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RESEARCH ARTICLE

To what degree patient-reported symptoms of central sensitization, kinesiophobia, disability, sleep, and life quality associated with 24-h heart rate variability and actigraphy measurements?

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[Correction added on 15 December 2023, after first online publication: The first three authors last and first names were wrongly swapped and were corrected in this version.]

Abstract

Objectives: Chronic musculoskeletal pain is associated with decreased parasympathetic and increased sympathetic activity in the autonomic nervous system. The objective of this study was to determine the associations between objective measures of heart rate variability (a measure of autonomic nervous system function), actigraphy (a measure of activity and sleep quality), respiration rates, and subjective patient-reported outcome measures (PROMs) of central sensitization, kinesiophobia, disability, the effect of pain on sleep, and life quality.
Methods: Thirty-eight study subjects were divided into two subgroups, including low symptoms of central sensitization ($n=18$) and high symptoms of central sensitization ($n=20$), based on patient-reported scores on the Central Sensitization Inventory (CSI). Heart rate variability (HRV) and actigraphy measurements were carried out simultaneously in 24 h measurement during wakefulness and sleep.
Results: A decrease in HRV during the first 2 h of sleep was stronger in the low CSI subgroup compared to the high CSI subgroup. Otherwise, all other HRV and actigraphy parameters and subjective measures of central sensitization, disability, kinesiophobia, the effect of pain on sleep, and quality of life showed only little associations.
Discussion: The high CSI subgroup reported significantly more severe symptoms of disability, kinesiophobia, sleep, and quality of life compared to the low CSI subgroup. However, there were only small and nonsignificant trend in increased sympathetic nervous system activity and poorer sleep quality on the high central sensitization subgroup. Moreover, very little differences in respiratory rates were found between the groups.

KEYWORDS
actigraphy, breathing rate, central sensitization, chronic musculoskeletal pain, heart rate variability, kinesiophobia, patient-reported outcome measure, sleep quality

OBJECTIVES

Chronic musculoskeletal pain (CMP) is defined by the International Association for the Study of Pain as "persistent pain that arises as part of a disease process directly affecting bone(s), joint(s), muscle(s), or related soft tissue(s) of more than 3 months duration".[1] CMP is a major societal, individual, and economic burden affecting between 13.5% and 47% of the general population in the world.[2,3] Multiple distinct changes in the central nervous system have been identified in subjects with CMP.[4–6] One of the major identified changes in subjects

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with CMP is decreased parasympathetic nervous system (PNS) activity and increased sympathetic nervous system (SNS) activity of the autonomic nervous system (ANS).[7–11]

Patient-reported outcome measures (PROMs) are standardized, validated, and subjective self-administrated questionnaires.[12,13] Numerous PROMs are used to evaluate various factors related to CMP.[14,15] Some widely used and validated CMP-related PROMs assess central sensitization,[16] kinesiophobia (fear of movement),[17] low back pain-related disability,[18] quality of life,[19] and effect of pain on sleep.[20] Research evidence of associations between CMP-related PROMs and function changes of the ANS are limited to three studies with 10 or fewer minutes of heart rate variability (HRV) measures. Results found weak-to-moderate correlations between HRV parameters and perceived level of disability, catastrophizing, kinesiophobia, and symptoms of central sensitization.[21–23]

Heart rate variability refers to the temporal variation of beat-to-beat intervals between heartbeats.[24] A growing body of literature suggests that organized variability in the heart rate pattern is a reasonable index of physical and emotional health.[25,26] HRV is a commonly used method for assessing the balance between the sympathetic and parasympathetic parts of the ANS.[24] Increased sympathetic nervous system activity is associated with "fight-or-flight" and decreased HRV. Conversely, increased parasympathetic nervous system activity is associated with the "rest and digest" activity of ANS and increased HRV.[27] In addition to the cardiovascular system, the ANS is part of the regulation system of wakefulness and sleep.[28] CMP and sleep disturbance are highly correlated, with more severe pain being associated with more severe impairment in sleep quality.[29,30] Studies have revealed that subjects with CMP often have difficulty with sleep initiation and maintenance during the night.[31] Actigraphy is a commonly used method to assess sleep quality parameters. It uses an acceleration-based method, often with wrist-worn devices, for measuring movement, which can help estimate sleep–wake patterns, sleep continuity versus fragmentation, and general sleep quality.[32] Actigraphy has shown over 90% sensitivity in detecting subjects' sleeping state compared to polysomnography, which is considered a gold standard method of assessing sleep.[32]

A faster breathing rate is identified in subjects with CMP.[33,34] Because of this, breathing exercises aimed to slow breathing rates are successfully incorporated into the treatment of various CMP syndromes.[33,35–37] However, despite strong evidence of a treatment effect of therapeutic breathing methods, respiration rate during the 24 h related to the most commonly studied CMP symptoms are not directly studied previously.

