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Disrupted Sleep is Associated with Altered Pain Processing by Sex and Ethnicity in Knee Osteoarthritis

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Abstract

Studies indicate that improving sleep decreases reported pain in patients with knee osteoarthritis (OA), but it is unclear if this association extends to experimentally-induced pain responses. A community-based sample of 88 African-American and 52 non-Hispanic white adults (45-76y) with knee OA completed the Insomnia Severity Index and the arousal subscale of the Sleep Hygiene and Practices Scale. Participants underwent quantitative sensory testing including measures of pain sensitivity and facilitation at the knee, and pain inhibition. Outcomes were analyzed with multiple Tobit, hierarchical regression models, with adjustment for relevant covariates. Ethnicity and sex by sleep interactions were also entered into the models. After

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covariate adjustment, main associations were not observed. However, sex interacted with insomnia severity to predict greater temporal summation of heat and punctate pressure pain among women and lower heat temporal summation among men. Men and women who engaged in frequent arousal-associated sleep behaviors demonstrated higher and lower heat temporal summation, respectively. Non-Hispanic whites with greater insomnia severity displayed lower pressure pain thresholds and pain inhibition. Our findings are the first to demonstrate that disrupted sleep is associated with altered pain processing differentially by sex and ethnicity/race among people with knee OA.

Keywords

quantitative sensory testing; knee osteoarthritis; insomnia; sleep; ethnicity

Introduction

Osteoarthritis (OA) is the most common form of arthritis and the leading cause of disability and work limitations in the United States,[10] with the knee being the most frequently affected joint. More than half of patients with OA experience pain during the night,[20] and suffer from some form of sleep disruption including poor sleep quality, sleep fragmentation, and frequent shifts between sleep stages.[29,31,39,53,61] Importantly, sleep disruption is also associated with significant daytime fatigue,[26]and reduced quality of life.[62] Further, about a third of OA sufferers report both clinically significant pain and insomnia.[35] Hence, comorbid insomnia and pain in OA represent a major deterrent to patient well-being.

Interactions between pain and sleep disturbance in pain populations were previously thought to be cyclical in nature.[24,25,51,52,58] However, a recent review suggests that sleep disruption may be a more consistent predictor of the incidence and augmentation of pain severity as opposed to pain causing difficulties in sleep.[21] A possible explanation for these observations is sleep disturbance may engage multiple pain modulatory circuits within the central nervous system through inflammatory mediators or N-methyl-D-aspartate receptor activation.[13,54] Consequently, activation of these mechanisms are associated with reductions in pain thresholds, pain inhibition and enhanced temporal summation of pain (i.e., enhanced pain in response to repeated noxious stimuli) as measured with laboratory-based quantitative sensory testing (QST). However, the nature of the association between sleep disruption and pain modulation is unclear among individuals with knee OA. The first paper in this area reported that among persons with knee OA, those with diagnosed insomnia, relative to those without insomnia, display significantly greater increases in IL-10 evoked by QST procedures suggesting support for the inflammatory mediation hypothesis.[42]

To better understand the relationship between sleep disruption and pain modulation, additional QST studies are needed. QST is a clinically-relevant method of pain assessment because the responses produced are related to clinical pain reports and treatment outcomes,[3,32,F34] and it provides mechanistic information on abnormal pain processing that can be used for more accurate diagnosis and tailored treatment.[11,18] QST responses are also associated with moderate to severe knee OA-related symptoms in comparison to patients

with mild symptom severity and persons with no knee OA.[27] The substantial relationship between QST measures and clinical pain reports among persons with knee OA is likely related to the finding that increases in clinical pain and QST procedures evoke enhanced activity in the same brain regions (i.e., thalamus, cingulate cortex, amygdala).[28] It should also be noted that among persons with knee OA, ethnic differences between African Americans and non-Hispanic whites in self-reports of pain intensity disappear after covariates (e.g., body mass index, socioeconomic status) are controlled.[1,12] However, ethnic differences on QST pain measures remain significant after these covariates are entered in analyses.[12,27] Thus, QST measures are particularly preferable to self-reports of pain in studies of ethnic differences in pain.

Only a few studies have implemented QST to examine whether sleep disruption is associated with pain facilitation in samples of relatively healthy persons and persons with chronic pain.[25,49] Schuh-Hofer and colleagues found that one night of sleep deprivation was unrelated to changes in temporal summation in healthy participants,[49] whereas Haack and colleagues reported lower temporal summation of heat pain in participants with insomnia compared to participants without insomnia.[25] Despite these mixed findings, there is reliable evidence that experimental sleep deprivation and poor sleep efficiency are related to reduced pain inhibition in healthy persons and those with chronic pain.[17,30,40,51] Thus, it is possible that sleep disruption is associated with increased pain sensitivity and enhanced pain facilitation in addition to reduced pain inhibition in persons with chronic pain such as knee OA.

Identifying the relationships between sleep and pain in knee OA is important because sleep is a highly modifiable behavior that may potentially alter pain. Evidence from a community-based study of patients with heterogeneous pain conditions revealed that patients with comorbid sleep disturbance engaged in more maladaptive behaviors for pain and sleep management (e.g., catastrophizing and activity avoidance) that, in turn, were associated with greater comorbid disease severity.[33] Alterations in maladaptive sleep-related behaviors are the cornerstone of cognitive-behavioral interventions for insomnia. Additionally, a recent outcome study of a cognitive-behavioral intervention for insomnia revealed improvements in sleep and decreases in clinical pain severity among elderly patients with comorbid insomnia and OA.[60] However, this study did not address whether specific, maladaptive sleep behaviors are associated with experimental pain responses in persons with knee OA.

The aim of the present study was to determine the relationships of self-reported insomnia severity and maladaptive sleep behaviors on QST measures of pain sensitivity, inhibition, and facilitation among persons with knee OA. We hypothesized that reports of greater insomnia severity and maladaptive sleep behaviors would be associated with lower pain thresholds and inhibition, and greater temporal summation of pain. Furthermore, both clinical pain and QST pain responses are known to differ by ethnicity/race and sex, such that ethnic minorities and women report heightened pain experiences.[8,9,12,14-16,19,45] There are also known sex and ethnic/racial differences in reports of sleep disruption [47,66]; however, these differences have not been investigated among persons with knee OA. Therefore, perceived sleep disturbance may be related to abnormal pain processing differentially by sex and ethnicity/race. As an exploratory aim to the study, we investigated the interactions of

ethnicity/race and sex with the sleep parameters on pain outcomes. Given the exploratory nature of this aim, no directional hypotheses were stated.

