women who completed 28-day daily diary from two study cohorts. Chronotype was estimated from daily diary data with the average mid-sleep time on weekends (MSW^{we}). SJL was calculated by subtracting the average mid-sleep time on weekdays from MSW^{we}. Sleep outcomes included diary assessments of sleep quality, sleep need met and restorative sleep during weekdays. In HCs, later chronotype was predictive of lower sleep quality ($\beta = -0.19$, $p < 0.01$), a perception of sleep need not met ($\beta = -0.17$, $p < 0.001$) and a less restorative sleep during weekdays ($\beta = -0.15$, $p = 0.073$), whereas SJL was not associated with sleep outcomes. Similar to HCs, earlier chronotypes in women with IBS-C reported better sleep quality and more sufficient sleep need met and restorative sleep during weekdays than later chronotypes (all $p > 0.05$). Compared to HCs, the relationships of chronotype with weekday sleep outcomes in the women with IBS-D were in the opposite directions (all $p < 0.05$). This exploratory study suggests that chronotype may be an important contributor to sleep outcomes in women with IBS-C and IBS-D, particularly sleep quality and sleep need met.

Keywords: Sleep, chronotype, social jetlag, circadian rhythm, symptom, irritable bowel syndrome

Introduction

Irritable bowel syndrome (IBS) is a prevalent chronic functional bowel disorder, affecting an estimated 11 % of the global population (Canavan, West et al., 2014). IBS is characterized by chronic, recurrent abdominal discomfort/pain related to bowel pattern alterations, and is more common in women than men (Drossman, 2016). The diagnosis of IBS is currently done with the Rome IV consensus-derived criteria (Drossman & Hasler, 2016). To guide clinical treatment, IBS is further classified into four subtypes based on stool consistency: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and IBS unclassified (IBS-U) (Drossman, 2016; Defrees & Bailey, 2017). IBS imposes a substantial economic burden on healthcare systems, and can adversely affect quality of life and reduce work productivity (Buono, Carson et al., 2017; Corsetti & Whorwell, 2017).

The etiology of IBS remains to be elucidated; it has been linked with genetics, dysregulation of the brain-gut axis, altered immune responses, altered microbiome (dysbiosis), psychological distress, as well as environmental and lifestyle risk factors (Guo, Zhuang et al., 2015; Drossman, 2016; Henström & D'Amato, 2016; Defrees & Bailey, 2017). Of these, lifestyle risk factors may be the most amenable to behavioral changes with subsequent improvement in symptoms and quality of life for individuals with IBS (Kang, Choi et al., 2011; Shahabi, Naliboff et al., 2016). A number of investigators have shown that sleep deficiency, including inadequate amount of sleep obtained and poor sleep quality, is a significant risk factor for IBS symptom exacerbations such as abdominal pain, fatigue and psychological distress (Buchanan, Cain et al., 2014; Lee, Yoon et al., 2017; Tu, Heitkemper et al., 2017; Ben, Ruqiao et

al., 2018). As such, sleep deficiency may be an important target for behavioral modifications to optimize IBS symptom management.

Circadian rhythms are endogenous physiological and behavioral processes that are entrained to the 24-hour external environment (Parkar, Kalsbeek et al., 2019). Inter-individual differences in circadian entrainment can be attributed to intrinsic (e.g. circadian genes, age, gender, health conditions, gut microbiome) and extrinsic factors (e.g. light exposure, eating behaviors, social timing) (Roenneberg, Kuehnle et al., 2007; Mattson, Allison et al., 2014; Fischer, Lombardi et al., 2017; Parkar, Kalsbeek et al., 2019), leading to different circadian phenotypes, known as chronotypes (Roenneberg, 2015). Chronotype is in part determined by an individual's phase of circadian entrainment relative to the external 24-hour environment (Roenneberg, 2015). Early chronotypes, "larks", prefer waking up and going to bed early while late chronotypes, "owls", prefer waking up and going to bed late. Whether these chronotype characteristics are associated with sleep quality and/or quantity in individuals with IBS remains to be examined.

Investigators have found that chronotype is an important determinant of sleep quality and quantity in multiple, other populations including students and employees with regular daytime work/school schedules. Specifically, late chronotypes are more likely to report poor sleep quality (Orr, Elsenbruch et al., 2000; Yun, Ahn et al., 2015; Chrobak, Nowakowski et al., 2018), less restorative sleep (Tutek, Molzof et al., 2017), shorter sleep duration (Soehner, Kennedy et al., 2011), insomnia (Ong, Huang et al., 2007; Merikanto, Kronholm et al., 2012) and daytime dysfunction symptoms (Chrobak, Nowakowski et al., 2018) compared to early chronotypes. Even though sleep deficiency is well-documented in individuals with IBS (Tu, Heitkemper et al., 2017; Ben, Ruqiao

et al., 2018), whether sleep deficiency symptoms are associated with chronotype and vary among IBS bowel pattern subgroups remains to be explored.

Habitual sleep bedtimes and risetimes are influenced by social factors such as work/school schedules and other social commitments. These social factors lead to a variance in bedtime and risetime timing between weekdays and weekends creating a circadian misalignment known as "social jetlag" (SJL) (Wittmann, Dinich et al., 2006; Roenneberg, Pilz et al., 2019). For example, after a weekend, on Monday individuals may experience symptoms consistent with jet lag associated with travelling across time zones (Roenneberg, Pilz et al., 2019). SJL is used as an estimate of the time discrepancy between endogenous circadian phase and imposed social timing, and it is considered the most common circadian misalignment in modern society (Beauvalet, Quiles et al., 2017). Adults with greater SJL are more likely to report poor sleep quality (Islam, Hu et al., 2019; Sűdy, Ella et al., 2019) and sleep less on weekdays (Rutters, Lemmens et al., 2014) as compared to those with less SJL. It remains to be determined whether individuals with IBS experience more SJL and whether SJL influences weekday sleep outcomes.

The aims of this secondary analysis were to (1) compare diary reported sleep-wake patterns (bedtimes, wake times, sleep duration) and sleep outcomes (sleep quality, sleep need met and restorative sleep) on weekdays and weekends by groups of women with IBS-C, IBS-D, and healthy controls (HC); (2) compare estimates of chronotype and SJL derived from daily diary entries of bedtimes and wake times on weekends and weekdays by groups; (3) examine relationships of chronotype and SJL with weekday sleep outcomes; and (4) test whether these relationships differ by IBS bowel pattern predominance subgroups compared to HCs. Given the importance of sleep deficiency in the exacerbation of IBS symptoms, a deeper understanding of how chronotype and SJL

influence sleep outcomes in women in IBS subgroups could have clinical implications for symptom management.

Materials and methods

Participants and procedures

This is a secondary data analysis of two studies of sleep in women with IBS and age-matched HC women, 18-45 years old, recruited through community advertisements. The details of recruitment and other procedures have been published elsewhere (Heitkemper, Jarrett et al., 2005; Heitkemper, Cain et al., 2012). The purpose of the first study ("SLP I") was to examine objective sleep measures (polysomnography, actigraphy) and self-reported sleep and symptoms in women with IBS and HCs (Heitkemper, Jarrett et al., 2005). The purpose of the second study ("SLP II") was to examine sleep, plasma adrenocorticotropic hormone and serum cortisol levels over the night in response to anticipation of a public speaking stressor in women with IBS and HCs (Heitkemper, Cain et al., 2012). Similar inclusion and exclusion criteria were used for both SLP I and II cohorts. In brief, eligibility criteria for women with IBS included: (1) a medical diagnosis of IBS and currently experiencing symptoms compatible with Rome-II (for SLP I) or Rome III (for SLP II) diagnostic criteria for IBS, (2) did not take specific medications for IBS on a regular basis, and (3) did not have a history of or current abdominal conditions other than IBS. HCs were eligible if they denied any history of GI disorders and any IBS symptoms meeting Rome II or III criteria. Exclusion criteria both for both IBS and HCs included: (1) any significant co-morbidity (i.e., cardiac dysrhythmia, sleep disorder [other than insomnia symptoms], pain disorder, and psychiatric disorders), (2) taking medications that could affect sleep (i.e., β-blockers, antihistamines, benzodiazepines, anti-depressants, and/or hypnotics), and (3) shift work or night shift only work.

Prior to data collection, eligible participants completed informed consent and were instructed on study procedures including how to complete the daily diary each evening for 28 consecutive days (over one menstrual cycle) at home. In addition, participants slept in an academic sleep laboratory setting for 3 consecutive nights. Given the purpose of this study, only women who completed at least 14 consecutive days (excluding sleep laboratory days) of the 28-day diary were included in data analyses. Less than 14 days was unlikely to present reliable estimates of chronotype and SJL. The final sample included 62 women with IBS and 58 HCs. Supplementary Table 1S provides a summary of sample characteristics and average sleep-wake patterns and sleep outcomes for each cohort (SLP I, II) and the cohorts combined.

Measures

Demographic and IBS measures

Demographic variables included self-reported age, body mass index (BMI), race, marital status, education and occupation. IBS subtypes in the present data analyses were categorized by predominant bowel habit on the basis of Rome III diagnostic criteria (Thompson, Drossman et al., 2006).

