Insomnia with Objective Short Sleep Duration in Women with Temporomandibular Joint Disorder: Quantitative Sensory Testing, Inflammation and Clinical Pain Profiles

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Abstract

Objectives/Background: Temporomandibular joint disorder (TMD) is a disabling facial pain syndrome with a high prevalence of insomnia that primarily affects women. Insomnia with objective short sleep duration (ISSD) is an emerging phenotype linked to cardiometabolic morbidity and increased mortality. The present report examines the association of ISSD on clinical and laboratory pain and systemic inflammation in TMD.

Methods: We collected baseline data from 128 women with TMD and insomnia as part of a clinical trial evaluating psychological interventions for sleep and pain. Participants completed self-report questionnaires, one-night polysomnography, a 2-week actigraphy assessment, quantitative sensory testing (QST) to assess cold pain tolerance, pain sensitivity and central sensitization and circulating Interleukin-6 levels were measured to assess systemic inflammation.

Results: 24.2% (n=31) of the sample met criteria for ISSD [polysomnography (sleep duration <6 hours)]. Compared to those with insomnia and normal sleep duration, ISSD were older (40.4 vs. 34.9, *p*<.05) and a greater proportion self-identified as Black (48.4% vs 11.3%, *p*<.001). Multivariate regressions revealed that ISSD endorsed higher self-report pain severity

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and functional limitation of the jaw. ISSD also demonstrated increased generalized pain sensitivity, enhanced central sensitization, cold pressor tolerance and higher resting interleukin-6 levels.

Conclusions: This is the first study to characterize the ISSD phenotype in a chronic pain sample and expand the scope of its negative health outcomes to chronic pain. ISSD may be an important chronic pain phenotype associated with a more severe clinical and laboratory pain profile, and future studies should focus on implications for treatment response and disease trajectory.

Keywords

Insomnia; objective sleep duration; phenotypes; chronic pain; temporomandibular disorder; quantitative sensory testing; inflammation; Central sensitization; pain tolerance

1. Introduction

Sleep disturbances, especially insomnia, are prevalent among individuals with temporomandibular disorder (TMD) [1] a chronic, idiopathic facial pain condition involving the temporomandibular joint and surrounding structures, primarily impacting women of child bearing age [2, 3]. Far from being a simple consequence of pain, insomnia has been identified as a major risk factor for the development of incident new onset TMD and symptom flares in individuals with chronic TMD [4–6]. There are numerous putative mechanisms by which insomnia symptoms are hypothesized to influence the development and maintenance of chronic pain [7, 8]. Here, we focus on the hypothesis that insomnia-related sleep loss contributes to a pro-inflammatory state and heightens pain processing, which in turn contributes to pain chronicity and morbidity [9, 10]. Central sensitization, defined as a hyper-excitability in central nervous system nociceptive pathways, that amplifies afferent nociceptive input, is believed to play a role in the pathophysiology of TMD and other idiopathic chronic pain disorders [11]. Interleukin-6 (IL-6), a key inflammatory cytokine is implicated in chronic inflammation, the regulation of pathological pain conditions, and central sensitization [12–14]. Work by our group and others demonstrates that sleep disruption with concomitant objective curtailment of sleep to 4 hours per night, as well as total sleep deprivation, alters pain sensitivity [15] and responsivity to psychophysical testing linked with central sensitization, especially in women [16–18].

Individuals with chronic insomnia often self-report short sleep, due to trouble initiating and maintaining sleep. However, insomnia nosology does not include sleep duration criteria and many patients with insomnia obtain relatively normative levels of sleep duration, when measured via objective means [19, 20]. By combining clinical features of insomnia with polysomnography (PSG)-assessed objective sleep duration, Vgontzas and colleagues [21] recently identified two phenotypes of insomnia with distinct features: insomnia with objective normal sleep duration (INSD; 6 hours a night), and insomnia with objective short sleep duration (ISSD; < 6 hours a night). With respect to morbidity, although both phenotypes are linked with adverse health outcomes and impaired quality of life, ISSD is the more severe phenotype, prominently linked with cardiometabolic risk [21]. Individuals with the ISSD phenotype are at an increased risk for developing cardiovascular disease [22], hypertension [23–25], type 2 diabetes [26], and cognitive deficits [27, 28], as well

as exhibiting reduced brain metabolites, such as glutamine in the left occipital cortex [29]. Although possible associations between the ISSD phenotype and immune markers of stress and inflammation have yet to be systematically investigated, at least one study found ISSD to be associated with elevated C-reactive protein in adolescents [30], a marker of systemic inflammation. In contrast to ISSD, the INSD phenotype is characterized by less physiological arousal, but with a clinical profile consistent with greater anxiety, rumination, dysfunctional beliefs, and sleep misperception and increased risk of depression [21, 31, 32].

Given the physiological and cognitive-affective differences found between these two chronic insomnia phenotypes and the role of sleep in regulating pain perception and inflammation [9, 33], we sought to evaluate, extend, and describe these phenotypes for the first time in insomnia occurring in the context of TMD. Specifically, we examined differences between the phenotypes in terms of TMD symptomatology, clinical pain, evoked pain sensitivity, central sensitization, interleukin-6 (IL-6), clinical pain and TMD symptomatology, as well as pain catastrophizing. It was hypothesized that the TMD patients with the ISSD phenotype will exhibit a more severe TMD, pain, and inflammatory profile.

2.   Material and Methods

The present ancillary study is derived from baseline data from a parent randomized clinical trial examining the efficacy and underlying mechanisms of different psychological interventions on sleep and pain in women with TMD and at least mild, clinically significant insomnia. (ClinicalTrials.gov Identifier: NCT01794624). The main outcome paper is currently in preparation.

