ORIGINAL ARTICLE

Sleep Science

Sleepiness comorbid to musculoskeletal pain is associated with worse quality of life and mood symptoms in a general population sample

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ABSTRACT

Objectives: Musculoskeletal (MSK) pain and hypersomnolence (HPS) are very disabling conditions that may share some pathophysiological factors. This study aimed to evaluate the interaction between MSK pain and HPS and its association with mood symptoms, fatigue, quality of life, and both objective and subjective sleep quality. **Design:** Cross-sectional study. **Setting:** General population based sample. **Participants:** 510 individuals from EPISONO cohort, São Paulo (Brazil). **Measurements:** All participants completed questionnaires, had clinical assessment and underwent a full-night polysomnography. HPS was defined according to Epworth Sleepiness Scale while the presence of MSK pain was defined by structured questionnaire. The sample was allocated into 4 groups: control (CTRL, n=281), HPS (n=141), MSK (n=50), and both conditions (HPS+MSK, n=38). **Results:** MSK pain and HPS by themselves were associated with worse mood symptoms and quality of life. However, individuals with both associated conditions (HPS+MSK) presented higher frequencies of moderate to severe depression (44.1%) and anxiety symptoms (45.7%), as well as an additional decrease in quality of life compared to the other groups. There were no differences between HPS+MSK and MSK groups in objective sleep pattern. With regard to subjective sleep, HPS+MSK presented a higher prevalence of sleep attacks and cataplexy compared to all other groups. **Conclusions:** The combination of MSK pain and HPS was associated with worse mood symptoms, quality of life and HPS-related features. This study suggests that sleepiness may be an important symptom to be investigated and treated in MSK pain-related conditions for a better quality of life.

Keywords: Sleep; Musculoskeletal Pain; Disorders of Excessive Somnolence; Mood Disorders; Quality of Life.

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INTRODUCTION

In adults, the incidence of chronic pain is around 10% per year, while its prevalence varies from 7% to 48%[1,2] depending on the population investigated. Population-based studies suggest that chronic pain can be associated with age, female gender, socioeconomic level, among other factors[3-5]. Specifically for chronic musculoskeletal pain (MSK), the associated risk factors include female gender, aging, family history, depression, nutritional status and sleep disturbances[6-8].

Sleep and pain present a bidirectional relationship[9,10]. Sleep deprivation has been consistently associated with hyperalgesia in both humans and animals[6], while sleep disorders frequently occur in pain-related conditions[11]. Nevertheless, other sleep disturbances such as hypersomnolence (HPS) have been much less studied in this context.

HPS is a transitory state between wake and sleep that can be defined as an exacerbated tendency of the subject to fall asleep briefly in a given time if circumstances permit[12,13]. The prevalence of diurnal HPS is estimated to affect 0.5%-5.0% of adults[14]. HPS has been associated with several psychiatric and medical conditions such as neurological and cardiovascular comorbidities, substance abuse, and psychotropic drug[13]. Among the central disorders of HPS, narcolepsy type 1 is the main sleep disturbance, characterized by the presence of excessive daytime sleepiness, cataplexy and other rapid eye movement (REM) sleep phenomena, such as sleep paralysis and hypnagogic hallucinations[15].

A few studies showed a relationship between HPS and MSK pain in adults[16,17]. Thus, we hypothesized that HPS could be negatively associated with physical, psychological and social well-being, as well as lower quality of life in patients with MSK pain when compared to those without HPS. Therefore, the aim of the current study was to evaluate the interaction between HPS and MSK pain on mood symptoms, sleep quality and sleep pattern, and quality of life in a general population sample.

MATERIAL AND METHODS

Study population and sampling procedures

This study comprises a secondary analysis of data from the EPISONO cohort[18], an epidemiological study performed in the city of São Paulo. It was used a three-stage cluster sampling method to get a representative sample of São Paulo's adult population according to age, gender and socioeconomic class. Detailed information about sampling methodology has been already described elsewhere[18]. The study was approved by the University's Institutional Ethics Committee (CEP#0593/06). As shown in Figure 1, the exclusion criteria of this study consisted of missing data for MSK pain and/or somnolence assessments; the presence of pain located in other locations than back, over the body, joints, and legs. Overall, EPISONO included 1,042 volunteers, from which 510 fitted the criteria of the current study, signed the informed consent form, answered questionnaires, had clinical assessment, and underwent a full-night polysomnography (PSG).

Sociodemographic and clinical evaluation

The sociodemographic data was collected by Datafolha Institute at the volunteer's house. Parameters such as age, sex, and monthly income were completed according to the Brazilian Economic Classification Criteria. In the Sleep Institute, all volunteers had their height and weight assessed by trained personnel for body mass index (BMI) calculation. Medical history was evaluated through structured questionnaires, including questions about smoking and drinking habits and the use of central nervous system (CNS)-acting medication.

