



Observational study

Perceived sleep deficit is a strong predictor of RLS in multisite pain – A population based study in middle aged females

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HIGHLIGHTS

- This study showed that sleep deficit and sleep fragmentation are strong predictors of RLS in multisite pain.
- This study identified other sleep characteristics in this RLS phenotype of females with multisite pain.
- This study characterized RLS and multisite pain together with impaired sleep quality as strong predictors for daytime sleepiness.

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ABSTRACT

Background: Chronic pain conditions as well as Restless Legs Syndrome (RLS) are known to be associated with subjectively and objectively disturbed sleep. RLS has been recently described as highly prevalent in multisite pain and the role of sleep as a modifying factor in this RLS phenotype is unknown. This study aimed to investigate if perceived sleep deficit and other sleep related parameters predict RLS in subjects with multisite pain.

Current knowledge/study rationale: We have recently demonstrated a strong association between Restless Legs Syndrome (RLS) and number of pain locations. In the current analysis we hypothesized that impaired sleep predicts RLS in subjects with multisite pain.

Method: Questionnaire-based data from 2727 randomly selected women aged 18–64 years were used to analyze RLS symptoms, self-reported sleep quality, and the degree of daytime sleepiness (Epworth Sleepiness Scale (ESS)) in relation to type, degree and localization of body pain. Potential confounders including anthropometrics, pain localization, co-morbidities, and medication were adjusted for in the Generalized Linear Models (GLM).

Results: Perceived sleep deficit ≥ 90 min (OR 2.4 (1.5–3.8), $p < 0.001$) and frequent nocturnal awakenings (OR 2.3 (1.4–3.6), $p < 0.001$) were the strongest sleep related predictors for RLS in subjects with multisite pain. Additional factors include prolonged sleep latency (≥ 30 min, OR 1.8 (1.1–2.8), $p = 0.01$) and daytime symptoms like elevated daytime sleepiness (ESS score ≥ 9 , OR 1.8 (1.2–2.7), $p = 0.005$). Accordingly, RLS diagnosis was associated with impaired sleep quality (TST (Total Sleep Time) -8.2 min, sleep latency $+8.0$ min, and number of awakenings from sleep $+0.4$, $p < 0.01$). ESS score increased with RLS diagnosis ($+0.74$, $p < 0.01$) and number of pain locations (0.5, 1.7, and 1.8 for 1, 3, and 5 pain areas, $p < 0.001$). In addition, confounders like pain severity, the history of psychiatric disease, and current smoking were associated with impaired sleep quality in this group of females.

Conclusions: Perceived sleep deficit and sleep fragmentation are the strongest sleep related predictors of RLS in multisite pain. Potential implication of our results are that clinical management programmes of RLS in subjects with multisite pain need to consider both sleep quality and sleep quantity for individually tailored treatment regimes.

Study impact: RLS, pain, and sleep disorders are highly interrelated. Our study strongly suggests that clinical management of RLS in patients with multisite pain needs to consider sleep quality as an independent risk factor.

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1. Introduction

Subjectively and objectively disturbed sleep are regarded as hallmark symptoms in chronic pain [1,2], a condition characterized by pain persisting beyond the expected time for tissue healing [3,4]. The relationship between pain and sleep disturbances is considered to be bidirectional. For example, sleep deprivation lowers the pain threshold [5] and both slow-wave sleep and REM-sleep modulation are known to affect pain perception during wakefulness [6]. Reciprocally, chronic pain may induce disturbed sleep which in the long-term is known to negatively further affect both pain perception and coping strategies with pain during daytime [7,8].

Restless Legs Syndrome (RLS), often described also as Willis Ekbohm Disease (WED), is defined as an unpleasant sensory experience in the extremities [9] characterized by a circadian peak incidence during the last third of the day. RLS causes an urge to move and symptoms are relieved following limb movement. Proposed underlying pathomechanisms in RLS include an altered dopaminergic transmission [10], potential micro-circulatory dysfunction with local hypoxia in the extremities [11,12], and central nervous system iron metabolic dysfunction [13,14]. RLS typically induces increased sleep latency or loss of sleep. As a consequence, patients may report difficulties in falling asleep or frequent awakenings which negatively affect overall sleep quality and daytime function [15,16].

Multisite pain and fibromyalgia are subtypes of chronic pain characterized by the spreading of pain areas over the entire body [17]. In a recent study we could, for the first time, demonstrate that spreading of pain was an independent and dose dependent predictor for RLS [18]. The pathophysiological link between the two conditions is currently not evident but other common factor in both pain and RLS may be poor sleep [10] and its impact on daytime functioning.

The aim of the current study was therefore to analyze the cross sectional association between RLS, sleep quality and daytime vigilance in women with and without pain. We further aimed to identify certain sleep variables indicative for comorbid RLS in multisite pain.

2. Method

2.1. Study population

The study design and study population have been described in detail elsewhere [18]. In short, a questionnaire was mailed to 10 000 females aged between 18 and 64 in the Swedish county of Dalarna. The study population was randomly selected from the population census (>80 000 females in the current age strata) by a blinded automated process. The subject's addresses were retrieved from the National Personal Registry and were randomly chosen by a computer based automated process performed by the Swedish Post Service. Selection has been made on women, living in Dalarna county, and a target group of 10 000 subjects equally distributed in the age range between 18 and 64 years. The study was approved by the regional ethics committee at the Uppsala University (Dnr. 2010/124).