2.1.   Participants

Participants had to meet criteria for both TMD and chronic insomnia and were recruited via fliers, radio advertisements, mailings and referrals from local dentists. Inclusion criteria included: (1) female between 18 and 60 years of age; (2) meeting research diagnostic criteria for TMD[34]; (3) reporting facial pain for at least 3 months; (4) reporting facial pain for at least 10 days out of the past 30 days; (5) average pain severity score over the past week of   3/10; (6) reporting scores   8 on both the Insomnia Severity Index [35] and Pain Catastrophizing Scale [36]; (7) reporting difficulties in initiating and/or maintaining sleep regularly (3 days/week) for at least 1 month; (8) consistent treatment regimen for the last 30 days, if using non-opioid medication for pain treatment; (9) if using an opioid for pain treatment or a benzodiazepine/benzodiazepine receptor agonist or sedating tricyclic antidepressant (e.g., trazodone, amitriptyline, doxepin) for sleep   3 days/week, willing to undergo a 4-week washout period prior to enrolling in the study; (10) agree to use contraception throughout the study, if of child-bearing potential; (11); and if post-menopausal, menopausal for at least 12 consecutive months prior to screening.

Exclusion criteria included: (1) body mass index (BMI) > 35; (2) history of temporomandibular joint (TMJ) surgery or TMJ growth disturbances, neoplasm or injury to the TMJ area in the past 6 months; (3) surgery scheduled for TMD during study period; (4) resting systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg (5) history of major medical conditions influencing sleep, the central nervous system

(e.g., COPD, seizure disorder, cancer), or peripheral neuropathy; (6) diagnosis of Raynaud's Syndrome; (7) history of unstable major psychiatric disorder (e.g., psychotic disorder, bipolar disorder); (8) active substance or alcohol abuse in the past 6 months; (9) regular use (3x/week) of opioids, benzodiazepines, or sedating tricyclic antidepressants; (10) stable preferred sleep phase between 10 am and 10 pm (e.g., night workers) or self-reported significant variability in sleep due to changes in work shifts; (11) scores 27 on Center for Epidemiologic Studies of Depression Scale [37] or current suicidal ideation; (12) positive urine toxicology screen test (i.e., barbiturates, THC, alcohol, cocaine, and other recreational drugs of abuse); (13) positive urine pregnancy test.

A total of 149 individuals met the inclusion and exclusion criteria and consented to participate in the parent study. Of those, 128 individuals completed a 1-night home PSG assessment and were included in the present study. A series of chi-square and t-tests were conducted to examine if there were any systematic demographic differences between those who completed PSG and those who did not. Results showed that there were no significant differences between the two groups in terms of age, race, ethnicity, education level, marital status and income. Approval for this study was granted by the Institutional Review Board in both Johns Hopkins School of Medicine and University of Maryland School of Dentistry.

2.2   Procedures

Participants who passed an initial phone screen, completed an in-person screening visit during which participants' medical and dental history were reviewed. A calibrated research dental hygienist conducted a standardized Diagnostic Criteria for TMD exam (DC-TMD) [34] to establish diagnosis. Individuals who passed the in-person screening visit were invited for a baseline study session consisting of questionnaires, quantitative sensory testing, blood sampling, and a brief sleep diagnostic interview. During the visit, a research staff member also trained participants on the use of the wrist actigraphy and the interactive voice recording system through which they completed sleep and pain diaries for two weeks after this baseline study visit. A Registered PSG Technician (RPSGT) then placed PSG sensors on the study participants, after which the participant was sent home via taxi/hired driver to complete the overnight PSG sleep study.

2.3.   Measures

2.3.1   Quantitative sensory testing (QST)

2.3.1.1   Pressure Pain Testing: Pressure pain thresholds (PPTh) for the trapezius, thumb, masseter, and forearm were measured using a SBmedic digital pressure algometer, with a 1 cm^2 surface area. Participants indicated when the steadily increasing pressure from the algometer (30 kPa per second) first became painful. The PPTh measurements were completed bilaterally with two trials on each side and with a ceiling of 1200 kPA to avoid bruising the participant's skin. Mean values were calculated averaging across side and trials.

2.3.1.2   Mechanical Pain Testing: Participants completed a mechanical temporal summation (MTS) task involving weighted pinprick stimulator with a 0.2 mm diameter contact area. The probes (256 and 512 mN) were separately applied to the dorsal surface of the nondominant middle finger 10 times, with an inter stimulus interval of Is. Peak

pain ratings were recorded after 1 stimulus and also after the 10th stimulus. The difference between the peak pain rating from the 10 repeated stimuli and single stimulus was calculated as the MTS score.

2.3.1.3   Thermal Pain Testing: Thermal tasks were used to assess pain threshold, pain tolerance, and thermal temporal summation using the 9 cm^2 Medoc Contact Heat-Evoked Potential Stimulator (CHEPS) placed on the ventral side of the dominant forearm. To determine Heat Pain Threshold (HPTh), participants indicated when a thermal stimulus ramping at 0.5°C/sec first became painful by pressing a button. Participants similarly reported when the ascending thermal stimulus became unbearable to determine Heat Pain Tolerance (HPTo). Thermal Temporal Summation (TTS) was measured by both phasic and tonic heat stimulus. For phasic TTS, participants responded to four series (temperatures: 45°C, 46°C, 48°C and the temperature that produced a pain level of 60 on a scale of 0 to 100) of 10 heat pulses with a 2.5 second inter stimulus interval and 70°C/second ramp rate. Pain ratings using a 0–100 numerical rating scale (NRS) were collected for each temperature. The Phasic TTS score was calculated as the difference between pain ratings from the first pulse and the maximum pain rating after the train of thermal pulses. For the Tonic TTS, two 1-min long stimuli (i.e., slow ramp and fast ramp) at the Pain-60 temperature was administered and pain ratings were recorded during the onset of each stimulus and then every 10 seconds. Both slow and fast ramp stimuli were used for the tonic stimulus which was completed on the dorsal side of the dominant forearm. The Tonic TTS score was calculated as the difference between the pain rating obtained at the onset of the thermal stimulus and the maximum pain rating during the one minute of the thermal stimulus. Lastly, after sensations were captured by pain ratings recorded 15 seconds following termination of each thermal task.