Sleep-wake patterns and sleep outcomes

All participants were asked to report each day of the week (Sunday, Monday, etc.) and the sleep-wake patterns and sleep outcomes for the prior night. Sleep-wake pattern variables include: (1) bedtime, defined as the time when participants reported as "went to sleep last night"; (2) wake time, defined as the time when participants reported as "woke up this morning"; and (3) sleep duration, defined as the total amount time between bedtime and wake time. Sleep variable outcomes included: (1) sleep quality, defined as a rating on the 5 point scale of 0 (very poor), to 4 (very good) to the statement "Overall the quality of my sleep was"; (2) perceived sleep need met, defined

as a rating on a five point scale of 0 (very poor) to 4 (very good) to the statement "For my needs, the number of hours I slept was"; and (3) restorative sleep, defined as a rating on a scale from 0 (not at all), 1 (minimally), 2 (mild), 3 (moderately) or 4 (extremely) to the statement "How rested did you feel when you woke up today?". To examine sleep-wake patterns and sleep outcomes on weekdays and weekends, each time period was coded as a weekday (bedtimes starting from Sunday to Thursday nights) or a weekend (bedtimes starting from Friday to Saturday nights) (Monk, Buysse et al., 2000; Gander, 2016; Fischer, Lombardi et al., 2017).

Chronotype and social jetlag

Typically, chronotype is calculated as the time of **M**id-**S**leep point on **F**ree days (**MSF**) without using an alarm clock. This marker of chronotype reflects the circadian phase of an individual because he/she is more likely to sleep and wake on the basis of the endogenous biological circadian timing due to less social constraints on free days (Wittmann, Dinich et al., 2006; Roenneberg, 2015; Roenneberg, Pilz et al., 2019). MSF is considered a reliable proxy for chronotype because it correlates well with dim light melatonin onset (DLMO), a marker of circadian phase (Kantermann, Sung et al., 2015). Given the lack of the information about participant's work/school schedules and use of alarm devices, we assumed that all participants had a typical five-day work/school schedule (Monday-Friday). As such, chronotype was calculated for each participant as the average of **M**id-**s**leep time for **W**eekends (Friday and/or Saturday nights) (**MSW^{we}**) (Fischer, Lombardi et al., 2017) and mid-sleep time was computed by the average midpoint between bedtimes and wake times. Thus, chronotype was viewed as a continuous variable in units of time**.** **SJL** was calculated for each participant by subtracting the average of mid-sleep time on weekdays from that on weekends (Roenneberg, Pilz et al., 2019).

Statistical analysis

Descriptive statistics were used for demographic and clinical characteristics, as well as daily diary data. Diary-measured sleep-wake patterns (bedtimes, wake times, sleep duration), sleep outcomes (sleep quality, sleep need met, restorative sleep) were averaged over weekdays and weekends, respectively, for IBS bowel pattern subtypes (IBS-C or IBS-D) and HCs. We used independent t test or χ^2/Fisher's exact tests to examine the differences between SLP I and SLP II cohorts in demographic and clinical characteristics. The significant differences in age, occupation (e.g., professional/managerial, homemaker) and IBS subtypes between study cohorts may indicate SLP I and SPL II were not comparable (Supplementary Table 1S). Age is a well-established factor influencing sleep outcomes as well as chronotype and SJL (Fischer, Lombardi et al., 2017; Roenneberg, Pilz et al., 2019). Therefore, age and study cohort (SLP II vs. SLP I) were included as covariates in the following data analyses. We used multiple linear regression analyses to compare weekday/weekend sleep-wake patterns and sleep outcomes (Aim 1) as well as chronotype (MSW^{we}) and SJL by groups (IBS-C, IBS-D, HCs) (Aim 2), statistically controlling for potential age and study cohort effects (SLP II vs. SLP I).

Multiple linear regression analyses were also used to assess the relationship of chronotype with each weekday sleep outcome (sleep quality, sleep need met and restorative sleep) in women with IBS compared to HCs (Block 1 tests only included the main effects of chronotype and IBS subgroups, q.v. Table 3) (Aim 3). Further, we assessed the chronotype-by-group interaction terms (MSW^{we}×IBS-C, MSW^{we}×IBS-D) to determine whether the relationship of chronotype with weekday sleep outcomes would differ by IBS subtypes compared to HCs (Block 2 tests adding chronotype-by-group interaction terms to the main effects, q.v. Table 3) (Aim 4). Similar multiple linear regression analyses and SJL-by-group interaction terms (SJL×IBS-C, SJL×IBS-

D) were used to examine the relationship of SJL with each of three weekday sleep outcomes. For Aim 3 and Aim 4, chronotypes (MSW^{we}), SJL and age were z-scored in all regression models to facilitate the interpretation of the comparison of the β coefficients in IBS subtypes compared to HCs. We made the scatter plots of each weekday sleep outcome vs. chronotype (MSW^{we}) stratified by group to visualize the relationships of chronotype with each weekday sleep outcome in IBS-C, IBS-D and HC groups.

The validity of the assumptions of multiple linear regression were studied by using scatter plots of the jackknife residuals vs. the fitted values to assess the linearity and equal variance assumptions, and identifying outliers or influential points. QQ-plots of the residuals were used to assess normality. Assessment of research design was used to examine the independence assumption. All statistical analyses were conducted in the statistical software package RStudio, version 3.6.1 (RStudio Team, 2019). All *p*-values were two-tailed and less than 0.05 were considered statistically significant.

Results

Participant demographics

Table 1 presents the demographic characteristics of the study sample. The mean age of the sample was 30.1 ± 7.2 years. Of the participants, 24.2 % (n = 29) met Rome III criteria for IBS-C and 27.5 % (n = 33) met Rome III criteria for IBS-D. Most participants were racially self-identified as white (75.8%), unmarried/unpartnered (71.7%), equal or greater than college-educated (67.2%), and 12.5% were unemployed.

Sleep-wake patterns and sleep outcomes

Table 2 shows the averages of weekday/weekend sleep-wake pattern variables and sleep outcome variables by IBS-C, IBS-D and HC groups with and without adjustment for age and cohort effects.

Sleep-wake patterns

Average bedtimes and wake times were later on weekends than weekdays in two bowel pattern IBS groups and HCs. On weekdays, the participants with IBS-C had, on average, an estimated 33 min earlier bedtime (β = -0.55, p = 0.022) and 32.4 min earlier wakeup time (β = -0.54, p = 0.035) than HCs, and the estimated weekday sleep duration was not significantly different between IBS-C and HC groups (β = 0.14, p = 0.939). The estimated weekday sleep-wake patterns did not differ between IBS-D and HCs, nor between IBS-C and IBS-D groups (all p values > 0.05). On weekends, no significant differences in the estimated variables of sleep-wake patterns were observed between any of the groups (all p values > 0.05).

Sleep outcomes

On weekdays, participants with IBS-C and IBS-D reported lower sleep quality (IBS-C vs. HCs: β = -0.28, p = 0.020; IBS-D vs. HCs: β = -0.52, p < 0.001), less sleep duration than needed (IBS-C vs. HCs: β = -0.29, p = 0.033; IBS-D vs. HCs: β = -0.42, p < 0.001), and less restorative sleep (IBS-C vs. HCs: β = -0.31, p = 0.020; IBS-D vs. HCs: β = -0.48, p < 0.001) compared to HCs. On weekends, participants with IBS-D reported worse ratings of sleep quality, sleep need met, and restorative sleep compared to HCs (all p values <0.001), whereas no group difference in weekend sleep outcomes was observed between IBS-C and HC groups (all p values > 0.05). Participants with IBS-D reported lower weekday sleep quality than those with IBS-C (IBS-D vs. IBS-C: β = -0.25, p = 0.029).

Chronotype and SJL in IBS bowel pattern subtypes and healthy women

Chronotype, estimated as mean MSW^{we}, was 4:12 a.m. (± 1:03 h:min) for the IBS-C group, 4:13 a.m. (± 1:05 h:min) for the IBS-D group and 4:36 a.m. (± 1:02 h:min) for HCs. The estimates of MSW^{we} were not significantly different from each other (IBS-C

vs. HCs: $p = 0.144$; IBS-D vs. HCs: $p = 0.423$). Averages of SJL in all three groups were less than 1 hr, and did not differ between any of the groups (IBS-C vs. HCs: $p = 0.297$; IBS-D vs. HCs: $p = 0.637$) (See Table 2).

Relationship of chronotype with sleep outcomes in IBS bowel pattern subtypes and healthy women

Table 3 summarizes the relationship between chronotype and weekday sleep outcomes in IBS subtypes compared to HCs. Multiple regression models of Block 1, which only included the main effect of MSW^{we} after adjusting for IBS subtype, age and cohort effects, showed chronotype was only a significant predictor of sleep quality ($\beta = -0.1$, $p = 0.018$) but not sleep need met ($\beta = -0.06$, $p = 0.234$) or restorative sleep ($\beta = -0.06$, $p = 0.329$).