Methods

Study Design and Sample

This study was part of a multi-site investigation at the University of Florida and the University of Alabama at Birmingham aimed at ascertaining ethnic/racial differences in knee OA-related pain sensitivity and limitations in African American and non-Hispanic white middle-aged to older adults (Understanding Pain and Limitations in OsteoArthritic Disease; UPLOAD Study). Participants with knee pain were recruited from the community through flyers, radio and print media ads, and word-of-mouth referral. Participants were eligible to participate in the study if they were between 45 and 85 years of age, self-reported race/ethnicity as African American or non-Hispanic white, and had unilateral or bilateral symptomatic knee OA based upon American College of Rheumatology clinical criteria.[2] Participants were excluded if they self-identified as belonging to any other ethnic group, if they had concurrent medical or arthritic conditions that could confound testing procedures, or coexisting disease that could preclude successful completion of the protocol. These conditions included systemic rheumatologic disease, a history of surgical knee replacement to both knees, uncontrolled hypertension (>150/95mmHg), decreased peripheral sensitivity to tuning fork vibration, peripheral neuropathy, recent acute myocardial infarction, heart failure, serious psychiatric disorder or active suicidal ideation, diminished cognitive function (as measured by Mini Mental Status Exam (MMSE) with score ≤ 22), drug or alcohol abuse, and daily opioid use. Participants were also excluded if they had a Kellgren-Lawrence score of four for knee OA severity. Nearly all of the participants had Kellgren-Lawrence scores of two while a small number of participants scored a three. All procedures were reviewed and approved by the institutional review boards at the University of Florida and University of Alabama at Birmingham. Participants provided written consent and were compensated for their participation.

Procedure

Participants completed two in-person visits. The first visit was a health assessment session designed to verify eligibility criteria and collect baseline information. This session consisted of a comprehensive medical history, physical examination by a rheumatologist or nurse practitioner, radiographic exam of the affected knee(s), anthropomorphic measures, cognitive status exam, review of current medications, vital signs, and a self-reported sleep assessment. The second visit was a QST session, which occurred within two to four weeks of the first visit. QST was comprised of basal responses to heat and mechanical (punctate and pressure) pain assessments, temporal summation as well as assessment of conditioned pain modulation. The order of heat and mechanical testing was randomized. The cold pain and conditioned pain modulation testing always occurred last. Participants were asked to withhold any opioid (taken as needed or PRN) or benzodiazepine medication for one week prior to the QST testing. Over-the-counter pain medications were permitted.

Sleep Measures

A subsample of participants (n = 140) completed two self-report sleep questionnaires up to seven days prior to the QST session: the Insomnia Severity Index (ISI) and the Sleep Hygiene and Practices Scale (SHPS). The subsample occurred because the questionnaires were introduced to the UPLOAD study in Year 3 of the investigation.

The ISI measures outcomes of perceived sleep difficulties and insomnia severity over the past two weeks.[37] The ISI has 7 items each measured on a Likert scale from 0 to 4 (range: 0-28). The validity and reliability of the ISI has been demonstrated,[5,38] and it has been used effectively across multiple populations with comorbid disease.[58] A clinical cut-off of 10 is sensitive and specific to differentiating normal sleepers from those with clinically significant insomnia among persons with medical conditions.[38]

The SHPS is a 30-item multifactorial scale designed to measure the practice of sleep habits over the past month likely to negatively impact sleep.[64] The scale has a four-factor structure of the following sleep habit subscales: a) behaviors interfering with sleep scheduling and timing; b) arousal-associated behaviors; c) eating/drinking habits; and d) environmental interferences.[64] Exploratory and confirmatory factor analyses have supported the validity of these subscales in normal sleepers, insomnia patients, and obstructive sleep apnea patients.[63,64] Total scores for each subscale are summed. The arousal-associated behaviors subscale (SHPS-A, range: 6-42) was the only subscale used for analysis because the behaviors (i.e., engaging in sleep-irrelevant activities in bed, pondering about unresolved matters, and worry about not being able to fall asleep) identified in this subscale are more highly related to sleep disturbance for both persons with insomnia and normal sleepers.[64] Considering the wide variation in behaviors within this subscale, the Cronbach's α coefficient of this subscale for the study sample was in the moderate range (0.63) which is acceptable for use.[50]

Quantitative Sensory Testing (QST)

QST was performed using standardized methodology that is common in the field, as previously reported.[12,27]

Thermal heat testing was conducted to assess pain threshold, pain tolerance, and temporal summation (5 pulses each at 44°C, 46°C, 48°C) with a computer-controlled Medoc Thermal Sensory Analyzer (Ramat Yishai, Israel) at three sites on the most symptomatic knee. Pain intensity ratings (0-100) were collected for the temporal summation procedure. Temporal summation involved administering five brief (700 msec) heat pulses at inter-stimulus intervals of 2.5 seconds, and participants rated the pain intensity experienced after each pulse. Temporal summation was calculated as the difference in pain intensity ratings between the first heat pulse and the maximum rating from any of the four subsequent heat pulses, as in previous studies.[23,27]

Pressure pain threshold was assessed three times each at two sites on the knee (medial and lateral joint lines). Order of sites was randomized and counterbalanced. Pressure was applied using a digital, handheld algometer (Medoc, Sollentuna Sweden) at a constant rate of 30 kilopascals (kPa)/second. The average amount of pressure required to evoke the first

sensation of pain (kPa) was assessed and pressure pain threshold was calculated by averaging the three trials for each site.

Temporal summation of punctate mechanical pain was assessed twice at the knee. For the procedure, a 300g nylon monofilament probe was applied to the skin for one second and then applied over a series of 10 taps. Participants rated the intensity of pain (0-100 scale) of the first tap and following the 10^{th} tap for both trials. To measure temporal summation, pain intensity ratings were averaged for the single and 10^{th} taps and then the difference was calculated (i.e., 10^{th} tap – single tap). The greater the difference score, the greater the temporal summation that occurred.

Cold sensitivity was measured after the thermal and mechanical tests with a modified cold pressor test. Participants were asked to immerse their right hand up to their wrist into a cold-water bath (Thermo Scientific Refrigerated Bath) three times each for one-minute at temperatures set at 16, 12, and 8°C, respectively. Participants were asked to verbalize when the cold sensation 'first became painful' (i.e., time of report represents pain threshold) as well as to report separate ratings of pain intensity and unpleasantness when pain tolerance occurred or at the end of the maximum 1-minute immersion period on a scale from 0 (no pain/unpleasantness) to 100 (the most intense/unpleasant pain sensation imaginable).

Conditioned pain modulation (CPM)—We used CPM as a marker of endogenous pain inhibition. CPM was assessed by determining the ability of a conditioning stimulus, immersion of the right hand into cold water, to diminish the experience of pain from a test stimulus (temporal summation of thermal heat) applied to the opposite ventral forearm. The temperatures of the water bath and the heat stimulus were tailored for each participant to achieve a stimulus that would produce moderate pain (i.e. pain intensity rating of 40-60 on the 0-100 scale). First, baseline heat pain ratings were initially assessed on the left ventral forearm. Next, participants immersed their right hand in the cold water bath for a maximum of 60 seconds. Immediately after removing their hand from the cold water bath, the heat stimulus was again applied to the left ventral arm and pain ratings obtained. In order to operationalize CPM, the average heat pain rating following cold water immersion was subtracted from the average pre-immersion heat pain rating, such that higher scores reflected greater pain inhibition.