2.3.1.4   Cold Pressor Testing: Pain tolerance and conditioned pain modulation tasks were conducted using a cold pressor. Participants placed their dominant hand in a circulating water bath set to 4°C. Pain ratings were collected every 20 seconds for a duration of 5 minutes. Participants had the ability to terminate the task at any time if the pain was intolerable in which case, the time of hand withdrawal was noted. For conditioned pain modulation (CPM), two baseline PPTh measurements recorded before the cold pressor task were compared to a PPTh measurement obtained while the participant submerged their dominant hand in the cold water bath to compute a difference score as previously described [1]. The new PPTh measurement was conducted on the non-dominant trapezius after 20 seconds of hand immersion. The CPM task was completed twice interspersed with a 2-minute rest period. A CPM difference score was created by subtracting the mean trapezius PPTh during water submersion (two trials) from mean trapezius PPTh prior to submersion. Higher numbers reflect greater pain inhibition capacity.

2.3.2   QST Outcome Measures—To reduce the number of pain tests for statistical analysis, we calculated two global metrics: a General Pain Sensitivity Index, and a Central Sensitization Index and also evaluated two specific pain sensitivity measures: Pressure Pain Threshold measured bilaterally at the masseter and Cold Pressor Pain Tolerance (CPPT; hand withdrawal latency). To compute the pain sensitivity index, each QST-derived

parameter (i.e., PPTh, MTS, HPTh, HPTo, TTS, average pain intensity from cold pressor test, CPM, and after sensation scores) was first z-scored (standardized). As higher pain sensitivity index scores indicate greater evoked-pain sensitivity; z-scores of QST-parameters (i.e., threshold/tolerance measures and CPM) for which the lower scores indicate low pain sensitivity were reversed by multiplying by −1. The Central Sensitization Index was calculated as the average of the following individually z-scored values: CPM, MTS, TTS, and the after-sensations. Our lab and others have employed this data reduction approach to compute these global QST outcomes [38]. We elected to focus on masseter PPTh because this is a primary site of local TMD pain. We selected cold pressor tolerance as a major focus because this test is widely known to provoke autonomic reactivity, originally developed as a cardiac stress test[39]. We hypothesized, therefore, given strong linkages of ISSD phenotype with sympathetic hyperarousal that this pain tolerance test might be especially relevant.

2.3.3   Blood Sampling for IL-6—Prior to the baseline visit, research assistants reminded participants to abstain from taking any pain medications (including NSAIDs) or caffeine at least 24 hours before the visit. To reduce circadian influences on IL-6 levels, all sessions started approximately at 12:00. An intravenous (IV) line was placed following the American Phlebotomy Association guidelines. The samples were collected with participants sitting at rest 30 minutes before QST. We also conducted blood draws halfway through QST, immediately following QST, 90 minutes post QST, and 150 minutes post QST. Up to 20 milliliters of blood was collected at each time point and samples were immediately centrifuged at 4°C for 15 minutes. Plasma was removed and stored in a −80°C freezer. Commercially available ELISA kits were used to assess IL-6 serum levels. Blood data for analysis was available for 86 participants. A series of chi-square and t-tests were conducted to examine if there were any systematic demographic differences between those who had blood data and those with missing data. Results showed that there were no significant differences between the two groups in terms of age, race, ethnicity, education level, marital status and income, as well as the proportion of INSD and ISSD phenotype.

2.3.4   Home Polysomnography (PSG)—We used an Embla N7000 ambulatory recording system (Natus) to acquire PSG data. The system permits 24-hour monitoring with data stored to flash memory. We recorded data from the following standard clinical montage: 6 channel electroencephalography, electrooocculography, electromyography (mentalis and submentalis), respiratory function (i.e. abdominal and thoracic strain gages, oral-nasal pressure transducers, thermocouple), pulse oximetry, body position sensors, and electrocardiogram [40], All RPSGTs were fully trained in the application of sensors to standard locations as described in the PSG procedure manual, which is consistent with the American Academy of Sleep Medicine guideline. The clinical diagnostic sensor montage was applied in the late evening in the lab and subjects were sent home to sleep ad libitum at their habitual bed and wake times. Data was scored using Remlogic PSG software by RPSGTs. All RPSGTs were trained to achieve 80% agreement with a standard set of records scored by an expert. All scored records were reviewed and finalized by a board-certified sleep medicine physician. Sleep continuity parameters, including sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST) and sleep efficiency (SE), and

respiratory parameters, as well as sleep architecture, apnea/hypopnea index (AHI) and respiratory disturbance index (RDI), were all scored.

2.3.5 Actigraphy—Participants were trained in wrist actigraphy monitoring and wore a triaxial wrist actigraph (Actigraph GT3X+; ActiGraph LLC, Pensacola, FL, USA) on their non-dominant wrist for 2 weeks (24 hours/day) to provide another objective index of SOL, WASO, TST, and SE. Data were integrated into 60-second epochs. Following the actigraphy scoring guidelines from the Society of Behavioral Sleep Medicine (SBSM) [41], sleep periods were first autoscored using the ActiLife software (Version 6.7.3; ActiGraph) based upon the Cole-Kripke's sleep algorithm. Then, those autoscored sleep periods were manually reviewed by trained research assistants to further remove artifact, off wrist periods and adjust sleep period based on the sleep diary data and actigraphy patterns as needed, according to standardized procedures developed by the lab and consistent with SBSM guidelines.

2.3.6 Other Measures

2.3.6.1 Insomnia Severity Index: Insomnia severity was assessed by the Insomnia Severity Index (ISI)[35], a self-report measure that has good psychometric properties. The total score of ISI was used and the Cronbach's α was 0.76.