When chronotype-by-group interaction terms (MSW^{we}×IBS-C, MSW^{we}×IBS-D) were added in regression analyses, the regression models of Block 2 showed that chronotype was significantly associated with weekday sleep quality ($\beta = -0.19$, $p = 0.003$), sleep need met ($\beta = -0.17$, $p = 0.037$), but not with weekday restorative sleep ($\beta = -0.15$, $p = 0.073$) in HCs. The interaction effects between MSW^{we} and IBS-C were not significant for sleep outcomes (all p values > 0.05), indicating the relationships of chronotype and these sleep outcomes in IBS-C group were not significantly different from these relationships in HCs. However, the interaction effects between MSW^{we} and IBS-D were significant for weekday sleep quality ($\beta = 0.23$, $p = 0.001$), sleep need met ($\beta = 0.23$, $p = 0.023$) and restorative sleep ($\beta = 0.25$, $p = 0.017$), indicating that the relationships of chronotype with these weekday sleep outcomes in IBS-D were significantly different from HCs.

As shown in Figures 1(A-C), the relationships of chronotype (MSW^{we}) with each of the weekday sleep outcomes were different in IBS-D as compared to HCs, but similar between IBS-C and HC groups. IBS-D participants with later chronotypes reported

better weekday sleep quality, more sufficient sleep need met and restorative sleep than IBS-D participants with early chronotypes, whereas the opposite relationship was observed in the IBS-C and HC groups.

Relationships of SJL with sleep outcomes in IBS bowel pattern subtypes and healthy women

Table 4 summarizes the relationships of SJL with weekday sleep outcomes in IBS subtypes compared to HCs. All linear regression models showed the main effect of SJL and SJL-by-group interaction terms were not significant for weekday sleep outcomes (all p values > 0.05).

Discussion

To the best of our knowledge, this study is the first to examine the potential relationships of chronotype (quantitatively assessed by average mid-sleep time on weekends) and SJL with weekday sleep outcomes (sleep quality, sleep need met and restorative sleep) in a sample of women with IBS-C and IBS-D in comparison to healthy (control) women using daily diary data. Our findings provide preliminary evidence that when IBS bowel pattern predominance subgroups are considered, chronotype is associated with weekday reports of sleep quality and sleep need met in both women with and without IBS, whereas SJL is not. Further, the relationship of chronotype with weekday sleep outcomes in women with IBS-C is similar to healthy women, but different from that of the IBS-D group.

Sleep-wake patterns

Our sample of women with IBS-C showed a trend of an earlier average weekday/weekend bedtime and wake time as compared to those with IBS-D and HCs. This finding is in contrast to the study by Okami, Kato et al. (2011) who found that Japanese female nursing and medical students with IBS-C had later bedtimes and wake times than those with IBS-D. The inconsistency in findings may be due to

sociodemographic (i.e., age) and/or the way sleep measures were obtained. Okami, Kato et al. (2011) used a single-time questionnaire to retrospectively assess sleep-wake patterns, as opposed to estimates based on daily diary data of bedtime and wake time. Self-reported diary data of sleep outcomes has been prefered to questionaire reports as it is less likely to be infludenced by multiple symptoms (i.e., insomnia, depressive mood, hostility) and the correlation with objective sleep measures (i.e., polysomnography, actigraphy) is stronger (Matthews, Patel et al., 2018; Mallinson, Kamenetsky et al., 2019).

Chronotype

The average MSW^{we} for each IBS subtypes and HCs in our sample was later compared to Fischer, Lombardi et al. (2017) who reported an average MSW^{we} of 3:54 a.m. among a general sample of US women at age 30 years. The later MSW^{we} in our sample could be attributed to latitude effects on chronotype as our participants were recruited from Northwest US residents. This conjecture is supported by Randler and Rahafar (2017) systematic review of a total of 87 datasets found that late chronotype predominance is associated with higher latitude. There is also evidence indicating the impact of seasonality on chronotype (Shawa, Rae et al., 2018). However, the later MSW^{we} in our sample is unlikely due to differences in calendar month photoperiod exposure since data collection was approximately equal for autumn/winter (IBS: 48.4 %; HCs: 48.3 %) as compared to spring/summer (IBS: 51.6 %; HCs: 48.3 %). Whether the later chronotype predominance in our Northwest US sample is due environmental and/or geographic factors is unknown in this secondary data analysis. For example, evening exposure to artificial light (e.g., use of electronic devices prior to bedtime) can inhibit melatonin secretion, a signal that marks the start of the biological night, and can delay the circadian clock, leading to an a later sleep and wake timing (Cajochen, Frey et al., 2011; Nesbitt & Dijk, 2014; Koo, Song et al., 2016).

Relationships of chronotypes with weekday sleep outcomes

Previous studies in general populations and among employees with consistent daytime work schedules report that those with early chronotypes experience better sleep quality, more sufficient sleep met and more restorative sleep on weekdays compared to later chronotypes (Ong, Huang et al., 2007; Soehner, Kennedy et al., 2011; Merikanto, Kronholm et al., 2012; Yun, Ahn et al., 2015; Tutek, Molzof et al., 2017; Chrobak, Nowakowski et al., 2018). This is in line with our findings in HC and IBS-C groups. However, an inverse relationship was found in the IBS-D group, in which later chronotypes experienced better weekday sleep outcomes. It may be that specific symptoms associated in the IBS-D (e.g., more frequent toileting in the evening) contributed to the unique sleep-wake behavioral patterns in IBS-D. Our findings highlight the importance of future studies integrating ecological momentary assessment to examine the 24-h temporal pattern of symptoms in IBS patients, specifically in women with IBS-D.

Social jetlag

SJL in our sample of women with IBS and HCs was less than 1 hr. This is considerably less than that reported in European and Japanese populations that included men and women (Roenneberg, Allebrandt et al., 2012; Islam, Hu et al., 2019). A lower average value of SJL in our sample could be attributed to women only sample. When compared to men, women are typically earlier chronotypes (Fischer, Lombardi et al., 2017) and SJL is usually lower in early chronotypes (Roenneberg, Pilz et al., 2019). Our operationalization of SJL which assumed all the women followed a consistent work/school schedule may account for the low SJL value in this secondary data analyses. Future research is warranted to collect workday and free day sleep-wake timing to confirm our SJL results in women with IBS-C and IBS-D as well as healthy women.

Relationships of social jetlag with weekday sleep outcomes

Our current study failed to find any significant relationship of SJL with weekday sleep outcomes. Prior studies showed that individuals with SJL > 1-2 hrs are at a higher risk of adverse health outcomes including sleep deficiency (Rutters, Lemmens et al., 2014; Beauvalet, Quiles et al., 2017). Given SJL < 1 hr was more common in both women with and without IBS, this limited SJL range may have accounted for the absence of an association between SJL and weekday sleep outcomes. Studies with a sample with a broader SJL distribution may reveal a relationship between SJL and sleep outcomes in IBS.

Strengths and limitations

The strengths of this study include a comparison sample of healthy control women and the use of daily diaries for as long as 28-days to measure sleep-wake patterns across weekdays and weekends. In this secondary data analyses, we separated weekday and weekend wake and bed times to examine chronotype and SJL as factors influencing weekday sleep outcomes. This approach provides insights into the question of whether weekend sleep-wake patterns (reflecting chronotype predominance) influence sleep outcomes during weekdays. However, a limitation is the lack of information about workdays vs. free days and the use of alarm devices. We used an average mid-sleep time on weekends to determine chronotype and this may not have corresponded to "free days." This alternative of chronotype would have contributed to an overestimated relationship of chronotype with sleep outcomes if we had included weekend sleep outcomes in data analysis. To prevent from this potential overestimation, we only used self-reports of weekday sleep evaluation as outcomes and average mid-sleep time on weekends as a predictor in order to avoid measuring a predictor and outcomes at the same time. Our mid sleep phase marker is drawn under the influence of daily environmental cycles (i.e., light/dark, fasting/feeding, temperature and social timing)

(Duffy & Dijk, 2002), and it does not allow to extract the pure endogenous circadian phase. Future studies are suggested to use a constant routine protocol and physiological measures such as DLMO to unmask circadian phase (Klerman et al., 2002), and assess if it differs between IBS subtypes and HCs. Even though daily diary data of sleep-wake timing is less invasive and more amenable for studies over an extended time period, the estimate of chronotype and SJL have not yet been validated against other reliable circadian markers in individuals with IBS.

Conclusion

In conclusion, our findings show that women with IBS-D experience more disrupted sleep across weekdays and weekends compared to healthy control women. The findings also indicate that chronotype may be an important contributor to weekday sleep outcomes for all women with and without IBS, whereas SJL is not. The direction of the association between chronotype and weekday sleep outcomes is influenced by IBS bowel pattern predominance subgroups. Disrupted sleep and inappropriate sleep practices are treatable through addressing sleep behavioral strategies and/or potential chronotherapy. Future research needs to validate our preliminary evidence about chronotype and SJL as well as their relationships, potentially incorporating physiological biomarkers and other measures of behavioral and environmental cues for circadian pattern on a constant routine protocol.

