

Original experimental

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The influence of restless legs symptoms on musculoskeletal pain in depression

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Abstract

Background and aims: Restless legs syndrome is a sensorimotor disorder associated with mental health conditions notably depression. Restless legs symptoms and depression are commonly associated with pain. The study investigated the influence of restless legs symptoms on musculoskeletal pain in patients with depression or with increased depressive symptoms.

Methods: A cross-sectional study of primary care patients in the Central Finland Hospital District. The prevalence of restless legs symptoms was studied in patients with depressive symptoms ($n=695$) and controls without a psychiatric diagnosis ($n=410$) by using a structured questionnaire. The depressive symptoms were evaluated with the Beck Depression Inventory and the psychiatric diagnosis was confirmed by means of a diagnostic interview (MINI). The prevalence and intensity of musculoskeletal

pain was captured with form-based questions. A single-question screen for restless legs symptoms was applied.

Results: There was a significant difference in the prevalence of continuous widespread musculoskeletal pain between the three study groups: the controls 4.6% (95% CI: 2.8–7.1), the patients with symptoms of depression without a diagnosis 16.0% (11.7–21.1), and the patients with diagnosed depression 22.1% (18.3–23.3) ($p=0.006$ after being adjusted for age, sex, smoking, use of alcohol, education years, body mass index, use of antidepressants, and physical activity, after multiple corrections, all groups were significantly different from each other). Compared with those not having restless legs symptoms, subjects with restless legs symptoms had more often continuous widespread musculoskeletal pain in the control subjects ($p=0.001$; 2.3% vs. 10.5%) and in the patients with depressive symptoms without a depression diagnosis ($p=0.024$; 9.1 vs. 18.7%) but not in those with diagnosed depression ($p=0.98$; 19.5 vs. 19.4%). The restless legs symptoms were associated with the intensity of pain in all groups ($p<0.001$).

Conclusions: Restless legs symptoms were related to continuous widespread musculoskeletal pain in subjects without depressive symptoms and in patients with depressive symptoms without a depression diagnosis. Pain intensity was higher in the subjects with restless legs symptoms regardless of depressive symptoms or depression.

Implications: Clinical management of pain in patients with restless legs symptoms should include an increased focus on the prevention and treatment of either conditions.

Keywords: restless legs syndrome; depressive disorder; depression; primary health care; musculoskeletal pain.

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1 Introduction

Depression impairs health substantially and is a major global burden [1]. Apart from a low-spirited mood and a frail quality of life, depressed patients have a more severe sense of pain compared to others [2]. The culprit

of depression is both biological and psychosocial stress. Genes and epigenetic mechanisms partly create the basis for depression [3]. Depression and pain have been found to be related to restless legs symptoms [4–6].

The restless legs symptoms are unpleasant sensations such as an urge to move and crawling or tingling in the lower limbs [7]. Moreover some patients experienced the symptoms as pain intrinsically without any other source of pain [8]. Often restless legs symptoms occur with widespread pain and distressing ailments such as tension-type headaches, migraines and fibromyalgia [9–13]. Knowledge of the pathophysiology and clinical experience of restless legs symptoms have increased during the last decade, but the definite pathophysiology is still not completely elucidated.

Several different theories such as the lack of folate, hormones, deficient dopaminergic neurotransmission, genetics, systemic inflammation, peripheral hypoxia and iron deficiency have been suggested [14–17]. Lack of iron metabolism is more about the central nervous system than the peripheral parts and inflicts dopaminergic function-disrupting monoamine neurotransmitter synthesis [18]. For an individual this could explicate depressive symptoms alongside restless legs symptoms [19]. It is suspected that in the depressed patients the number of dopamine receptors has increased [20]. Dopamine agonists are effective treatments for symptoms of restless legs syndrome besides gabapentin, pregabalin, and opioids [21–23]; in addition to these are apposite medications to treat severe or chronic pain.

2 Aim

Due to non-existent data on the correlation between restless legs symptoms, a diagnosis, or symptoms of depression and musculoskeletal pain, we sought to characterize this relationship in a geographically defined sample of patients with depressive symptoms with and without clinical depression and population-based control subjects without a psychiatric diagnosis. We hypothesized that pain prevalence and intensity have an association with the presentation of restless legs symptoms among subjects with depressive symptoms.