2.3.6.2 Pain Severity and Pain Interference: The Brief Pain Inventory (BPI)[42] was used to measure pain severity and interference. For pain severity a composite of four items ("average," "worst," "least" pain past 7-days, and pain "right now") derived from 0-10 numerical rating scales was computed by taking the average. Pain interference was measured by the mean of five items that assessed the extent to which an individual experienced pain that interfered with their general activity, relationship with other people, mood, sleep, and enjoyment of life in the past week. Cronbach's alphas for these two subscales were 0.88 and 0.93, respectively.

2.3.6.3 Pain Catastrophizing: The Pain Catastrophizing Scale (PCS)[36] consists of 13 items with a 5-point Likert scale ranging from 0 (not at all) to 4 (all the time). Participants are asked to rate the degree to which they have experienced feelings and thoughts when experiencing pain. The total score of PCS was used and the Cronbach's α was 0.91.

2.3.6.4 Depressive Symptoms: The Center for Epidemiologic Studies Depression (CES-D)[37] Scale is a well-validated 20-item questionnaire that assesses how often participants experienced depressive symptoms in the past week using a 4-point scale. The total score was used and the Cronbach's α was 0.84.

2.3.6.5 Anxiety Symptoms: The General Anxiety Disorder – 7 item scale (GAD-7)[43] is a brief scale that is designed to to assess the severity of GAD symptoms. Participants are asked to rate how much they were affected by anxiety symptoms in the past two weeks. Each item is scored on a 4-point Likert scale, ranging from 0 (not at all) to 3 (nearly every day). Total score was used and the Cronbach's alpha was 0.85.

2.3.6.6   Functional Limitation of the Jaw: The Jaw Function Limitation Scale-20 item version (JFLS-20)[44] consists of three sub-constructs for assessing the functional status of the masticatory system: (a) mastication, (b) vertical jaw mobility and (c) emotional and verbal expression. Each item was rated on a 0–10 point scale, where "0" indicating no limitation and "10" indicating extreme limitation. We used the total score of JFLS and the Cronbach's alpha was 0.93.

2.3.6.7   Baseline Blood Pressure: Baseline resting systolic and diastolic blood pressure were measured at rest prior to the QST session.

2.4   Data Analytic Plan

Participants were first dichotomized into the ISSD and INSD phenotypes based upon the previous literature using PSG-assessed TST < 6 hours as a cutoff [23]. To examine differences in sample socio-demographics, sleep, and physical and mental health characteristics between individuals with ISSD vs. INSD, a series of chi-square and t-tests were conducted. For main outcome analyses, multiple linear regression models were employed to assess the association of ISSD vs. INSD on laboratory pain assessed by QST (i.e., pain sensitivity index, central sensitization index, cold pressor tolerance, and PPTh on masseter), baseline IL-6 levels, and clinical pain-related experiences (i.e., pain severity, pain interference, pain catastrophizing, and functional limitation of the jaw). As the IL-6 variable was quite highly skewed (skewness = 1.54), we log transformed this variable prior to the regression analysis (skewness after log transformation = −0.57). Each main outcome model controlled for age and BMI which are known for their associations with pain-related experiences and IL-6[45, 46]. To explore the extent to which group differences were driven by race, race was added as a covariate in an additional step to all regression models. In addition, to explore the extent to which group differences were maintained when using an objective measure alternative to PSG, supplementary analyses using actigraphy to define insomnia phenotypes were conducted. These analyses defined ISSD vs. INSD using both < 6 and < 6.5 hour thresholds, given actigraphy's tendency to overestimate TST [47, 48].

For all analyses, the threshold for statistical significance was set at $p < 0.05$ (two-tailed). Given the exploratory nature of these analyses, we did not adjust for multiple comparisons to avoid type 2 error in this first extension of the ISSD phenotype to pain, consistent with the extant literature [49]. All analyses were conducted in R.

3.   Results

3.1   Insomnia Phenotype Categorization

Based upon the PSG TST < 6 hours benchmark, 24.2% (n = 31) of the participants were identified as ISSD and slept for 280.8 (SD = 56.3) minutes, while those with INSD (n = 96) slept for 466.4 (SD = 56.1) minutes.

3.2   Socio-Demographic Differences by Insomnia Phenotypes

A detailed summary of socio-demographic comparisons by insomnia phenotypes can be found in Table 1. Significant phenotypic differences in age ($p = 0.02$) and race ($p < 0.001$)

were observed. Individuals who were classified as ISSD were older and a greater proportion self-identified as Black compared to those with INSD.

3.3 Sleep and Physical and Mental Health Characteristics by Insomnia Phenotypes

As shown in Table 2, there were significant sleep continuity and architecture differences between insomnia phenotypes, except for stage N1 duration. Overall, ISSD showed worse sleep profiles than INSD. No significant phenotype group differences were observed on Apnea Hypopnea Index (AHI), Respiratory Disturbance Index (RDI), BMI, duration of TMD, diagnosis of TMD, anxiety symptoms, or depressive symptoms. However, individuals with ISSD exhibited higher resting systolic ($p = 0.007$) and diastolic ($p = 0.003$) blood pressure levels and greater insomnia severity ($p = 0.003$), compared with those with INSD.

3.4 Main Outcome Finding #1: Differences in QST Profiles between Insomnia Phenotypes

As shown in Table 3, regression analyses controlling for age and BMI as covariates showed significant group differences in the General Pain Sensitivity Index ($p = 0.049$), Central Sensitization Index ($p = 0.045$), and cold pressor pain tolerance ($p = 0.002$), such that individuals with ISSD presented greater pain sensitivity, central sensitization characteristics, and lower cold pain tolerance, compared with those with INSD. There were no significant differences in PPTh in the masseter ($p = 0.405$) between the two groups. R-squared results showed that both the insomnia phenotype predictor and covariates explained 4.2%, 6.8%, 1.3%, and 9.8% of the variances of General Pain Sensitivity Index, Central sensitization index, PPTh in masseter, and cold pain tolerance, respectively.