The objective of this work was to study the associations between PROMs of central sensitization, disability, kinesiophobia, the effect of pain on sleep, and quality of life and 24-h ambulatory HRV and actigraphy measurements during wakefulness and sleep. In addition, we studied association between PROMS and respiration rate during wakefulness and sleep. To the best of our knowledge, these objectives have not been previously studied simultaneously with HRV and actigraphy measurements in 24-h measurement.

MATERIALS AND METHODS

Ethical approval and consent to participate

Ethical approval for the study was obtained from the Research Ethics Committee of the Northern Savo Hospital District with identification number 1106/13.02.00/2018. Written informed consent was received from all subjects before the data collection. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were adhered to in this study.[38]

Data collection and subjects

The subjects were recruited from a cross-cultural validation study of the Central Sensitization Inventory (CSI). This study was carried out partly simultaneously in a single chiropractic clinic in Helsinki Finland from May 2019 to March 2020.[39] The subjects completed an online demographic form including age, gender, height, and weight. Body mass index was calculated in the data analysis phase from subject-reported height and weight data. All subjects included in this study met the following inclusion criteria: (a) Age between 18 and 65 years and (b) Proficient in written and spoken Finnish language. Exclusion criteria were as follows: (a) History of a malignant tumor; (b) History of diagnosed trauma potentially negatively affecting the central nervous system (including whiplash or mild traumatic brain injury); (c) History of diagnosed disease negatively affecting the central nervous system (including multiple sclerosis, Alzheimer's disease, Parkinson's disease, and dementia); (d) chronic obstructive pulmonary disease; (e) bundle-branch block or chronic arrhythmias; (f) spinal surgery in the last 12 months; (g) a cardiac pacemaker; and (h) not completing online form of demographic data.

For each subject in this study, a collection of physiological measurements of actigraphy and HRV were carried out between December 2019 and March 2020 and between August 2020 and November 2020. The break in data collection was due to the COVID-19 outbreak in Finland. From a total of 229 subjects recruited in the CSI validation study,[39] those with CSI scores ≤30 (low CSI subgroup) and CSI scores ≥40 (high CSI subgroup) were invited to participate in this study. Group scores were based on previously established clinically relevant severity levels of CSI, where the score of ≤30 clinically

translates as mild and ≥40 as severe.[40] The recruitment process was stopped when the required 20 subjects per group were recruited. After data collection began, two additional subjects with low CSI scores were excluded due to the poor quality of HRV data, which left 18 subjects in the low CSI subgroup and 20 subjects in the high CSI subgroup. Subjects also completed an online form of pain history and PROMs on the same day, or the following day, as the physiological 24-h measurements were carried out. A flowchart of subjects is presented in Figure 1.

Subject-reported pain-related variables

Pain history

All subjects completed a structured web-based pain history assessment with binary questions (yes/no), including the presence of chronic low back pain (CLBP), referral to a leg (if yes to CLBP), the experience of other ongoing chronic musculoskeletal pain, and presence of chronic headaches. The subjects were further divided into three pain history groups (a) pain-free control group (no CLBP, pain intensity 0, no other chronic musculoskeletal pain, and no chronic headache), (b) pain in a single body area (CLBP group with or without leg referral or other chronic musculoskeletal pain or chronic headache), and (c) multisite chronic pain (two or more of the following: CLBP with or without radiculopathy, other chronic musculoskeletal pain and/or chronic headache). CLBP is the most common CMP diagnoses[41] and is defined as pain present for more than 3 months and more than 3 days per week.[42] Generally, subjects with CMP tend to have PROMs scores indicating more severe related CMP symptomology, but not without exceptions,[13] which also have been confirmed in previously published studies of this same cohort.[39,43,44] Moreover, subjects with multisite pain distribution tend to have more comorbid biopsychosocial health issues.[45] In this study, we concentrated not only on associations between HRV/actigraphy measurements and PROMs, but also included pain status to inform the pain history of subjects.