Other Measures

Depressive symptomatology was measured with the Center for Epidemiologic Studies Depression Scale (CES-D, range: 0-60), a well-validated and reliable measure of current frequency of depressive symptoms.[43] Clinical pain was measured with the Western Ontario and McMaster Universities Arthritis Index (WOMAC), a well-validated measure of symptoms of clinical pain, stiffness and physical functioning over the preceding 48 hours among patients with osteoarthritis.[6] The WOMAC has demonstrated high construct validity and test-retest reliability.[7] In the present study the total score of all items was used as the main outcome measure (range: 0-96). Higher scores indicate greater symptoms of clinical pain, stiffness, and poor physical functioning.

Statistical Analysis

Descriptive statistics of measures of central tendency and dispersion were calculated for all study variables. Ethnicity/race and sex comparisons were conducted with *t* tests for continuous variables and Chi square tests of independence for categorical variables. Likely confounding variables considered in the association between sleep and pain responses included sociodemographic information such as age, sex, ethnicity/race (African American or non-Hispanic white), and education (≤ high school degree vs. some college or more). Health factors often related to sleep disturbance were also considered including body mass index (BMI), depressive symptomatology, and clinical pain levels.

The distributions for all experimental pain outcomes were not normally distributed with the exception of CPM. Temporal summation scores, in particular, are often subject to difference scores of 0 (i.e., no temporal summation occurred). A temporal summation difference score of zero occurred among 62.5%, 41.4%, 30.2%, and 7.5% of the participants at the heat testing temperatures of 44°C, 46°C, and 48°C, and the punctate mechanical test, respectively. Censoring at the upper limit of mechanical threshold (600.1 kPA) at the lateral and medial knee joint lines occurred among 7.4% and 6.6% of the participants respectively. Censoring at the upper limit for cold pain threshold (60.1 seconds of hand immersion) at 16°C, 12°C, and 8°C occurred among 22.5%, 7.2%, and 1.5% of participants, respectively. Censoring at the upper limit for cold pain unpleasantness (100 on a scale from 0 to 100) at 16°C, 12°C, and 8°C occurred among 5.1%, 24.1%, and 32.6% of participants, respectively. Censoring at the upper limit for cold pain intensity (100 on a scale from 0 to 100) at 16°C, 12°C, and 8°C occurred among 4.4%, 19.9%, and 29.5% of participants, respectively. For these reasons all experimental pain outcomes, with the exception of CPM, were explored with hierarchical Tobit regression models to estimate their relationships with the sleep measures controlling for the covariates above.[48,55] Tobit regression models allow for left or right censoring of the dependent variable. The error distributions of the models were examined to determine level of heteroscedasticity. Variables were entered into the model in the following sets:

- Model 1 included all sociodemographic and health-related information
- Model 2 = Model 1 + SHPS-A score
- Model 3 = Model 2 + ISI scores
- Model 4a = Model 3 without ethnicity/race + separate interactions between ethnicity/race and SHPS-A and ISI scores
- Model 4b = Model 3 without sex + separate interactions between sex and SHPS-A and ISI scores.

SHPS-A scores were entered into the model prior to ISI scores because ISI scores were hypothesized to mediate the association between arousal-associated sleep behaviors and pain responses. The correlation between the two variables was $r = 0.48$, hence the risk of multicollinearity was low. Prior to the creation of the interaction terms, the sleep parameters were centered. An alpha level of $p < 0.05$ was considered statistically significant. In all, eighteen models were constructed to address each QST outcome separately as has been

previously done.[8,12,27] The Tobit regression analyses were conducted using the PROC QLIM statement in SAS 9.4 (SAS Institute, Inc., Cary, North Carolina). Significant main effects or interactions with insomnia severity on any of the outcomes were further explored with rank analysis of covariance to test whether these relationships differentiated between participants with and without clinically significant insomnia severity (cutoff of 10 on the ISI).[41]

Results

Sample Characteristics

Table 1 presents descriptive characteristics of the total sample (n = 140) and each ethnic group. On average, the sample was middle-aged, had BMI > 30, and had subclinical levels of depression symptomatology ($M < 16$). Fifty percent of the sample were experiencing clinical levels of insomnia severity (ISI score ≥10). The sample was balanced by sex and represented diverse levels of education. About 60% of the total sample was African-American (n = 88). WOMAC scores ranged from 0 to 87 with an average score of 37.0, indicating moderate OA symptoms.[27] In addition, the median duration of knee pain experienced by the participants was 72 months (*Interquartile Range*: 36 - 180). Compared to non-Hispanic whites, African-Americans were significantly younger, less educated, reported greater levels of clinical pain and disability on the WOMAC, and engaged more frequently in arousal-associated sleep behaviors. Men and women did not differ on any of the descriptors. Missing data were minimal for all variables (<4%).

Heat Pain Outcomes

Multiple, hierarchical Tobit regression analyses were conducted to evaluate how well the sleep parameters predicted heat pain sensitivity (Supplementary Table 1) and facilitation (see Table 2). There were no significant relationships between any of the sleep parameters and heat pain threshold and tolerance (Supplementary Table 1). After adjustment for variables in Model 1 (i.e., sociodemographic information, BMI, WOMAC score, and CES-D score), scores on the SHPS-A and ISI were not significantly related to temporal summation of heat pain at any of the temperature levels in Models 2 and 3, respectively (Table 2).

Mechanical Pain Outcomes

A multiple, hierarchical Tobit regression analysis was conducted to evaluate how well the sleep parameters predicted temporal summation of punctate pressure pain at the knee (Table 3). After adjustment for variables in Model 1, scores on the SHPS-A and ISI were not significantly related to temporal summation of punctate pressure pain in Models 2 and 3, respectively.

Pressure Pain Thresholds at the Knee

Multiple, hierarchical Tobit regression analyses were conducted to evaluate how well the sleep parameters predicted pressure pain thresholds at the medial and lateral knee joint line (Table 3). After adjustment for variables in Model 1 (i.e., sociodemographic information, BMI, WOMAC score, and CES-D score), scores on the SHPS-A and ISI were not

significantly related to pressure pain thresholds at either knee site in Models 2 and 3, respectively.

Cold Sensitivity

Multiple hierarchical regression analyses were conducted to evaluate how well the sleep parameters predicted measures of cold sensitivity. Neither of the sleep parameters were significantly associated with any of the cold sensitivity measures (Supplementary Tables 2-4).