3.5 Main Outcome Finding #2: Differences in Baseline IL-6 Levels between Insomnia Phenotypes

As shown in Table 3, regression analysis controlling for age and BMI as covariates showed significant group differences in baseline IL-6 levels ($p = 0.011$), such that individuals with ISSD presented higher baseline IL-6 level, compared with those with INSD. R-squared results showed that both insomnia phenotype predictor and covariates explained 22.3% of the variances of baseline IL-6 level.

3.6 Main Outcome Finding #3: Differences in Self-Reported Pain and Jaw function Profiles between Insomnia Phenotypes

As shown in Table 4, regression analysis controlling for age and BMI as covariates showed significant group differences in pain severity ($p = 0.001$) and limitation in jaw functioning ($p < 0.001$), such that individuals with ISSD presented greater pain severity and limitations in jaw functioning, compared with those with INSD. There was no significant difference in pain interference ($p = 0.101$) and pain catastrophizing ($p = 0.060$) between the two groups. R-squared results showed that both insomnia phenotype predictor and covariates explained 15.1%, 5.2%, 6.3%, and 10.8% of the variances of pain severity, pain interference, pain catastrophizing, and functional limitation of the jaw, respectively.

3.7 Post-Hoc Analyses of Blood Pressure

As blood pressure is closely associated with age and BMI[50, 51], we further explored phenotype group differences in blood pressure while controlling for these variables. We found that even after including age and BMI as covariates, individuals with ISSD exhibited higher resting systolic ($p = 0.027$) and diastolic ($p = 0.014$) blood pressure levels than those with INSD.

3.8 Post-Hoc Analyses of Racial Differences

As individuals who were classified as ISSD had much greater proportion of individuals identifying themselves as Black (46.7%) compared to those with INSD (11.3%), we included race as an additional covariate to the main regression models. Compared to Black, White individuals presented better profiles on all main outcomes. More specifically, individuals who are White presented lower general pain sensitivity ($B = -0.56$, $SE = 0.13$, $p < 0.001$), central sensitization characteristics ($B = -0.54$, $SE = 0.13$, $p < 0.001$), higher cold pain tolerance ($B = 70.57$, $SE = 20.66$, $p < 0.001$), higher pressure pain threshold in masseter ($B = 35.51$, $SE = 10.63$, $p = 0.001$), lower baseline IL-6 levels ($B = -0.24$, $SE = 0.12$, $p = 0.04$), pain severity ($B = -1.57$, $SE = 0.36$, $p < 0.001$), pain interference ($B = -1.88$, $SE = 0.46$, $p < 0.001$), pain catastrophizing ($B = -7.49$, $SE = 2.26$, $p = 0.001$), and limitations in jaw functioning ($B = -17.90$, $SE = 7.37$, $p = 0.02$) compared to Black individuals.

After including race as a covariate, significant ISSD vs. INSD differences were only maintained in limitations in jaw functioning ($B = 18.69$, $SE = 6.78$, $p = 0.007$). Marginally significant differences were observed in cold pressor tolerance ($B = -35.94$, $SE = 19.02$, $p = 0.061$), baseline IL-6 levels ($B = 0.22$, $SE = 0.11$, $p = 0.050$) and pain severity ($B = 0.65$, $SE = 0.34$, $p = 0.055$). There were no longer statistically significant differences between individuals with ISSD and INSD in terms of General Pain Sensitivity Index ($B = 0.06$, $SE = 0.12$, $p = 0.610$) and Central Sensitization Index ($B = 0.09$, $SE = 0.12$, $p = 0.474$).

We further explored the effects of racial differences by conducting main regression analyses separately for White and Black race subgroups[1]. The results showed that there were no significant differences between ISSD and INSD on all main outcomes (p-values ranging from 0.302 ~ 0.946) among Black race subgroup. On the other hand, in the case of White race subgroup, we found that there were significant differences between individuals with ISSD and INSD on cold pressor tolerance ($B = -54.79$, $SE = 26.85$, $p = 0.044$), baseline IL-6 levels ($B = 0.30$, $SE = 0.15$, $p = 0.048$), and functional limitations of the jaw ($B = 23.17$, $SE = 7.38$, $p = 0.002$).

3.9 Supplementary Analyses Using Actigraphy instead of PSG to define Insomnia Phenotypes

Based upon 111 participants who completed two weeks of actigraphy monitoring, we categorized the insomnia phenotypes using both < 6 and < 6.5 hour thresholds. Then, we conducted the same set of analyses presented above. Average TST based upon two-week

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[1]We did not formally test race by sleep phenotype interaction, as this was post-hoc exploratory analysis and we did not have adequate statistical power to detect moderation effects.

actigraphy assessment (M = 426.17, SD = 53.3) was slightly longer than that based upon PSG (M = 421.5, SD = 97.5). Correlation of TSTs between PSG and actigraphy was moderate ($r = 0.48$, $p < 0.01$). Using < 6 and < 6.5 hours of actigraphy-based TST as cutoff criteria, 11.7% (n = 13) and 18.0% (n = 20) of the participants were classified as ISSD, respectively. The percent agreement between the PSG- and actigraphy-derived insomnia phenotype categorization was 86% and 81.1%, respectively.

