# AN EXAMINATION OF PAIN'S RELATIONSHIP TO SLEEP FRAGMENTATION AND DISORDERED BREATHING ACROSS COMMON SLEEP DISORDERS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2017

ACKNOWLEDGMENTS

I would like to thank the members of my committee and especially my research mentor, Dr. Michael Robinson, for their guidance and support in completing this research. I would also like to thank Dr. Stephan Eisenschenk and the staff at the UF Health Sleep Center for their assistance during the recruitment process. Finally, I am grateful to have had the support of my lab mates, friends, and family.

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LIST OF ABBREVIATIONS

| | |
|---|---|
| AASM | American Academy of Sleep Medicine |
| AHI | Apnea-hypopnea index |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| BMI | Body mass index |
| CBT-I | Cognitive behavioral therapy for insomnia |
| CPAP | Continuous positive airway pressure |
| CSA | Central sleep apnea |
| ESS | Epworth Sleepiness Scale |
| ISI | Insomnia Severity Index |
| MCV | Medical College of Virginia Pain Questionnaire |
| MSLT | Multiple Sleep Latency Test |
| OSA | Obstructive sleep apnea |
| PAP | Positive airway pressure |
| PSG | Polysomnography |
| REM | Rapid eye movement |
| $SaO_2$ | Arterial oxygen saturation |
| SDB | Sleep disordered breathing |
| TMD | Temporomandibular disorder |
| UF | University of Florida |
| VAS | Visual analog scale |

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

# AN EXAMINATION OF PAIN'S RELATIONSHIP TO SLEEP FRAGMENTATION AND DISORDERED BREATHING ACROSS COMMON SLEEP DISORDERS

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December 2017

Chair: Michael Robinson
Major: Psychology

Short sleep duration and insomnia have been linked to higher pain and an increased risk of developing chronic pain, but relatively little research has examined the contribution of sleep disordered breathing (SDB) to pain. This study examined the unique contributions of SDB and insomnia to chronic pain. Patients who presented to the University of Florida Health Sleep Center for overnight polysomnography were invited to participate, provided they had no history of using positive airway pressure. Participants (*N* = 105) completed additional questionnaires about their sleep (Insomnia Severity Index) and pain (Medical College of Virginia Pain Questionnaire, pain locations, chronic pain diagnoses) before undergoing overnight polysomnography. They subsequently completed an online sleep/pain diary for two weeks. Physicians diagnosed 52.38% with obstructive sleep apnea (OSA) and 4.76% with insomnia, though 20.95% were classified as having chronic insomnia based on sleep diaries used for the study. In a hierarchical regression, polysomnography-measured total sleep time, but not measures of sleep fragmentation (apnea-hypopnea index, spontaneous arousals) or hypoxemia ($SaO_2$ nadir), was related to pain. The majority of participants

(80.00%) reported chronic pain, with musculoskeletal pain (28.57%) and chronic headaches (24.76%) being the most frequent. Although the likelihood of having chronic pain did not differ by sleep disorder, there was a significant difference in pain intensity; individuals with comorbid OSA/insomnia (12.38% of the sample) reported an average pain intensity that was 20 points (out of 100) higher than individuals with insomnia or no diagnosis and 28 points higher than those with OSA, controlling for participant sex (*p*s < .05). Thus, although polysomnography measures of SDB severity were unrelated to pain intensity, individuals with comorbid OSA/insomnia had the most severe pain.

# CHAPTER 1
# INTRODUCTION

## Sleep Disordered Breathing and Insomnia

### Prevalence

Sleep disordered breathing (SDB) and insomnia represent the most common sleep disorders, affecting millions of individuals in the United States. Estimates of prevalence vary due to differences in research diagnostic criteria, but studies have shown that approximately 2-4% of adults have some form of SDB, most commonly obstructive sleep apnea (OSA).[1] The prevalence of insomnia with associated daytime impairment among adults is approximately 10-15%, though 33-50% of adults report some insomnia symptoms.[56] Although extensive literatures exist on each disorder, a relatively small number of studies have examined comorbid SDB and insomnia. These studies have demonstrated high rates of co-occurrence, though estimates again vary considerably due to inconsistent criteria. Among individuals with OSA, 22-55% have comorbid insomnia[1], but estimates for the broader category of SDB reach up to 84%.[52] For individuals with insomnia, the rates of SDB and OSA range from 16-83% and 7-75%, respectively.[1, 52] However, as insomnia researchers commonly screen out individuals with SDB symptoms, these numbers likely underestimate the true prevalence of SDB among individuals with insomnia.[52]

### Clinical Presentation

In terms of symptoms and daytime impairments, SDB and insomnia are both characterized by fragmented sleep and a shortened sleep duration, associated with complaints of impaired daytime function such as fatigue or sleepiness.[22, 56] While individuals with SDB are often unaware of these awakenings, individuals with insomnia

are by definition aware of—and often distressed by—their awakenings. While both SDB and insomnia may be accompanied by subjective reports of daytime fatigue, typically only SDB is characterized by objective sleepiness (i.e., the propensity to fall asleep if given an opportunity).[22, 32] Although individuals with insomnia may report being sleepy, they tend not to fall asleep during the daytime due to an elevated level of physiological arousal. By contrast, individuals with apnea fall asleep quite easily, even in situations when it is dangerous to do so, such as while driving. While both conditions share some aspects of fragmentation and daytime impairments, the key distinguishing feature is the cause of the sleep disturbance. In the case of SDB, awakenings are caused by the repeated cessation of breathing. Insomnia, by contrast, is characterized by difficulty falling or staying asleep due to elevated physiological arousal and sleep-interfering habits (e.g., consumption of caffeine or other stimulants, bright light exposure, learned associations).

**Assessment and Treatment**

Patients with SDB and insomnia are both likely to present with complaints of unrefreshing and inadequate sleep. However, different treatments are indicated for each disorder in order to target the unique underlying causes of the presenting complaints. SDB is typically treated with positive airway pressure (PAP), while insomnia can be alleviated with cognitive behavioral therapy or sedating medications.[22, 56] A thorough assessment and accurate diagnosis is therefore crucial to determine the best course of treatment. This is typically accomplished by means of a clinical interview and a sleep study (polysomnography; PSG), which quantifies the frequency and type of apneic events. PSG can readily identify the presence of SDB, but daily sleep diaries are necessary in order to adequately assess for symptoms of insomnia. As sleep may vary

greatly from night to night in insomnia, standard research practice includes the completion of two weeks of sleep diaries.[56] Insomnia-related sleep disturbance includes subjective perceptions of difficulty falling asleep, staying asleep, or waking too early. In addition to sleep disturbance, a diagnosis of insomnia requires self-reported daytime impairment (fatigue, concentration, occupational functioning, mood, etc.).[2]

**Interaction of Sleep Disordered Breathing and Insomnia**

Despite the fact that these conditions frequently co-occur, researchers have typically examined one or the other in isolation. However, recent investigations have highlighted the comorbidity of SDB and insomnia and proposed possible mechanisms for a bidirectional interaction. Given evidence that treating OSA often improves nocturia, OSA may precipitate and perpetuate insomnia via its impact on nocturia.[1] It is also possible that restricted airflow leads to insomnia-like alpha intrusions and sympathetic activation which make resuming sleep more difficult.[51, 72] Such repeated awakenings from SDB itself or from poor tolerance to PAP treatment may also lead to the development of dysfunctional sleep behaviors that perpetuate insomnia (e.g., ruminating in bed during awakenings).[6] Conversely, it is also conceivable that insomnia may exacerbate sleep apnea. Specifically, sleep deprivation and fragmentation have been shown to reduce pharyngeal muscle tone, and this mechanism could potentially link insomnia to an increase in obstructive apneic events.[1, 6] These hypotheses remain to be tested empirically, however.[1, 52]

The treatment of comorbid SDB and insomnia also deserves further attention, as there are presently no treatment standards for this population.[52] Researchers have suggested that SDB should be addressed first[1], though treating both conditions is likely to lead to the best outcomes.[42] Some studies have highlighted possible complications of

treating comorbid SDB and insomnia. Studies have found that initial[7] and middle[7, 72] insomnia predict poorer adherence to PAP. Bjornsdottir and colleagues[7] also demonstrated that while initial and late insomnia tended to persist regardless of PAP use, middle insomnia was most likely to improve significantly with PAP use. This finding may suggest that for some individuals, frequent awakenings associated with middle insomnia may be better characterized as a symptom of untreated OSA. This same study revealed that new cases of insomnia among PAP users were most likely to be late insomnia, potentially due to being awakened by the PAP machine itself during the lighter stages of sleep which predominate at the end of the night.