Musculoskeletal pain assessment

MSK pain was defined as diffuse pain or pain located in the back, joints or limbs as previously described[19]. The screening was accomplished by 2 questions answered at the Sleep Institute. The first question was: "Did you feel pain over your body, associated with tiredness during the day in the last 6 months?" with only 2 possible answers: "generally yes" and "generally no". When the volunteer answered "generally yes", a second question about pain location was considered with the following possible answers: back, head, chest, over the body, joints, legs, mouth, face, teeth and other place.

Subjects who answered back, joints and legs or over the body (diffuse pain) were included in the MSK group, while the other types of responses were excluded from the study. Subjects that answered "generally no" in the first question and have not reported any pain were included as control (CTRL) group. Subjects that did not answer one of the questions were excluded from the study, being considered as missing data (Figure 1).

Somnolence evaluation

Epworth Sleepiness Scale (ESS) was used to assess excessive daytime somnolence. It consists in 8 questions involving everyday situations[20]. The patient has to score from 0 to 3 the possibility of falling asleep. ESS was validated for use in Brazil, and its use allows evaluating the subjective somnolence. In the present study, individuals were considered as having HPS if they presented ESS score higher or equal to 10, and scores of 10-24 represent increasing levels of excessive daytime sleepiness[20]. Volunteers with scores lower or equal to 9 were considered as without HPS.

Groups

According to the evaluation of pain and somnolence, the sample was allocated into 4 groups. CTRL: individuals that had ESS score ≤9 and did not report MSK pain; MSK: individuals that had ESS score ≤9 and reported MSK pain; HPS: individuals that had ESS score ≥10 and did not report MSK pain; HPS+MSK: individuals that had ESS score ≥10 and reported MSK pain.

Mood and quality of life assessments

Anxiety and depression symptoms were assessed by the Portuguese validated version of Beck Anxiety Inventory[21] and Beck Depression Inventory[22], respectively. The quality of life

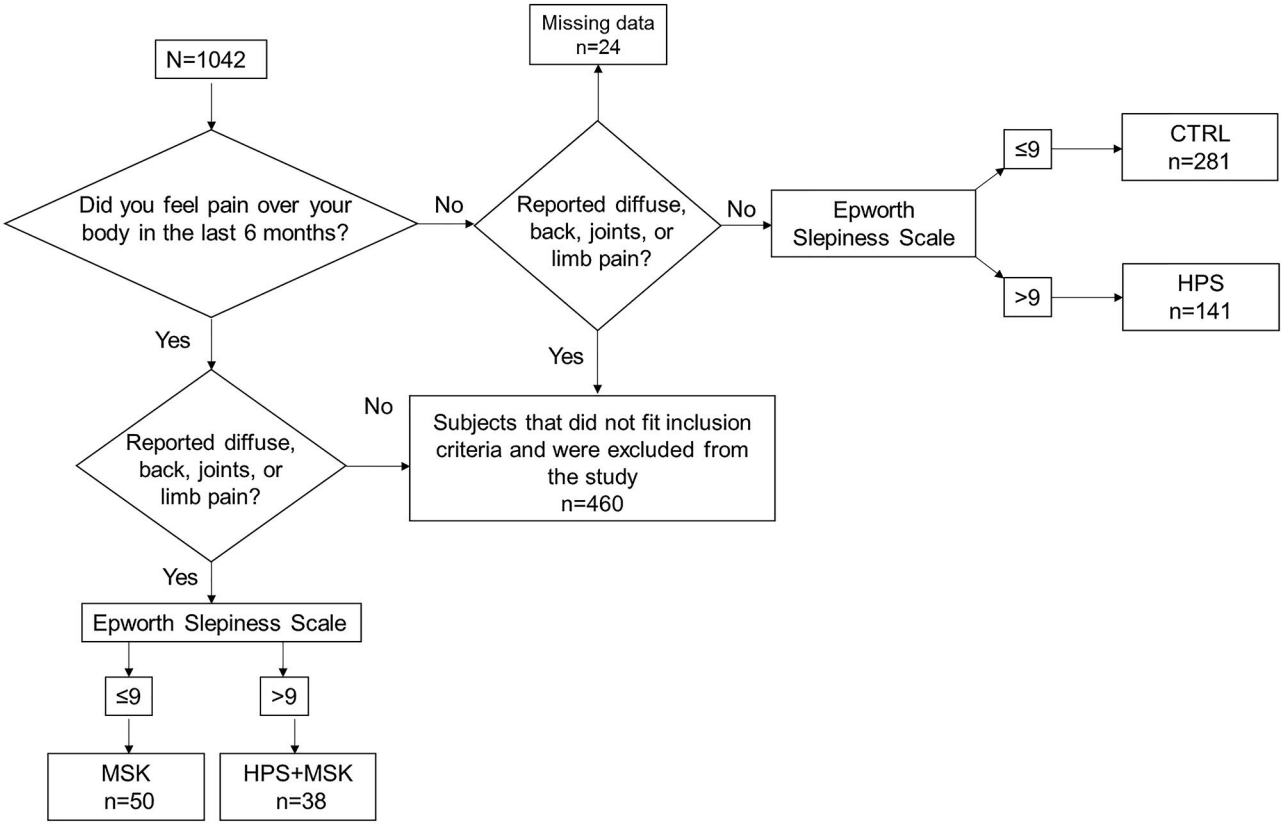

Figure 1. Flowchart of the study. Flowchart illustrates the experimental design of the study and the inclusion and exclusion criteria. CTRL: individuals without hypersomnolence and pain; HPS: individuals with hypersomnolence and no pain; MSK: individuals with pain and no hypersomnolence; HPS+MSK: individuals with both conditions.