Conditioned Pain Modulation

A hierarchical regression analysis was conducted to evaluate how well the sleep parameters predicted changes in CPM (Table 4). There were no main associations between the sleep parameters and CPM.

Exploratory Interactions with Sex and Ethnicity/Race

Heat Pain Outcomes—There were no significant interactions between any of the sleep parameters and ethnicity/race for any of the temperature levels. However, there were significant interactions between ISI score and sex on temporal summation at 46°C ($p = 0.02$) and 48°C ($p < 0.001$). There also was a significant interaction between SHPS-A and sex at 48°C ($p < 0.001$). In Figure 1, the simple slopes were plotted, but not the true intercepts on the original temporal summation response scale (1-100) because the sleep parameters and the interaction terms were centered. Figure 1a represents the sex by ISI score interaction for temporal summation at 46°C. Men demonstrated a borderline significant (negative) relationship between ISI score (greater insomnia severity) and lower temporal summation at 46°C (simple slope = −1.16, SE = 0.59, $t = -1.97$, $p = 0.052$) but women did not ($p = 0.20$). A rank analysis of covariance indicated a strong but non-significant trend for the interaction between sex and clinical levels of insomnia severity (i.e., ISI score cutoff of 10), $F(1,125) = 2.92$, $p = 0.09$. Figure 1b represents the sex by ISI score for temporal summation at 48°C. Among men, greater insomnia severity was associated with lower temporal summation (simple slope = −1.89, SE = 0.52, $t = -3.63$, $p = 0.0004$), whereas for women greater insomnia severity was associated with higher temporal summation (simple slope = 1.51, SE =0.67, $t = 2.28$, $p = 0.025$). A rank analysis of covariance indicated a significant interaction between sex and clinical levels of insomnia severity such that men and women with clinically significant insomnia severity differed significantly in temporal summation compared to those within their sex that did not have insomnia, $F(1,121) = 3.93$, $p = 0.05$. Figure 1c displays the sex by SHPS-A subscale score interaction for temporal summation at 48°C. Among men, frequent arousal-associated sleep behaviors were associated with greater temporal summation (simple slope= 1.82, SE = 0.62, t = 2.92, $p = 0.004$), whereas among women, these behaviors were associated with lower temporal summation (simple slope = −1.24 SE = 0.55), t = −2.28, $p = 0.025$).

To understand which arousal-associated behaviors were dominant in these relationships, correlations by item were conducted for both sexes. For men, watching television/listening to music (r = .26, $p = 0.04$), or exercising vigorously before bed (r = .36, $p = 0.003$) were

associated with greater temporal summation. For women, frequently pondering about unresolved matters in bed was related to less temporal summation (r = −.28, $p = 0.02$).

Mechanical Pain Outcomes—There were no significant interactions between any of the sleep parameters and ethnicity/race. However, there was a significant interaction between ISI score and sex ($p = 0.01$). Figure 2a displays a significant association between greater insomnia severity and temporal summation of punctate pressure pain for women (simple slope = 1.50, SE = 0.51, $t = 2.95$, $p = 0.004$) but not men ($p = 0.88$). A rank analysis of covariance indicated a strong but non-significant trend for the interaction between sex and clinical levels of insomnia severity, $F(1,129) = 3.86$, $p = 0.052$. In other words, temporal summation was differentiated between women with clinically significant insomnia compared to women without insomnia.

Pressure Pain Thresholds at the Knee—There were no significant interactions between any of the sleep parameters and sex for either knee site. However, there were significant interactions between ISI score and ethnicity/race for pressure pain thresholds at both the medial and lateral joint lines ($p's < 0.001$). In Figure 2, the simple slopes for these interactions are plotted. In both Figures 2b and 2c, the simple slopes indicate significant associations between greater insomnia severity and lower pressure pain thresholds at both knee sites for non-Hispanic whites (Lateral joint line: simple slope = −15.95, SE = 4.57), $t = -3.49$, $p = 0.007$; Medial joint line: simple slope = −16.32, SE = 4.35, $t = -3.76$, $p = 0.0003$) but not for African-Americans (Lateral joint line: $p = 0.69$; Medial joint line: $p = 0.61$). A rank analysis of covariance indicated significant interactions between ethnicity/race and clinical levels of insomnia severity for pressure pain threshold at the lateral joint line ($F(1,127) = 7.86$, $p = 0.006$), and at the medial joint line, $F(1,128) = 13.76$, $p = < 0.001$, such that pressure pain thresholds were significantly different between non-Hispanic whites with clinically significant insomnia severity compared to non-Hispanic whites without insomnia.

Conditioned Pain Modulation—After adjustment for variables in Models 1, 2, and 3, there was a significant interaction between insomnia severity and ethnicity/race on CPM ($p = 0.009$). Lower pain inhibition was associated with greater insomnia severity in non-Hispanic whites ($n = 52$, simple slope: −2.31 (0.88), $t = -2.62$, $p = 0.009$) but not African Americans ($n = 88$, simple slope: −1.02 (2.75), $t = -0.37$, $p = 0.71$) (Figure 3). A rank analysis of covariance indicated there was no significant interaction between ethnicity/race and clinical levels of insomnia severity, $F(1,128) = 1.11$, $p = 0.29$. No significant interactions between the sleep parameters and sex were observed.

Discussion

In a sample of middle-aged to older adults with knee OA, self-reported insomnia severity is associated with altered pain processing and central sensitization. The associations varied across multiple stimuli, and were moderated either by sex or ethnicity/race. Among women, greater insomnia severity was related to greater temporal summation of thermal and mechanical pain, whereas for men, greater insomnia severity was related to less summation of thermal pain and was unrelated to mechanical pain summation. Among non-Hispanic

whites, greater insomnia severity was related to lower pressure pain thresholds as well as diminished pain inhibition in response to the CPM task, which was not true of their African American counterparts. Contrary to our expectations, frequent arousal-associated sleep behaviors were related to greater temporal summation of thermal pain among men, and lower thermal pain summation among women. None of the sleep parameters was related to cold and thermal pain threshold, tolerance or sensitivity. Overall, the study hypotheses predicting disturbed sleep would be associated with greater pain facilitation, sensitivity, and lower pain inhibition were partially confirmed in certain subgroups and for specific pain stimuli.