Independently, SDB and short sleep duration have each been linked to an increased risk for a number of health problems, including cancer, cardiovascular disease, diabetes, and obesity.[13, 16, 26, 28-31] However, little is known about the combined impact of comorbid SDB and insomnia on health outcomes. Therefore, the goal of the present study is to examine the relationship of these two common sleep disorders to chronic pain, which is itself an extremely common health problem affecting nearly one-third of the population of the United States.[33]

## Sleep Disturbance and Pain

The relationship of pain with short sleep duration or insomnia has been characterized fairly extensively. However, relatively little is known regarding how SDB impacts chronic pain. Furthermore, it is unclear how pain is related to different types of SDB (i.e., obstructive vs. central apnea) or different features of SDB (i.e., fragmentation vs. hypoxemia).

**Sleep Duration, Insomnia, and Pain**

Cross-sectionally, high rates of comorbidity between chronic pain and sleep problems have been observed. Half of patients with insomnia have chronic pain, and between 50-88% of patients with chronic pain have sleep disturbance.[24, 65] A great deal of evidence suggests there is a bidirectional relationship between sleep and pain[58], though research in the last decade has more strongly supported the role of sleep in predicting pain than vice versa.[24] Evidence for the interaction of sleep and pain, including the temporal trajectory, comes from studies on short-term sleep deprivation, longitudinal observations, and treatment studies.

Experimental manipulation of sleep has demonstrated that acute sleep deprivation (either partial or total deprivation) results in increased pain sensitivity the following day. This has been shown in healthy (i.e., pain-free) individuals as well as those with pre-existing chronic pain using a number of different experimental pain protocols, including heat, cold, and laser-induced pain (e.g., [4, 11, 27]). There is even some evidence that individuals with chronic pain are more sensitive to the hyperalgesic effects of sleep deprivation. A study by Irwin and colleagues[34] found a greater degree of hyperalgesia in individuals with rheumatoid arthritis compared to healthy individuals.

Some studies have examined whether selectively depriving individuals of particular sleep stages has greater effects on pain perception. Results have been mixed, though there is some evidence that, controlling for total sleep time, selective deprivation of rapid eye movement (REM) or slow wave sleep is enough to increase pain sensitivity.[24] Some research points to disrupted sleep architecture in individuals with chronic pain conditions, though results have not been entirely consistent. For example, rheumatic conditions have been associated with problems in nearly all

aspects of sleep, including total sleep time, sleep onset latency, wake time, and arousals.[40] The primary complaint of many chronic pain patients, particularly fibromyalgia, is unrefreshing or nonrestorative sleep. It has been suggested that this may be related to increased number of arousals during slow wave sleep, but this has not been borne out by all published PSG studies.

Observational studies have shown that short sleep predicts greater next day pain. This has been demonstrated in the general population[21] as well as individuals with chronic pain.[53, 63] Microlongitudinal studies with daily measurement of pain and sleep have shown that sleep reliably predicts next day pain, while pain does not necessarily predict sleep that same night.[21, 63] In a sample representative of the general population, average daytime pain predicted sleep duration[21], but in a heterogeneous chronic pain sample, presleep pain did not predict subsequent sleep.[63] Sleep has also been found to predict pain months later, while pain generally has not shown the same predictive power for later sleep disturbance. However, there are exceptions to this, such as a study of individuals hospitalized for burns.[59] In that sample, sleep at discharge predicted later pain, and pain at discharge also predicted later sleep. In studies that have observed participants for months or years, baseline sleep predicts the onset of new pain as well as the exacerbation of existing pain.[24] Conversely, restorative sleep at baseline has been shown to predict the resolution of chronic widespread pain.[15]

Sleep complaints are also intimately tied to many headache disorders and seem to be both a symptom as well as a potential exacerbating factor.[8] Some headaches have circadian patterns, suggesting their occurrence is tied to aspects of the sleep cycle. Hypnic headaches occur only during sleep, usually at the same time each night.

Migraine headaches occur more frequently in the morning and can be triggered by sleep loss or alleviated with sleep.

Despite evidence of a relationship between sleep and pain, insomnia treatment studies have generally not demonstrated significant improvements in pain. Although cognitive behavioral therapy for insomnia (CBT-I) improves sleep among those with comorbid chronic pain and insomnia, only a couple of studies have shown any effect on pain. One study showed improvement in pain-related functional impairment.[43] Another study showed that although pain was not initially improved in patients with osteoarthritis, sleep improvement at post-treatment predicted improvement at later assessments (9 and 18 months).[67] In that same study, pain improvement at post-treatment was not associated with later sleep improvement. Thus, similar to observational studies showing delayed effects of good sleep on pain, there is some evidence that improvement in insomnia may lead to improved pain if long enough follow-up is available.

Some pharmacological treatments for chronic pain are believed to impact pain partially through their ability to improve sleep. For example, gabapentin and tricyclic antidepressants lead to increased slow wave sleep and more consolidated sleep.[50] Sodium oxybate, a drug only available for narcolepsy at this time due to abuse concerns, has shown promising preliminary results for fibromyalgia patients in terms of increasing slow wave sleep and producing sleep that is subjectively rated as more refreshing.[61, 62]

The accumulation of research during recent years supports the conclusion that insufficient or poor sleep serves as an exacerbating factor for most types of acute and chronic pain. Data on the relationship between pain and insomnia or short sleep

duration suggests that there is a bidirectional relationship, but that sleep is a stronger and more reliable predictor of pain.[24]

**Sleep Disordered Breathing and Pain**

Although a great deal of research has demonstrated connections of pain with insomnia and sleep duration, less research has focused on SDB. Thus far, results have been mixed in terms of whether SDB is related to increased or decreased pain, perhaps owing to the fact that SDB involves both fragmentation and hypoxemia, which may exert opposite effects on pain sensitivity.

Cross-sectional studies have shown that the presence of OSA is linked to higher odds of pain and vice versa. In one study, a decrease in minimum $SaO_2$ (arterial oxygen saturation) from 92% to 72% doubled the odds of pain (i.e., morning headaches, sleep-disrupting pain, or chest pain while in bed).[17] Similarly, another study demonstrated an association between lower oxygen saturation and higher sensitivity during fibromyalgia tender point testing.[66] Interestingly, there was no relationship between AHI and pain in that study. In terms of comorbidity, it has been reported that patients with fibromyalgia were more than twice as likely to have a diagnosis of OSA than controls matched for age, sex, and body mass index (BMI).[71] Likewise, compared to those without chronic pain, a higher percentage of individuals with chronic musculoskeletal pain were classified as having clinically probable OSA based on a self-report screening measure (48% vs. 69%).[47] Conversely, Nadeem and colleagues[46] found that 51% of individuals with OSA had comorbid chronic musculoskeletal pain. Prospective studies have shown that the presence of OSA predicts a greater likelihood of later developing temporomandibular disorder (TMD)[55] and bladder pain.[12]

In contrast, several studies have found that SDB is either not associated with pain or is associated with decreased pain. In a sample of individuals with OSA, the severity of OSA was not related to either pain intensity or pain duration.[3] A recent study showed mixed results such that more severe apnea (as indicated by AHI and desaturation) predicted higher pain intensity but lower pain sensitivity (forearm pressure pain threshold) the next morning.[70] Results of this study also suggested a long-term hypoalgesic effect of SDB, as more severe AHI and desaturation were associated with lower pain intensity over the preceding day and six months (based on retrospective reporting of pain on the Brief Pain Inventory and Chronic Pain Grade Scale, respectively). Smith and colleagues[60] found that while insomnia was related to hyperalgesia (i.e., decreased pain threshold during thermal and mechanical pain protocols), apnea was related to hypoalgesia (during the mechanical protocol only). Additionally, in a study of women with TMD, higher average pain was related to fewer respiratory event related arousals.[19] Another experiment showed an association between lower minimum $SaO_2$ and increased analgesic response to remifentanil, suggesting that hypoxemia potentiates the analgesic effect of opioids.[18] The investigators propose that upregulation of μ-opioid receptors in response to hypoxemia may be the mechanism underlying this effect, which has been observed in other studies.[9, 10]

Opioid pain medications represent one mechanism by which pain may interact with SDB. Research has found that opioids have a dose-dependent effect on SDB and other measures of sleep disturbance.[38, 50] Opioids depress respiration and therefore represent a risk factor for SDB, particularly central sleep apnea (CSA). Recent

summaries have concluded that opioid use increases the frequency of central apneic events (i.e., those caused by a cessation of respiratory effort due to central nervous system factors) but does not increase obstructive apneic events (i.e., those caused by loss of muscle tone or physical obstruction).[23, 38] Contrary to earlier literature suggesting that individuals become tolerant to the respiratory depressive effects of opioids, newer evidence suggests that patients on long-term opioid therapy continue to have increased rates of SDB.[69]

Treatment studies have been mixed but provide some support for the impact of improved SDB on pain. A retrospective examination of veterans using CPAP did not find reductions in ether pain intensity or opioid consumption after 12 months.[35] However, in pain-free patients with OSA, treatment with PAP has been shown to decrease experimental pain sensitivity.[39, 49] In one study[39], when PAP was temporarily stopped after two months of use, pain sensitivity increased nearly to baseline levels but went down again after resuming PAP use. These studies provide evidence that improving OSA leads to improvement in pain sensitivity—at least in individuals free of chronic pain—and parallel research findings on the negative implications of insomnia or short sleep duration for pain.