was measured by the Portuguese validated version of the World Health Organization Quality of Life (WHOQoL)-bref[23].

Subjective sleep assessment

Sleep quality: To assess the perception of sleep quality, the volunteers completed the Pittsburgh Sleep Quality Index (PSQI)[24]. Cut-off for PSQI was ≤5 (good sleepers) and >5 (poor sleepers).

The narcolepsy-related questions below were created by a panel of sleep specialists from the Sleep Institute (São Paulo), and were asked by trained instructors with yes/no as answers:

Sleep attacks: The individuals were asked if they had "uncontrollable sleep attacks, sleeping suddenly" in the last 6 months.

Cataplexy: the cataplectic-like symptom question covered the occurrence of an event in the last 6 months. The individuals were asked if they had "any event of sudden weakness or difficultly in speaking in situations of strong emotion (such as joy, anger, fear, or surprise) without unconsciousness".

Objective sleep assessment

All PSG were done at the Sleep Institute (São Paulo, Brazil), a sleep laboratory with 80 beds (www.sono.org.br), always respecting the usual time the participants went to bed. Participants were asked about their sleep routines and wake-up times during the week, at weekends and on holidays. The PSG was scheduled according to the availability of the volunteers, and most of them were performed during weekdays (64%). The scheduling of PSG took into consideration the availability of the participants.

A type 1 PSG was performed using a digital system (EMBLA® N7000, Embla Systems Inc., Broomfield, CO, USA). The following physiological tests were performed: electroencephalography (EEG, C3-A2, C4-A1, O1-A2, O2-A1), electrooculography (EOG, EOG-Left-A2, EOG-Right-A1), electromyography (EMG, muscle of the submentonian region, tibialis anterior muscle, masseter region, and 17th intercostal space), electrocardiography (ECG, derivation V1 modified), and airflow detection by a thermocouple and by nasal pressure. In addition, the following physiological parameters were evaluated: respiratory effort using thoracic and abdominal x-trace belts, snoring and body position by EMBLA sensors, and percutaneous oxygen saturation (SpO_2) and pulse rate by an EMBLA oximeter. All PSG exams were visually scored by a registered and trained PSG technologist. All sleep stages were scored according to standardized criteria for investigating sleep[25]. EEG arousals and leg movements were scored according to the criteria established by the American Academy of Sleep Medicine (AASM) Manual for Scoring Sleep and Associated Events[26]. Four percent of the PSG results were randomly rescored by a registered PSG technologist to confirm that all of the PSG scoring had been executed correctly (agreement rate of 93.36±5.1%, k=0.91±0.03).

Statistical analysis

All continuous data were tested for normal distribution. If non-parametric, the variables were standardized for logarithmic scale (Log10). Categorical variables were compared using Pearson chi-square test, and the possible differences were identified by the adjusted residual. Continuous parameters were compared using two-way analysis of covariance (ANCOVA), considering MSK pain and HPS as fixed factors and controlling for age, sex, BMI, use of CNS-acting medication, alcohol consumption and smoking. When significant interaction effect between MSK pain and HPS was found, Bonferroni's post-hoc test was applied. Data analysis was performed using SPSS 21 software (Chicago, IL). All data are presented as mean ± standard error or percentage within group. The statistical significance was set as $p<0.05$.

RESULTS

From the total sample (n=1,042), 510 met the inclusion criteria (Figure 1) and were enrolled in the current study. Of these, 55.1% were considered as control without MSK pain (CTRL, n=281), 9.8% as control with MSK pain (MSK, n=50), 27.6% as HPS without MSK pain (HPS, n=141), and 7.5% as HPS with MSK pain (HPS+MSK, n=38).

Table 1 demonstrates the comparison of sociodemographic parameters among the groups. Groups with MSK pain presented higher frequency of women (MSK 68% and HPS+MSK 73.7%), while HPS group presented more men (60.3%) when compared to the others. MSK and HPS+MSK groups also reported to use more CNS-acting medication. Weekly to monthly smoking was significantly associated with

Table 1. Sample characterization. Sociodemographic and clinical profile of subjects without hypersomnolence and pain (CTRL), with hypersomnolence and no pain (HPS), with pain and no hypersomnolence (MSK) and with both conditions (HPS+MSK) in the EPISONO cohort.