2.2. Classification of pain

In the current analysis, pain characteristics were assessed by means of a validated pain screening questionnaire used in pain centres [19]. The questionnaire asked for pain intensities, pain qualities, the time line of pain location, and included significant parts of the Brief Pain Inventory (Swedish version). Relevant for the analysis, pain intensity was graded using validated VAS scales for the

categories no/mild (VAS 0–4), moderate (VAS 5–6) and severe pain (VAS 7–10) [20]. Pain duration was dichotomized in short-term (<3 months) and long-term (≥ 3 months) pain [21]. Localization of pain was stratified for five pain zones (neck, shoulders/arms, upper back region, lower back region and legs). Number of pain locations was defined according to the number of areas affected (between 0 and 5 areas) and grouped into three categories (0 zone = no number of pain locations, 1–2 zones = limited number of pain locations, 3–5 zones = extended number of pain locations).

2.3. Classification of RLS symptoms

Standardized and validated criteria were used for the four characteristic symptoms of RLS: (I) dysaesthesia and/or urge to move the limbs, (II) difficulties in resting, (III) worsening of symptoms at rest and improvement by movement, (IV) worsening at night [22]. The questionnaire was based on the classification of RLS according to the contemporary recommendations, and an RLS diagnosis was assigned if all 4 criteria were met [13]. Finally, RLS symptom frequency (rare, sometimes, often, always) was also assessed.

2.4. Quantification of sleep and sleep disordered breathing

The history of sleep and daytime function was assessed by means of the Basic Nordic Sleep Questionnaire [23] which included questions on mean subjective sleep latency, actual and preferred sleep duration, and the number of nocturnal awakenings. The variable "perceived sleep deficit" was calculated as the difference between subjective mean and preferred sleep time. Loud snoring was used as a categorical variable (always, 4–5 times a week, 2–3 times a week, 1–2 times a week and 1 time or less) in order to provide a proxy for obstructive sleep disordered breathing.

2.5. Assessment of daytime sleepiness

Daytime sleepiness was assessed by means of the established and validated Epworth Sleepiness Scale (ESS). A score of 11 or higher was considered as subjective excessive daytime sleepiness according to current practice [24].

2.6. Clinical data and confounding factors

Anthropometric data (age as a voluntary information available in 1339 out of 2727 individuals, length, body weight) and important comorbidities (cardiovascular (CVD), metabolic, neurological) were assessed. "Psychiatric disorder" was defined as self-reported depression, anxiety, and/or severe sleep disturbance. Concomitant medication was assessed and classified according to the Anatomical Therapeutic Chemical (ATC) system. Alcohol intake was quantified according to the frequency of intake (never, 1–3 times a month, 1–2 times a week, 3–4 times a week and more often). Smoking status (current or non-smoking) was also assessed.

2.7. Statistical analysis

Statistical analysis was performed using IBM-SPSS version 20.0 software (Illinois, USA). A p -value of <0.05 was considered as statistically significant. Descriptive statistics was used to evaluate sleep variables categorized for pain duration, intensity and spreading. RLS was also categorized (diagnosis yes/no, frequency of symptoms). Frequency distributions for sleep related symptoms were compared using the Chi-Square test whereas continuous variables were compared using ANOVA test (normally distributed variables) or the Kruskal Wallis test (not normally distributed data).

Independent associations were analyzed using Generalized Linear Model (GLM) analysis. Continuous sleep variables as well as the

Table 1
Anthropometrics and clinical data.

Anthropometric and clinical data of the study cohort (N = 2727)	Mean values ± standard deviation or % of the cohort
Female gender	100%
Age (years) ^a	50.5 ± 11.0
Length (cm)	166.4 ± 6.0
Weight (kg)	72.2 ± 14.9
Body Mass Index (kg m ⁻²)	26.1 ± 5.2
Current smokers	15.6%
Frequent alcohol use (>3 times/week)	3.7%
Self-reported comorbidities	
• Psychiatric disease	20.6%
• Neurological disease	16.8%
• Cardiovascular disease	14.0%
• Metabolic disease	12.3%
Concomitant medication (ATC code)	
• Analgesic (N02)	12.6%
• NSAID (M03)	9.3%
• Psycho-analeptic (N06)	8.4%
• Antihistamines (R06A)	1.6%
• Antiepileptics (N03A)	1.2%
• Dopaminergic medication (N04B)	1.0%
Pain	
• Acute	24.2%
• Chronic	50.2%

NSAID, non steroidal anti-inflammatory drug; ATC: Anatomic-Therapeutic-Chemical.

^a N = 1339.

ESS score were used as linear response variables. Predicting factors included RLS diagnosis (all 4 symptoms fulfilled), number of pain locations (0–5 pain zones), pain intensity (3 categories mild to severe), and pain duration (short- and long-term). Further, frequent snoring and witnessed apnea, psychiatric, neurologic, metabolic, and cardiovascular co-morbidity as well as intake of medication according to ATC codes N05 (psycholeptics), N06 (psychoanaleptics), N02 (analgesics), M01A (anti-inflammatory/NSAID), frequent alcohol consumption (at least 4 days/week), marital status (yes/no), current smoking and Body Mass Index (BMI) were added as potential predictors. In addition, quantitative sleep variables were included as covariates in the analyses of daytime sleepiness and body fatigue.