3 Methods

The study (Finnish Depression and Metabolic Syndrome in Adults, FDMSA) was conducted in municipalities of the

Central Finland Hospital District and 706 patients were involved. The patients were 35 years or older and they went to a depression nurse case manager on their own or were referred by a general practitioner. The patients were included in this study if they were treated by a depression nurse case manager in 2008–2009 and had depressive symptoms and a score of at least 10 on the 21-item Beck's Depression Inventory (BDI) [24]. Notification was based on written and oral patient information and written consent was obtained before any study procedures. The study protocol was approved by the Ethics Committee of the Central Finland Hospital District.

The control group comprised 426 subjects over 35 years old. They were selected to the control group using random sampling in 2008–2009. The random sample was stratified by age, sex and community representing the population in the study. The tool for collecting the random sample was Statistics of Finland (<http://www.stat.fi>), which is an independent organization under the Ministry of Finance that manages data registers in Finland. After excluding participants with missing values (e.g. restless legs symptoms, missing values, $n=27$) the study population of the present study included 695 patients and 410 controls.

The data were collected with a questionnaire that included questions about use of medication, previously diagnosed somatic disorders, smoking, years of education, and use of alcohol (number of drinks per week). Leisure-time physical activity (number of 30-min exercise sessions) was delineated with the question: "How often do you engage in physical activity for at least half an hour so that you are out of breath and sweating?" Replies were classified as low (0–2 sessions per month), moderate (1–2 sessions per week), or high (three or more sessions per week) [16, 25].

The BDI was used for evaluating the severity of depression symptoms [24, 26], but the psychiatric diagnosis was confirmed with a diagnostic interview (Mini-International Neuropsychiatric Interview; MINI.; [27]) performed by a duly educated study nurse [28]. Of the patients with a BDI score of 10 or higher, 439 subjects had a confirmed depression diagnosis determined by a MINI [27, 29]. Altogether 256 subjects did not fulfill the diagnostic criteria since they had depressive symptoms without a depression diagnosis.

Musculoskeletal pain was captured by enquiring: "Do you have pain?" with the response categories: (1) not at all; (2) I have pain rarely or temporarily; and (3) I have pain frequently or continuously in the joints, back, neck, or multisite. The prevalence of the continuous widespread pain was based on answer category 3 (frequent or continuous

pain in the joints, back, neck, or multisite). Pain intensity was formed based on three pain-related questions. Participants were asked if they have had (1) pain or stiffness in joints; (2) neck pain; or (3) back pain during the last 4 weeks. Answers (0, have not had; 1, have had mild pain; 2, have had difficult pain; 3, have had severe pain) were summed up into a total score (scale ranging between 0 and 9), which accounted for pain intensity [30].

The restless legs symptoms were investigated by means of a structured and tested question: “When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?”. The question took into account an urge to move the legs, primarily during rest or inactivity, and partial or total relief with movement, with presence or worsening exclusively in the evening or at night. Reported by a previous validation study, the questionnaire had 100% sensitivity and 96.8% specificity [31].

The quality of sleep was determined by questions about sufficient sleep and feeling rested in the morning. Sufficient sleep was evaluated by the question: “Do you think that your sleep is sufficient (1=yes, almost always; 2=yes, often; 3=rarely or hardly ever; 4=I cannot say)”. Subjects responding “almost” or “often” were regarded as having sufficient sleep. Feeling rested in the morning was evaluated by the question: “How tired do you feel during the first 30 min after you have woken up in the morning (1=very tired; 2=quite tired; 3=quite rested; 4=I feel fresh)?” Subjects responding “quite rested” or feeling fresh were regarded as rested in the morning.

3.1 Statistical analysis

Data are presented as means with range or standard deviations (SD) or calculated as percentages. Statistical significance between groups was tested by analysis of variance (ANOVA) or a χ^2 -test. When adjusting for confounding factors, an analysis of covariance (tested variable was continuous) or logistic regression model (tested variable was categorical) was applied; models included age, sex, smoking, use of alcohol, education years, body mass index, use of antidepressants, and physical activity as covariates. In the case of violation of the assumptions (e.g. non-normality), a bootstrap-type test was used. The significance for pairwise comparisons were correct for multiplicity using Hommel’s multiple comparison procedure (at a significance level of 0.05). The normality of the variables was tested by using the Shapiro-Wilk W test. The

Stata 15.1, StataCorp LP (College Station, TX, USA) statistical package was used for the above analyses.

4 Results

A total of 1105 subjects participated in our study: 363 (32.9%) men and 742 (67.1%) women. Of these subjects, 410 were controls with no psychiatric diagnosis (mean BDI scores = 3.2 ± 2.7 points) and 256 were patients with depressive symptoms without a depression diagnosis (mean BDI scores = 17.8 ± 6.4 points). Of all the patients, 439 received a depression diagnosis (mean BDI scores = 23.4 ± 8.2 points). All the subjects with elevated depressive symptoms had lower leisure time physical activity than the controls. Furthermore, the prevalence of current smoking was higher in the patient groups than in the controls.