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Declaration of interest

All authors have no conflicts of interest with this publication.

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Data availability statement

The data that support the findings are available from the senior author (M.M.H), upon reasonable request.

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References

Beauvalet JC, Quiles CL, de Oliveira MAB, Ilgenfritz CAV, Hidalgo MPL, Tonon AC. 2017. Social jetlag in health and behavioral research: a systematic review. ChronoPhysiology and Therapy. 7:19-31.

Ben W, Ruqiao D, Liping D. 2018. Prevalence of sleep disorder in irritable bowel syndrome: A systematic review with meta-analysis. Saudi J Gastroenterol. 24:141-150.

Buchanan DT, Cain K, Heitkemper M, Burr R, Vitiello MV, Zia J, Jarrett M. 2014. Sleep measures predict next-day symptoms in women with irritable bowel syndrome. J Clin Sleep Med. 10:1003-1009.

Buono JL, Carson RT, Flores NM. 2017. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. Health Qual Life Outcomes. 15:35.

Cajochen C, Frey S, Anders D, Spati J, Bues M, Pross A, Mager R, Wirz-Justice A, Stefani O. 2011. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. J Appl Physiol (1985). 110:1432-1438.

Canavan C, West J, Card T. 2014. The epidemiology of irritable bowel syndrome. Clin Epidemiol. 6:71-80.

Chrobak AA, Nowakowski J, Zwolinska-Wcislo M, Cibor D, Przybylska-Felus M, Ochyra K, Rzeznik M, Dudek A, Arciszewska A, Siwek M, Dudek D. 2018. Associations between chronotype, sleep disturbances and seasonality with fatigue and inflammatory bowel disease symptoms. Chronobiol Int. 35:1142-1152.

Corsetti M, Whorwell P. 2017. The global impact of IBS: time to think about IBS-specific models of care? Therap Adv Gastroenterol. 10:727-736.

Defrees DN, Bailey J. 2017. Irritable bowel syndrome: epidemiology, pathophysiology, diagnosis, and treatment. Prim Care. 44:655-671.

Drossman DA. 2016. Functional gastrointestinal disorders: history, pathophysiology, clinical Features, and Rome IV. Gastroenterology. 150:1262-1279.e1262.

Drossman DA, Hasler WL. 2016. Rome IV—functional GI disorders: disorders of gut-brain interaction. Gastroenterology. 150:1257-1261.

Duffy JF, Dijk DJ. 2002. Getting through to circadian oscillators: why use constant routines? J Biol Rhythms.17:4-13.

Fischer D, Lombardi DA, Marucci-Wellman H, Roenneberg T. 2017. Chronotypes in the US – Influence of age and sex. PLoS One. 12:e0178782.

Gander PH. 2016. Differences in circadian phase and weekday/weekend sleep patterns in a sample of middle-aged morning types and evening types AU - Paine, Sarah-Jane. Chronobiol Int. 33:1009-1017.

Guo YB, Zhuang KM, Kuang L, Zhan Q, Wang XF, Liu SD. 2015. Association between diet and lifestyle habits and irritable bowel syndrome: a case-control study. Gut Liver. 9:649-656.

Heitkemper MM, Cain KC, Deechakawan W, Poppe A, Jun SE, Burr RL, Jarrett ME. 2012. Anticipation of public speaking and sleep and the hypothalamic-pituitary-adrenal axis in women with irritable bowel syndrome. Neurogastroenterol Motil. 24:626-631, e270-621.

Heitkemper MM, Jarrett M, Burr R, Cain KC, Landis C, Lentz M, Poppe A. 2005. Subjective and objective sleep indices in women with irritable bowel syndrome. Neurogastroenterol Motil. 17:523-530.

Henström M, D'Amato M. 2016. Genetics of irritable bowel syndrome. Mol Cell Pediatr. 3:7.

Islam Z, Hu H, Akter S, Kuwahara K, Kochi T, Eguchi M, Kurotani K, Nanri A, Kabe I, Mizoue T. 2019. Social jetlag is associated with an increased likelihood of having depressive symptoms among the Japanese working population: the Furukawa Nutrition and Health Study. Sleep. 43.

Kang SH, Choi SW, Lee SJ, Chung WS, Lee HR, Chung KY, Lee ES, Moon HS, Kim SH, Sung JK, Lee BS, Jeong HY. 2011. The effects of lifestyle modification on symptoms and quality of life in patients with irritable bowel syndrome: a prospective observational study. Gut Liver. 5:472-477.

Kantermann T, Sung H, Burgess HJ. 2015. Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the Dim Light Melatonin Onset. J Biol Rhythms. 30:449-453.

Koo YS, Song JY, Joo EY, Lee HJ, Lee E, Lee Sk, Jung KY. 2016. Outdoor artificial light at night, obesity, and sleep health: Cross-sectional analysis in the KoGES study. Chronobiol Int. 33:301-314.

Lee SK, Yoon DW, Lee S, Kim J, Choi K-M, Shin C. 2017. The association between irritable bowel syndrome and the coexistence of depression and insomnia. J Psychosom Res. 93:1-5.

Mallinson DC, Kamenetsky ME, Hagen EW, Peppard PE. 2019. Subjective sleep measurement: comparing sleep diary to questionnaire. Nat Sci Sleep. 11:197-206.

Matthews KA, Patel SR, Pantesco EJ, Buysse DJ, Kamarck TW, Lee L, Hall MH. 2018. Similarities and differences in estimates of sleep duration by polysomnography, actigraphy, diary, and self-reported habitual sleep in a community sample. Sleep health. 4:96-103.

Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, Malaisse WJ, Mosley M, Notterpek L, Ravussin E, Scheer FA, Seyfried TN, Varady KA, Panda S. 2014.

Meal frequency and timing in health and disease. Proc Natl Acad Sci U S A. 111:16647-16653.

Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Lahti T, Partonen T. 2012. Relation of chronotype to sleep complaints in the general Finnish population. Chronobiol Int. 29:311-317.

Monk TH, Buysse DJ, Rose LR, Hall JA, Kupfer DJ. 2000. The sleep of healthy people--a diary study. Chronobiol Int. 17:49-60.

Nesbitt AD, Dijk DJ. 2014. Out of synch with society: an update on delayed sleep phase disorder. Curr Opin Pulm Med. 20:581-587.

Okami Y, Kato T, Nin G, Harada K, Aoi W, Wada S, Higashi A, Okuyama Y, Takakuwa S, Ichikawa H, Kanazawa M, Fukudo S. 2011. Lifestyle and psychological factors related to irritable bowel syndrome in nursing and medical school students. J Gastroenterol. 46:1403-1410.

Ong JC, Huang JS, Kuo TF, Manber R. 2007. Characteristics of insomniacs with self-reported morning and evening chronotypes. J Clin Sleep Med. 3:289-294.

Orr WC, Elsenbruch S, Harnish MJ. 2000. Autonomic regulation of cardiac function during sleep in patients with irritable bowel syndrome. Am J Gastroenterol. 95:2865-2871.

Parkar SG, Kalsbeek A, Cheeseman JF. 2019. Potential Role for the Gut Microbiota in Modulating Host Circadian Rhythms and Metabolic Health. Microorganisms. 7:41.

Randler C, Rahafar A. 2017. Latitude affects Morningness-Eveningness: evidence for the environment hypothesis based on a systematic review. Sci Rep. 7:39976.

Roenneberg T. 2015. Having trouble typing? what on earth is chronotype? J Biol Rhythms. 30:487-491.

Roenneberg T, Allebrandt KV, Merrow M, Vetter C. 2012. Social jetlag and obesity. Curr Biol. 22:939-943.

Roenneberg T, Kuehnle T, Juda M, Kantermann T, Allebrandt K, Gordijn M, Merrow M. 2007. Epidemiology of the human circadian clock. Sleep Med Rev. 11:429-438.

Roenneberg T, Pilz LK, Zerbini G, Winnebeck EC. 2019. Chronotype and Social Jetlag: A (Self-) Critical Review. Biology (Basel). 8.

RStudio Team. 2019. RStudio: Integrated Development for R. In. Boston, MA. : RStudio, Inc.

Rutters F, Lemmens SG, Adam TC, Bremmer MA, Elders PJ, Nijpels G, Dekker JM. 2014. Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? J Biol Rhythms. 29:377-383.

Shahabi L, Naliboff BD, Shapiro D. 2016. Self-regulation evaluation of therapeutic yoga and walking for patients with irritable bowel syndrome: a pilot study. Psychol Health Med. 21:176-188.

Shawa N, Rae DE, Roden LC. 2018. Impact of seasons on an individual's chronotype: current perspectives. Nat Sci Sleep. 10:345-354.

Soehner AM, Kennedy KS, Monk TH. 2011. Circadian preference and sleep-wake regularity: associations with self-report sleep parameters in daytime-working adults. Chronobiol Int. 28:802-809.

Sűdy ÁR, Ella K, Bódizs R, Káldi K. 2019. Association of Social Jetlag With Sleep Quality and Autonomic Cardiac Control During Sleep in Young Healthy Men. Front Neurosci. 13:950-950.