Finally, the predictive capacity of sleep-related predictors for “RLS in multisite pain” (pain in all 5 body zones) were obtained by a binary ordinal regression analysis using GLM. The third tertile of the four continuous sleep variables and the ESS score, as well as the previously identified factors for RLS in multisite pain (pain in the legs, psychiatric comorbidity) [18] were allowed as predictors in the model. Odds ratios with 95% confidence intervals (CI) for “RLS in multisite pain” were calculated. The analysis was performed in the entire study population and in the subgroup of females with RLS/multisite pain or RLS/no pain.

3. Results

3.1. Response rate and data completeness in the survey

As previously reported, the response rate to the questionnaire was 40.3% in the entire study and the final analysis cohort on this study data comprised 2727 females (27.3%) with available data on pain, RLS, and sleep variables (Table 1, Fig. 1). Subjects who did not fill in questionnaires, especially sleep issues, sufficiently well were excluded from the study.

A questionnaire and phone based non-responder analysis identified “no RLS and/or pain”, “linguistic problems”, “lack of time”, and “lack of interest” as leading factors to non-response in the survey.

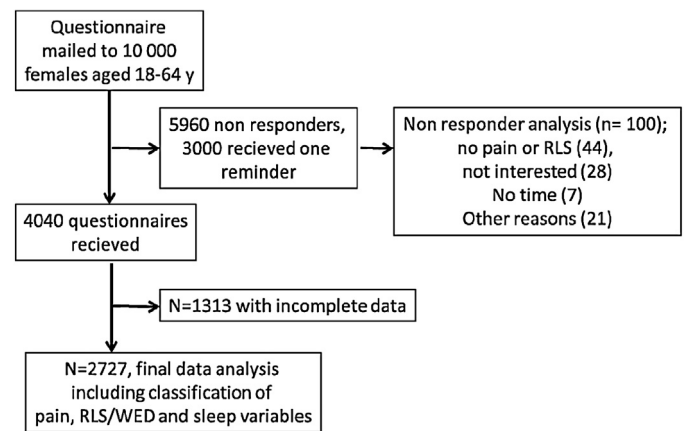


Fig. 1. Study flow chart. The questionnaire was sent out to 10 000 females and 27.3% of the initial target population were included into the final analysis cohort of this study. RLS, Restless Legs Syndrome; WED, Willis Ekblom Disease (synonym of RLS); y, year; n, number.

3.2. Association between pain characteristics and sleep

Pain intensity (no/mild, moderate, severe) was associated with shorter sleep duration (TST 419.3 ± 57.8, 389.4 ± 73.0, 385.1 ± 93.3 min, $p < 0.001$, respectively), increased sleep latency (20.4 ± 26.5, 35.2 ± 39.3, 41.8 ± 47.9 min, $p < 0.001$, respectively), more frequent nocturnal awakenings (1.8 ± 1.4, 2.6 ± 1.6, 3.1 ± 1.8 n/night, $p < 0.001$, respectively), and a higher degree of sleep loss (44.6 ± 57.7, 76.3 ± 68.4, 88.7 ± 84.9 min, $p < 0.001$, respectively). Further, higher dissemination of pain (no/limited/extended) was associated with shorter sleep duration (425.6 ± 55.6, 409.5 ± 67.9, 384.9 ± 79.1 min, $p < 0.001$, respectively), prolonged sleep latency (17.1 ± 21.6, 25.9 ± 32.7, 38.9 ± 44.2 min, $p < 0.001$, respectively) and more frequent nocturnal awakenings (1.5 ± 1.3, 2.1 ± 1.5, 3.0 ± 1.7 n/night, $p < 0.001$, respectively).

Mean perceived sleep deficit was lower in patients with short-term versus those with long-term pain, 46.2 ± 60.8 vs. 71.7 ± 71.4 min, $p < 0.001$, respectively. In addition, perceived sleep deficit increased sharply along with the degree of number of pain locations (35.5 ± 53.5 min (no pain), 56.2 ± 64.9 min (limited pain spread, 1–2 areas), and 86.8 ± 74.4 min (extensive pain spread 3–5 areas), $p < 0.001$, respectively). However, the localization of pain (neck, shoulder, upper back, lower back, and legs) had no specific influence on the reported sleep variables (sub-analysis in 643 subjects with single pain localization, data not shown).

3.3. Association between RLS and sleep

A diagnosis of RLS was associated with shortened sleep time (392.4 ± 78.9 vs. 415.9 ± 63.1 min), prolonged sleep latency (37.9 ± 46.9 vs. 20.8 ± 25.5 min), more frequent awakenings from sleep (2.8 ± 1.7 vs. 1.9 ± 1.5 n/night), and enlarged perceived sleep deficit (76.4 ± 74.5 vs. 47.7 ± 60.9 min, all comparisons $p < 0.001$, respectively).

The frequency of RLS (rare ($n = 119$), sometime ($n = 277$), often ($n = 248$), always ($n = 43$)) negatively influenced all four sleep variables in a dose dependent manner. For example, the perceived sleep deficit increased along with RLS symptom frequency (50.7 ± 58.6, 69.2 ± 64.9, 88.2 ± 81.4, and 121.4 ± 93.7 min, $p < 0.001$, respectively).