The lowest sufficiency and quality of sleep was perceived by the subjects with diagnosed depression. The patient groups used antidepressant medication and different kinds of medications (opioids, NSAID and paracetamol) more often than the control group (Table 1). Restless legs symptoms were present in 433 of all the study subjects. Subjects without a psychiatric diagnosis (BDI < 10) had the lowest prevalence of restless legs symptoms (25%). Patients with depressive symptoms without a depression diagnosis had a 43% prevalence of restless legs symptoms. The highest prevalence of restless legs symptoms, 50%, was found among the patients with diagnosed depression (Table 1).

Figure 1 shows adjusted (for age, sex, smoking, use of alcohol, education years, body mass index, use of antidepressants, and physical activity) prevalence of continuous widespread musculoskeletal pain and restless legs symptoms between the three study groups: the controls, the patients with symptoms of depression without diagnosis, and the patients with diagnosed depression. There was a significant difference in the prevalence of continuous widespread musculoskeletal pain between the three study groups: the controls 4.6% (95% CI: 2.8–7.1), the patients with symptoms of depression without diagnosis 16.0% (11.7–21.1), and the patients with diagnosed depression 22.1% (18.3–23.3) ($p=0.006$ after adjusted for age, sex, smoking, use of alcohol, education years, body mass index, use of antidepressants, and physical activity). After multiple corrections, all groups were significantly different from each other. Compared with those not having restless legs symptoms, subjects with restless legs symptoms had more often continuous widespread musculoskeletal pain

Table 1: Demographic and clinical traits of the subjects.

	Controls	BDI ≥ 10		<i>p</i> -Value
	N = 410	Without depression N = 256	Depression N = 439	
Female, number	245 (60)	189 (74)	308 (70)	<0.001
Age, mean (SD)	53 (10)	53 (11)	51 (10)	<0.001
Education years, mean (SD)	12.0 (3.4)	11.0 (3.3)	11.1 (3.0)	<0.001
Body Mass Index, mean (SD)	26.8 (4.6)	27.9 (5.9)	28.1 (5.9)	0.002
Smoking, n (%)	67 (16)	59 (23)	142 (32)	<0.001
Alcohol use dose, n (%)				0.048
0	66 (16)	61 (24)	103 (23)	
1–9	292 (71)	168 (66)	280 (64)	
≥ 10	52 (13)	27 (11)	56 (13)	
Leisure time physical activity, n (%)				<0.001
Low	49 (12)	43 (17)	108 (25)	
Moderate	181 (44)	122 (48)	179 (41)	
High	180 (44)	90 (35)	150 (34)	
BP, mmHg, mean (SD)				
Systolic	129 (16)	130 (16)	131 (16)	0.29
Diastolic	81 (10)	81 (10)	82 (11)	0.33
Use of antidepressant, n (%)	24 (6)	125 (49)	303 (69)	<0.001
Use of pain medication, n (%)	10 (2)	67 (26)	143 (33)	<0.001
NSAID	7 (2)	38 (15)	99 (23)	
Paracetamol	1 (1)	26 (10)	45 (10)	
Opioids	4 (1)	16 (6)	30 (7)	
Felt rested in the morning, n (%)	355 (87)	158 (62)	213 (49)	<0.001
Sufficiency of sleep, n (%)	348 (85)	150 (59)	175 (40)	<0.001
Restless legs symptoms, n (%)	101 (25)	111 (43)	221 (50)	<0.001
BDI points, mean (SD)	3.2 (2.7)	17.8 (6.4)	23.4 (8.2)	<0.001

Results in the table shown as numbers (percentage) and means (standard deviation).

SD = standard deviation; BMI = body mass index; alcohol dose, 12 grams of pure alcohol; BP = blood pressure; NSAID = nonsteroidal anti-inflammatory drugs; BDI = 21-Item Beck Depression Inventory.

in the control subjects ($p=0.001$; 2.3% vs. 10.5%) and in the patients with depressive symptoms without a depression diagnosis ($p=0.024$; 9.1 vs. 18.7%) but not in those with diagnosed depression ($p=0.98$; 19.5 vs. 19.4%).