Thompson WG, Drossman D, Talley N. 2006. Rome III diagnostic questionnaire for the adult functional GI disorders (including alarm questions) and scoring algorithm. Rome III.917-951.

Tu Q, Heitkemper MM, Jarrett ME, Buchanan DT. 2017. Sleep disturbances in irritable bowel syndrome: a systematic review. Neurogastroenterol Motil. 29.

Tutek J, Molzof HE, Lichstein KL. 2017. Multilevel modeling of chronotype and weekdays versus weekends to predict nonrestorative sleep. Chronobiol Int. 34:1401-1412.

Wittmann M, Dinich J, Merrow M, Roenneberg T. 2006. Social jetlag: misalignment of biological and social time. Chronobiol Int. 23:497-509.

Yun JA, Ahn YS, Jeong KS, Joo EJ, Choi KS. 2015. The relationship between chronotype and sleep quality in Korean firefighters. Clin Psychopharmacol Neurosci. 13:201-208.

Table 1. Demographic characteristics in women with IBS and healthy women

Variables	HC (*n* =58)	IBS-C (*n*=29)	IBS-D (*n* =33)	Total sample (*n* =120)
Age, years, mean (SD)	30.7 (7.3)	30.9 (6.9)	28.4 (7.4)	30.1 (7.2)
BMI, kg/m^2, mean (SD)	24.4 (4.9)	22.6 (2.7)	25.0 (4.6)	24.1 (4.4)
Race, white, *n* (%)	46 (79.3)	21 (72.4)	24 (72.7)	91 (75.8)
Married/partnered, *n* (%)	16 (27.6)	10 (34.5)	8 (24.2)	34 (28.3)
Education, college or greater, *n* (%)	41 (70.7)	18 (62.1)	21 (63.6)	80 (67.2)
Occupation				
Professional, managerial, *n* (%)	15 (25.9)	10 (34.5)	10 (30.3)	35 (29.2)
Technical, service, sales, *n* (%)	20 (34.5)	5 (17.2)	10 (30.3)	35 (29.2)
Student, *n* (%)	2 (3.5)	0 (0.00)	1 (3.0)	3 (2.5)
Homemaker, *n* (%)	12 (20.7)	7 (24.1)	7 (21.2)	26 (21.7)
Others, *n* (%)	2 (3.5)	3 (10.3)	1 (3.0)	6 (5.0)
Unemployed, *n* (%)	7 (12.1)	4 (13.8)	4 (12.1)	15 (12.5)
Study seasons‡				
Spring (Mar-May), *n* (%)	13 (22.4)	11 (37.9)	4 (12.1)	28 (23.3)
Summer (Jun-Aug), *n* (%)	15 (25.9)	8 (27.6)	9 (27.3)	32 (26.7)
Autumn (Sep-Nov), *n* (%)	17 (29.3)	4 (13.8)	11 (33.3)	32 (26.7)
Winter (Dec-Feb), *n* (%)	13 (22.4)	6 (20.7)	9 (27.3)	28 (23.3)

Note. BMI= body mass index, HC= healthy controls, IBS= irritable bowel syndrome, IBS-C= IBS constipation, IBS-D= IBS diarrhea.

‡ participant's study season was based on the majority of diary days studied in seasons.

Table 2. Comparisons of weekday/weekend sleep-wake patterns and sleep outcomes, chronotype and social jetlag by IBS subtypes and healthy women

Measures	HC n = 58		IBS-C n = 29		IBS-D n = 33		IBS-C vs. HC†			IBS-D vs. HC†			IBS-D vs. IBS-C†		
	M	SD	M	SD	M	SD	β	SE	*p*	β	SE	*p*	β	SE	*p*
Sleep-wake patterns															
Weekday															
Bedtime	0:02	1:05	23:27	1:02	0:06	1:17	-0.55	0.24	**0.022**	-0.08	0.25	0.743	0.48	0.27	0.084
Wake time	7:43	1:14	7:05	1:02	7:41	1:26	-0.54	0.25	**0.035**	-0.16	0.28	0.553	0.36	0.28	0.194
Sleep duration (hr)	7.68	0.74	7.63	0.76	7.59	0.82	0.14	0.18	0.939	-0.08	0.18	0.660	-0.11	0.21	0.602
Weekends															
Bedtime	0:34	1:04	0:06	1:11	0:33	1:16	-0.44	0.25	0.097	-0.16	0.24	0.511	0.28	0.28	0.322
Wake time	8:39	1:10	8:19	1:09	8:34	1:15	-0.28	0.27	0.314	-0.21	0.27	0.314	0.08	0.28	0.776
Sleep duration (hr)	8.08	0.90	8.23	1.00	8.02	0.72	0.19	0.23	0.485	-0.05	0.19	0.800	-0.26	0.25	0.368
Sleep outcomes															
Weekday															
Sleep quality	3.01	0.49	2.68	0.52	2.47	0.33	-0.28	0.12	**0.020**	-0.52	0.08	**<0.001**	-0.25	0.11	**0.029**
Sleep need met	2.84	0.58	2.52	0.59	2.43	0.50	-0.29	0.13	**0.033**	-0.42	0.13	**<0.001**	-1.67	0.15	0.278
Restorative sleep	2.70	0.53	2.31	0.69	2.21	0.51	-0.31	0.15	**0.020**	-0.48	0.11	**<0.001**	-0.16	0.16	0.341
Weekend															
Sleep quality	3.04	0.57	2.83	0.55	2.61	0.40	-0.17	0.14	0.231	-0.41	0.10	**<0.001**	-0.26	0.13	0.056
Sleep need met	2.91	0.64	2.78	0.67	2.58	0.58	-0.13	0.16	0.409	-0.35	0.13	**0.007**	-0.26	0.17	0.129
Restorative sleep	2.82	0.59	2.51	0.76	2.38	0.53	-0.27	0.16	0.111	-0.40	0.12	**<0.001**	-0.16	0.17	0.361
Predictors															
MSW^{we}	4:36	1:02	4:12	1:03	4:13	1:05	-0.36	0.24	0.144	-0.18	0.23	0.423	0.18	0.29	0.484
Social jetlag (hr)	0.73	0.73	0.94	0.73	0.65	0.83	0.19	0.18	0.297	-0.08	0.17	0.637	-0.26	0.20	0.189

Note. IBS= irritable bowel syndrome, HC= healthy controls, IBS-C= IBS constipation, IBS-D= IBS diarrhea, MSF^{we}=time of mid-sleep on weekends, Bedtimes, wake times and MSW^{we} were presented as local time, h:mm. Boldface indicates statistical significance ($p < 0.05$).†Adjusted for age (Z-scored) and cohort effects.

Table 3. Multiple linear regression with chronotype predictor for weekday sleep outcomes

	Sleep Quality						Sleep Need Met						Restorative Sleep					
	Block 1			Block 2			Block 1			Block 2			Block 1			Block 2		
	β	SE †	*p*	β	SE †	*p*	β	SE †	*p*	β	SE †	*p*	β	SE †	*p*	β	SE †	*p*
Coefficients																		
Intercept	3.11	0.07	***	3.11	0.07	***	2.89	0.10	***	2.89	.096	***	2.77	0.09	***	2.77	.086	***
Age	-0.12	0.06	*	-0.12	0.06	*	-0.12	0.07	.081	-0.12	.072	.092	-0.07	0.07	.365	-0.07	.075	.421
Cohort (SLP II)‡	-0.19	0.09	*	-0.16	0.09	.082	-0.08	0.12	.479	-0.06	.114	.603	-0.13	0.12	.269	-0.10	.114	.359
IBS-C¶	-0.31	0.12	**	-0.34	0.12	**	-0.31	0.14	*	-0.34	.143	*	-0.37	0.15	*	-0.40	.157	*
IBS-D¶	-0.54	0.09	***	-0.57	0.08	***	-0.43	0.12	***	-0.46	.119	***	-0.49	0.11	***	-0.52	.110	***
MSW^{we} (Z)	-0.10	0.04	*	-0.19	0.06	**	-0.06	0.05	.234	-0.17	.080	*	-0.06	0.06	.329	-0.15	.075	.073
MSW^{we}× IBS-C				0.04	0.09	.663				0.07	.120	.563				0.03	.136	.831
MSW^{we}× IBS-D				0.23	0.07	**				0.26	.112	*				0.25	.103	*

Note. *N*=120 (HCs= 58, IBS-C= 29, IBS-D= 33). Block 1 F-change test df = 5, 114; Block 2 df = 7, 112. IBS= irritable bowel syndrome, IBS-C= IBS constipation, IBS-D= IBS diarrhea, MSW^{we}= time of mid-sleep on weekends and presented as local time, h:mm. Age and MSW^{we} predictors standardized into z-scores.† SE, robust SE. ‡ Cohort is coded (SLP I=0, SLP II=1).¶ HC is a reference for group comparisons with IBS subtypes.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 4. Multiple linear regression with social jetlag predictor for weekday sleep outcomes