Table 2

Generalized Linear Model. Independent influence of number of pain locations and RLS on quantitative sleep variables ($n = 2587$). Shown are beta-values of the four different final GLM for the sleep variables assessed. Beta values show the independent influence of the cofactor on the predicted variable, p -value < 0.01 for all reported values.

Factor in the GLM analysis	Sleep latency (min)	Total sleep time (min)	Nocturnal awakenings (n/night)	Perceived sleep deficit (min)
RLS diagnosis, reference category: No RLS				
RLS diagnosis	8.0	−8.2	0.4	8.8
Number of pain locations, reference category: No pain area				
1 pain area	4.3	−10.7	0.4	12.4
2 pain areas	5.9	−14.7	0.5	20.0
3 pain areas	10.3	−26.2	1.0	28.4
4 pain areas	9.9	−24.6	1.1	36.1
5 pain areas	9.0	−40.9	1.5	47.4
Psychiatric comorbidity, reference category: No psychiatric comorbidity				
Psychiatric disease	21.0	−22.1	0.7	−35.0
Smoking status: reference category: Non smoker				
Current smoker	6.1	−9.0	−0.3	n.s.

Factors not included in the four models: pain intensity, pain duration, frequent snoring and witnessed apnea, neurologic, metabolic, and cardiovascular co-morbidity, intake of medication according to ATC codes N05 (psycholeptics), N06 (psychoanaleptics), N02 (analgesics), M01A (anti-inflammatory/NSAID), frequent alcohol consumption, marital status (yes/no), and Body Mass Index.

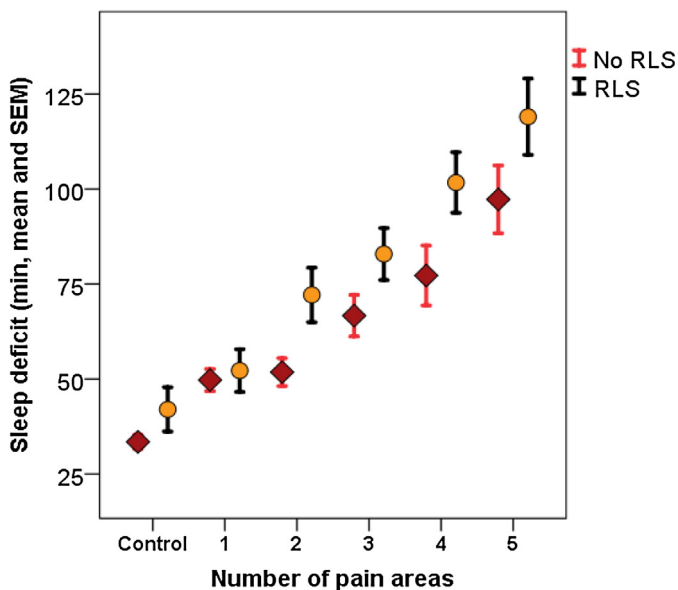


Fig. 2. The perceived sleep deficit (min, mean and standard error of mean (SEM), y-axis) in relation to the number of reported pain locations (x-axis) for two groups (RLS and no RLS). The means differed significantly for both factors (ANOVA analysis, $p < 0.001$, respectively).

3.4. Independent influences of pain and RLS on sleep

GLM analyses suggested an independent association between number of pain locations/RLS and the sleep variables like “sleep duration”, “sleep latency”, and “nocturnal awakenings” (Table 2).

The influence of number of pain locations and RLS was particularly strong for the variable perceived sleep deficit (Fig. 2, $p < 0.001$ for factors “number of pain locations” and “RLS”).

Psychiatric co-morbidity was also a strong predictor for sleep quality and quantity in the final model whereas neither cardiovascular disease, alcohol and current nicotine consumption, anthropometrics nor pain duration reached statistical significance. Medications did not independently influence RLS prevalence or sleep variables. Sensitivity analysis with two additional

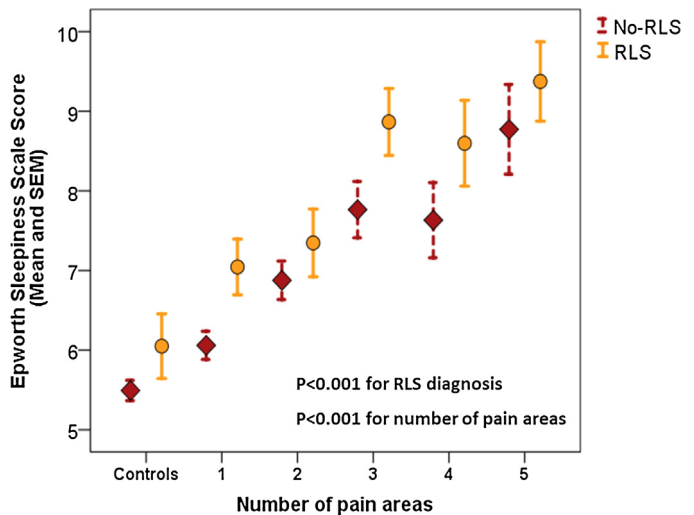


Fig. 3. Influence of number of pain locations and RLS frequency on Epworth Sleepiness Scale score (means and standard error of mean (SEM), ANOVA analysis).

sub-analyses were performed. First, when age ($n = 1146$ data points) was added into the model, the independent influence of number of pain locations and RLS on sleep variables, except the influence of RLS on sleep duration, remained unchanged (data not shown). Second, we excluded all patients with a localization of pain in the legs to reduce the risk of overlap between “painful RLS” and “pain other than RLS”. In essence, results of the GLM model were similar ($n = 1805$, data not shown).