**Sleep Disordered Breathing, Insomnia, and Pain**

Given conflicting findings in the literature on SDB and pain, there is not yet a clear understanding of how sleep apnea and its component features interact with chronic pain. Smith and Finan[57] recently noted the physiological connections between regulation of respiration and pain in the brainstem and suggested that “nocturnal hypoxemia and sleep fragmentation are distinct sleep-disordered breathing phenotypes that may exert potentially differential effects on pain sensitivity and symptoms

expression” (p. 1012). However, studies of SDB and pain have to date focused on respiration and not examined the contribution of SDB-related fragmentation to pain. Additionally, although SDB and insomnia frequently co-occur in clinical samples, they are usually studied in isolation. However, they both present with some degree of fragmented and shortened sleep, and it remains unknown whether disruptions associated with each disorder have similar effects on pain.

## Aims and Hypotheses

The present study aimed to address these gaps in the literature by examining the relationship of pain to both SDB- and insomnia-related sleep disturbance. In order to better understand the unique contributions of each disorder to pain, this study included individuals with symptoms of SDB and insomnia.

**Aim 1:** To investigate whether SDB-related sleep fragmentation and nocturnal hypoxemia are uniquely related to pain.

**Hypothesis 1A:** Controlling for total sleep time, sleep fragmentation will be positively related to pain intensity.

**Hypothesis 1B:** Controlling for total sleep time, hypoxemia will be negatively related to pain intensity.

**Aim 2:** To examine whether SDB- and insomnia-related sleep fragmentation are uniquely related to pain.

**Hypothesis 2:** Controlling for total sleep time and hypoxemia, both SDB- and insomnia-related sleep fragmentation will contribute to higher pain intensity. Given limited prior research linking SDB to pain, no hypothesis is made as to whether SDB or insomnia will more strongly predict pain.

**Aim 3:** To determine whether the presence of both SDB and insomnia creates an increased risk for pain.

**Hypothesis 3:** Compared to individuals with either SDB or insomnia in isolation, individuals with both sleep disorders will report higher pain intensity and will be more likely to report having a chronic pain condition.

# CHAPTER 2
# METHODS

## Participants

Patients referred to the University of Florida (UF) Health Sleep Center for overnight PSG were recruited to participate in this study. Individuals were eligible for participation if they met the following criteria: a) 18 years of age or older, b) scheduled to undergo diagnostic PSG (i.e., measurement only, no PAP administration) or split-night PSG (i.e., PAP administered during the latter portion of the night) at the Sleep Center, c) access to a computer with internet in order to complete daily sleep diaries, and d) able to read and write English. Individuals were excluded from participation for the following reasons: a) previous and/or current treatment with PAP or b) undergoing treatment PSG (i.e., PAP administered the entire night).

Individuals were not included/excluded on the basis of pain type or duration; the study aimed to sample a broad range of pain types and the hypotheses did not specify different predictions based on pain type. Similarly, potential participants could present with any type of sleep complaint, as the study sought to examine continuous measures of sleep-related respiration and fragmentation that may be found in a variety of disorders.

## Measures

Some data for this study were taken from measures routinely administered to patients undergoing PSG at the UF Health Sleep Center. Participants were also asked to complete additional measures on the night of the PSG and two weeks of sleep diaries following the PSG, as described below.

## Demographics and Medical History

Basic background information collected from clinic paperwork included sex, age, marital status, shift work, body mass index, caffeine intake, medications, and medical history. Study-specific measures asked for race, ethnicity, and education level.

## Polysomnography

PSG was performed and scored by registered polysomnographic technologists according to American Academy of Sleep Medicine (AASM) scoring guidelines. Final diagnoses of OSA, CSA, parasomnias, periodic limb movements, or other sleep disorders was determined by physicians at the UF Health Sleep Center. The following PSG channels were recorded: frontal, central, and occipital electroencephalography (used in the determination of sleep stages); electro-oculography (measures eye movements associated with REM sleep); chin electromyography (measures muscle tone, which decreases during REM); electrocardiogram; respiration (airflow [nasal-oral airflow by thermal sensor], nasal pressure, and respiratory effort; to detect apneas, hypopneas, and other sleep-related breathing problems); arterial oxygen saturation ($SaO_2$; to determine severity of sleep related breathing disorders); leg electromyography (measures leg movements associated with restless legs syndrome and periodic limb movement disorder); and body position (to determine whether apnea is exacerbated in the supine position). For a small number of patients, daytime assessment (Multiple Sleep Latency Test; MSLT) was also performed during the day following PSG in order to assess for narcolepsy. MSLT raw data were not used for the present study, though the results of MSLT were used by physicians in determining patient diagnoses.

**Sleep Questionnaires**

Clinic questionnaires provided information on the participant's typical sleep schedule, nighttime and daytime symptoms, and responses to the Epworth Sleepiness Scale (ESS). The ESS asks respondents to rate their propensity to fall asleep in various situations, such as while watching television.[36] Adequate internal consistency has been reported, Chronbach's α = .88.[37]

Study participants were also asked to complete the Insomnia Severity Index (ISI) on the night of their PSG. The ISI is a brief measure used for insomnia screening and assessing treatment outcomes. Adequate internal consistency has been demonstrated among patients referred to a sleep disorders center, Chronbach's α = .74[5], and among primary care patients, Chronbach's α = .92.[25]

**Sleep Diaries**

Insomnia was further assessed via two weeks of sleep diaries, in keeping with suggested guidelines.[56] In order to ease participant burden and encourage timely completion, participants received a daily email with a link to complete the sleep diary using the REDCap web application. The daily sleep diaries yielded the following variables which were used in statistical analyses for aim 3: time in bed, total sleep time, sleep onset latency, wake time after sleep onset, sleep efficiency (the percentage of time in bed spent sleeping), number of awakenings, and sleep quality rating (1 = "very poor" to 5 = "excellent").

The presence or absence of chronic insomnia was determined from sleep diary data. Based on the International Classification of Sleep Disorders – Third Edition[2] and research diagnostic criteria[41], participants were diagnosed with insomnia if they reported difficulty initiating or maintaining sleep (a) lasting > 30 minutes[41], (b) occurring at least

three nights per week[2, 41], and (c) having persisted for at least three months[2] along with (d) a complaint of daytime distress or dysfunction due to insomnia.[2, 41]

### Pain

Pain intensity and unpleasantness ratings were also obtained from the daily online survey. On the night of the PSG, participants were asked to complete the Medical College of Virginia (MCV) Pain Questionnaire.[54, 68] The MCV provides visual analog scale (VAS) ratings of pain intensity, pain unpleasantness, the impact of pain on the respondent's life, and negative emotions related to pain (depression, anxiety, frustration, anger, fear). Participants also indicated whether they had any chronic pain conditions, the name of the condition(s), and the location(s) of their pain during the last three months.

## Procedures

All procedures were approved by the UF Institutional Review Board. Recruitment took place at the UF Health Sleep Center during the evening when patients arrived for overnight PSG. A technologist asked the patient for permission to be approached by a researcher, who described the study and provided time for the patient to review the informed consent form. Individuals who consented to participate were asked to complete questionnaires (described above) and to complete daily sleep diaries online during the next two weeks. Compensation (a $25 gift card) was provided to participants after all procedures were completed.