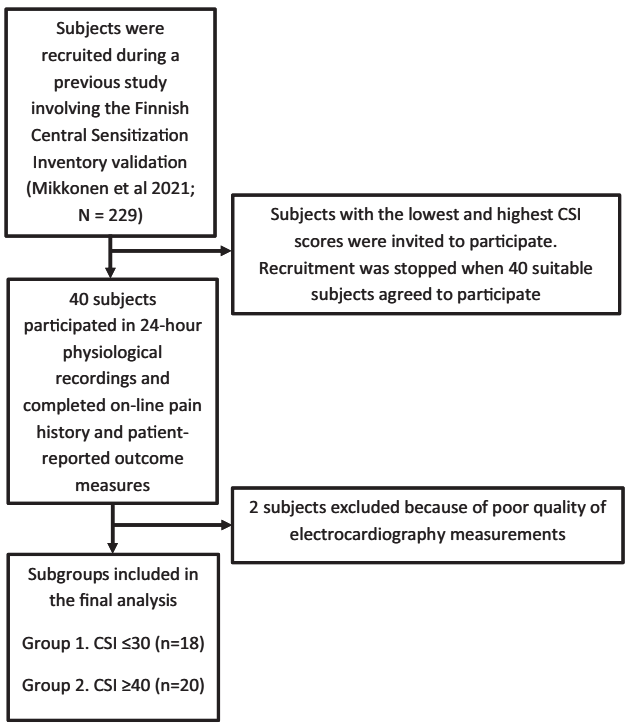

FIGURE 1 Flowchart.

PROMs

The Central Sensitization Inventory (CSI) was developed as a screening tool for symptoms related to central sensitization.[16] It is considered the leading PROM for assessing CS-related symptomology.[46] The CSI is a two-part questionnaire. Part A includes 25 questions about CS-related symptomology, with a total score range of "0" to "100." Items are rated on the Likert scale: 0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = always. A ≥40 cutoff score has been proposed for reliable discrimination of subjects whose presenting symptomology is likely related to central sensitization.[16,40] Part B contains questions about previously diagnosed Central Sensitization syndromes and related disorders in the form of "No/Yes, and year diagnosed." CSI part B is only for additional information and is not scored. It includes binary questions (yes/no) and year of previous diagnoses such as fibromyalgia, neck injury, restless legs syndrome, temporomandibular joint disorder, or migraine/tension headaches.[16] In this study, we extracted the number of subjects who reported previous fibromyalgia diagnoses from CSI part B for further analysis. A Finnish version of the CSI, which has been previously translated and cross-culturally validated in a Finnish population.[39]

The Tampa Scale of Kinesiophobia (TSK) evaluates kinesiophobia (fear of movement). The TSK is a 17-item questionnaire used to assess subjective kinesiophobia on a Likert scale: 1 = strongly disagree, 2 = disagree, 3 = agree, and 4 = strongly agree. The range of scores is from 17 to 68. Higher scores indicate a more severe level of kinesiophobia.[47] A Finnish version of the TSK, which has previously been translated into Finnish and validated in the Finnish population, was used in this study.[48]

The Roland–Morris Disability Questionnaire (RMDQ) is a 24-item measure designed to evaluate the perceived level of disability related to chronic low back pain.[49] For each item, disability in performing specific daily activities is indicated by "yes" or "no." The RMDQ is scored by adding up the number of items checked "yes." Total scores range from 0 to 24, with higher scores indicating a higher level of disability related to low back pain.[50]

The Pain and Sleep Questionnaire 3-Item Index (PSQ-3) assesses the impact of pain on sleep during the past week.[51] It is measured on a numerical 11-point rating scale from 0 to 10. Zero indicates "never" and 10 indicates "always." Thus, the final score range is from 0 to 30. A Finnish version of the PSQ-3, which has been previously translated and cross-culturally validated in a Finnish population, was used in this study.[43]

The EuroQol (EQ-5D-5L) assesses health-related quality of life in the five dimensions.[52] The dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response levels: 0 = no problems, 1 = slight problems, 2 = moderate problems, 3 = severe problems, and 4 = unable to /extreme problems. A second part of the EQ-5D-5L is the EQ visual analog scale (EQ VAS).[52] Because there is currently no Finnish standard value set available, a value set from Denmark was used to calculate the index value as recommended by the EuroQol EQ-5D-5L User Guide.[53]