3.5. Predictors of daytime sleepiness

The degree of daytime sleepiness was assessed as ESS score (mean 6.4 ± 4 in non RLS and 7.9 ± 4 in RLS subjects, $p < 0.001$). ESS score was linearly associated with both the number of pain locations and a RLS diagnosis (Fig. 3, ANOVA, $p < 0.001$ for both factors RLS and number of pain locations). Increased daytime sleepiness (ESS scores ≥ 11) was found in 15.9% of non-RLS and 26.3% of RLS subjects, $p < 0.001$.

Additional confounding factors and covariates for ESS score included history of psychiatric disease, frequent snoring (> 3 nights/week), increased perceived sleep deficit/sleep latency, marital status, and intake of NSAID medication (ATC code M01A) (Table 3). We controlled even for other types of analgesic medication as they also may affect sleepiness. However, very few individuals used opioids and we could not establish any effect on daytime sleepiness in our analysis.

3.6. Sleep as a predictor for RLS in multisite pain

Altogether, 106 females fulfilled the criteria for RLS in multisite pain. Perceived sleep deficit and frequent nocturnal awakenings independently predicted RLS in multisite pain with odds ratios of 2.4 and 2.3, respectively ($p < 0.001$, Table 4a).

Other significant predictors included prolonged sleep latency (≥ 30 min), increased daytime sleepiness after control for cofounders like psychiatric comorbidity and pain in the legs. In a sub analysis, we substantially reduced the analyzed population and compared RLS in multisite pain and RLS without any comorbid pain. Again, perceived sleep deficit together with daytime sleepiness were out as the strongest sleep related predictors for RLS in multisite pain (Table 4b).

Table 3Independent predictors of Epworth Sleepiness Scale score in the final Generalized Linear Model (GLM) ($n = 2618$).

Variable	<i>B</i>	95% confidence interval		Sig. level
		Lower	Upper	
Number of pain locations (reference no pain)				
5 reported pain areas	1.79	1.10	2.48	.000
4 reported pain areas	1.34	.68	2.00	.000
3 reported pain areas	1.69	1.16	2.23	.000
2 reported pain areas	.81	.35	1.26	.001
1 reported pain area	.47	.06	.88	.026
RLS diagnosis	.74	.38	1.11	.000
Psychiatric disease	.76	.35	1.17	.000
Frequent snoring (≥3 nights/week)	1.14	.68	1.59	.000
Sleep latency (min)	−.02	−.02	−.01	.000
Perceived sleep deficit (min)	.01	.01	.01	.000
Nocturnal awakenings (n/night)	.10	−.01	.21	.078
Marital status	.50	.11	.88	.012
Intake of NSAID pain medication	.60	.07	1.13	.027

Factors not included in the model: pain intensity (VAS scale), pain duration ≥ 3 months, cardiovascular, neurological, and metabolic disease history, current nicotine use, frequent alcohol consumption, BMI, sleep duration, intake of psychoanaleptic (ATC code N06), psycholeptic (N05), and analgesic (N02) medication.

Table 4aSleep related predictors for RLS in multisite pain ($n = 106$) compared with the remaining study population ($n = 2552$).

Sleep variable (highest tertile)	Sig.	Exp(<i>B</i>)	95% Wald confidence interval for Exp(<i>B</i>)	
			Lower	Upper
Perceived sleep deficit ≥ 90 min, $n = 907$	<.0001	2.4	1.5	3.8
Nocturnal awakenings ≥ 3 /night, $n = 938$	<.0001	2.3	1.4	3.6
Daytime sleepiness (ESS score ≥ 9), $n = 828$	.005	1.8	1.2	2.7
Sleep latency ≥ 30 min, $n = 895$	.01	1.8	1.1	2.8

The final model was adjusted for the effects of psychiatric comorbidity. Shortened sleep duration (≤ 6 h) and pain in the legs were excluded from the GLM due to non-significance.

Table 4bSleep related predictors for RLS in multisite pain ($n = 106$) compared with RLS without pain ($n = 88$).

Sleep variable	Sig.	Exp(<i>B</i>)	95% Wald confidence interval for Exp(<i>B</i>)	
			Lower	Upper
Perceived sleep deficit ≥ 90 min	<.001	3.8	1.8	8.2
Daytime sleepiness (ESS score ≥ 9)	.004	3.1	1.4	6.6
Nocturnal awakenings ≥ 3 /night	.031	2.3	1.0	4.8
Sleep latency ≥ 30 min	.155	1.7	.8	3.8

The final model was adjusted for the effects of psychiatric comorbidity. Shortened sleep duration (≤ 6 h) was excluded from the GLM due to non-significance.