## Statistical Analyses

Analyses were performed using SPSS v22.0 (SPSS Inc., Chicago, IL, USA). For participants who underwent split-night PSG (*n* = 23), only data from the diagnostic

portion of the PSG were used (e.g., the AHI reflects the value during the untreated portion of the night, not the value during PAP titration).

**Aims 1 and 2**

Aims 1 and 2 examined 1) whether prominent characteristics of SDB (i.e., fragmentation and nocturnal hypoxemia) were uniquely related to pain and 2) whether SDB- and insomnia-related sleep fragmentation were uniquely related to pain. These aims were examined with a single hierarchical regression with the outcome variable of average pain intensity obtained via daily diaries. The predictors entered into the regression were obtained from PSG. In order to control for total sleep time, it was entered in the first predictor block of the regression. The second block added minimum $SaO_2$ as a measure of nocturnal hypoxemia, spontaneous arousals as a measure of insomnia-related fragmentation, and the apnea-hypopnea index (AHI) as a measure of SDB-related fragmentation. Prior research has shown that the AHI correlates strongly ($r$ = .97, $p$ < .0001) with the number of respiratory arousals.[64]

**Aim 3**

For the final aim, the relationship of SDB and insomnia to pain was examined in several ways. To begin, sleep was examined from the standpoint of conventional diagnostic categories. Although sleep disorder diagnoses use somewhat arbitrary cutoffs, they are nonetheless useful in that they identify what is believed to represent clinically significant levels of sleep disturbance. Examining individuals who fall into these categories provides a picture of the differences in pain experienced by clinical populations. We first used a one-way ANOVA to compare the pain intensity (mean obtained from sleep diaries) of individuals with no sleep diagnosis and those meeting diagnostic criteria for OSA, insomnia, comorbid OSA/insomnia, or no sleep disorder.

Secondly, chi-square was used to compare the likelihood of individuals in those same diagnostic categories having chronic pain (i.e., self-report of pain more days than not during the preceding three months).

Finally, as an exploratory analysis, we performed a cluster analysis. In contrast to using diagnostic categories, this data-driven approach is useful for identifying potential subtypes within the categories of SDB and insomnia.[45, 73] A hierarchical agglomerative method (Ward's method with squared Euclidian distance as a measure of similarity) was used in order to identify clusters of individuals based on a number of sleep variables, including daytime sleepiness (ESS total score) and insomnia severity (ISI total score). PSG-derived variables included total sleep time, apnea-hypopnea index, duration of oxygen desaturation less than or equal to 88% (duration as a percentage of total sleep time), minimum $SaO_2$, spontaneous arousals, and REM latency. The following sleep diary variables derived from sleep diaries were included: total wake time, total sleep time, and sleep quality. After clusters were identified, they were validated by examining the distribution of sleep disorders across clusters. Cluster differences were characterized through a series of ANOVAs on the clustering variables. ANOVAs were also used to examine differences in continuous demographic variables (age, BMI) and pain-related mood (depression, anxiety). A chi-square analysis examined differences in the sex distribution across clusters. A discriminant function analysis was performed to determine which variables had contributed most strongly to the formation of clusters. To address the hypothesis of this aim, differences in pain intensity were examined using an ANOVA and the likelihood of each group endorsing the presence of chronic pain was examined using chi-square.

# CHAPTER 3
# RESULTS

## Participant Characteristics

A total of 105 individuals were enrolled in the study, with 94 participants completing all study procedures. Of the 105 enrolled participants, 41.90% were male and 58.10% were female. The age of participants ranged from 18 to 81, with a mean age of 43.83 (*SD* = 16.52). Participants self-identified as belonging to the following racial and ethnic groups: 70.48% White, 17.14% Black/African American, 5.71% Hispanic/Latino, and 5.71% Asian/Asian American. A summary of other demographic characteristics (education, employment status, relationship status) can be found in Table 3-1.

## Sleep Characteristics

### Sleep Disordered Breathing

Diagnoses of sleep related breathing disorders and other sleep disorders were made by physicians at the UF Health Sleep Center. OSA represented the most common diagnosis, comprising 52.38% of the sample (*n* = 55). A substantial proportion of individuals—many of whom were referred for suspected sleep apnea—were given no diagnosis (*n* = 36, 34.29%). See table 3-2 for a complete list of diagnoses given to participants by physicians following PSG (and MSLT, if applicable).

### Insomnia

Physicians infrequently made a diagnosis of insomnia (*n* = 5, 4.76%) based on a patient's PSG results. This is perhaps not surprising, given standards of practice dictating that insomnia is best evaluated through a detailed sleep history and sleep diaries rather than PSG.[56] Using sleep diaries and other self-report data obtained for the

study, a diagnosis of chronic insomnia was assigned based on AASM criteria[2] and research diagnostic criteria[41], as specified above. Using these criteria, 22 participants (20.95%) were classified as having chronic insomnia. The duration of insomnia ranged from 6 months to 55 years with a mean of 10.89 years (*SD* = 13.03). Over half of those with insomnia (59.09%) had a comorbid diagnosis of OSA from their physician (*n* = 13, 12.38% of the total sample). There were no other comorbidities among individuals determined to have chronic insomnia. Scores from the ISI indicated that 14.29% of all participants could be classified as not having clinically significant insomnia, while 40.95% had subthreshold insomnia, 35.24% had moderately severe clinical insomnia, and 9.52% had severe clinical insomnia.

### Pain Characteristics

Participants indicated the body regions in which they had pain more days than not over the preceding three months (see Table 3-3). On this basis, 80.00% of the sample was determined to have chronic pain in at least one body region. Lower back pain was the most common, with nearly half of the sample reporting chronic pain on the left side (*n* = 51, 48.57%) and the right side (n = 49, 46.67%). Participants also reported what diagnoses, if any, they had received with regard to their chronic pain. The most common diagnoses were musculoskeletal pain (*n* = 30, 28.57%) and chronic headaches (*n* = 26, 24.76%). These data are available in Table 3-4. Using the visual analog scales of the MCV (0-100, with 0 representing none), participants reported their usual pain intensity (*M* = 36.41, *SD* = 24.24) and usual pain unpleasantness over the preceding week (*M* = 33.98, *SD* = 25.78). Table 3-5 provides additional information on participants' ratings of lowest and highest pain as well as negative emotions that accompanied their pain.

### Aims 1 and 2: Contributions of Fragmentation and Hypoxemia to Pain

A hierarchical regression was conducted to determine whether sleep fragmentation and nocturnal hypoxemia contributed uniquely to pain intensity (above and beyond total sleep time). As expected, PSG-measured total sleep time was a significant predictor of pain intensity, $F(1, 95) = 4.00$, $p = .05$, $R^2 = .04$. However, measures of fragmentation (AHI, spontaneous arousals) and hypoxemia ($SaO_2$ nadir) were not significant predictors (see Table 3-6). Table 3-7 provides a correlation matrix for these variables.

### Aim 3: Risk of Pain Across Sleep Disorders

#### Differences in Pain Intensity by Sleep Diagnosis

A one-way ANOVA revealed significant differences in pain intensity (mean obtained from daily diaries) among individuals with OSA, insomnia, comorbid OSA/insomnia, or no sleep diagnosis, $F(3, 84) = 6.00$, $p < .01$, $\eta_p^2 = .18$. Bonferroni-corrected post-hoc comparisons showed that the comorbid group had a significantly higher ($p < .001$) pain intensity than the OSA group and the no diagnosis group ($p = .05$). Group means are reported in table 3-8.

Potential covariates were examined, and neither age nor BMI were significantly correlated with pain intensity ($ps > .05$). However, there was a significant sex difference in pain intensity, $t(86) = -2.57$, $p < .05$ (male $M = 20.25$, $SD = 21.07$; female $M = 33.42$, $SD = 25.95$). Sex was subsequently added to the model as a covariate. In this ANCOVA, sex was significantly related to pain intensity, $F(1, 83) = 4.26$, $p < .05$, $\eta_p^2 = .05$. After controlling for sex, there continued to be a significant effect of diagnostic group on pain intensity, $F(3, 83) = 5.14$, $p < .01$, $\eta_p^2 = .16$. With the addition of sex as a

covariate, Bonferroni-corrected post-hoc comparisons continued to show significantly higher pain intensity in the comorbid group compared to those with OSA or no diagnosis (*p*s < .01). Additionally, the comorbid group had higher pain intensity compared to the insomnia group ($p < .05$). Covariate adjusted means are reported in table 3-8.