	Sleep Quality						Sleep Need Met						Restorative Sleep					
	Block 1			Block 2			Block 1			Block 2			Block 1			Block 2		
	β	SE †	*p*	β	SE †	*p*	β	SE †	*p*	β	SE †	*p*	β	SE †	*p*	β	SE †	*p*
Coefficients																		
Intercept	3.09	0.07	***	3.09	0.07	***	2.87	.095	***	2.87	.097	***	2.76	.084	***	2.75	.085	***
Age	-0.07	0.05	.154	-0.07	0.05	.158	-0.09	.066	.172	-0.09	.067	.171	-0.04	.066	.564	-0.04	.114	.291
Cohort (SLP II)‡	-0.18	0.09	.053	-0.18	0.09	.052	-0.07	.113	.512	-0.08	.115	.505	-0.12	.112	.281	-0.12	.114	.291
IBS-C¶	-0.27	0.12	*	-0.27	0.12	*	-0.28	.140	*	-0.29	.143	*	-0.34	.153	*	-0.35	.159	*
IBS-D¶	-0.53	0.08	***	-0.53	0.08	***	-0.42	.117	***	-0.43	.118	***	-0.48	.112	***	-0.48	.115	***
SJL	-0.03	0.04	.488	-0.001	0.08	.942	-0.05	.058	.376	-0.06	.096	.524	-0.04	.053	.495	-0.06	.084	.478
SJL× IBS-C				-0.04	0.12	.731				0.05	.141	.748				0.05	.150	.756
SJL× IBS-D				-0.05	0.09	.619				<.001	.140	.992				0.04	.116	.727

Note. N=120 (HCs= 58, IBS-C= 29, IBS-D= 33). Block 1 F-change test df = 5, 114; Block 2 df = 7, 112. HC= healthy controls, IBS= irritable bowel syndrome, IBS-C= IBS constipation, IBS-D= IBS diarrhea, SJL= social jetlag. Age and SJL predictors standardized into z-scores.† SE, robust SE. ‡ Cohort is coded (SLP I=0, SLP II=1).¶ HC is a reference for group comparisons with IBS subtypes.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

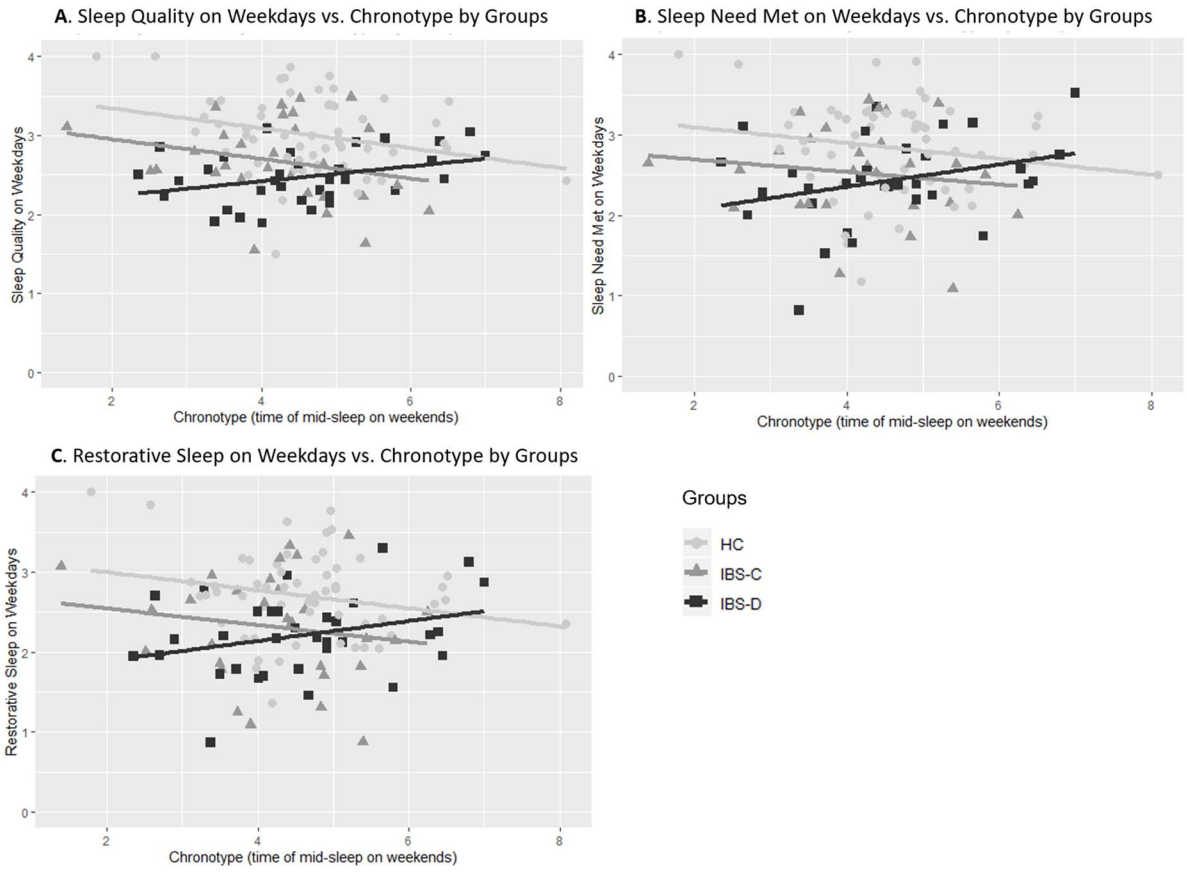

Figure 1. Relationships of chronotype (time of mid sleep on weekends, MSW^{we}) with weekday sleep outcomes in women with IBS-C and IBS-D in comparison to HC women. Scatter plots display chronotype (as time-of-day in hours, presented as local time) and against (A) sleep quality, (B) sleep need met, (C) restorative sleep on weekdays by groups (IBS-C, IBS-D, HCs). IBS= irritable bowel syndrome, IBS-C= IBS constipation, IBS-D= IBS diarrhea, HC=healthy controls.

Appendix

Supplementary Table 1S. Descriptive Characteristics between SLP I and SLP II Studies

Variables	SLP I (*n* =53)	SLP II (*n* =67)	Total sample (*n* =120)	*p*†
Age, years, mean (SD)	32.4 (7.6)	28.3 (6.5)	30.1 (7.2)	**.002**
BMI, kg/m^2, mean (SD)	24.7 (5.3)	23.7 (3.6)	24.1 (4.4)	.193
Race, white, *n* (%)	37 (69.8)	54 (80.6)	91 (75.8)	.201
Married/partnered, *n* (%)	15 (28.3)	19 (28.4)	34 (28.3)	1.000
Education, college or greater, *n* (%)	31 (58.5)	49 (74.2)	80 (67.2)	.079
Occupation				**<0.001**
Professional, managerial, *n* (%)	14 (26.4)	21 (31.3)	35 (29.2)	
Technical, service, sales, *n* (%)	27 (50.9)	8 (11.9)	35 (29.2)	
Student, *n* (%)	3 (5.7)	0 (0)	3 (2.5)	
Homemaker, *n* (%)	0 (0.0)	26 (38.8)	26 (21.7)	
Others, *n* (%)	0 (0.0)	6 (9.0)	6 (5.0)	
Unemployed, *n* (%)	9 (17.0)	6 (9.0)	15 (12.5)	
Study seasons‡				0.247
Spring (Mar-May), *n* (%)	13 (24.5)	15 (23.9)	28 (22.4)	
Summer (Jun-Aug), *n* (%)	10 (18.9)	22 (38.8)	32 (32.8)	
Autumn (Sep-Nov), *n* (%)	14 (26.4)	18 (26.9)	32 (26.9)	
Winter (Dec-Feb), *n* (%)	16 (30.2)	12 (17.9)	28 (17.9)	
Bowel pattern predominance				**<0.01**
Healthy controls, *n* (%)	34 (64.2)	24 (35.8)	58 (48.3)	
IBS-C, *n* (%)	8 (15.1)	21 (31.3)	29 (24.2)	
IBS-D, *n* (%)	11 (20.8)	22 (32.8)	33 (27.5)	

Note. IBS= irritable bowel syndrome, *IBS-C*= IBS constipation, *IBS-D*= IBS diarrhea, *MSW^{we}*= time of mid-sleep on weekends, *SJL*= social jetlag. Bedtimes, wake times and MSW^{we} were presented as local time, h:mm. Boldface indicates statistical significance ($p < 0.05$).

†*p* values for testing differences of descriptive characteristics between SLP I and SLP II studies, calculated by independent t test for continuous variables and $\chi 2$/Fisher's exact tests for categorical variables.

‡ participant's study season was based on the majority of diary days studied in seasons.