4. Discussion

Our data, representing the general population, provide three novel findings in females with RLS and multisite pain: First, sleep quality was deteriorated by number of pain locations in a dose dependent manner and RLS had a further independent negative influence on sleep quality further, particularly in those with multisite pain. Second, daytime sleepiness was enhanced, independent from confounders, in subjects reporting RLS and multisite pain. Third, we consistently identified sleep-deficit as the strongest sleep related predictor for RLS in subjects with multisite pain. Our data strongly suggests that the effect of sleep enhancing remedies should be further explored in patients with RLS and multisite pain.

4.1. Restless legs and sleep disturbances

RLS symptoms were strongly associated with disturbed sleep, in particular more pronounced perceived sleep deficit and more prevalent sleep fragmentation, in the current study. These findings are in line with previous findings of increased sleep latency and a more pronounced reduction of sleep duration [25]. Indeed, studies using polysomnography suggest that sleep typically is fragmented by arousals induced by periodic leg movements or underlying cyclic alternating patterns [26] in patients with RLS. According to

these studies, approximately 80% of patients with RLS also have periodic limb movements (PLM) as a potential sleep disturbing phenomenon. PLM can only be quantified by polysomnographic studies and cannot be screened by questionnaire data.

4.2. Pain and sleep

The current study also demonstrates a strong dose dependent association between pain intensity/number of pain locations and the degree of sleep disturbance. Indeed, a close relationship between sleep duration and increased pain sensitivity at the day following two or three nights with sleep restriction was first demonstrated by Kleitman in the 1930s [27]. Nociception increased progressively during periods of sleep deprivation. In a more recent study, the nociceptive response to heat stimuli increased in healthy volunteers following a regimen of sleep reduction from 8 h to 4 h per night. Conversely, extension of sleep time to 10 h over a period of 4 nights reduced pain sensitivity [1]. Not only sleep length but also sleep quality interacted with pain rating in several studies. Experimental sleep disruption has been shown to be associated with an increase in pain rating [25,28,29]. Prospective population based data suggest that more than 40% of individuals with insomnia symptoms reported at least one chronic painful physical condition [7]. A further, sleep disturbance may lead to a spreading of pain

perceived as increase in the number of pain areas [30]. A recent study [31] identified sleep quality as the only factor that significantly related to inhibitory conditioning of pain. This raises the possibility that a sleep disturbance may relate to deficient pain inhibition. In addition, a very recent prospective study showed that individuals with widespread pain had a 2.1 fold increased risk of developing insomnia [32] indicating a bidirectional causality between pain and sleep complaints.

4.3. Daytime sleepiness and RLS/pain

Sleepiness during daytime is a disabling symptom which adversely affects the quality of life. Previous findings showed that pain has a major influence on daytime sleepiness [33,34]. Increased daytime sleepiness has also been reported in RLS. Indeed, randomized controlled trials of dopaminergic treatment in patients with moderate to severe RLS have consistently shown improvement of daytime sleepiness expressed as an ESS score. In our study we could, for the first time, show that the number of pain locations and RLS independently associated with daytime sleepiness [35].

4.4. RLS and multisite pain conditions, including fibromyalgia

We recently reported an elevated RLS prevalence in females with multisite pain [18,36]. The current analysis, which addresses the same population, clearly showed that perceived sleep deficit is a major sleep related predictor of RLS in multisite pain independent from confounders. This notion is supported by data suggesting that sleep deprivation in healthy pain-free volunteers enhances pain sensitivity and lowered the pain threshold [29]. Objective recordings demonstrate impaired sleep quality and quantity due to sleep fragmentation in patients with RLS [37] and the possibility of amplified pain processing was recently proposed to occur in these patients [38].

4.5. Strengths of the study

The strengths of the current study reside in the large number of subjects with different degree and localization of pain and RLS and a substantial number of controls without the two conditions. In addition, the recruitment was population based which increases generalizability of our findings. We used validated and comprehensive questionnaires assessing pain conditions, RLS symptoms, sleep quality/quantity, and established measures of daytime sleepiness. The analysis accounted for the confounder psychiatric disease which may interact with sleep, pain perception and RLS [39–41].

4.6. Study limitations

It is important to recognize that the response rate in the current study was limited and in the range of approximately 40% and only data from 27% of the original target population were included in the current analysis. Indeed, the non-responder analysis suggested a potential oversampling of subjects with pain and also possibly with RLS symptoms. However, even if an oversampling of subjects with pain did occur, our study aimed to describe the interrelation between pain phenotypes, RLS symptoms, and sleep variables. In fact, our study population included a substantial number of control individuals without pain ($n = 784$ individuals reported no pain during the past 3 weeks) and without RLS ($n = 2039$). The intention was not to compute absolute prevalence of RLS, sleep disturbances or pain prevalence in the original population. It is therefore unlikely that a bias with respect to study recruitment severely affected our conclusions on the relation between sleep and RLS in multisite pain. Another potential weakness is that assessment of sleep quality and quantity, and daytime sleepiness all were questionnaire based.