**Likelihood of Chronic Pain by Sleep Diagnosis**

The prevalence of chronic pain was 81.25% among the subset of participants ($n = 96$) with either OSA, insomnia, comorbid OSA/insomnia, or no sleep disorder. The prevalence of chronic pain within diagnostic groups was as follows: OSA 76.19%, insomnia 88.89%, comorbid OSA/insomnia 100%, and no diagnosis 78.13%. Based on a chi-square analysis, there was no significant difference in the likelihood of individuals in these diagnostic categories having chronic pain, $\chi^2(3) = 4.26$, $p = .24$, $w = .43$.

**Identification and Validation of Sleep Disorder Clusters**

The agglomeration coefficients for the hierarchical cluster analysis showed a large increase between four and five clusters. We therefore used a four-cluster solution which appeared—based on group means on the variables used to create clusters—to roughly correspond to the following sleep diagnostic groups: 1) OSA, $n = 48$; 2) insomnia, $n = 11$; 3) comorbid OSA/insomnia, $n = 12$; and 4) other/no diagnosis, $n = 26$. Figure 3-1 shows the profiles of the four clusters with the standardized means plotted for each of the variables. A chi-square was performed to determine if the distribution of sleep disorders differed across clusters. The chi-square was significant, $\chi^2(12) = 42.26$, $p < .001$. Inspection of the standardized residuals confirmed that each of the clusters had higher than expected frequencies of the diagnoses corresponding to the labels given them (e.g., cluster 2 had significantly more individuals with insomnia than expected). Figure 3-2 shows the frequency of sleep disorders in each cluster.

To better characterize the clusters and understand which variables contributed to the formation of the clusters, we conducted a series of one-way ANOVAs on each of the variables. All of these ANOVAs were significant (*p*s < .05). Bonferroni-corrected pairwise comparisons showed that cluster 2 (insomnia) had significantly lower PSG and diary total sleep time and higher diary total wake time than all other clusters (*p*s < .01). Cluster 3 (comorbid OSA/insomnia) was unique in terms of the severity of apnea-related variables; this cluster demonstrated significantly worse AHI, percent time below 88% $SaO_2$, and minimum $SaO_2$ than all other groups (*p*s < .001). Finally, cluster 4 (other/no diagnosis) reported higher levels of daytime sleepiness on the ESS than all other groups ($p < .05$). Cluster means for all variables are presented in Table 3-9.

A discriminant function analysis was also performed in order to determine which variables had the greatest contribution to the clusters. Function 1 was significant ($\chi^2[33] = 255.96$, $p < .001$) with a canonical correlation of .85. Based on the standardized canonical coefficients, the AHI was the strongest predictor of cluster membership (-.77), followed by diary total wake time (.48), minimum $SaO_2$ (.47), daytime sleepiness (.46), and PSG total sleep time (-.39).

We further characterized the clusters by examining differences in demographic variables (sex, age, BMI) and pain-related mood (depression, anxiety). A chi-square analysis indicated a significant difference in sex distribution across clusters, $\chi^2(3) = 19.10$, $p < .001$, $w = .53$. Based on standardized residuals, men were overrepresented in the OSA cluster and underrepresented in the insomnia and other/no diagnosis clusters. Figure 3-3 shows the frequencies of males and females across clusters. An ANOVA showed that age also differed across clusters, $F(3, 93) = 3.48$, $p < .05$, $\eta_p^2 = .10$,

with the other/no diagnosis cluster being on average significantly younger than the OSA cluster ($p < .05$; Bonferroni-corrected for this and all subsequent comparisons). The ANOVA for BMI was also significant, $F(3, 93) = 4.48$, $p < .01$, $\eta_p^2 = .13$, and post-hoc analyses showed that the comorbid OSA/insomnia cluster had a significantly higher BMI than the OSA and other/no diagnosis clusters ($p$s ≤ .05). Pain-related depression differed significantly among the clusters, $F(3, 88) = 5.55$, $p < .01$, $\eta_p^2 = .16$, as did pain-related anxiety, $F(3, 90) = 5.82$, $p < .01$, $\eta_p^2 = .16$. The OSA cluster displayed lower depression than the insomnia and OSA/insomnia clusters ($p$s < .05). Individuals in the OSA cluster were also less anxious compared to all other clusters ($p$s ≤ .05). Cluster means for age, BMI, depression, and anxiety are available in Table 3-10.

**Differences in Pain Intensity by Cluster**

An ANOVA demonstrated that the clusters differed significantly on pain intensity (mean obtained from daily diaries), $F(3, 93) = 6.21$, $p < .01$, $\eta_p^2 = .17$. Specifically, Bonferroni-corrected post-hoc comparisons showed that the OSA cluster had significantly lower pain ($M = 18.19$, $SD = 19.76$) than the insomnia ($M = 45.70$, $SD = 31.21$) and other/no diagnosis clusters ($M = 33.99$, $SD = 22.17$). The pain intensity of the comorbid OSA/insomnia cluster did not differ from other groups ($M = 35.02$, $SD = 26.00$).

Potential covariates were examined for inclusion in an ANCOVA. Among the participants included in the cluster analysis ($n = 97$), pain intensity was unrelated to age ($r = -.14$, $p = .18$) but significantly related to BMI ($r = .21$, $p < .05$). Additionally, females reported higher average pain intensity, $t(95) = -2.75$, $p < .01$ (male $M = 19.74$, $SD = 21.04$; female $M = 33.17$, $SD = 25.31$). When BMI and sex were added to the model as

covariates, the clusters continued to differ significantly on pain intensity $F(3, 91) = 3.88$, $p < .05$, $\eta_p^2 = .11$. In Bonferroni-corrected post-hoc comparisons, the only significant ($p < .05$) group comparison that remained after the inclusion of covariates was a higher pain intensity for the insomnia cluster (covariate-adjusted $M = 42.10$, $SE = 6.95$) compared to the OSA cluster (covariate-adjusted $M = 19.60$, $SE = 3.34$).

Table 3-1. Demographic characteristics for all enrolled participants (*N* = 105).

| | *n* | % | Mean | *SD* |
|---|---|---|---|---|
| Age | -- | -- | 43.83 | 16.52 |
| | | | | |
| Male | 44 | 41.90 | | |
| Female | 61 | 58.10 | | |
| | | | | |
| White | 74 | 70.48 | | |
| Black or African American | 18 | 17.14 | | |
| Hispanic or Latino | 6 | 5.71 | | |
| Asian or Asian American | 6 | 5.71 | | |
| | | | | |
| Education | | | | |
| Did not complete high school | 5 | 4.76 | | |
| High school | 42 | 40.00 | | |
| Associate's degree | 16 | 15.24 | | |
| Bachelor's degree | 20 | 19.05 | | |
| Master's degree | 13 | 12.38 | | |
| Doctoral degree | 9 | 8.57 | | |
| | | | | |
| Employment status | | | | |
| Working | 57 | 54.29 | | |
| Disabled | 15 | 14.29 | | |
| Student | 12 | 11.43 | | |
| Retired | 10 | 9.52 | | |
| Unemployed (looking for work) | 5 | 4.76 | | |
| Homemaker | 4 | 3.81 | | |
| | | | | |
| Relationship status | | | | |
| Married | 51 | 48.57 | | |
| Single | 22 | 20.95 | | |
| Divorced | 12 | 11.43 | | |
| Cohabiting | 10 | 9.52 | | |
| Widowed | 5 | 4.76 | | |
| Dating | 4 | 3.81 | | |

Table 3-2. Frequencies of sleep disorders.

| Diagnosis | *n* | % |
|---|---|---|
| Obstructive sleep apnea | 55 | 52.38 |
| Insomnia (diaries)* | 22 | 20.95 |
| Insomnia | 5 | 4.76 |
| Periodic limb movement disorder | 4 | 3.81 |
| Idiopathic hypersomnia | 3 | 2.86 |
| Narcolepsy | 2 | 1.90 |
| Restless legs syndrome | 2 | 1.90 |
| REM behavior disorder | 1 | 0.95 |
| Central sleep apnea | 1 | 0.95 |
| No diagnosis | 36 | 34.29 |

Note: Five participants received two diagnoses from their physicians.
* Frequency of insomnia as classified using sleep diaries (based on AASM and research diagnostic criteria). All other categories represent diagnoses made by Sleep Center physicians following polysomnography (and Multiple Sleep Latency Test, if applicable).