Twenty-four-hour physiological measurements

Measurements always began on Tuesday afternoon and ended ~24 h later on Wednesday. The physiological measurement equipment was setup by a trained colleague at the clinic and the equipment was returned via mail. Simultaneous electrocardiography (ECG) and acceleration-based actigraphy data were recorded for 24 h. The ECG was recorded with a Bittium Faros 180 Holter device (Bittium Oyj, Oulu, Finland) with a 250 Hz sampling rate using three wet gel electrodes (BlueSensor VLC, Ambu A/S, Ballerup, Denmark) placed under the left and right collarbones and below the left rib cage. Simultaneously, actigraphy was measured with an ActiGraph GT9X link research-grade activity bracelet (ActiGraph LLC., Pensacola, FL) with a 30 Hz sampling rate.

Heart rate variability (HRV) measures

Heart rate variability analyses were carried out using Kubios HRV Premium 3.5 software (Kubios Oy, Kuopio, Finland). The software automatically detects RR intervals (time intervals between successive ECG R-waves), and corrects missed, extra, and misaligned (including ectopic) beats using a validated algorithm.[54,55] Furthermore, periods of noisy measurement data were automatically identified and excluded from HRV analysis. Finally, very low-frequency components were removed from the HRV data since the baseline drift of ambulatory HRV data is not directly related to the short-term regulation of heart rate by the sympathetic and parasympathetic branches of the ANS.[56] All HRV analyses were carried out by a trained data analyst (SK), who also visually verified that only good-quality sinus rhythm data were analyzed.

Heart rate variability was assessed using the mean RR interval (mean RR), the standard deviation of normal-to-normal beat intervals (SDNN), the root mean square of successive RR interval differences (RMSSD), and the ratio of the standard deviations SD2 and SD1 from the Poincaré plot (SD2/SD1). In addition, an estimate of the respiratory rate derived from the ECG data was obtained from the Kubios HRV software. The respiratory rate estimate is based on analyzing the respiration-induced changes in the ECG R-wave amplitude and RR interval time series.[57] The descriptions of the HRV parameters are given in Table 1.

Sleep-time HRV analysis was conducted using two approaches. First, HRV variables were assessed for the entire duration of sleep, commencing at bedtime and concluding upon awakening, to evaluate sleep-time HRV across different study groups. Second, recognizing the inherent interindividual variability in HRV parameters,[58] a 15-min baseline HRV was established for each subject, starting from the time they went to bed. Individual HRV changes from this baseline were subsequently evaluated during the initial 4 h of sleep at 15-min intervals. Essentially, the first 4 h of sleep were partitioned into nonoverlapping 15-min segments, HRV variables were computed for each segment, and changes in HRV from the baseline were analyzed in relation to time. This latter analysis aimed to identify potential group differences in the initiation of sleep.

Actigraphy measures

The actigraphy data were analyzed with Actilife 6.0 analysis software (ActiGraph LLC., Pensacola, FL). Actilife uses the Cole–Kripke algorithm[59] for sleep scoring. In this work, the sleep–awake patterns were analyzed with a 60-s window. The sleep quality parameters were evaluated using the Actilife implementation of the Tudor-Locke method.[60] Sleep quality was assessed through total sleep time (TST), sleep efficiency (SE), number of awakenings (NOA), and wake after sleep onset (WASO). The sleep quality parameters are described in more detail in Table 1. In addition, actigraphy data were used to determine the daytime activity levels. Activity levels were evaluated with cut points described by Freedson et al.[61] The cut points were 0–99 counts for sedentary, 100–1951 for light, 1952–5724 for moderate, 5725–9498 for vigorous, and 9499 and above for very vigorous activity.

Diary

In addition to the physiological measures, subjects kept an activity diary during the 24-h measurement period. They were asked to document their prescribed

TABLE 1 Heart rate variability and actigraphy measures.