However, recent studies suggest that subjectively assessed sleep quality reasonably complies with polysomnographic sleep study results [42,43]. In addition, there is no data suggesting that the subjective report of sleep variables and the ESS scale were systematically influenced by number of pain locations or the occurrence of RLS. In addition, multisite pain classification was based on different body zones and RLS diagnosis was based on 4 criteria without excluding the mimics according to the most recent recommendations. In large-sample community-based surveys using the minimal IRLSSG criteria is the most feasible approach for the estimation of the prevalence of RLS. The specificity of the IRLSSG criteria has been estimated as 84% since there are some mimicking conditions that are not distinguishable by the four items in the criteria [44]. We also re-investigated 36 females randomly selected from the study population stratified for multisite pain 24 months after the first assessment. Following personal interviews and clinical investigations the RLS diagnosis was verified in close to 80% of cases and the multisite pain diagnosis was confirmed in 100%. Several new cases with RLS occurred during follow up phase and in one case RLS symptoms had disappeared spontaneously. Further, we performed additional analysis with exclusion of patients with pain ratings in the legs in order to reduce the risk of any such potential misdiagnosis. These findings suggest that the current RLS and multisite pain classifications are reasonably valid. In line with the previous arguments, our different statistical approaches (GLM and logistic regressions analyses) provided comparable results which argue for a high consistency of our findings. Finally, data on age was only available in only 1339 of the 2727 individuals. Age information was a voluntary information in the questionnaires and only half of the participants filled in that information. As age is an important confounder for sleep quality, we performed sensitivity analysis including age and found comparable influences of RLS diagnosis and number of pain areas on the sleep variables reported above.

4.7. Implications of our findings for treatment and research on RLS, pain, and sleep

Further research is needed to entangle the mechanisms behind the association between RLS, multisite pain, and sleep loss. The recognition of a potential negative prognostic influence of sleep disturbances on chronic pain appears to be poor. Very few subjects in our study received specific treatment for RLS, which raises the question why RLS in pain conditions is so severely under-treated. Future research needs to explore if treatment of sleep disturbances may contribute to a better RLS and pain control and prevention of a chronic condition in patients suffering from pain. Indeed, several treatment options may be implemented in pain treatment and pain management programmes to target symptom control in sleep disorders and RLS [45]. For example, RLS may be successfully treated by dopamine agonists or Alpha-2-Delta ligands; obstructive sleep apnea may be controlled by nasal ventilation (CPAP) or oral appliance therapy, and insomnia symptoms may be significantly reduced by cognitive behavioural therapy or sleep promoting medication. For example, pregabalin has shown to increase the percentage of slow-wave sleep and sleep efficiency in insomnia [46].

5. Conclusion

In summary, our study has demonstrated that perceived sleep deficit, sleep fragmentation and daytime sleepiness are strong predictors for RLS in subjects with multisite pain. Despite the fact that this cross sectional study only can show associations but not the causal direction between disturbed sleep and RLS, our findings advocate the identification of co-morbid sleep disorders in

patients seeking medical attention for RLS, multisite pain, or the combination of both.

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Conflicts of interest

The authors have no conflict of interest.