CHAPTER 5: CONCLUSION

The overall purpose of this dissertation was to examine the relationships among sleep, circadian rhythms, social timing and symptoms in adults living with a health condition, specifically adults with acute respiratory failure (ARF) and irritable bowel syndrome (IBS). The dissertation included three independent manuscripts. The first manuscript aimed to examine sleep and rest-activity circadian rhythms in ARF survivors after discharge. The second manuscript used structural equation modeling (SEM) to examine the potential indirect effects of sleep on abdominal pain simultaneously through psychological distress and daytime dysfunction in 332 adults with IBS. The third manuscript explored the relationships of chronotype and social jetlag (SJL) with sleep outcomes during weekdays in women with IBS in a comparison with healthy control (HC) women.

Summary of manuscript one

The first manuscript provides preliminary data regarding sleep and rest-activity circadian rhythms after discharge among ARF survivors. At three months post discharge, our cohort of ARF survivors exhibited subclinical and clinical insomnia symptoms, supported by findings from actigraphy (sleep fragmentation) and sleep diaries (reduced sleep time and quality). Survivors' rest-activity circadian rhythms displayed less stability and lower amplitude compared to that of a published community-dwelling population. To the best of our knowledge, this is the first study to identify persistent circadian rhythm disruption in ARF survivors after hospital discharge.

Our cohort of ARF survivors reported moderately impaired sleep time and sleep efficiency on their sleep diaries, but these findings were less notable in the actigraphy data. Subjective sleep disturbance was pronounced, similar to prior questionnaire studies in ICU survivors (1). However, standard actigraphy measures of sleep (total sleep time and sleep efficiency) were

fairly normal on a basis of the National Sleep Foundation recommendations. There are several possible reasons for these findings. First, sleep diary may align better with subjective sleep impairment than standard actigraphy measures, and sleep diary tends to underestimate sleep time and efficiency compared to actigraphy (2-4). Second, identifying circadian abnormalities requires specialized analyses that take into account the timing of the sleep period, which is not reflected in standard actigraphy parameters. Untreated circadian disruption may contribute to insomnia (5), and effective treatment must take account both sleep and circadian components. While limited in size and scope, this pilot study provides an intriguing potential insight into a circadian contribution to the subjective sleep complaints commonly described among survivors of critical illness (6-8).

Our cohort exhibited multiple circadian abnormalities in several respects compared to the community-dwelling US adult sample with similar age and BMI distribution. Left untreated, rest-activity circadian disruption may exacerbate cognitive and psychological comorbidities in ARF survivors. ARF survivors often experience persistent impairments in physical activity and social functioning (9-11), both of which have been found to be associated with low activity and weak circadian strength (12, 13). In populations other than ICU survivors, cognitive impairment has been associated with disrupted rest-activity circadian rhythms (i.e., less stability, more fragmentation or lower rest-activity amplitude) (13-17). Future studies are needed to identify if rest-activity circadian disruption may be a contributor to long-term cognitive deficits among ARF survivors.

Summary of manuscript two

Manuscript two focused on examining a hypothesized model to test the potential indirect effects of sleep (poor sleep quality and unrefreshed sleep) on pain simultaneously through psychological

distress and daytime dysfunction (fatigue, sleepiness, and hard to concentrate) among adults with IBS by using SEM approach. SEM allows for the inclusion of multiple indicators to measure the multifaceted symptom constructs of sleep deficiency, psychological distress, daytime dysfunction and abdominal discomfort/pain(18-20), and further to reduce measurement error of these four multifaceted symptoms of interest(21). Also, SEM is able to include analyses of multiple relationships simultaneously (i.e., direct and indirect effects) to build a more sophisticated statistical model (21, 22).

SEM analyses found a strong indirect effect of poor sleep on abdominal pain via daytime dysfunction, but not psychological distress. More than 95% of the total effect of nighttime sleep complaints on abdominal pain is indirect. The directional relationships among sleep, abdominal pain, psychological distress and daytime dysfunction symptoms in the hypothesized SEM model were supported by our prior sleep studies of women only with IBS,(23, 24); the current study utilized a cross-sectional SEM approach and thus temporal sequences among these latent variables in IBS cannot be established due to the current sample size limitations. There might be alternative models fitting the data equally well. For example, another alternative SEM model with the direct and indirect effect of sleep on daytime dysfunction through psychological distress and abdominal discomfort/pain symptoms could be considered. The directionality of these relationships of symptom clusters in IBS needs confirmation by experimental research or a cross-lagged panel analysis in a prospective study design with a large sample size. Despite this limitation of temporal sequencing, this study made a significant contribution to a better understanding of how sleep deficiency, abdominal discomfort/pain, daytime dysfunction and psychological distress interact to optimize symptom management in IBS populations.

Summary of manuscript three

Manuscript three centered on exploring the relationships of chronotype (quantitatively assessed by average mid-sleep time on weekends) and social jetlag (SJL) with weekday sleep outcomes (sleep quality, sleep need met and restorative sleep) in a sample of women with IBS predominant constipation (IBS-C, n=29) and IBS with predominant diarrhea (IBS-D, n=33) in comparison to healthy control (HCs, n=58) women using daily diary data. The results showed that in HCs, later chronotype was predictive of lower sleep quality ($\beta = -0.19$, $p < 0.01$), a perception of sleep need not met ($\beta = -0.17$, $p < 0.001$) and a less restorative sleep during weekdays ($\beta = -0.15$, $p = 0.073$), whereas SJL was not associated with sleep outcomes. Similar to HCs, earlier chronotypes in women with IBS-C reported better sleep quality and more sufficient sleep need met and restorative sleep during weekdays than later chronotypes (all $p > 0.05$). Compared to HCs, the relationships of chronotype with weekday sleep outcomes in the women with IBS-D were in the opposite directions (all $p < 0.05$).

Previous studies in general populations and among employees with consistent daytime work schedules report that those with early chronotypes experience better sleep quality, more sufficient sleep met and more restorative sleep on weekdays compared to later chronotypes (25-30). This is in line with our findings in HC and IBS-C groups. However, an inverse relationship was found in the IBS-D group, in which later chronotypes experienced better weekday sleep outcomes. It may be that specific symptoms associated in the IBS-D (e.g., more frequent toileting in the evening) contributed to the unique sleep-wake behavioral patterns in IBS-D. The findings included in this manuscript highlight the importance of future studies integrating ecological momentary assessment to examine the 24-h temporal pattern of symptoms in IBS patients, specifically in women with IBS-D.

Our current study failed to find any significant relationship of SJL with weekday sleep outcomes. Prior studies showed that individuals with SJL > 1-2 hrs are at a higher risk of adverse health outcomes including sleep deficiency (31, 32). Given SJL < 1 hr was more common in both women with and without IBS, this limited SJL range may have accounted for the absence of an association between SJL and weekday sleep outcomes. This limited SJL range in our sample could be attributed to our women only sample. When compared to men, women are typically earlier chronotypes (33) and SJL is usually lower in early chronotypes (34). Our operationalization of SJL which assumed all the women followed a consistent work/school schedule may account for the low SJL value in this secondary data analyses. Future research is warranted to collect workday and free day sleep-wake timing to confirm our SJL results in women with IBS-C and IBS-D as well as healthy women.

Implications

These three manuscripts in this dissertation have made a significant contribution to a better understanding of the relationships among sleep, circadian rhythms, social timing (weekdays vs. weekends) and symptoms in adults living with a healthy condition specifically among ARF survivors and adults with IBS.

The findings from the manuscript one show that sleep and circadian disruption is common in ARF survivors even in 3 months after hospital discharge. Sleep and circadian disruption are potentially treatable through chronotherapy (e.g., light, melatonin) as well as behavioral strategies (e.g., set a regular daily routine). Sleep improvement and circadian rhythm regularity may be a promising approach to improve quality of life and daytime function in ARDS survivors. Future research is warranted in larger samples to validate these findings, their

association with quality of life, and to target specific chronotypes with effective circadian interventions.

The findings from the manuscript two have important implications for understanding and managing IBS symptoms. As nighttime sleep complaints directly predicted both daytime dysfunction and psychological distress, treating nighttime sleep complaints may alleviate both of these symptom clusters. However, an intervention only targeting sleep without taking account of daytime function (fatigue, tiredness, cognitive dysfunction) might be less effective for treating abdominal discomfort/pain. Our results suggest that daytime dysfunction is a critical target for IBS symptom management. Among adults with IBS, adequate daytime functioning essentially could reduce or remove poor sleep during the night as a risk factor for abdominal discomfort/pain symptoms even after adjusting for psychological distress. If adults with IBS experience poor sleep quality and/or psychological distress but they can maintain appropriate daytime functioning, the impact of poor sleep on abdominal discomfort/pain can be minimized. These results provide a potential avenue to optimize personalized and hybrid intervention through addressing daytime functioning and sleep behaviors for IBS populations. Additional work is warranted to address the issue of the causality and directionality as well as to understand a shared mechanism among these symptom constructs.

The findings from the manuscript three suggest that chronotype may be an important contributor to sleep outcomes in women with IBS-C and IBS-D, particularly sleep quality and sleep need met, whereas SJL is not. The direction of the association between chronotype and weekday sleep outcomes is influenced by IBS bowel pattern predominance subgroups. Disrupted sleep and inappropriate sleep practices are treatable through addressing sleep behavioral strategies and/or potential chronotherapy. Targeting lifestyle risk factors of sleep deficiency may

be the most amenable to behavioral changes with subsequent improvements in symptoms and quality of life for individuals with IBS. Future research needs to validate our preliminary evidence about chronotype and SJL as well as their relationships, potentially incorporating physiological biomarkers and other measures of behavioral and environmental cues for circadian pattern on a constant routine protocol.