Measure/parameter	Units	Description	Clinical interpretation
Heart rate variability (HRV)			
Mean RR intervals	ms	RR refers to the intervals between successive heartbeats, which is inversely proportional to mean heart rate	PNS↑ and SNS↓
Standard deviation of normal–normal intervals (SDNN)	ms	SDNN demonstrate overall HRV variability	PNS↑ and SNS↕
Root mean square of successive differences (RMSSD)	ms	RMSSD demonstrate HRV beat-to-beat variation	PNS↑
Poincaré SD2/SD1		The Poincaré plot ratio is a nonlinear measure of ANS balance.	PNS↓ and SNS↑
Respiration rate	breaths/min	Electrocardiogram-derived mean respiration rate	
Actigraphy			
Sleep efficiency (SE)	%	The ratio between the total sleep time and the time spent in bed	>85% is considered good sleep quality
Total sleep time (TST)	min	The amount of time the participant has been asleep during the intended sleep period	General recommendation 7–9 h per night
Number of awakenings (NOA)		The number of 1-min or longer awakenings during the sleep period	≤2 awakenings of duration over 5 min are considered good sleep quality
Awake after sleep onset (WASO)	min	The cumulative time spent awake in bed after sleep onset	≤20 min indicates good sleep quality

Abbreviations: ANS, autonomic nervous system; PNS, Parasympathetic nervous system; SNS, sympathetic nervous system.

medications, daily activities and estimated time of sleep onset, and estimated rising time in the precision of 30 min. The beginning and end of sleep were extracted for each subject based on their HRV and actigraphy data and diary notes.

Statistical methods

Statistical analysis of demographics and subject-reported data was performed using the SPSS version 27 (IBM SPSS Statistics for Windows, Version 27.0. IBM Corp, Armonk, NY). Statistical significance was defined as $p < 0.05$. Data were shown as N (%) or mean (95% confidence interval lower and upper bound or standard deviation). Normal or non-normal data distribution was evaluated by Shapiro-Wilks tests and histograms. Group comparisons for non-normally distributed data were calculated by Mann–Whitney U-test. Categorical variables were compared by Pearson Chi-square (χ^2) tests. Physiological measurements were analyzed by comparing the HRV, sleep quality parameters, and activity levels between the low CSI (≤30) and high CSI (≥40) subgroups of scores. The statistical differences were evaluated by one-way-ANOVA using a built-in function anova1 on MATLAB (version R2022a, MathWorks inc., Natick, MA). Before ANOVA, a one-sample Kolmogorov–Smirnov normality test was applied for each parameter using the kstest function with the default 0.05 significance level on MATLAB. There are no previous studies with similar 24-h HRV measurement protocol study association with PROMs used in this study. Hence, group sample sizes were not based on sample size calculation.

RESULTS

Demographic characteristics of the sample

Demographic and subject-reported symptoms are presented in Table 2. There were no differences in age, gender, height, weight, and BMI between the low and high CSI groups. However, significant differences were found between the two groups in all pain parameters and subject-reported symptoms on the PROMs.

Wakefulness HRV and activity

Wakefulness HRV and activity results for the study groups are presented in Table 3. No significant differences were found in wakefulness HRV parameters, respiration rate, and activity levels between the two groups.

Sleep-time HRV and sleep quality

Night-time HRV and sleep quality were assessed for the entire night, starting from the detected beginning of sleep at bedtime and ending at the detected wake-up

TABLE 2 Group comparison of baseline data ($N=38$).

Variable	Group 1: CSI ≤ 30 ($n=18$)	Group 2: CSI ≥ 40 ($n=20$)	Group comparison (p-value)
Pain history			
Pain-free control	8 (44%)	2 (10%)	<0.01*
Single site chronic pain	7 (39%)	1 (5%)	<0.01*
Multisite chronic pain	3 (17%)	17 (85%)	<0.01*
Demographics			
Age	45.3 (39.4–51.2)	48.2 (42.4–53.9)	0.41
Gender: Female, *N* (%)	14 (85%)	18 (90%)	0.63
Height (cm)	170.4 (166.2–174.7)	169.9 (166.6–173.2)	0.9
Weight (kg)	72.8 (66.1–78.5)	75.6 (69.7–81.5)	0.38
BMI (kg/m^2)	24.8 (23.2–26.4)	26.2 (24.3–28.2)	0.32
Patient-reported outcome measures			
CSI part A	22.3 (19.6–24)	51.7 (47.8–55.5)	<0.01*
CSI part B	0.4 (0.1–0.7)	1.9 (1.2–2.6)	<0.01*
Fibromyalgia diagnosis	0	2 (10%)	
TSK	24.3 (22.3–26)	35.5 (32.1–38.9)	<0.01*
RMDQ	1.1 (0.2–1.9)	3.5 (2.1–4.8)	<0.01*
PSQ-3	3.8 (0.0–7.7)	10.6 (7.7–13.6)	<0.01*
EQ-5D-5L	0.85 (0.80–0.89)	0.73 (0.66–0.80)	<0.01*

Note: Data presented as *N* (%) or mean (95% confidence interval lower and upper bound). Central Sensitization Inventory (CSI part A), number of central sensitivity-related diagnoses (CSI part B). Group comparison with Mann–Whitney and Pearson Chi-square (χ^2) tests, statistical significance $p<0.05$*.