Table 3-3. Frequency of chronic pain across body regions.

| | Left | | Right | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Hand | 18 | 17.14 | 19 | 18.10 |
| Arm | 10 | 9.52 | 14 | 13.33 |
| Shoulder | 29 | 27.62 | 29 | 27.62 |
| Neck | 28 | 26.67 | 30 | 28.57 |
| Head | 20 | 19.05 | 21 | 20.00 |
| Face | 5 | 4.76 | 4 | 3.81 |
| Chest | 10 | 9.52 | 10 | 9.52 |
| Stomach | 8 | 7.62 | 10 | 9.52 |
| Upper back | 18 | 17.14 | 19 | 18.10 |
| Lower back | 51 | 48.57 | 49 | 46.67 |
| Pelvis | 13 | 12.38 | 12 | 11.43 |
| Hip | 20 | 19.05 | 18 | 17.14 |
| Knee | 25 | 23.81 | 26 | 24.76 |
| Leg (other than knee) | 19 | 18.10 | 16 | 15.24 |
| Foot | 30 | 28.57 | 26 | 24.76 |
| Ankle | 18 | 17.14 | 15 | 14.29 |

Table 3-4. Chronic pain diagnoses reported by participants.

| Diagnosis | *n* | % |
|---|---|---|
| Musculoskeletal pain | 30 | 28.57 |
| Chronic headaches | 26 | 24.76 |
| Osteoarthritis/Degenerative Joint Disease | 19 | 18.10 |
| Neuropathic pain | 14 | 13.33 |
| Chronic Fatigue Syndrome | 6 | 5.71 |
| Irritable Bowel Syndrome | 6 | 5.71 |
| Fibromyalgia | 5 | 4.76 |
| Rheumatoid Arthritis | 4 | 3.81 |
| Chronic pelvic pain | 3 | 2.86 |
| Temporomandibular disorder | 3 | 2.86 |
| Inflammatory Bowel Disease | 2 | 1.90 |
| Cancer pain | 2 | 1.90 |
| Spondylitis | 2 | 1.90 |
| Pain due to another medical condition | 4 | 3.81 |

Table 3-5. MCV ratings of pain and accompanying negative emotions for the preceding week.

| Scale* | Usual Mean (*SD*) | Lowest Mean (*SD*) | Highest Mean (*SD*) |
|---|---|---|---|
| Pain intensity | 36.41 (24.24) | 21.32 (19.66) | 52.60 (27.99) |
| Pain unpleasantness | 33.98 (25.78) | 22.72 (21.81) | 52.47 (29.92) |
| Depression | 24.79 (29.62) | -- | -- |
| Anxiety | 31.30 (30.85) | -- | -- |
| Frustration | 42.91 (31.93) | -- | -- |
| Anger | 26.57 (30.76) | -- | -- |
| Fear | 20.86 (27.56) | -- | -- |

* All scales rated using a 0-100 visual analog scale (0 = none).

Table 3-6. Hierarchical regression predicting average pain intensity.

| PSG-derived predictors | $R^2$ change | *F* change | *B* | *SE B* | ß | *t* | *p* |
|---|---|---|---|---|---|---|---|
| Model 1 | .04 | 4.00 | | | | | |
| Total sleep time | | | .08 | .04 | .20 | 2.00 | .05 |
| Model 2 | .01 | .18 | | | | | |
| Total sleep time | | | .07 | .04 | .20 | 1.78 | .08 |
| Minimum $SaO_2$ | | | .21 | .37 | .08 | .58 | .57 |
| Spontaneous arousals/hour | | | -.10 | .38 | -.03 | -.27 | .79 |
| Apnea-hypopnea index | | | .02 | .19 | .01 | .08 | .93 |

Table 3-7. Correlation matrix for pain intensity and polysomnography variables.

| | Pain intensity | Total sleep time | Minimum $SaO_2$ | Spontaneous arousals/hour |
|---|---|---|---|---|
| Total sleep time | .20* | -- | -- | -- |
| Minimum $SaO_2$ | .04 | -.11 | -- | -- |
| Spontaneous arousals/hour | -.11 | -.37** | -.00 | -- |
| Apnea-hypopnea index | -.04 | .02 | -.61** | .22* |

* $p < .05$
** $p < .001$

Table 3-8. Pain characteristics by sleep diagnosis.

| Diagnosis | *n* | Pain intensity | | Covariate-adjusted pain intensity* | | Chronic pain | |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SE | n | % |
| OSA | 42 | 18.89 | 19.33 | 20.28 | 3.60 | 32 | 76.19 |
| Insomnia | 9 | 32.91 | 26.03 | 28.24 | 7.79 | 8 | 88.89 |
| OSA/insomnia | 13 | 49.17 | 25.99 | 48.56 | 6.21 | 13 | 100.00 |
| None | 32 | 28.31 | 24.92 | 28.10 | 4.39 | 25 | 78.13 |

Note: OSA = obstructive sleep apnea.
* Means controlling for participant sex as a covariate.

Table 3-9. Means for variables used in hierarchical cluster analysis.

| Variable | Cluster 1 (OSA) | Cluster 2 (Insomnia) | Cluster 3 (OSA/insomnia) | Cluster 4 (Other/no diagnosis) |
|---|---|---|---|---|
| | Mean (*SD*) | Mean (*SD*) | Mean (*SD*) | Mean (*SD*) |
| ESS | 7.18 (4.12) | 8.09 (5.44) | 10.25 (4.45) | 14.80 (4.06) |
| ISI | 10.85 (5.01) | 17.36 (5.25) | 14.25 (7.18) | 17.15 (4.28) |
| TST (PSG) | 367.27 (54.22) | 301.09 (103.64) | 415.50 (33.97) | 403.11 (43.8) |
| AHI | 11.80 (12.82) | 2.39 (2.75) | 43.20 (24.84) | 2.04 (2.24) |
| Time <88% | 4.14 (6.88) | 0.90 (1.78) | 19.89 (26.12) | 0.17 (0.12) |
| Minimum $SaO_2$ | 85.64 (6.49) | 90.54 (4.41) | 70.75 (10.73) | 90.73 (3.21) |
| Spont. Arousals | 12.17 (8.97) | 10.40 (7.14) | 8.35 (3.59) | 7.48 (3.46) |
| REM latency | 127.54 (77.41) | 211.90 (106.21) | 167.91 (88.91) | 107.19 (41.57) |
| TWT (diary) | 49.37 (28.08) | 194.41 (92.39) | 79.27 (67.4) | 77.08 (35.48) |
| TST (diary | 433.40 (58.28) | 321.80 (83.21) | 403.57 (108.41) | 419.12 (38.66) |
| Quality | 3.15 (0.59) | 2.51 (0.65) | 3.01 (0.78) | 2.86 (0.43) |

Notes: ESS = Epworth Sleepiness Scale, ISI = Insomnia Severity Index, TST = total sleep time (minutes), PSG = polysomnography, AHI = apnea/hypopnea index, Time <88% = percentage of total sleep time with arterial oxygen saturation below 88%, Spont. Arl. = spontaneous arousals per hour, REM latency = rapid eye movement latency (minutes), TWT = total wake time (minutes), Quality = sleep quality rating.

Table 3-10. Cluster means for demographic and mood variables.

| Variable | Cluster 1 (OSA) | Cluster 2 (Insomnia) | Cluster 3 (OSA/insomnia) | Cluster 4 (Other/no diagnosis) |
|---|---|---|---|---|
| | Mean (*SD*) | Mean (*SD*) | Mean (*SD*) | Mean (*SD*) |
| Age | 47.94 (17.85) | 48.27 (14.90) | 43.25 (11.93) | 35.88 (14.12) |
| BMI | 32.58 (8.19) | 36.34 (10.35) | 39.81 (7.02) | 29.95 (8.10) |
| Depression | 13.70 (18.82) | 41.36 (36.46) | 43.00 (40.22) | 31.60 (32.83) |
| Anxiety | 18.55 (24.04) | 44.36 (34.28) | 46.27 (36.40) | 40.68 (29.85) |