References

- [1] Roehrs TA, Harris E, Randall S, Roth T. Pain sensitivity and recovery from mild chronic sleep loss. *Sleep* 2012;35:1667–72.
- [2] Davies KA, Macfarlane GJ, Nicholl BI, Dickens C, Morriss R, Ray D, McBeth J. Restorative sleep predicts the resolution of chronic widespread pain: results from the EPiFUND study. *Rheumatology (Oxford)* 2008;47:1809–13.
- [3] Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005;9:463–84.
- [4] Woolf AD, Zeidler H, Haglund U, Carr AJ, Chaussade S, Cucinotta D, Veale DJ, Martin-Mola E. Musculoskeletal pain in Europe: its impact and a comparison of population and medical perceptions of treatment in eight European countries. *Ann Rheum Dis* 2004;63:342–7.
- [5] Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep Med Rev* 2006;10:357–69.
- [6] Roehrs T, Roth T. Sleep and pain: interaction of two vital functions. *Semin Neurol* 2005;25:106–16.
- [7] Ohayon MM. Relationship between chronic painful physical condition and insomnia. *J Psychiatr Res* 2005;39:151–9.
- [8] Ohayon MM. Observation of the natural evolution of insomnia in the American general population cohort. *Sleep Med Clin* 2009;4:87–92.
- [9] Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005;165:1286–92.
- [10] Trenkwalder C, Paulus W, Walters AS. The restless legs syndrome. *Lancet Neurol* 2005;4:465–75.
- [11] Larsson BW, Kadi F, Ulfberg J, Aulin KP. Skeletal muscle morphology in patients with restless legs syndrome. *Eur Neurol* 2007;58:133–7.
- [12] Salminen AV, Rimpila V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). *Neurology* 2014;82:1856–61.
- [13] Earley CJ, Connor J, Garcia-Borreguero D, Jenner P, Winkelman J, Zee PC, Allen R. Altered brain iron homeostasis and dopaminergic function in Restless Legs Syndrome (Willis-Ekbom Disease). *Sleep Med* 2014;15:1288–301.
- [14] Grote L, Leissner L, Hedner J, Ulfberg J. A randomized, double-blind, placebo controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome. *Mov Disord* 2009;24:1445–52.
- [15] Kallweit U, Siccoli MM, Poryazova R, Werth E, Bassetti CL. Excessive daytime sleepiness in idiopathic restless legs syndrome: characteristics and evolution under dopaminergic treatment. *Eur Neurol* 2009;62:176–9.
- [16] Abetz L, Allen R, Follet A, Washburn T, Earley C, Kirsch J, Knight H. Evaluating the quality of life of patients with restless legs syndrome. *Clin Ther* 2004;26:925–35.
- [17] Goldenberg DL. Diagnosis and differential diagnosis of fibromyalgia. *Am J Med* 2009;122(Suppl.):S14–21.
- [18] Stehlik R, Ulfberg J, Hedner J, Grote L. High prevalence of restless legs syndrome among women with multi-site pain: a population-based study in Dalarna, Sweden. *Eur J Pain* 2014;18:1402–9.
- [19] Andersson HI. Increased mortality among individuals with chronic widespread pain relates to lifestyle factors: a prospective population-based study. *Disabil Rehabil* 2009;31:1980–7.
- [20] Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;17:45–56.
- [21] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain TA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160–72.
- [22] Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101–19.
- [23] Partinen M, Gislason T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. *J Sleep Res* 1995;4:150–5.
- [24] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540–5.
- [25] Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT. Duration of sleep contributes to next-day pain report in the general population. *Pain* 2008;137:202–7.
- [26] Winkelman JW, Redline S, Baldwin CM, Resnick HE, Newman AB, Gottlieb DJ. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. *Sleep* 2009;32:772–8.
- [27] Kleitman N. Sleep and wakefulness. Revised and enlarged edition, 2. impr. ed. Chicago: The University of Chicago Press; 1963. x, 552 s. p.
- [28] Roehrs T, Hyde M, Blaisdel B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 2006;29:145–51.
- [29] Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res* 2001;10:35–42.
- [30] Burton E, Campbell C, Robinson M, Bounds S, Buenaver L, Smith M. (322) Sleep mediates the relationship between central sensitization and clinical pain. *J Pain* 2016;17(Suppl.):S56.
- [31] Paul-Savoie E, Marchand S, Morin M, Bourgault P, Bissette N, Rattanavong V, Cloutier C, Bissonnette A, Potvin S. Is the deficit in pain inhibition in fibromyalgia influenced by sleep impairments? *Open Rheumatol J* 2012;6:296–302.
- [32] Tang NK, McBeth J, Jordan KP, Blagojevic-Bucknall M, Croft P, Wilkie R. Impact of musculoskeletal pain on insomnia onset: a prospective cohort study. *Rheumatology (Oxford)* 2015;54:248–56.
- [33] Zautra AJ, Fasman R, Parish BP, Davis MC. Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Pain* 2007;128:128–35.
- [34] Okura K, Lavigne GJ, Huynh N, Manzini C, Filipini D, Montplaisir JY. Comparison of sleep variables between chronic widespread musculoskeletal pain, insomnia, periodic leg movements syndrome and control subjects in a clinical sleep medicine practice. *Sleep Med* 2008;9:352–61.
- [35] Zintzaras E, Kitsios GD, Papatheanasiou AA, Konitsiotis S, Miligkos M, Rodopoulou P, Hadjigeorgiou GM. Randomized trials of dopamine agonists in restless legs syndrome: a systematic review, quality assessment, and meta-analysis. *Clin Ther* 2010;32:221–37.
- [36] Stehlik R, Arvidsson L, Ulfberg J. Restless legs syndrome is common among female patients with fibromyalgia. *Eur Neurol* 2009;61:107–11.
- [37] Bogan RK. Effects of restless legs syndrome (RLS) on sleep. *Neuropsychiatr Dis Treat* 2006;2:513–9.
- [38] Edwards RR, Quartana PJ, Allen RP, Greenbaum S, Earley CJ, Smith MT. Alterations in pain responses in treated and untreated patients with restless legs syndrome: associations with sleep disruption. *Sleep Med* 2011;12:603–9.
- [39] Seidel MF, Muller W. Differential pharmacotherapy for subgroups of fibromyalgia patients with specific consideration of 5-HT₃ receptor antagonists. *Expert Opin Pharmacother* 2011;12:1381–91.
- [40] Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, Gracely RH, Clauw DJ. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. *Arthritis Rheum* 2003;48:2916–22.
- [41] de Souza JB, Potvin S, Goffaux P, Charest J, Marchand S. The deficit of pain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms. *Clin J Pain* 2009;25:123–7.
- [42] Gooneratne NS, Bellamy SL, Pack F, Staley B, Schutte-Rodin S, Dinges DF, Pack AI. Case-control study of subjective and objective differences in sleep patterns in older adults with insomnia symptoms. *J Sleep Res* 2011;20:434–44.
- [43] Diaz-Piedra C, Catena A, Sanchez AI, Miro E, Martinez MP, Buena-Casal G. Sleep disturbances in fibromyalgia syndrome: the role of clinical and polysomnographic variables explaining poor sleep quality in patients. *Sleep Med* 2015;16:917–25.
- [44] Hening WA, Allen RP, Washburn M, Lesage SR, Earley CJ. The four diagnostic criteria for Restless Legs Syndrome are unable to exclude confounding conditions (“mimics”). *Sleep Med* 2009;10:976–81.
- [45] Mäntyselkä P. Sleeping with pain – a nightmare. *Scand J Pain* 2014;3:208–9.
- [46] Bazil CW, Dave J, Cole J, Stalvey J, Drake E. Pregabalin increases slow-wave sleep and may improve attention in patients with partial epilepsy and insomnia. *Epilepsy Behav* 2012;23:422–5.