Abbreviations: EQ-5D-5L, the EuroQol 5-level EQ-5D version; PSQ-3, Pain and Sleep Questionnaire Three-Item Index; RMDQ, Roland-Morris Disability Questionnaire; TSK, Tampa scale of kinesiophobia.

TABLE 3 Group comparison of wakefulness HRV and activity levels ($N=38$).

Variable	Group 1: CSI ≤ 30 ($n=18$)	Group 2: CSI ≥ 40 ($n=20$)	Group comparison (p-value)
Wakefulness HRV			
Mean RR (ms)	787 (747–827)	769 (724–814)	0.54
SDNN (ms)	38.1 (27.6–48.4)	30.4 (24.6–36.3)	0.18
RMSSD (ms)	29.8 (17.7–41.9)	23.6 (17.6–29.7)	0.33
Poincaré SD2/SD1	2.7 (2.5–3.0)	2.8 (2.5–3.0)	0.93
Respiration rate in minute	17.9 (17.1–18.7)	17.6 (16.6–18.5)	0.61
Wakefulness activity levels			
Sedentary (min)	212 (176–248)	254 (205–302)	0.16
Light (min)	474 (433–514)	429 (390–468)	0.11
Moderate (min)	194 (155–233)	224 (179–269)	0.30
Vigorous (min)	17.8 (9.6–26.1)	18.7 (7.7–29.7)	0.90
Very vigorous (min)	2.6 (−0.2 to 5.5)	1.5 (−0.4 to 3.4)	0.50

Note: Data presented as *N* (%) or mean (95% confidence interval lower and upper bound). The standard deviation of normal-to-normal beat intervals (SDNN), the root mean square of successive RR interval differences (RMSSD), and the ratio of the standard deviations SD2 and SD1 from the Poincaré plot (SD2/SD1).

and rising time. Night-time HRV and sleep quality for the study groups are presented in Table 4. There were no statistically significant differences in night-time HRV or sleep quality variables between the study groups. Though nonsignificant, the mean RR was somewhat longer (lower HR), sleep efficiency was about 2% higher, and total sleep time was about 36 min longer for group 1 compared to group 2.

In addition to the whole night HRV analysis, we analyzed the first 4 h of sleep in 15-min windows to see how the HRV changed at the beginning of the sleep. This time trend analysis was carried out because subjects with CMP may have challenges in sleep initiation.[31] Since the magnitude of HRV at rest is highly interindividual,[58] the HRV parameter time trends are reported as changes from the first 15-min window, that is, as differences to

TABLE 4 Group comparison in HRV during sleep and on actigraphy-based sleep quality parameters ($N=38$).

Variables	Group 1: CSI ≤ 30 ($n=18$)	Group 2: CSI ≥ 40 ($n=20$)	Group comparison (p-value)
HRV during sleep			
Mean RR (ms)	1028.6 (960.9–1096.3)	973.0 (917.5–1028.4)	0.19
SDNN (ms)	49.4 (31.5–67.4)	40.6 (30.6–50.6)	0.36
RMSSD (ms)	47.5 (25.5–69.5)	40.1 (26.8–53.4)	0.54
Poincaré SD2/SD1	2.1 (1.9–2.4)	2.0 (1.8–2.3)	0.65
Respiration rate in minute	14.8 (13.7–16.0)	14.3 (13.4–15.2)	0.46
Sleep quality			
Sleep efficiency	85.8 (83.0–88.6)	83.7 (80.7–86.7)	0.29
TST	418.8 (389.5–448.1)	383.2 (350.5–415.9)	0.10
WASO	63.9 (50.3–77.5)	71.1 (54.5–87.6)	0.49
NOA	23.3 (19.5–27.2)	23.1 (18.3–27.8)	0.93