	CTRL (n=281)	MSK (n=50)	HPS (n=141)	HPS+MSK (n=38)	*p* HPS*MSK
Age (years)	42.07±15.33	45.56±12.67	42.79±14.01	42.45±15.9	0.265
BMI (kg/m²)[a]	26.61±5.34	27.43±5.57	27.1±5.06	25.44±5.44	0.066
Gender, %(n)					
Female	45.2 (127)	68.0 (34)§	39.7 (56)	73.7 (28)§	<0.0001
Male	54.8 (154)	32.0 (16)	60.3 (85)†	26.3 (10)	
Monthly income, %(n)					
Low	40.2 (113)	52.0 (26)	29.8 (42)	39.5 (15)	0.160
Medium	47.0 (132)	44.0 (22)	57.4 (81)	50.0 (19)	
High	11.0 (31)	2.0 (1)	12.1 (17)	7.9 (3)	
Refused to answer	1.8 (5)	2.0 (1)	0.7 (1)	2.6 (1)	
Marital status, %(n)[b]					
Single	32.3 (90)	22 (11)	28.8 (40)	29.7 (11)	0.848
Consensual union	12.2 (34)	10 (5)	11.5 (16)	10.8 (4)	
Married	47.3 (132)	64 (32)	48.2 (67)	51.4 (19)	
Separated/Divorced	4.7 (13)	2 (1)	7.2 (10)	5.4 (2)	
Widower/Widow	3.6 (10)	2 (1)	4.3 (6)	4.3 (6)	
Comorbidities					
Diabetes[c]	6 (17)	8 (4)	5 (7)	0 (0)	0.671
Heart attack	2.1 (6)	0 (0)	0.7 (1)	2.6 (1)	0.747
Neurological disease	4.6 (13)	8 (14)	2.1 (3)	10.5 (4)	0.292
Stroke	1.4 (4)	2 (1)	1.4 (2)	0 (0)	0.940
CNS-acting medication, %(n)[d]					
Users	34.1 (94)	18 (9)§	36.5 (50)	63.2 (50)§	<0.0001
Smoking, %(n)					
Weekly to monthly	4.6 (13)	0 (0)	2.8 (4)	15.8 (6)§	0.017
Daily	22.4 (63)	18.0 (9)	22.0 (31)	15.8 (6)	
Alcohol consumption, %(n)					
Monthly	18.5 (52)	12.0 (6)	14.2 (20)§	15.8 (6)	0.043
Weekly	38.4 (108)	28.0 (14)	51.1 (72)	36.8 (14)	
Daily	7.8 (22)	4.0 (2)	7.10 (10)	7.9 (3)	

Two-way analysis of variance (ANOVA), followed by Bonferroni's post hoc test, with data presented by mean ± standard error, or Pearson's Chi-square test with data presented by percentage (%) and number of individuals (n); †observed frequency higher than expected frequency (adjusted residuals higher than 2 and lower than 3); §observed frequency higher than expected frequency (adjusted residuals higher than 3).

BMI: body mass index; kg: kilogram; m²: square meter; CNS: central nervous system.

Sample size varied among comparison due to number of missing data: [a]MSK n=1; [b]CTRL=2, HPS n=2, HPS+MSK n=1; [c]CTRL n=3; [d]CTRL n=5, HPS n=4.

HPS+MSK group whilst monthly alcohol consumption was significantly associated with HPS group. There was no significant difference among the groups considering age, BMI, monthly income, marital status and other comorbidities.

Regarding objective sleep, ANCOVA analysis did not demonstrate any interaction effect between MSK pain and HPS in sleep parameters (Table 2). The analyses of total sleep time, sleep latency, sleep efficiency, and REM sleep stage showed only HPS effect. Groups with HPS had increased total sleep time, sleep efficiency and REM sleep as well as lower sleep latency compared to those without HPS regardless the presence of MSK pain (Table 2).

Table 3 illustrates the subjective indicators of mood symptoms and sleepiness adjusted for confounders. According to the Beck Anxiety Inventory score, we found HPS*MSK pain interaction effect ($F_{1,464}$=363.9, p<0.05), showing that MSK pain and HPS+MSK groups presented more anxiety symptoms than CTRL and HPS groups, respectively. Among MSK pain groups, the association with HPS led to significantly higher anxiety symptoms. Considering its frequency, there was a significant higher prevalence of moderate to severe anxiety symptoms in both HPS+MSK (45.7%) and MSK (30.6%) groups. Regarding Beck Depression Inventory score, our results showed only isolated effects of MSK pain and HPS. Nevertheless, considering the frequency of depressive symptoms, we found higher prevalence of moderate to severe depression symptoms in HPS+MSK (44.1%), followed by MSK group (18.8%). In addition, ANCOVA analysis revealed MSK pain effect on PSQI global score. Higher frequency of poor sleepers was observed in HPS+MSK (64.9%) and MSK groups (72.0%).