Overall, a similar pattern of group differences emerged in terms of socio-demographics (see Tables S1a and S1b). When the actigraphy-derived TST cutoff was < 6.5 hours, a significant phenotype difference in marital status was found. In terms of sleep and physical mental health characteristics, the patterns of phenotype group differences were quite different depending on the TST cutoff scores (see Tables S2a and S2b). With a cutoff of < 6 hours, there was a significant TST and SE % difference between ISSD and INSD. However, with a cutoff of < 6.5 hours, no significant sleep continuity differences were found, except for TST. In terms of sleep architecture, there were significant group differences in stage N2 and REM duration in both cutoffs. Based upon the < 6 hour cutoff, we found significant AHI and RDI differences between ISSD and INSD, but not with the < 6.5 hour cutoff. Based upon the < 6 hour cutoff, we did not find significant systolic and diastolic blood pressure differences between ISSD and INSD, but found significant differences in these with the < 6.5 hour cutoff.

Main outcome findings, however, were quite consistent across different TST cutoffs (see Tables S3a–S4b). These results were also similar to PSG-derived results. Controlling for age and BMI as covariates, we found that there were significant group differences in the General Pain Sensitivity Index, Central Sensitization Index, and cold pressor pain tolerance, such that individuals with actigraphy-derived ISSD presented greater pain sensitivity, central sensitization characteristics, and lower cold pain tolerance, compared with those with actigraphy-derived INSD. Significant group differences were also found in baseline IL-6 levels, such that individuals with actigraphy-derived ISSD presented higher baseline IL-6 level, compared with those with actigraphy-derived INSD. Group differences in self-report pain measures were only found in pain severity, such that individuals with actigraphy-derived ISSD presented greater pain severity compared with those with actigraphy-derived INSD. While there was no significant difference in the functional limitation of the jaw between groups with the cutoff of < 6 hours, there was a significant difference with the cutoff of < 6.5 hours. When race was included as an additional covariate in these main outcome models, all of the previously significant group differences became non-significant.

4. Discussion

This is the first study, of which we are aware, to characterize the ISSD phenotype in women with TMD and comorbid insomnia, highlighting its relevance to QST, inflammation, and self-report clinical pain and TMD symptoms. Specifically, our findings demonstrated that women with TMD who exhibit the ISSD phenotype showed increased general pain sensitivity, central sensitization and reduced cold pain tolerance, higher baseline IL-6 levels and increased self-report pain severity and jaw function limitation, as compared to those

with INSD. Moreover, the ISSD group demonstrated higher resting blood pressure and a greater proportion of Black participants.

Our main finding that women with TMD and ISSD show a more severe laboratory and clinical pain profile suggests that the combination of insomnia and short sleep duration, as observed in other clinical and non-clinical populations [21, 23, 24, 26, 28, 30], also has an additive burden in the context of pain. This is consistent with the literature demonstrating the adverse impact of short sleep duration on the maintenance and possibly the development of chronic pain [9, 52, 53]. Not only does the ISSD group report higher pain severity and functional jaw limitation, but also show increased pain sensitivity and central sensitization, and reduced cold pain tolerance. Interestingly, we found no group difference in pressure pain threshold measured at the masseter which is the regional muscle most commonly involved in symptomatic TMD [54], implying that a more general underlying mechanism is responsible for the difference in pain profiles between the insomnia phenotypes. Our finding on central sensitization is also consistent with previous reports that individuals with insomnia and other chronic pain conditions, such as knee osteoarthritis, demonstrate increased central sensitization [38].

The ISSD group in our study was comprised of a much higher proportion of Black participants (48.4%) than the INSD group (11.3%), which led us to explore the potential role of race in the insomnia phenotypes by including race as a covariate in our models. When race was controlled in our models, only limitations in jaw functioning remained significantly different between the two phenotypes and the difference in cold pressor tolerance and pain severity became marginally significant. This suggests a complex relationship between race, objective sleep duration phenotypes and pain profiles. To our knowledge, this is a novel observation in the insomnia phenotype literature that requires replication and further investigation. Our finding is consistent with other studies which demonstrated that Black individuals show shorter sleep duration both by self-report and objective measures, such as PSG and actigraphy [55]. In addition, Black individuals with insomnia are more likely to self-report short sleep duration and have a greater cardiometabolic and psychiatric illness burden than White counterparts [56]. The source of racial sleep disparities [55, 57–61] are still poorly understood but likely a number of factors may have been implicated, such as neighborhood disadvantage [62] and perceived racial discrimination [63, 64]. Previous work shows that perceived discrimination is also associated with report of greater clinical and experimental pain, as well as access and utilization of treatment for pain [65, 66], suggesting that discrimination might play an even greater role in individuals who suffer from comorbid chronic pain and insomnia. The majority of studies focusing on the insomnia duration phenotypes did not explore the role of race, thus it is necessary to utilize more racially diverse study samples in future studies and include multidimensional measures of racial discrimination.

Despite the increased cardiometabolic risk of the ISSD phenotype [21], only one study has assessed the role of circulating inflammatory cytokines in the insomnia phenotypes and found elevated C-reactive protein levels in adolescents with ISSD [30]. Consistent with this line of evidence, our TMD patients with ISSD demonstrated elevated levels of IL-6, one of the key inflammatory cytokines that serves an important role in chronic

inflammation and the regulation of pathological pain conditions (e.g., neuropathic pain and cancer related pain [12, 13]), as well as in central sensitization [14]. In the context of sleep, IL-6 has been implicated in sleep disturbances [67, 68] and interestingly, sleep restriction has been associated with heightened pain via an increase in IL-6 [33]. More recently, a study demonstrated that improvement in insomnia symptoms attenuated IL-6 reactivity in response to evoked pain testing [69]. A few studies explored the association between IL-6 and TMD in particular, suggesting that individuals with TMD may have a blunted IL-6 reactivity in response to stress [70] and genetic IL-6 polymorphisms are associated with lower quality of life among individuals with TMD [71]. Our finding of elevated resting IL-6 levels among individuals with ISSD even after controlling for pertinent factors such as age and BMI, shed further light on the complex relationships among inflammation, sleep and pain. Examining the role of the ISSD phenotype in other chronic pain populations is warranted in future studies.