Insomnia Severity, Gender, and Temporal Summation of Pain

Greater insomnia severity was associated with greater thermal (at 46°C and 48°C) and mechanical temporal summation for women. The likely reason for the lack of an association between insomnia severity and temporal summation at 44°C was the perceived painfulness at this stimulus level was low. The majority (75%) of the pain ratings for each heat pulse were mild (i.e. pain rating of < 40). This finding of greater insomnia severity associated with greater temporal summation is consistent with evidence that adult women with insomnia report more pain and somatic symptoms than women without insomnia and men with and without insomnia.[65] On the other hand, men with greater insomnia severity showed less thermal temporal summation though there was no relationship with mechanical temporal summation. Similarly, Haack and colleagues,[25] reported that persons with insomnia showed decreases in temporal summation of heat pain compared to healthy, good sleeping controls. They hypothesized that persons with insomnia may have a constantly activated pain inhibition system. This constant activation may counteract heightened responses to noxious stimuli. In general, activation of the pain inhibition system decreases with age and tends to diminish in persons with knee OA.[4,44] Activation of this system may remain more intact for men than women with knee OA. Previous reports do find that men demonstrate less thermal temporal summation than women.[19] Thus, men with knee OA and sleep disturbance tend to exhibit lower temporal summation, which is then coupled with a chronically activated pain inhibition system, possibly leading to the present findings. This explanation, however, does not reveal why greater insomnia severity was related to heat temporal summation but not mechanical temporal summation in men. Heat temporal summation is mediated by responses of dorsal horn neurons to c-fiber input, whereas punctate mechanical pain depends primarily on a-fiber nociceptor input.[67] The relationship between insomnia severity and temporal summation among men may be pronounced only for c-fiber mediated pain responses, which may be more strongly influenced by endogenous pain inhibition.

Insomnia Severity, Ethnicity/Race, and Pain Sensitivity and Inhibition

Among African Americans insomnia severity was unrelated to pain inhibition and pressure pain thresholds, while for to non-Hispanic whites high insomnia severity predicted poorer pain inhibition and lower pressure pain thresholds. Thus, insomnia may confer increased mechanical sensitization among whites but not African Americans with knee OA. The mechanisms underlying this finding are not clear; however, this suggests that alternative mechanisms may contribute to pressure pain sensitivity in African Americans. For example, we previously reported that African Americans showed significantly lower vitamin D levels

compared to non-Hispanic whites, and these lower levels of vitamin D mediated the greater pressure pain sensitivity of African Americans.[22] Alternatively, if pain were driving insomnia, this effect might differ for African Americans and non-Hispanic whites. That is, insomnia may be more strongly related to knee pain among non-Hispanic whites, which would also be associated with lower pressure pain thresholds. In contrast, insomnia may be driven by other factors in African Americans, such as environmental conditions (e.g. noise, temperature) or other health-related factors, rather than knee pain. Regarding the pain inhibition results, African Americans tended to show pain facilitation rather than inhibition, which may have created a floor effect preventing insomnia from reducing pain inhibition. However, in non-Hispanic whites, the presence of higher insomnia predicted pain facilitation similar to their African American counterparts.

Maladaptive Sleep Behaviors and Pain

A major aim of the present study was to determine if a set of maladaptive sleep behaviors would significantly predict pain responses. Additionally, we hypothesized that maladaptive sleep behaviors would mediate the association between insomnia severity and responses to painful stimuli. However, this scenario did not occur for any of the models analyzed. It is possible the great diversity of arousal-associated sleep behaviors presented in the SHPS-A may have weakened the true nature of the relationship, accounting for the lack of results in the sample. Further, the SHPS-A has not been previously validated in this population.

In our exploratory analyses, however, a significant interaction emerged between the SHPS-A and sex on heat temporal summation. This relationship indicated frequent maladaptive behaviors in men were related to greater temporal summation, yet less temporal summation among women. This finding is in opposition to the results of the insomnia severity and sex interaction on heat temporal summation. Logic would suggest that *both* greater insomnia severity and maladaptive sleep behaviors among men would predict less temporal summation. Therefore, these results should be interpreted with caution. To understand this relationship more clearly we analyzed each item of the SHPS-A by sex. Greater temporal summation among men was most associated with vigorous exercise before bed. Vigorous exercise before bed among men with knee OA may lead to poorer sleep, particularly if the exercise activates knee joint nociceptors, such as running or playing sports (weight-bearing on the knee joint) versus swimming that is gentle on the knee joint. Such knee-demanding exercises may lead to increased clinical knee pain along with greater central sensitization of pain through activation of pro-inflammatory cytokines or N-methyl-D-aspartate (NMDA) receptors. One study found that strenuous, aerobic exercise was related to increases in heat temporal summation in persons with fibromyalgia, effects that were opposite to those observed in the no pain controls.[57] No data on this relationship among individuals with knee OA are available; however, increased temporal summation after exercise may generalize to other pain conditions including knee OA.

In contrast to the positive relationship between insomnia severity and SHPS-A scores in the present sample, and specifically among women (data not presented), heightened temporal summation was not related to frequent maladaptive sleep behaviors despite its relationship with insomnia severity. Female participants with greater insomnia severity produced higher

pain ratings to the first heat pulse than those with less insomnia severity (data not presented). Hence, the relationship between SHPS-A scores and temporal summation was likely attenuated because there was less of a range in pain ratings to report as the temporal summation procedure continued. This likely created the observed inverse relationship.

Strengths and Limitations

Our study has notable strengths that contribute to the current literature. This study is one of only a few that have explored the associations between disrupted sleep, sleep-related behaviors, and responses to QST in people with knee OA. Our sample also had greater ethnic/racial diversity than previous studies evaluating this pain population. Much of the sample was recruited from the community and had comorbidities similar to that of the general population with the exception of severe or acute conditions. Therefore, the results may be generalizable to the broader knee OA population.

There are several limitations within this study that are worth discussing. First, sleep disruption was measured via retrospective self-report with the ISI. The ISI is limited in scope because it does not assess many other sleep factors that might be related to pain modulation such as objective short sleep duration, which, coupled with insomnia has been associated with numerous poor health outcomes.[56] To facilitate a greater understanding of the role of disturbed sleep and central pain processing, prospective assessment of sleep with both objective and subjective measures of sleep (i.e., polysomnography, actigraphy, sleep diaries, and questionnaires) is needed in this patient population. Second, chronicity of insomnia severity was not determined. The biological consequences of the stress from short-term vs. chronic insomnia symptoms on pain responses likely differ.[36] Third, the SHPS-A subscale was not previously validated in this population. Although the intra-class coefficient in the present sample was similar to the validation sample, the coefficient was in the acceptable range likely reflecting the diversity of arousal-associated sleep behaviors that persons with sleep disturbance tend to engage in. Fourth, we performed a large number of statistical tests without correction, which increases the risk of obtaining significant findings due to chance alone. Last, the present study was cross-sectional and does not present data on the causality of the relationship between sleep and pain.