Note: Data presented as N (%) or mean (95% confidence interval lower and upper bound). The standard deviation of normal-to-normal beat intervals (SDNN), the root mean square of successive RR interval differences (RMSSD), and the ratio of the standard deviations SD2 and SD1 from the Poincaré plot (SD2/SD1).
Abbreviations: NOA, number of awakenings; SE, sleep efficiency; TST, Total sleep time; WASO, wake after sleep onset.

the in-bed time HRV. Changes in HRV parameters for the first 4 h of sleep are illustrated in Figure 2. Mean RR increased (HR decreases) faster for group 1 compared to group 2 and was significantly different ($p=0.03$) between the groups at 1 h 45 min after in-bed time. In addition, the overall HRV measured by SDNN increased faster for group 1 compared to group 2, being significant at two time points around 2 h after bedtime ($p=0.03$ and $p=0.02$). It must be noted that only 5% (three out of 60) of 15-min windows HRV comparisons were significantly different.

DISCUSSION

Subjects were initially divided into low CSI and high CSI subgroups. Only very few significant associations were found between the subgroups in measures of 24-h HRV, 24-h actigraphy, and subjective symptoms of central sensitization, kinesiophobia, low back pain-related disability, pain-related sleep disturbance, and quality of life. However, there was overall little trend toward increased sympathetic nervous systems activity and poorer sleep quality in the higher score CSI subgroup. Clinically, this was the most pertinent finding because the associations between subjective central sensitization and HRV had not been studied before. Previously, higher scores of CSI have shown weak or no associations between objective other measures of nociceptive sensitivity of pain threshold, heat pain threshold, conditioned pain modulation, and temporal summation.[62]

The recent high-quality study demonstrated a similar lack of significant HRV findings with pain intensity.[63] Hence, our findings challenge the use of HRV measurements as an objective outcome measurement in future clinical trials related to CMP conditions, because there is only little association with the subjective core outcome measures of pain intensity, disability, and quality of life.[64]

It is known that demographic factors, such as sex, age, and body mass index have major effects on HRV results.[65] In our cohort, there were no significant intergroup differences in demographics or activity levels during waking hours or baseline values of sleep quality between the two groups, which may have affected our findings.

The most marked finding was a stronger decrease in heart rate and an increase in HRV parameters during the first 2 h of sleep in subjects who reported lower levels of central sensitization. This indicates higher parasympathetic recovery, which has previously been linked to better sleep quality and shorter sleep latency.[66] However, the overall trend showed smaller differences in HRV and there were only little subgroup differences in sleep quality measured by actigraphy.

We also investigated the association between respiration rates and subjective symptoms between the low and high CSI groups. No significant differences in respiratory rates were found between the groups, either during wakefulness or during sleep. These negative findings challenge the common understanding that CMP and contributing factors are meaningfully associated with faster mean respiration rates.[33,34]

Heart rate variability measurement methods vary greatly in studies involving subjects with CMP.[8] Only three previous studies have directly assessed the association of PROMs to HRV in CMP subjects. They all used very short HRV measurement protocols (10 min or less) and found little associations with central sensitization, catastrophizing, fear of movement, and disability.[21–23]

A previous meta-analysis of HRV studies comparing chronic pain subjects with pain-free controls showed evident differences in HRV measures.[8] The results of this meta-analysis were heavily influenced by studies that