In contrast to the literature suggesting that individuals with the INSD phenotype exhibit higher anxiety and ruminative traits, lower mood, and more dysfunctional sleep-related beliefs [21, 31, 32], we did not find insomnia phenotype group differences in symptoms of depression, anxiety, or pain catastrophizing, which includes a ruminative component and is robustly associated with depression and anxiety [72]. This discrepancy could be attributed to the focus of previous studies on non-clinical populations [21, 31] or primary insomnia clinical samples without any comorbidity [32], while it is likely that in the TMD population pain itself may contribute to elevated anxiety, lower mood and other cognitive-emotional characteristics regardless of insomnia phenotype.

In the current study, our primary categorization of the insomnia phenotype groups was based upon the PSG assessment of sleep duration, which is consistent with the majority of existing literature [21]. Few studies have compared actigraphy-derived insomnia phenotypes and, thus, supplementary analyses utilized actigraphy as an inexpensive, ecological measure that could replace PSG when identifying these insomnia phenotypes. Relatively high match rates (86% and 81.% for < 6 and < 6.5 hours cutoffs, respectively) were observed in terms of individuals identified as ISSD or INSD between PSG and actigraphy, as well as largely consistent pattern of findings in the main outcomes when using actigraphy and PSG derived insomnia phenotypes. A few discrepancies were observed in sociodemographic/clinical factors (marital status, AHI, and RDI) and in the self-report of jaw functioning. These inconsistencies might stem from differences in statistical power given that fewer individuals completed actigraphy than PSG and actigraphy yielded a much smaller group of ISSD, possibly related to the tendency of actigraphy to overestimate total sleep time [47, 48]. Discrepancies might also stem from the fact that PSG was measured over a single night, while actigraphy was averaged across 14 days. Nevertheless, it appears that the use of a more affordable and less cumbersome device to estimate objective sleep duration, such as actigraphy, could provide valuable information in the categorization of insomnia phenotypes. Future studies that measure both PSG and actigraphy for multiple nights would allow for further refinement of the insomnia phenotype assessment, such as determining the optimal number (e.g., 7 vs. 14 nights) or type of nights needed (weekdays/workdays vs. weekends/ days off) or the optimal threshold to define short sleep duration (e.g., < 6 vs. < 6.5 hours).

Our findings have a number of clinical and research implications for the treatment of individuals with TMD and insomnia. First, the ISSD phenotype appears to be associated with poorer pain-related outcomes and physiological morbidity, suggesting that this clinical group could benefit from earlier and more integrative intervention, targeting central sensitization, systemic inflammation, and autonomic arousal. Second, there is also evidence that individuals with ISSD might be less likely to respond to cognitive-behavior therapy for insomnia [21], although the results have been mixed. Four studies found that individuals with ISSD have lower remissions rate after CBT-I than those with the INSD phenotype [73–76], while three other studies reported similar remission rates after CBT-I between the two phenotypes [77–79]. In one of these latter studies, however, response rates were significantly lower in the ISSD phenotype than the INSD phenotype [78]. Future studies should evaluate whether insomnia phenotype may be a moderating factor for pain-related treatment response to cognitive-behavioral interventions, as well as for pharmacological interventions given the unique pain and heightened inflammatory profile shown in our study. Lastly, as Black individuals were more likely to present with the ISSD phenotype in our study, these findings underscore the importance of addressing structural social inequalities that contribute to more severe sleep health disparities.

There were a number of limitations in the present study and they should be considered when interpreting our findings. Objective sleep duration derived from PSG was collected through a single-night of an at-home PSG. One night of PSG might not sufficiently represent habitual sleep patterns. While sleeping at home might be a more ecologically valid assessment for participants compared to sleeping in a laboratory, an increased variability in sleep for individuals with insomnia has been reported when using at-home PSG [80]. Second, our study sample only included women with TMD selected to have at least subthreshold insomnia (ISI   8) and pain catastrophizing (PCS   8). Generalization of our results to men and those less severe ISI scores or with other chronic pain conditions may be limited. In addition, it is possible that the pain profile of a more general chronic pain sample with low pain catastrophizing may differ from what we found in the present study. Despite these limitations, our results suggest that estimation of objective sleep duration through PSG or actigraphy can identify a subgroup of individuals with insomnia who are at risk for poor pain-related outcomes and higher circulating IL-6 levels.

5.   Conclusions

In conclusion, women with TMD and the ISSD phenotype demonstrated a unique pain profile of increased clinical and laboratory pain, as well as elevated baseline inflammation which further supports the distinction between the two insomnia phenotypes based on objective sleep measures. Our findings broaden the scope of the negative health outcomes associated with the ISSD phenotype in the context of chronic pain. Early assessment of these phenotypes may possibly improve the ability to identify individuals at risk for poor pain outcomes and assist in designing more effective and personalized treatment procedures. Future studies should also examine racial disparities within the insomnia phenotypes, as well as the role of the ISSD phenotype in treatment response to behavioral and pharmacological sleep and pain treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data Availability Statement:

The data underlying this article are available in the article and in its online supplementary material.

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Highlights

- Women with objective short sleep duration insomnia have a more severe pain profile

- Objective short sleep duration insomnia is associated with elevated IL-6 levels

- Greater proportion of Black participants exhibited short sleep duration insomnia

- Black participants showed significantly worse pain profiles than White participants

Table 1.