Conclusions

The severity of sleep disruption appears to be associated with altered pain processing and central sensitization depending on the pain stimulus used as well as the sex and ethnicity/race of participants. These data, taken with compelling evidence indicating poor sleep is predictive of future pain provide further support that sleep interventions for individuals with knee OA-related pain are warranted. Study of potential mechanisms for this relationship such as neuroendocrine and pro-inflammatory mediators as indicated by Quartana and colleagues,[42] psychosocial factors, and endogenous systems involving dopamine, opioid, serotonin and noradrenaline would greatly enrich the literature and inform the refinement of interventions that improve sleep and influence associated mechanisms of action. Cognitive behavioral therapies specifically focused on sleep may have the greatest potential to make an impact. These therapies have already been found to initially improve sleep in patients with comorbid insomnia and OA, and those initial improvements predicted long-term reductions

in clinical pain severity, sleep disruption, and fatigue.[59] These types of interventions should be systematically evaluated for their effects on responses to QST among knee OA patients with clinical and subclinical insomnia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspective

This article presents the association between insomnia severity, maladaptive sleep behaviors, and experimentally-induced pain responses among people with knee osteoarthritis. Disrupted sleep was associated with altered pain processing by sex and ethnicity/race. Offering sleep interventions may help ameliorate pain, but treatment may need to be tailored by sex and ethnicity/race.

Highlights

- We studied the link between sleep and experimental pain in knee osteoarthritis
- Sleep disruption was related to altered pain processing by sex and ethnicity/race
- Disrupted sleep was related to greater heat and pressure pain facilitation in women
- Compared to African Americans, whites with poor sleep had less pain inhibition
- Whites with poor sleep had less pressure pain thresholds than African Americans.

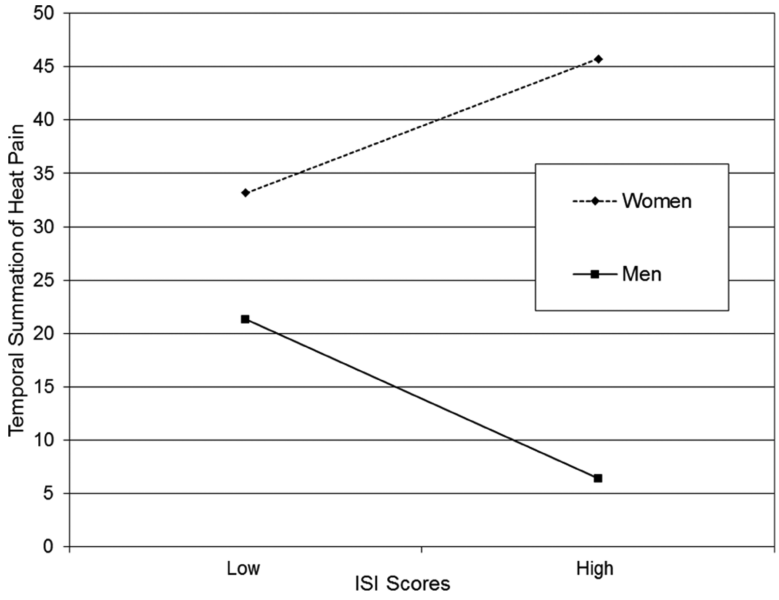

Figure 1a.
Gender by ISI Scores Interaction on Temporal Summation of Heat Pain at 46°C

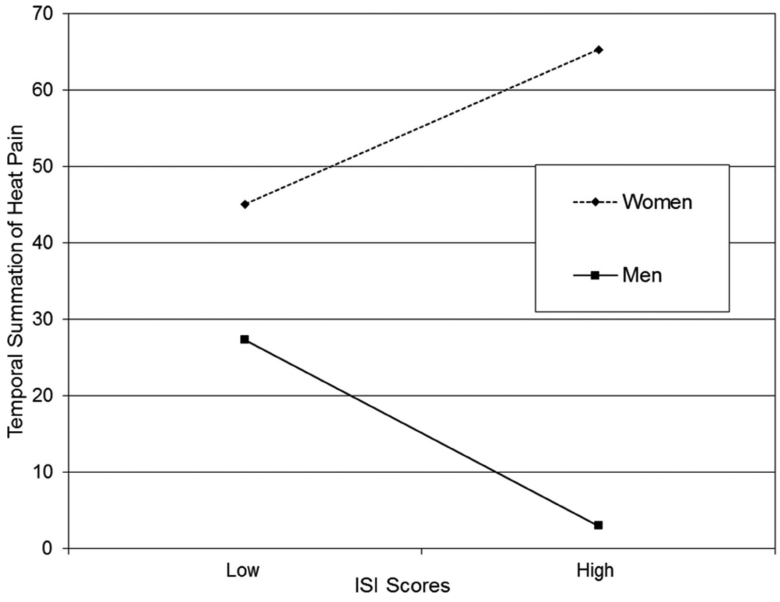

Figure 1b.
Gender by ISI Scores Interaction on Temporal Summation of Heat Pain at 48°C

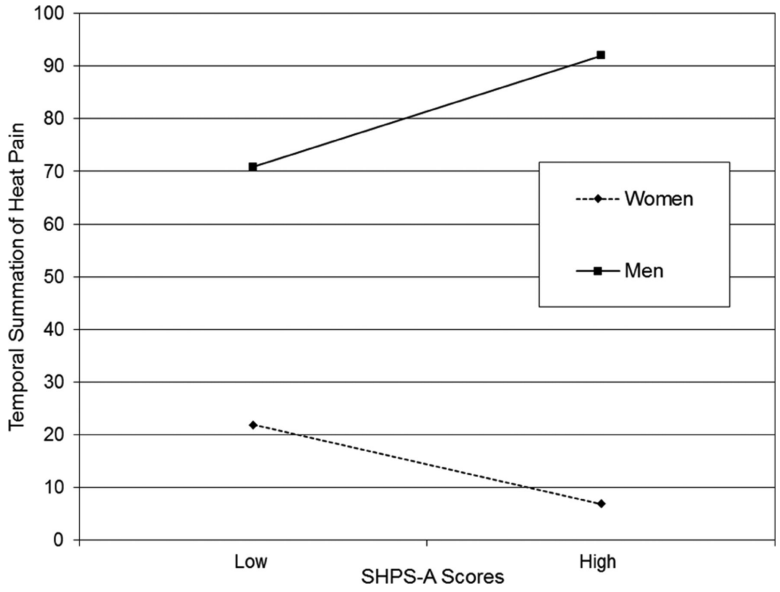

Figure 1c.
Gender by SHPS-A Scores Interaction on Temporal Summation of Heat Pain at 48°C