Notes: BMI = body mass index

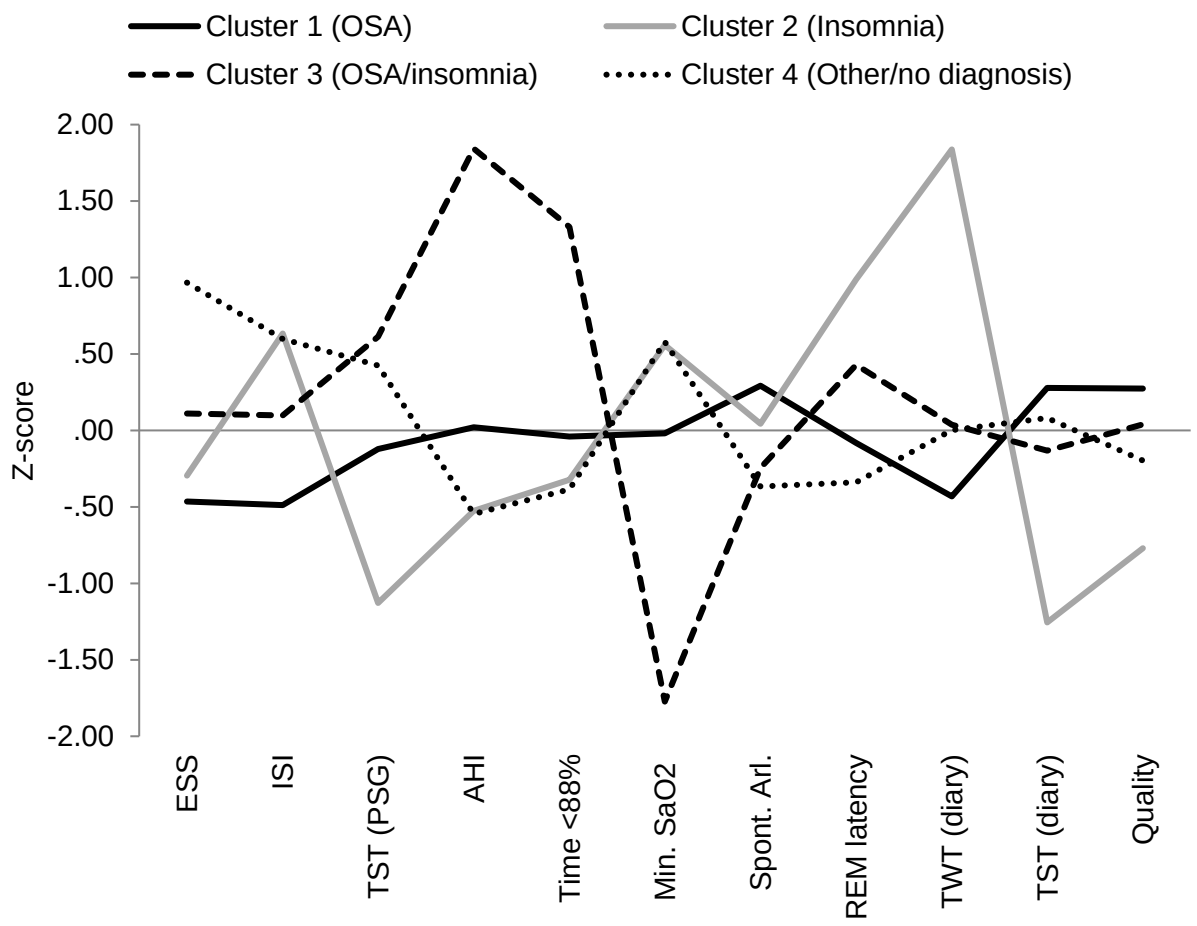


Figure 3-1. Standardized means for variables used in hierarchical cluster analysis.

Notes: ESS = Epworth Sleepiness Scale, ISI = Insomnia Severity Index, TST = total sleep time, PSG = polysomnography, AHI = apnea/hypopnea index, Time <88% = percentage of total sleep time with arterial oxygen saturation below 88%, Spont. Arl. = spontaneous arousals per hour, REM = rapid eye movement, TWT = total wake time, Quality = sleep quality rating.

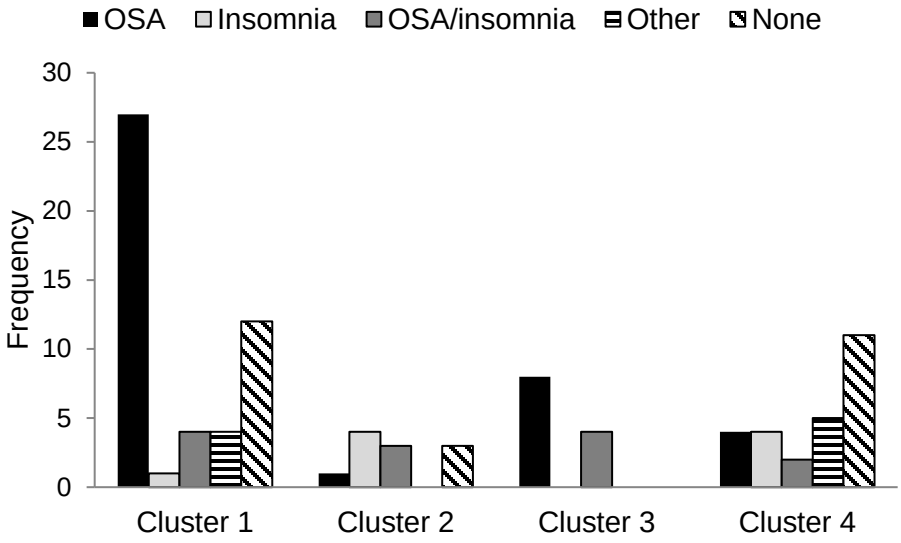


Figure 3-2. Frequency of sleep disorders in groups identified through hierarchical cluster analysis.

Note: OSA = obstructive sleep apnea

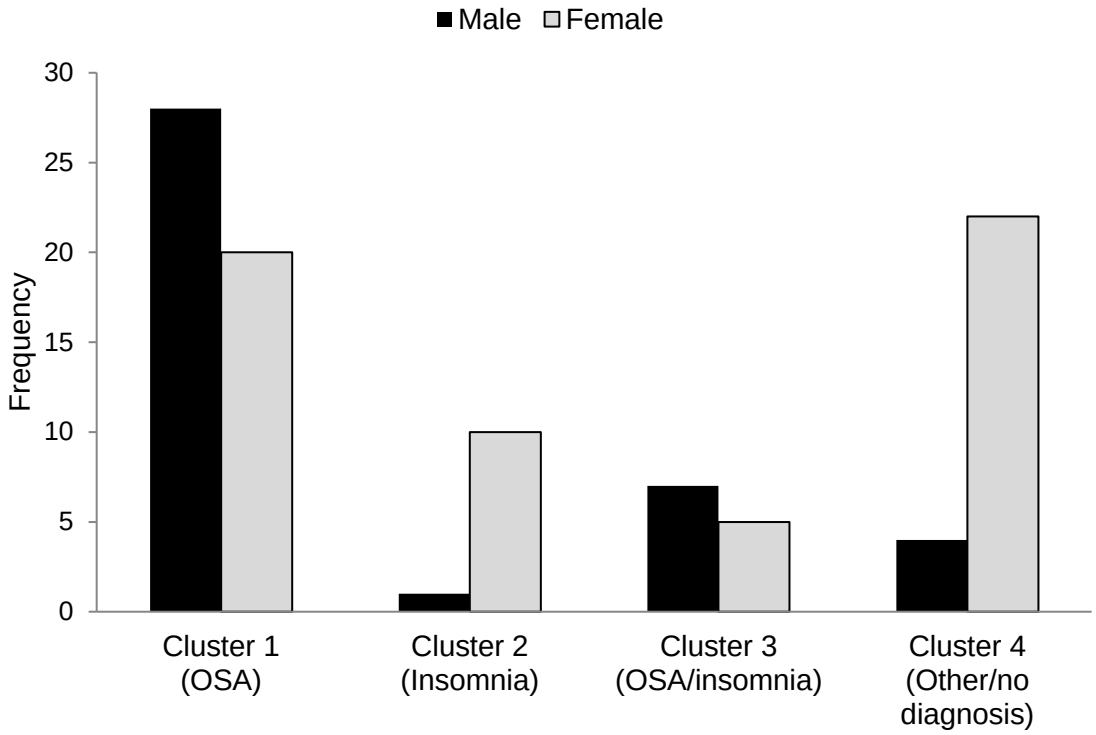


Figure 3-3. Sex distribution across groups identified through hierarchical cluster analysis.