As expected, the analyzes of the Epworth Sleepiness Scale presented only HPS effect, as both groups with HPS had more somnolence compared to those without HPS, regardless the presence of MSK pain (Table 3). The self-report of sleep attacks (64.9%) and cataplexy (34.2%) were significantly associated with HPS+MSK group compared to the others.

Quality of life was evaluated according to WHOQoL-bref questionnaire, which has 4 domains (Figure 2). Physical domain showed HPS*MSK pain interaction effect ($F_{1,464}$=3.6, p<0.05) and also isolated effects of HPS and MSK. Post-hoc analysis revealed that both MSK pain and HPS+MSK pain groups had lower quality of life in the physical domain compared to CTRL and HPS groups, respectively. Moreover, among MSK pain groups, the presence of HPS was associated with worse physical health quality of life (Figure 2A). In the psychological domain, it was observed only MSK pain effect (Figure 2B). Social domain showed HPS*MSK pain interaction effect ($F_{1,464}$=1.3, p<0.05) and also an isolated MSK pain effect. The post-hoc analysis demonstrated that both MSK and HPS+MSK groups had lower quality of life in the social domain compared to CTRL and HPS, respectively (Figure 2C). Additionally, among MSK pain groups, the presence of HPS was associated with worse social quality of life. Environmental domain presented only MSK pain effect (Figure 2D).

Table 2. Polysomnographic parameters. Sleep-related parameters adjusted for covariates from subjects without hypersomnolence and pain (CTRL), with hypersomnolence and no pain (HPS), with pain and no hypersomnolence (MSK) and with both conditions (HPS+MSK) in the EPISONO cohort.

	CTRL (n=281)	MSK (n=50)	HPS (n=141)	HPS+MSK (n=38)	*p*		
					MSK	HPS	HPS*MSK
Total sleep time (min)	338.00±4.44	323.96±10.68	351.72±6.31*+	357.84±12.18*+	0.665	**0.008**	0.258
Sleep latency (min)	19.29±1.42	21.64±3.42	14.68±2.02*+	14.85±3.42*+	0.667	**0.046**	0.703
REM sleep latency (min)[a]	101.23±3.19	107.27±7.62	101.70±4.52	102.96±8.69	0.576	0.763	0.707
Sleep efficiency (%)	80.67±0.72	78.72±1,73	84.46±1.02*+	83.53±1.97*+	0.331	0.003	0.720
Stage N1 (%)	4.96±0.22	5.20±0.53	4.24±0.31	4.34±0.61	0.708	0.075	0.866
Stage N2 (%)	54.33±0.55	55.17±1.32	54.51±0.78	55.57±1.51	0.404	0.794	0.923
Stage N3 (%)	21.85±0.48	21.86±1.15	21.57±0.68	20.15±1.32	0.474	0.302	0.457
REM sleep stage (%)	18.86±0.38	17.75±0.91	19.67±0.54*+	19.95±1.04*+	0.592	**0.049**	0.364
Arousal index (number/h)	14.83±0.64	13.00±1.54	16.02±0.91	13.99±1.76	0.145	0.396	0.939
Apnea-hypopnea index (number/h)	7.77±0.71	6.20±1.71	10.44±1.01	5.91±1.95	0.402	0.512	0.712
Basal SpO_2 (%)	95.78±0.78	96.17±0.19	95.96±0.11	95.83±0.21	0.403	0.599	0.099
Mean SpO_2 (%)	95.05±0.09	95.38±0.21	95.16±0.13	95.13±0.24	0.407	0.683	0.329
Lowest SpO_2 (%)	88.75±0.42	89.12±0.71	87.55±0.42	87.98±0.82	0.471	0.061	0.977
Time SpO_2<90% (%)	7.05±1.34	7.01±3.17	7.26±1.34	9.83±3.62	0.489	0.080	0.093
Dessaturation index (number/h)[b]	6.36±0.65	5.09±1.59	8.73±0.92	5.25±1.81	0.084	0.339	0.401
Periodic limb movements (number/h)	1.43±0.32	0.88±0.77	0.49±0.46	1.35±0.88	0.813	0.707	0.275

Two-way analysis of covariance (ANCOVA), followed by Bonferroni's post hoc test, with data presented by mean ± standard error. Covariates adjusted were: age, sex, body mass index, use of CNS-acting medication, alcohol consumption and smoking. *Statistically different from CTRL group;
#Statistically different from HPS group; +Statistically different from MSK group.
REM: rapid eye movement; SpO_2: oxygen saturation.
Sample size varied among comparison due to number of missing data: [a]CTRL n=5, HPS n=1; [b]CTRL=3, HPS n=2; [c]HPS n-1; [d]CTRL n=9, HPS n=3; [e]CTRL n=47, HPS n=22, MSK n=9, HPS+MSK n=7.

Table 3. Anxiety, depression and sleepiness. Symptoms of anxiety, depression, sleep quality and hypersomnolence-related parameters adjusted for covariates among subjects without hypersomnolence and pain (CTRL), with hypersomnolence and no pain (HPS), with pain and no hypersomnolence (MSK) and with both conditions (HPS+MSK) from the EPISONO cohort.