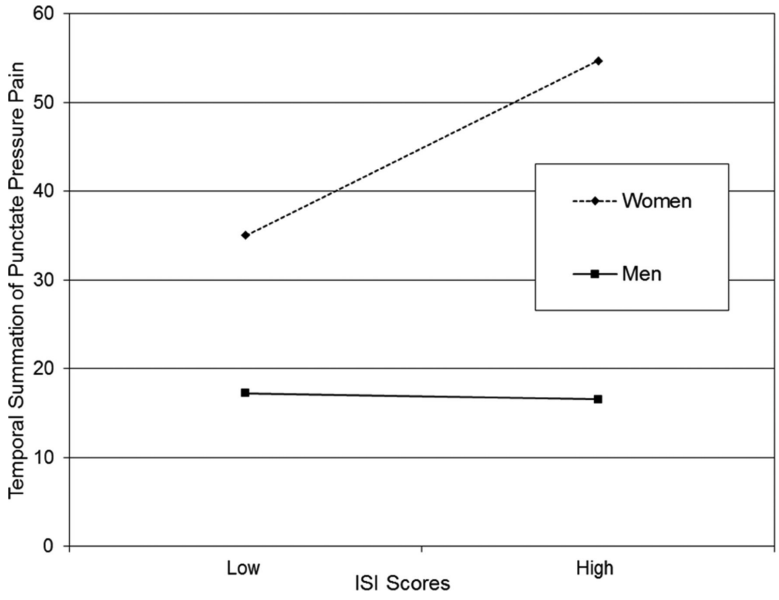

Figure 2a.
Gender by ISI Scores Interaction on Temporal Summation of Punctate Pressure Pain

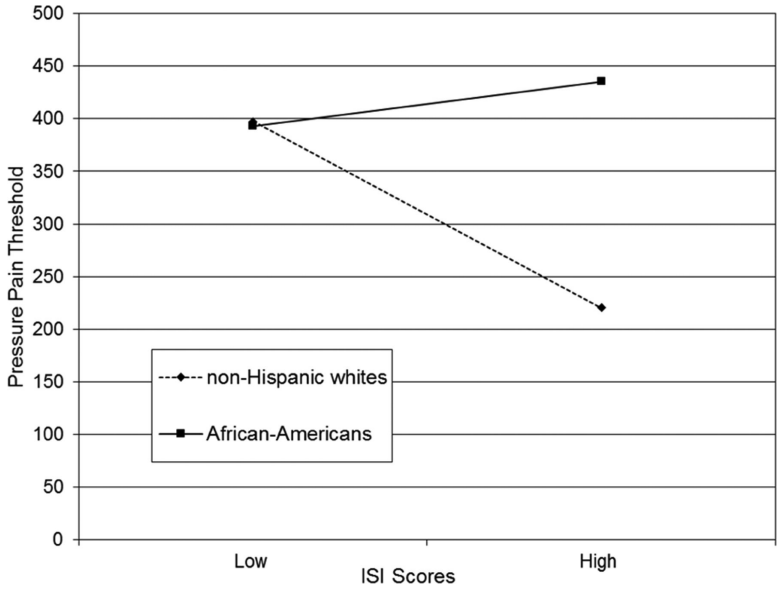

Figure 2b.
Ethnicity by ISI Scores Interaction on Pressure Pain Threshold at the Patella

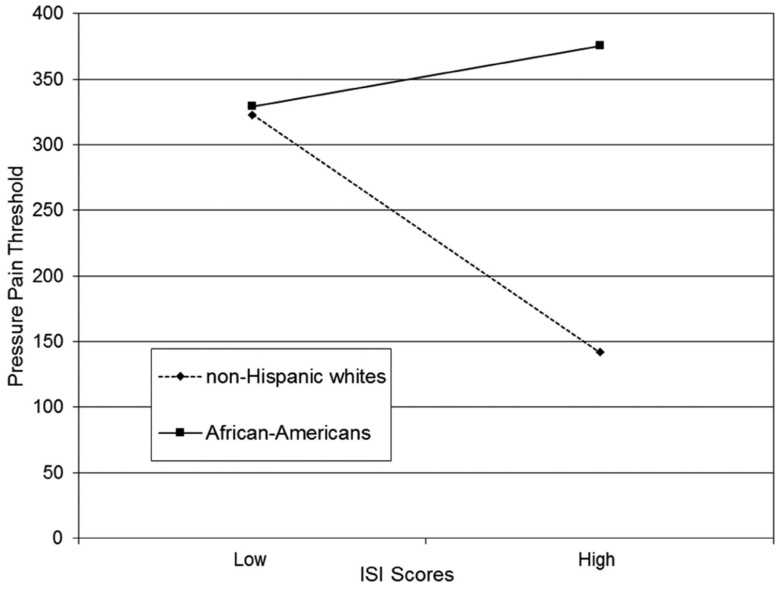

Figure 2c.
Ethnicity by ISI Scores Interaction on Pressure Pain Threshold at the Tibial Tuberoscity

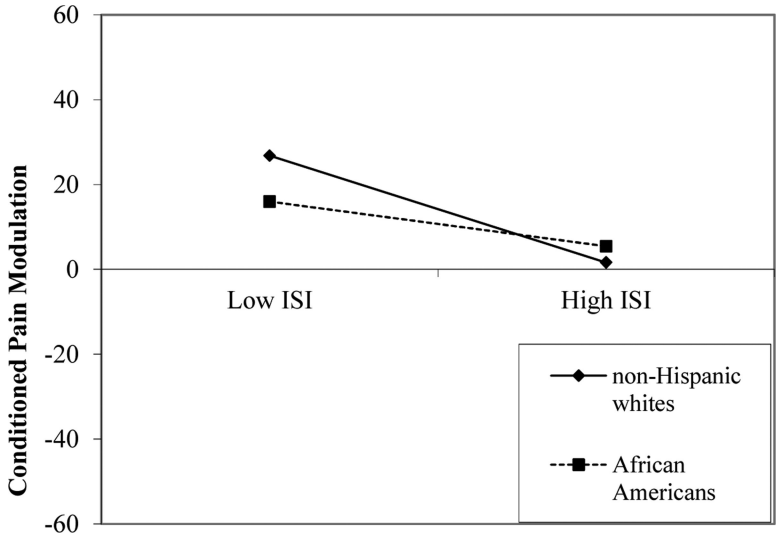

Figure 3.
Ethnicity by ISI Scores Interaction on Conditioned Pain Modulation

Table 1

Descriptive Characteristics of the Total Sample and by Ethnicity and Sex[a]