Note: OSA = obstructive sleep apnea

# CHAPTER 4
# DISCUSSION

## Contributions of Sleep Characteristics and Disorders to Pain

This study investigated the unique contributions of sleep disorders and their distinct features, particularly symptoms of SDB, to pain. There was a high prevalence of chronic pain in this sample (80.00%), and—perhaps in part due to this high base rate of chronic pain—the likelihood of having chronic pain did not differ by sleep diagnosis. However, controlling for participant sex, individuals with comorbid OSA/insomnia reported an average pain intensity that was 20 points (out of 100) higher than individuals with insomnia or no diagnosis and 28 points higher than those with OSA. This magnitude of difference is likely to be noticeable and meaningful to patients[20] and as such would have implications for clinical care (discussed below). The results of this study thus indicate that there is a high likelihood that any patient being referred for sleep evaluation has chronic pain but that patients who meet criteria for both OSA and insomnia may have significantly higher pain than their counterparts with a single sleep disorder.

A small number of prior studies have found mixed associations of SDB with pain intensity or experimental pain sensitivity, including indications that nocturnal hypoxemia and SDB-related fragmentation may differ in their relationships to pain. Our study found no relationship between SDB-related variables (AHI, $SaO_2$ nadir) and clinical pain intensity in a sample of individuals referred to a sleep clinic. Additionally, a measure of non-apnea fragmentation (spontaneous arousals) was not related to pain intensity. Although these specific aspects of sleep were unrelated to pain, lower PSG-measured total sleep time predicted higher pain intensity.

The hierarchical cluster analysis identified four groups that coalesced roughly around sleep diagnostic categories. However, this classification method provided groups that were empirically-derived from a variety of objective and self-report measures rather than being based on arbitrary cutoffs used in traditional diagnoses. An examination of the sleep, demographic, and mood characteristics of the four groups allowed us to better characterize the unique features of these groups beyond a diagnostic label. Specifically, cluster 1 (OSA) had a disproportionate number of men and reported lower pain-related anxiety and depression than the other groups. The insomnia group (cluster 2) was notable for having the least amount of sleep on both objective and subjective measures as well as for consisting almost entirely of females. Cluster 3 (comorbid OSA/insomnia) had more severe apnea than all other groups, including cluster 1. This group also had a higher average BMI. Finally, cluster 4 (other/no diagnosis) was predominantly female, younger than the other groups, and reported the highest daytime sleepiness. The latter finding perhaps represents the fact that this group contained four of the five individuals diagnosed with idiopathic hypersomnia or narcolepsy. In terms of pain intensity, after controlling for confounding variables (BMI and participant sex), only one significant group difference was evident—the insomnia cluster reported pain intensity 22.50 points higher (on a 100-point scale) than the OSA cluster. As noted above, the insomnia cluster had the lowest total sleep time, and the higher pain intensity among this group therefore mirrors the results of the hierarchical regression which found that total sleep time was a significant predictor of pain intensity.

## Clinical Implications

In this sample of patients referred to a sleep center, most were diagnosed with OSA (52.38%). Although physicians diagnosed only 4.76% with insomnia, the inclusion of sleep diaries in this study allowed us to classify 20.95% as meeting criteria for chronic insomnia. Of particular interest for this study, we found that 12.38% of participants had comorbid OSA/insomnia. Although these results may only generalize to other sleep clinics and not the general population, our rates of comorbidity fall within the ranges previously reported.[1, 52] Specifically, we found that 23.64% of participants with OSA also met criteria for insomnia, and 59.09% of those with insomnia also met criteria for OSA. Most individuals with insomnia were not identified as such though the standard sleep center evaluation, suggesting the potential importance of more thorough insomnia assessment through either screening measures or sleep diaries when feasible. Effective treatments exist for both OSA and insomnia, but it is important to identify whether both disorders are present in an individual, as this may complicate treatment. Initial and middle insomnia are associated with poorer PAP adherence[7, 72], and it may therefore be necessary to treat insomnia concurrently. Additionally, insomnia comorbid with OSA is likely to require treatment, as previous research has shown that insomnia (with the possible exception of middle insomnia) tends to persist and may even emerge (in the case of late insomnia) with PAP treatment.[7]

The high frequency of chronic pain (80.00%) in a population referred for sleep evaluation is striking but nonetheless aligns with what is already known about high rates of chronic pain in patients with sleep disorders.[24] Musculoskeletal pain (28.57%) and chronic headaches (24.76%) were the most common types of pain reported. In keeping with population norms[48], the back was the most frequently reported location of chronic

pain (48.57%). The high frequency of chronic pain in this sample is of clinical importance for treating sleep disorders, as pain intensity has been shown to predict PAP nonadherence.[35] In the present study, the majority of patients diagnosed with OSA had chronic pain (81.82%). Moreover, individuals with insomnia in addition to OSA had significantly higher average pain intensity than individuals with only OSA. Thus, while pain may be a barrier to PAP adherence in many patients with OSA, adherence is likely to be especially challenging among individuals with comorbid OSA/insomnia. Improved management of a comorbid pain condition would therefore be indicated when pain impedes adherence to treatment for a sleep disorder. Similarly, initial or concurrent treatment of comorbid insomnia may aid adherence to OSA treatment, though this remains to be tested in clinical trials.[52]

### Limitations and Future Directions

The results of this study may apply only to the population from which they were drawn—a tertiary sleep center—and may not generalize to the broader population or even to patients seen in other medical settings.

Specific chronic pain diagnoses used to characterize the sample were solicited from participants and were not verified by providers or with medical records. However, diagnoses were collected only in order to characterize the sample, and determination of the presence of chronic pain was accomplished through separate questions ascertaining whether the participant had experienced persistent pain in any body part over the preceding three months. This study did not explore whether associations between sleep features and pain are modified by the type of pain condition. In our broad clinical sample, we did not find evidence that SBD-related fragmentation and hypoxemia are associated with pain intensity. However, future researchers may be interested in

exploring relationships between SDB characteristics and pain in specific pain populations, such as individuals with spinal conditions noted to have higher rates of OSA than the general population.[44] Such investigations may shed light on the mechanisms of the sleep-pain interaction.

The present study did not find associations of pain to specific SDB symptoms, but it did reveal that individuals who had comorbid OSA/insomnia had more intense pain than individuals with either disorder in isolation. This population deserves further study in order to better understand what mechanisms might account for the higher pain associated with comorbid OSA/insomnia. Additionally, an important area for future research concerns the clinical care of patients with comorbid OSA/insomnia. Treatment may be complicated by the presence of a comorbid sleep disorder, and future research (such as an ongoing clinical trial by Ong and colleagues[14]), should aim to develop empirically-based guidelines regarding whether comorbid OSA and insomnia are best treated concurrently or in succession, including the optimal order for treatment, which may depend on the type of insomnia (i.e., initial, middle, or late).

## Conclusions

This investigation found that PSG-measured total sleep time, but not measures of sleep fragmentation or hypoxemia, was related to pain intensity among individuals referred to a sleep center. The majority of participants reported chronic pain. Although the likelihood of chronic pain did not differ by sleep disorder, individuals with comorbid OSA/insomnia had significantly higher average pain than their counterparts with OSA, insomnia, or no sleep diagnosis. This suggests that the most severe pain is likely to be found in individuals whose sleep is disturbed in a greater number of ways—at least when looking at the most common sleep disorders—rather than a specific pain to type

of sleep disturbance relationship. This study highlights the importance of identifying individuals with comorbid OSA/insomnia, as effective treatment of their sleep problems may be complicated by the existence of comorbid sleep disorders[7, 72] and chronic pain,[35] which is likely to be present in this population.

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## BIOGRAPHICAL SKETCH

Jennifer Mundt earned her B.A. in psychology—with a minor in sociology—from Seattle Pacific University in 2005. She subsequently attended Central Washington University, earning an M.S. in mental health counseling with additional certification in school counseling. Her master's thesis research was on the topic of empathy and bullying among adolescents. After graduating in 2008, she worked as a Research Associate for a Seattle e-learning company. Her work there involved project management and study coordination for CDC- and NIH-funded projects related to chronic pain, including a CBT-based self-help program for patients with chronic low back pain and continuing education for health professionals on topics related to pain management. In 2012, she began studying clinical health psychology at the University of Florida as part of Dr. Christina McCrae’s Sleep Research Lab and later (after Dr. McCrae’s departure from UF) as part of Dr. Michael Robinson’s Center for Pain Research and Behavioral Health. She completed her Ph.D. in 2017. Her research and clinical interests are focused on the area of health and chronic illness, particularly the interaction of sleep and pain.