	CTRL (n=281)	MSK (n=50)	HPS (n=141)	HPS+MSK (n=38)	*p*		
					MSK	HPS	HPS*MSK
Beck Anxiety Inventory[a]	5.35±0.43	12.83±1.02*	5.48±0.63	17.67±1.19*#+	**<0.0001**	**0.004**	**0.007**
Minimal anxiety symptoms	81.5 (212)§	49.0 (24)	80.6 (104)†	28.6 (10)			
Mild anxiety symptoms	11.2 (29)	20.4 (10)	17.1 (22)	25.7 (9)	**<0.0001**		
Moderate to severe anxiety symptoms	7.3 (19)	30.6 (15)§	2.3 (3)	45.7 (16)§			
Beck Depression Inventory[b]	6.51±0.43	14.41±1.02*#	7.54±0.62*	17.04±1.20*#	**<0.0001**	**0.035**	0.355
Minimal depressive symptoms	88.6 (226)§	54.2 (26)	84.4 (108)	47.1 (16)			
Mild depressive symptoms	7.1 (18)	27.1 (13)§	10.9 (14)	8.8 (13)	**<0.0001**		
Moderate to severe depressive symptoms	4.3 (11)	18.8 (9)†	4.7 (6)	44.1 (15)§			
Pittsburgh Sleep Quality Index[c]	4.98±0.20	8.32±0.47*#	4.97±0.28	8.24±0.54*#	**<0.0001**	0.908	0.938
Good sleepers	66.1 (181)§	28.0 (14)	68.8 (97)	35.1 (13)	**<0.0001**		
Poor sleepers	33.9 (93)	72.0 (36)§	31.2 (44)	64.9 (24)§			
Epworth Sleppiness Scale	4.88±0.16	5.59±0.38	12.97±0.23*+	13.37±0.44*+	0.079	**<0.0001**	0.588
Sleep attacks self-report	7.8 (22)	18.0 (9)	19.9 (28)†	64.9 (24)§	**<0.0001**		
Cataplexy self-report	7.9 (22)	14.0 (7)	7.8 (11)	34.2 (13)§	**<0.0001**		

Two-way analysis of covariance (ANCOVA), followed by Bonferroni's post hoc test, with data presented as mean ± standard error. Covariates adjusted: age, sex, body mass index, use of CNS-acting medication, alcohol consumption and smoking; or Pearson's Chi-square test with data presented as percentage (%) and number of individuals (n); *Statistically different from CTRL group; #Statistically different from HPS group; +Statistically different from MSK group; †observed frequency higher than expected frequency (adjusted residuals higher than 2 and lower than 3); §observed frequency higher than expected frequency (adjusted residuals higher than 3).
Sample size varied due to number of missing data: [a]CTRL n=26, HPS n=13, MSK n=2, HPS+MSK n=4; [b]CTRL n=21, HPS n=12, MSK n=1, HPS+MSK n=3; [c]CTRL n=7, HPS+MSK n=1.