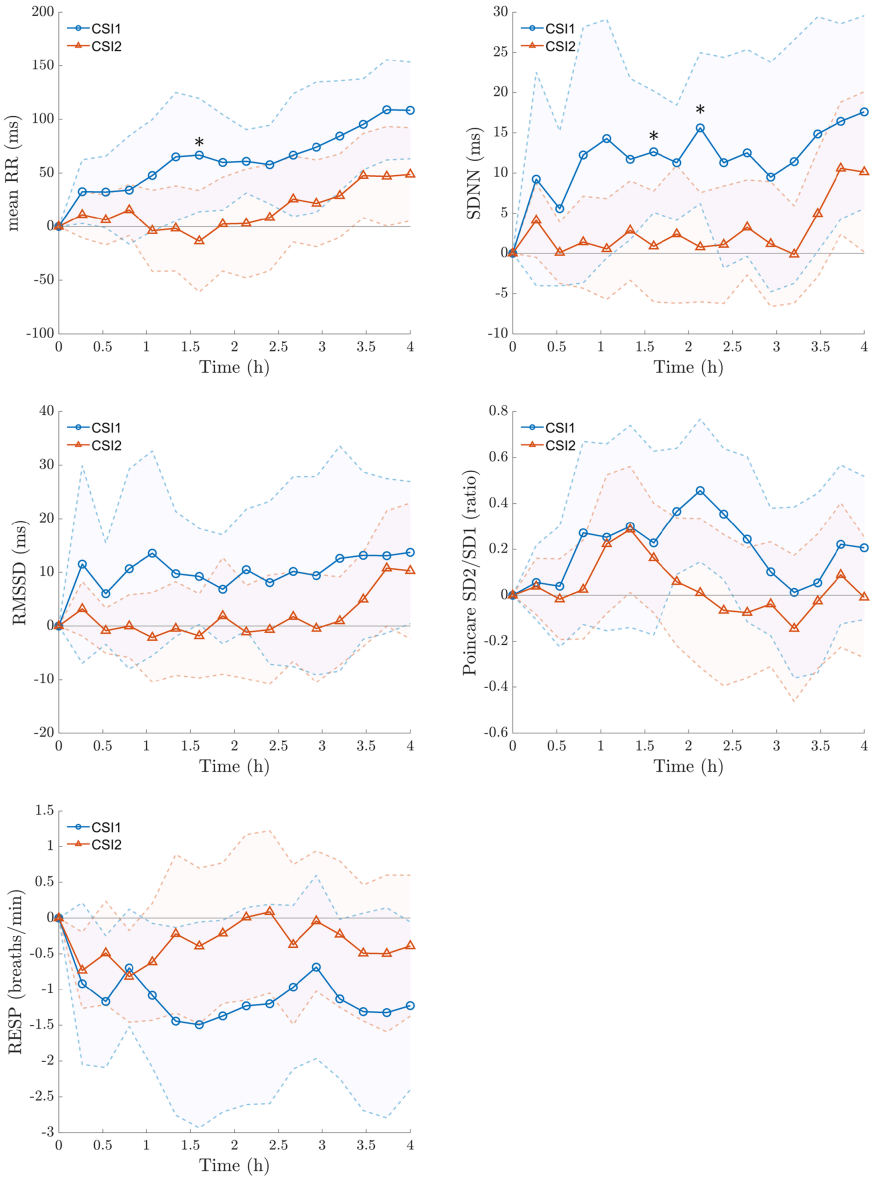

FIGURE 2 The changes in HRV parameters and respiration rate during the first 4 h of sleep for the two study groups. Data presented as mean (bold lines) and 95% confidence intervals (dash lines).

included subjects with fibromyalgia, which was not the case in our study. Only 10% of subjects in the high subjective symptoms group, and none of the subjects in the low symptom group, reported a previous fibromyalgia diagnosis in CSI part B. This difference may partially explain our more marginal results compared to this meta-analysis. It should also be noted that the meta-analysis compared chronic pain subjects with healthy controls, which was not the case in this study.

STRENGTHS

This study had several strengths, including (a) strict inclusion and exclusion criteria; (b) well-defined study groups; (c) a state-of-the-art 24-h HRV measurement protocol, including simultaneous actigraphy; and (d) reliable differentiation between periods of sleep and wakefulness.

LIMITATIONS

Most of the study subjects were females (84%), which limits the generalization of results to male populations. HRV measurements differ greatly between individuals and across the studies, leading to the unavoidable situation where the variability of the results is large.[58] This trend was observable also in our results, and hence, it is likely that our study cohort was too small for the adequately powered study. However, previous studies with similar cohort sizes have shown

meaningful ANS function differences between subjects with CMP and pain-free controls on HRV[8] and actigraphy measures.[67,68] Another limitation is that we did not incorporate medication use as a factor in our analysis. Almost half of the study participants (18/38) reported regular use of one or more medications. Medication use was more common in group 2 (14/20) compared to group 1 (4/18). However, as there were no significant differences between the groups in the daytime HRV, it appears that the medications used did not have a significant effect on HRV.

CONCLUSION

Almost all HRV and actigraphy parameters and subjective measures of central sensitization, disability, kinesiophobia, the effect of pain on sleep and quality of life showed only little association during wakefulness and sleep. Overall, there were small and nonsignificant trend for increased sympathetic nervous system activity and poorer sleep quality in the high central sensitization subgroup.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data of this study are available from the corresponding author upon reasonable written request.

DISCLAIMER

We declare that this article is original, has not been published before, and is not currently being considered for publication elsewhere. As corresponding author, I confirm that this article has been read and approved for submission by all the named authors.

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