Socio-demographic comparisons by insomnia phenotypes

>	INSD n = 97	ISSD n = 31	p-value[1]
Age	34.9 (11)	40.4 (11.1)	**.02**
Race			**<.001**
Black	11.3%	46.7%	
White	78.3%	50.0%	
Others	10.3%	3.3%	
Ethnicity			.28
Hispanic or Latino	7.2%	0%	
Not Hispanic or Latino	92.8%	100%	
Education			.053
Some high school	1.0%	0%	
High school graduate/GED	5.1%	24.1%	
Technical school graduate	1.0%	0%	
Some college	18.6%	31.0%	
College graduate	45.4%	27.6%	
Master's degree	25.7%	13.8%	
Doctoral degree	3.1%	3.4%	
Marital Status			.43
Divorced	4.2%	3.7%	
Living with Partner	5.2%	7.4%	
Married	38.5%	37.0%	
Separated	1.0%	3.7%	
Single	51.0%	44.4%	
Widow/Widower	0%	3.7%	
Income			.94
$25,000 or less	38.5%	34.5%	
$25,001 to $50,000	33.0%	37.9%	
$50,001 to $75,000	16.5%	13.8%	
$75,001 or over	12.1%	13.8%	

[1] Statistical tests performed: t-test; chi-square test

Table 2.

Sleep, and physical and mental health characteristics comparisons by insomnia phenotypes

	INSD n = 97	ISSD n = 31	p-value[1]
Sleep Continuity			
TST	466.4 (56.1)	280.8 (56.3)	< **.001**
SOL	21.7 (29.0)	40.4 (44.2)	**.033**
WASO	37.4 (36.1)	68.3 (65.4)	**.017**
SE%	89.2 (7.5)	73.8 (16.0)	< **.001**
Sleep Architecture			
Stage N1 Duration	19.9(10.6)	15.8 (13.3)	.12
Stage N2 Duration	244.4 (48.2)	143.3 (40.5)	< **.001**
Stage N3 (SWS) Duration	91 (34.9)	64.2 (29.9)	< **.001**
REM Duration	111.1 (35.6)	57.4 (28.8)	< **.001**
Apnea Hypopnea Index (AHI)	1.3 (1.9)	2.2 (2.3)	.053
Respiratory Disturbance Index (RDI)	2.6 (3.4)	4.0 (3.8)	.056
BMI	27.9 (5.4)	28.8 (5.5)	.44
TMD Duration (months)	65.1 (69)	57.7 (66.3)	.62
TMD Diagnosis			1.0
Myalgia only	2.2%	0%	
Arthralgia only	0%	0%	
Combined (Myalgia + Arthralgia)	97.8%	100%	
Systolic Blood Pressure (baseline)	107 (12.7)	114.2 (12.3)	**.007**
Diastolic Blood Pressure (baseline)	70 (10.9)	76.4 (9.8)	**.003**
Insomnia Severity Index (ISI)	15.3 (3.8)	18.0 (4.3)	**.003**
Depressive Symptoms (CES-D)	17.9 (7.5)	18.7 (8.9)	.60
Anxiety Symptoms (GAD-7)	8.8 (4.7)	8.8 (4.4)	.99

Note.

[1] Statistical tests performed: t-test; chi-square test of independence.

TST = Total Sleep Time, SOL = Sleep Onset Latency, WASO = Wake After Sleep Onset, SE % = Sleep Efficiency Percentage, SWS = slow-wave sleep, CES-D, Center for Epidemiological Studies Depression scale. GAD-7, Generalized Anxiety Disorder-7 item scale.

Table 3.

Association of ISSD with QST and IL-6

Predictors	General Pain Sensitivity Index				Central Sensitization Index				PPTh Masseter				Cold Pressor Tolerance				Baseline IL-6			
	B	SE	95% CI	p	B	SE	95% CI	p	B	SE	95% CI	p	B	SE	95% CI	p	B	SE	95% CI	p
Intercept	−.27	.27	−.82–−.27	.324	−.57	.28	−1.13–−.01	**.046**	117.92	22.44	73.51–162.33	**<.001**	26.55	43.73	−60.03–113.12	.545	−.73	.24	−1.21–−.24	**.004**
ISSD vs. INSD	.23	.12	.00–46	**.049**	.24	.12	.01–48	**.045**	−7.89	9.44	−26.57–10.79	.405	−57.20	18.47	−93.77–−20.62	**.002**	.27	.10	.06–.47	**.011**
Age	−.00	.00	−.01–−.01	.878	−.00	.00	−.01–.01	.886	−.07	.37	−.81–.66	.842	−.27	.74	−1.73–1.19	.717	−.01	.00	−.01–.00	.197
BMI	.01	.01	−.01–.03	.296	.02	.01	.00–.04	**.043**	.75	.75	−.73–2.22	.320	2.69	1.46	−0.20–5.57	.067	.03	.01	.01–.05	**<.001**

Note. ISSD, insomnia with short sleep duration. INSD, insomnia with normal sleep duration. QST, quantitative sensory testing. PPTh, pressure pain thresholds. IL-6, interlukin-6.

Table 4.

Association of ISSD with self-reported pain and jaw function outcomes

Predictors	Pain Severity			Pain Interference			Pain Catastrophizing			Functional Limitation of the Jaw		
	B	SE	95 % CI	p	B	SE	95 % CI	p	B	SE	95 % CI	p	B	SE	95 % CI	p
Intercept	2.26	.79	.69 – 3.82	**.005**	2.33	1.00	.36 – 4.30	**.021**	28.08	4.77	18.64 – 37.52	**<.001**	38.07	15.25	7.88 – 68.26	**.025**
ISSD vs. INSD	1.14	.33	.48 – 1.80	**.001**	.69	.42	–.14 – 1.52	.101	3.80	2.01	–.17 – 7.77	.060	24.29	6.42	11.59 – 36.99	**<.001**
Age	.02	.01	–.00 – .05	.080	.02	.02	–.01 – .06	.160	.08	.08	–.08 – .23	.343	–.10	.25	–.60 – .40	.705
BMI	.03	.03	–.02 – .09	.208	.01	.03	–.05 – .08	.656	–.32	.16	–.64 – –.01	**.045**	.26	.51	–.75 – 1.26	**.610**

Note. ISSD, insomnia with short sleep duration. INSD, insomnia with normal sleep duration.