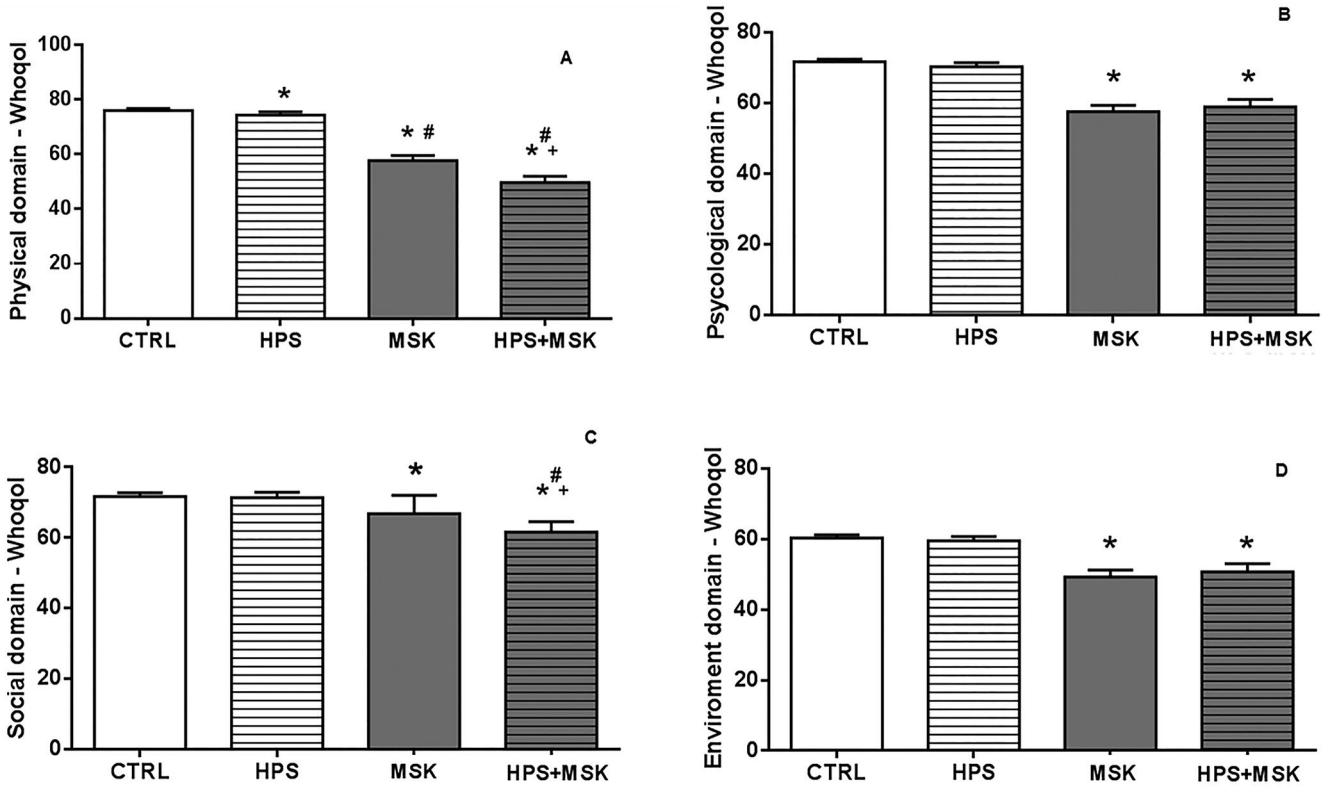

Figure 2. Quality of life. Domains of World Health Organization Quality of Life (WHOQoL) questionnaire adjusted for covariates in subjects without hypersomnolence and musculoskeletal pain (CTRL), with hypersomnolence and no musculoskeletal pain (HPS), with musculoskeletal pain and no hypersomnolence (MSK) and with both conditions (HPS+MSK) from the EPISONO cohort.
*Statistically different from CTRL group; #Statistically different from HPS group; +Statistically different from MSK group. $p<0.05$.
Sample size varied due to number of missing data: CTRL n=21, HPS n=12, MSK n=1, HPS+MSK n= 3.

DISCUSSION

In the current study, we demonstrated an interaction of MSK pain and HPS on mood symptoms, as higher frequencies of moderate to severe depression symptoms and higher anxiety symptoms were found in the MSK+HPS group compared to the MSK alone. The quality of life of both physical and social domains were significantly lower in the MSK+HPS group compared to all other groups. It is important to emphasize that physical and social well-being were domains impaired by MSK pain and/or HPS, and not life quality as a whole. Regarding sleep quality, groups with MSK pain presented worse sleep quality, independently of HPS. Additionally, individuals from HPS+MSK group reported higher frequencies of both sleep attacks and cataplexy, which are narcolepsy-related symptoms. All these findings were completely independent from confounders.

In our sample, the coexistence of both MSK pain and HPS was independently associated with higher levels of anxiety and depression symptoms, suggesting that the influence of mood symptoms on HPS may depend on MSK pain. Hypersomnolence and mood disorders often coexist[27]. Anxiety and depression symptoms are important determinants of pain intensity and disability in MSK pain conditions[28]. In our investigation, mood disorders were highly affected by both MSK pain and HPS factors, independently. Anxiety and depression symptoms have been described as predictors of incident HPS in women[29], while depression symptoms has been associated with hypersomnolence in middle-aged adults[30]. Depression seems to play a significant role in MSK pain[31] and may be involved in the relationship between sleep disorders and the development of chronic pain[7].

Hypersomnolence was highly prevalent in MSK pain (43%) in our adult general population sample, corroborating previous literature[17]. Pain records and perceptions seem to be linked to sleep quantity and depression symptoms in narcolepsy patients[14]. Chronic pain was also associated with the incidence of HPS[32]. In a recent investigation conducted in our group, we found that both types of narcolepsy (types 1 and 2) presented a high frequency of chronic pain (84.84% type 1 versus 75.75% type 2), with indistinct pain characteristics between them. In addition, chronic pain emerged as a co-morbidity never reported before in type 2. Depression possibly influences pain perception in these patients[33]. Narcolepsy comorbidities include chronic pain conditions[34]. The presence of comorbidities before and after narcolepsy was evaluated in another investigation, using a clinical database. The authors found that MSK conditions, such as low back pain, arthrosis, and arthritis, were conditions emerging after diagnosis, indicating that narcolepsy increased the incidence of MKS pain[35]. Chronic low back pain has increased probabilities to occur both at identification and at the end of a 9-year observation period of narcoleptic patients[36]. Regardless of these results, the scientific evidence is still unfounded as to whether pain conditions can act as a cause or consequence of narcolepsy[37], despite its association.