Variable	Total Sample (n=140)	African Americans (n=88)	Non-Hispanic Whites (n=52)	*t* or X^2	*p*	Males (n=68)	Females (n=72)	*t* or X^2	*p*
Age	56.2 (7.3)	55.1 (7.1)	58.1 (7.3)	2.3	.02	56.2 (6.9)	56.2 (7.8)	−.02	.98
Sex (n,% women)	72 (51.4)	48 (54.5)	24 (46.2)	0.9	.34	--	--	--	--
Race (n,% AA)	88 (62.9)	--	--	--	--	40 (58.8)	48 (66.7)	0.9	.34
Education (n,%)				25.4	<.001			4.2	.24
< HS Degree	14 (10.1)	12 (13.8)	2 (3.8)			7 (10.4)	7 (9.7)		
HS Degree	58 (41.7)	44 (50.6)	14 (26.9)			33 (49.3)	25 (34.7)		
2-4 Yr College	51 (36.7)	29 (33.3)	22 (42.3)			19 (28.4)	32 (44.4)		
> 4 Yr College	16 (11.5)	2 (2.3)	14 (26.9)			8 (11.9)	8 (11.9)		
BMI	32.1 (7.2)	32.5 (7.3)	31.4 (7.1)	−0.9	.39	31.2 (7.4)	32.9 (7.1)	1.4	.17
WOMAC	37.0 (19.8)	39.6 (20.9)	32.7 (17.3)	−2.0	.046	36.6 (20.0)	37.4 (19.8)	0.2	.82
CES-D	11.0 (8.7)	11.3 (8.9)	10.3 (8.5)	−0.7	.51	11.5 (8.4)	10.5 (9.0)	−0.7	.52
SHPS-A	24.1 (5.9)	25.1 (5.7)	22.4 (5.8)	−2.7	.008	23.6 (5.6)	24.5 (5.9)	0.9	.35
ISI	9.8 (6.6)	10.4 (6.9)	8.8 (5.8)	−1.4	.16	10.9 (7.0)	8.8 (5.9)	−1.9	.056

AA = African Americans; BMI = Body mass index; CES-D = Center for Epidemiological Studies - Depression scale; ISI = Insomnia Severity Index; SHPS-A = Sleep Hygiene and Practices Scale arousal associated behaviors subscale; WOMAC = Western Ontario and McMaster Universities Arthritis Index

[a]means and standard deviations are presented unless otherwise noted.

Table 2

Tobit Hierarchical Regression Analysis of Association of Sleep measures and Temporal Summation of Heat Pain at Affected Knee[a]

	44°C			46°C			48°C		
Variable	**Estimate**	***t***	**Pseudo-R^2**	**Estimate**	***t***	**Pseudo-R^2**	**Estimate**	***t***	**Pseudo-R^2**
Model 1			0.09			0.10			0.09
Age	0.29	0.79		0.46	1.46		0.73*	2.35	
Sex	−3.76	−1.04		−4.72	−1.08		−7.21‡	−1.67	
Ethnicity/Race	2.65	0.39		9.50	1.90‡		6.97	1.40	
Education	−2.43	−1.19		−1.06	−0.55		−0.46	−0.24	
CES-D	0.84*	3.10		0.74	2.74*		0.42	1.49	
WOMAC	−0.10	−0.79		−0.09	−0.72		−0.13	−1.05	
Model 2			0.09			0.09			0.09
SHPS-A	0.07	0.17		0.37	0.88		0.02	0.04	
Model 3			0.09			0.10			0.10
ISI	−0.27	−0.57		−0.36	−0.77		−0.54	−1.17	
Model 4a			0.09			0.16			0.12
Ethnicity/Race × SHPS-A	0.34	0.40		−1.51‡	−1.73		−1.07	−1.24	
Ethnicity/Race × ISI	−0.59	−0.65		−0.28	−0.30		−0.15	−0.17	
Model 4b			0.09			0.09			0.23
Sex × SHPS-A	−0.19	−0.22		0.77	0.87		3.06*	3.75	
Sex × ISI	−0.57	−0.66		−2.10*	−2.33		−3.41*	−4.26	

CES-D = Center for Epidemiologic Studies – Depression Scale; Eth = Ethnicity/Race; SHPS-A = Sleep Hygiene & Practices Scale, arousal-associated behaviors subscale; WOMAC = Western Ontario and McMasters Universities Arthritis Index

*$p < 0.05$

‡$p < 0.1$

[a]Variables in Models 2-4 are centered.

Table 3

Tobit Hierarchal Regression Models of Sleep and Mechanical Pain Outcomes[a]

	Temporal Summation at Knee			Pain Threshold at Knee Lateral Joint Line			Pain Threshold at Knee Medial Joint Line		
Variable	**Estimate**	***t***	**Pseudo-R^2**	**Estimate**	***t***	**Pseudo-R^2**	**Estimate**	***t***	**Pseudo-R^2**
Model 1			0.16			0.27			0.30
Age	0.19	0.76		−2.01	−1.06		0.36	0.19	
Sex	−10.9*	−3.24		140.12*	5.11		146.62*	5.51	
Ethnicity/Race	8.86*	2.30		−53.92‡	−1.71		−43.58	−1.43	
Education	2.03	1.34		15.76	1.26		−8.49	−0.70	
CES-D	0.32	1.50		−2.85	−1.67		−3.30*	−2.01	
WOMAC	0.16	1.62		−0.38	−0.49		−1.27‡	−1.72	
BMI	−0.14	−0.60		−4.08	−2.12		−2.89	−1.57	
Model 2			0.16			0.28			0.32
SHPS-A	−0.22	−0.65		0.28	0.11		1.96	0.77	
Model 3			0.18			0.29			0.32
ISI	0.52	1.51		−3.43	−1.28		−3.38	−1.30	
Model 4a			0.18			0.35			0.39
Ethnicity × SHPS-A	−0.23	−0.32		−4.52	−0.85		−5.26	−1.03	
Ethnicity × ISI	0.17	0.25		17.13*	3.33		17.73*	3.63	
Model 4b			0.22			0.29			0.33
Sex × SHPS-A	0.57	0.83		−1.79	−0.32		0.94	0.18	
Sex × ISI	−1.56*	−2.50		4.02	0.83		0.91	0.19	

BMI = body mass index; CES-D = Center for Epidemiologic Studies - Depression Scale; Eth = Ethnicity/Race; SHPS-A = Sleep Hygiene & Practices Scale, arousal-associated behaviors subscale; WOMAC = Western Ontario and McMasters Universities Arthritis Index

*$p < 0.05$

‡$p < 0.1$

[a]Variables in Models 2-4 are centered.

Table 4

Tobit Hierarchical Regression Analysis of Sleep measures and Conditioned Pain Modulation[a]

Variable		Estimate	*t*	R^2
Model 1				0.03
	Age	−0.13	−0.75	
	Sex	−1.56	−0.64	
	Ethnicity/Race	−3.10	−1.11	
	Education	−0.84	−0.77	
	CES-D	−0.14	−0.95	
	WOMAC	0.08	1.19	
Model 2				0.04
	SHPS-A	0.23	0.96	
Model 3				0.04
	ISI	−0.07	−0.03	
Model 4a				0.09
	Ethnicity/Race × SHPS-A	−0.33	−0.67	
	Ethnicity/Race × ISI	1.29*	2.65	
Model 4b				0.04
	Sex × SHPS-A	−0.32	−0.62	
	Sex × ISI	0.29	0.65	

‡ $p < 0.1$

CES-D = Center for Epidemiologic Studies – Depression Scale; SHPS-A = Sleep Hygiene & Practices Scale, arousal-associated behaviors subscale; WOMAC = Western Ontario and McMasters Universities Arthritis Index

* $p < 0.05$

[a] Variables in Models 2-4 are centered.