Nurse scientists are well-positioned to explore the relationships among sleep, circadian rhythms, social timing and symptoms among adults living a health condition. A better understanding of sleep and circadian rhythms as well as their interactions with symptoms can help nurse scientists and clinicians to develop a more tailored and personalized approach to enable self-management of sleep and symptoms. Taking into account an individual's chronotype preference may inform intervention development to promote self-management of sleep and symptoms in adults with a health condition, specifically ARF survivors and adults with IBS and improve health outcomes.

References

1. Altman MT, Knauert MP, Pisani MA. Sleep Disturbance after Hospitalization and Critical Illness: A Systematic Review. Ann Am Thorac Soc. 2017;14(9):1457-68 DOI: 10.1513/AnnalsATS.201702-148SR.
2. Schwab KE, Ronish B, Needham DM, To AQ, Martin JL, Kamdar BB. Actigraphy to Evaluate Sleep in the Intensive Care Unit. A Systematic Review. Ann Am Thorac Soc. 2018;15(9):1075-82 DOI: 10.1513/AnnalsATS.201801-004OC.
3. Harvey AG, Tang NK. (Mis)perception of sleep in insomnia: a puzzle and a resolution. Psychol Bull. 2012;138(1):77-101 DOI: 10.1037/a0025730.
4. Hartmann JA, Carney CE, Lachowski A, Edinger JD. Exploring the construct of subjective sleep quality in patients with insomnia. J Clin Psychiatry. 2015;76(6):e768-73 DOI: 10.4088/JCP.14m09066.
5. Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. J Sleep Res. 2016;25(2):131-43 DOI: 10.1111/jsr.12371.
6. Lee CM, Herridge MS, Gabor JY, Tansey CM, Matte A, Hanly PJ. Chronic sleep disorders in survivors of the acute respiratory distress syndrome. Intensive Care Medicine. 2009;35(2):314-20 DOI: 10.1007/s00134-008-1277-3.
7. Dhooria S, Sehgal I, Agrawal A, Agarwal R, Aggarwal A, Behera D. Sleep after critical illness: Study of survivors of acute respiratory distress syndrome and systematic review of literature. Indian Journal of Critical Care Medicine. 2016;20(6):323-31 DOI: 10.4103/0972-5229.183908.
8. Parsons EC, Kross EK, Caldwell ES, Kapur VK, McCurry SM, Vitiello MV, et al. Post-discharge insomnia symptoms are associated with quality of life impairment among survivors of acute lung injury. Sleep Med. 2012;13(8):1106-9 DOI: 10.1016/j.sleep.2012.05.010.

9. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med. 2016;42(5):725-38 DOI: 10.1007/s00134-016-4321-8.
10. Bein T, Weber-Carstens S, Apfelbacher C. Long-term outcome after the acute respiratory distress syndrome: different from general critical illness? Current Opinion in Critical Care. 2018;24(1):35-40 DOI: 10.1097/mcc.0000000000000476.
11. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293-304 DOI: 10.1056/NEJMoa1011802.
12. Innominato PF, Komarzynski S, Palesh OG, Dallmann R, Bjarnason GA, Giacchetti S, et al. Circadian rest-activity rhythm as an objective biomarker of patient-reported outcomes in patients with advanced cancer. Cancer Medicine. 2018;7(9):4396-405 DOI: 10.1002/cam4.1711.
13. Carvalho-Bos SS, Riemersma-van der Lek RF, Waterhouse J, Reilly T, Van Someren EJ. Strong association of the rest-activity rhythm with well-being in demented elderly women. Am J Geriatr Psychiatry. 2007;15(2):92-100 DOI: 10.1097/01.JGP.0000236584.03432.dc.
14. Luik AI, Zuurbier LA, Hofman A, Van Someren EJW, Tiemeier H. Stability and Fragmentation of the Activity Rhythm Across the Sleep-Wake Cycle: The Importance of Age, Lifestyle, and Mental Health. Chronobiol Int. 2013;30(10):1223-30 DOI: 10.3109/07420528.2013.813528.
15. Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Annals of Neurology. 2011;70(5):722-32 DOI: 10.1002/ana.22468.

16. Journal of neurogastroenterology and motilityWu JQ, Li P, Stavitsky Gilbert K, Hu K, Cronin-Golomb A. Circadian Rest-Activity Rhythms Predict Cognitive Function in Early Parkinson's Disease Independently of Sleep. Mov Disord Clin Pract. 2018;5(6):614-9 DOI: 10.1002/mdc3.12692.
17. Cochrane A, Robertson IH, Coogan AN. Association between circadian rhythms, sleep and cognitive impairment in healthy older adults: an actigraphic study. J Neural Transm (Vienna). 2012;119(10):1233-9 DOI: 10.1007/s00702-012-0802-2.
18. Han CJ, Pike K, Jarrett ME, Heitkemper MM. Symptom-based latent classes of persons with irritable bowel syndrome. Res Nurs Health. 2019;42(5):382-91 DOI: 10.1002/nur.21974.
19. Whibley D, AlKandari N, Kristensen K, Barnish M, Rzewuska M, Druce KL, et al. Sleep and pain: a systematic review of studies of mediation. Clin J Pain. 2019;35(6):544-58 DOI: 10.1097/AJP.0000000000000697.
20. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain. 2013;14(12):1539-52 DOI: 10.1016/j.jpain.2013.08.007.
21. Kline RB. Principles and practice of structural equation modeling. 4th ed: Guilford publications; 2016.
22. Naliboff BD, Kim SE, Bolus R, Bernstein CN, Mayer EA, Chang L. Gastrointestinal and psychological mediators of health-related quality of life in IBS and IBD: a structural equation modeling analysis. Am J Gastroenterol. 2012;107(3):451-9 DOI: 10.1038/ajg.2011.377.
23. Buchanan DT, Cain K, Heitkemper M, Burr R, Vitiello MV, Zia J, et al. Sleep measures predict next-day symptoms in women with irritable bowel syndrome. J Clin Sleep Med. 2014;10(9):1003-9 DOI: 10.5664/jcsm.4038.

24. Jarrett M, Heitkemper M, Cain KC, Burr RL, Hertig V. Sleep disturbance influences gastrointestinal symptoms in women with irritable bowel syndrome. Dig Dis Sci. 2000;45(5):952-9.

25. Chrobak AA, Nowakowski J, Zwolinska-Wcislo M, Cibor D, Przybylska-Felus M, Ochyra K, et al. Associations between chronotype, sleep disturbances and seasonality with fatigue and inflammatory bowel disease symptoms. Chronobiol Int. 2018;35(8):1142-52 DOI: 10.1080/07420528.2018.1463236.

26. Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Lahti T, Partonen T. Relation of chronotype to sleep complaints in the general Finnish population. Chronobiol Int. 2012;29(3):311-7 DOI: 10.3109/07420528.2012.655870.

27. Ong JC, Huang JS, Kuo TF, Manber R. Characteristics of insomniacs with self-reported morning and evening chronotypes. J Clin Sleep Med. 2007;3(3):289-94.

28. Soehner AM, Kennedy KS, Monk TH. Circadian preference and sleep-wake regularity: associations with self-report sleep parameters in daytime-working adults. Chronobiol Int. 2011;28(9):802-9.

29. Tutek J, Molzof HE, Lichstein KL. Multilevel modeling of chronotype and weekdays versus weekends to predict nonrestorative sleep. Chronobiol Int. 2017;34(10):1401-12 DOI: 10.1080/07420528.2017.1373118.

30. Yun JA, Ahn YS, Jeong KS, Joo EJ, Choi KS. The relationship between chronotype and sleep quality in Korean firefighters. Clin Psychopharmacol Neurosci. 2015;13(2):201-8 DOI: 10.9758/cpn.2015.13.2.201.

31. Rutters F, Lemmens SG, Adam TC, Bremmer MA, Elders PJ, Nijpels G, et al. Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? J Biol Rhythms. 2014;29(5):377-83 DOI: 10.1177/0748730414550199.
32. Beauvalet JC, Quiles CL, de Oliveira MAB, Ilgenfritz CAV, Hidalgo MPL, Tonon AC. Social jetlag in health and behavioral research: a systematic review. ChronoPhysiology and Therapy. 2017;7:19-31.
33. Fischer D, Lombardi DA, Marucci-Wellman H, Roenneberg T. Chronotypes in the US – Influence of age and sex. PLoS One. 2017;12(6):e0178782 DOI: 10.1371/journal.pone.0178782.
34. Roenneberg T, Pilz LK, Zerbini G, Winnebeck EC. Chronotype and Social Jetlag: A (Self-) Critical Review. Biology (Basel). 2019;8(3) DOI: 10.3390/biology8030054.