Higher sleep attacks were also observed in MSK+HPS group compared to the other groups, suggesting a possible influence of MSK pain on sleepiness. Sleep has an important role in pain processing as sleep disruption has been shown to decrease the activity of the descending inhibitory pain pathways in healthy individuals[38].

Of note, one of our main findings was the interaction of HPS*MSK pain factors found in both the physical and social domains of quality of life. These results suggest that for both domains, the presence of comorbid HPS in MSK pain may potentiate the impairment on the patient's quality of life by modulation of, at least in part, sleep quality and mood symptoms. Taking into consideration that 43% of the MSK pain individuals from our cohort presented HPS, defined by Epworth Sleepiness Scale score ≥10, our results may indicate a relevant role for HPS as a sign of poor quality of life in MSK pain-related conditions, independently from sleep-disordered breathing, a well-known source of HPS.

Unfortunately, there is no available study to contrast our data yet. However, evidence from a clinical trial showed that an intervention with hydrotherapy in patients with fibromyalgia improved physical function, anxiety and depression symptoms, pain intensity, fatigue, and the quality of life. Moreover, the treatment also significantly reduced daytime sleepiness (assessed by Epworth Sleepiness Scale)[39], indicating an important correlation between the improvement in MSK pain, mood disorders and the HPS.

Regarding sleep pattern, our findings showed only HPS-mediated differences, represented by increased total sleep time, sleep efficiency and REM sleep stage, as well as a reduction in sleep onset latency in HPS groups compared to no-HPS groups. Longer sleep duration was found by Plante et al.[40] in patients with major depressive disorder and co-occurring HPS, but not in controls *versus* HPS groups, contrary to our findings[40]. We observed a lack of differences in objective sleep parameters among the groups with and without MSK, differently from subjective sleep. Other authors have also addressed inconsistencies among objective and subjective sleep quality. In a population-based study, subjects with chronic fatigue reported unrefreshing sleep and poorer sleep quality more often than non-fatigued controls[41]. However, there were no significant differences in sleep architecture between the groups when measured by PSG[41]. We could speculate that possible changes in sleep architecture could be present at a microstructure level, but not macrostructure. Currently, the literature about objective sleep and MSK pain is very scarce, with most evidence coming from female clinical samples and showing shorter sleep duration, lower delta power in the EEG of NREM sleep and higher sleep fragmentation[42].

It is important to emphasize that all findings of the current study were adjusted for age, sex, BMI, use of CNS-acting medication, alcohol consumption and smoking. Moreover, there was no influence of sleep-disordered breathing, another potential source of HPS, as all groups had no differences in all sleep-related respiratory parameters. Second, unlike other epidemiological studies on pain, the enrollment process of this study did not focus on pain, but on a general population[18]. Thus, the possibility of sampling bias of individuals who were motivated by their pain condition was minimal.

This study has some limitations. First, we did not have an objective measurement of HPS as its definition was based solely on a subjective instrument, the ESS questionnaire. It is known that Multiple Sleep Latency Test (MSLT) is considered the gold standard measure of HPS[43]. Since the primary aim of the EPISONO cohort study was not related to HPS, MSLT was not performed. However, recent evidence demonstrated divergent associations between subjective and objective HPS and depression symptoms in the Wisconsin Sleep Cohort Study[44]. In that cohort, subjective sleepiness, defined by ESS, was associated with increased odds of depression symptoms; but MSLT-measured objective sleep propensity was associated with the opposite[44]. Thus, these data underscore important limitations of the MSLT as a measure of HPS in mood disorders.

Second, besides no significant changes were observed in the objective sleep pattern, we must address the lack of an adaptation night due to the epidemiological framework of the study.

Third, we cannot ascertain isolated cases of inaccuracy in the self-report of MSK pain; nevertheless, this issue was addressed by the population-based method of the study. Additionally, neither the topography nor the pain intensity were investigated, due to the coexistence of pain in different body regions and lack of evaluation of pain intensity.

Fourth, control participants scored on the criteria for sleep attack and cataplexy in our sample, as we did not expect that. We we assumed that there was a misinterpretation of the volunteers to both questions.

Fifth, the assessment of MSK pain in this investigation was done by a non-validated instrument, as it was measured by one question and should be done in further studies by validated questionnaires on MSK pain.

Lastly, although there was an association between MSK+HPS and worse psychological and well-being parameters, we cannot infer causality since the design of the study was cross-sectional. Additional prospective studies and clinical trials will be necessary to establish a possible temporal relationship between HPS, MSK pain, mood disorders and quality of life.

CONCLUSIONS

Our study showed that subjects with musculoskeletal pain and comorbid hypersomnolence presented a worse clinical picture compared to those without hypersomnolence due to higher frequencies of severe depression, elevated anxiety levels, increased prevalence of sleep attacks and cataplexy, and lower quality of life. This study suggests that the investigation and management of subjective sleepiness may be clinically relevant in patients with chronic musculoskeletal pain for a better quality of life.

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