Figure 2 illustrates adjusted (for age, sex, smoking, use of alcohol, education years, body mass index, use of antidepressants, and physical activity) intensity of pain and restless legs symptoms between the study groups. There was an insignificant relationship between increased intensity of pain and the study groups. However, restless legs symptoms have an association with increased intensity of pain in all groups ($p < 0.001$).

5 Discussion

The main finding was that restless legs symptoms had a significant relationship with continuous widespread musculoskeletal pain in the subjects without depressive

symptoms and the patients with depressive symptoms without a depression diagnosis. However, restless legs symptoms were not associated with widespread musculoskeletal pain in patients with a depression diagnosis albeit they have the most pain. We found that the subjects with restless legs symptoms and depression symptoms without clinical depression may suffer from continuous widespread musculoskeletal pain as frequently as the patients with a depression diagnosis. The second finding was that in addition to depression, restless legs symptoms aggravated the intensity of pain.

Previous studies have found that restless legs symptoms may have a recurrent affiliation with pain. Widespread pain has been linked to restless legs symptoms in patients with asthma, severe bronchitis and emphysema; and they additionally often had a tension-type headache, migraine and fibromyalgia [9–12]. The hypothesis assumed either the mechanisms of pain intensity defused restless legs symptoms or the symptoms compounded the sense of pain. Restless legs symptoms were associated

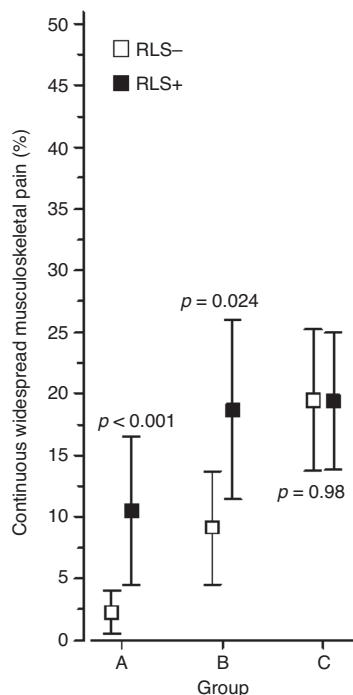


Fig. 1: Prevalence of continuous widespread musculoskeletal pain according to restless legs symptoms in controls (A), subjects with depressive symptoms without a depression diagnosis (B), and clinically depressed patients (C) (adjusted for age, sex, smoking, use of alcohol, education years, body mass index, use of antidepressants, and physical activity).

with psychosomatic symptoms, notably somatization [32]. Subjects with restless legs syndrome have hyperalgesia and more long-term and intense pain; also, Parkinson's disease patients with restless legs symptoms reported a sense of pain more repeatedly than those without the symptoms [33–35].

Restless legs symptoms independently aggravated the intensity of pain. Restless legs symptoms are subsumed to the dopaminergic dysfunction and it had a bidirectional effect on chronic pain and depression [36]. However, restless legs symptoms added widespread musculoskeletal pain only in healthy subjects and patients with depressive symptoms without a depression diagnosis. The patients with depressive symptoms without a depression diagnosis had widespread musculoskeletal pain as much as the patients with a depression diagnosis but the patients with a depression diagnosis had a high prevalence of restless legs symptoms excluding acknowledgement of pain [6]. One explanation for the present findings could be that depression spontaneously increased the susceptibility to widespread musculoskeletal pain whereupon restless legs symptoms did not intensify the pain among the patients with depression. However, restless legs symptoms in the

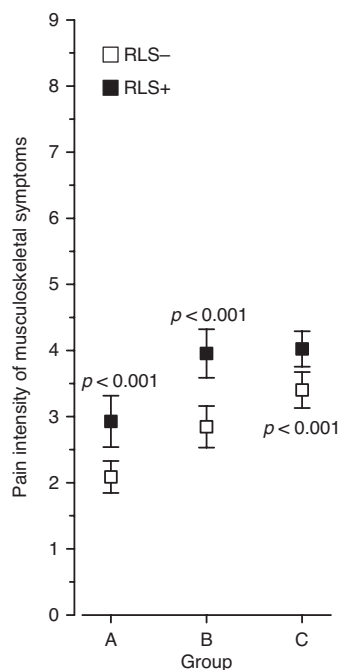


Fig. 2: Intensity of pain according to restless legs symptoms in controls (A), subjects with depressive symptoms without a depression diagnosis (B), and clinically depressed patients (C) (adjusted for age, sex, smoking, use of alcohol, education years, body mass index, use of antidepressants, and physical activity).

patients with depressive symptoms without a depression diagnosis may cause an exacerbation of widespread pain. Those patients could experience restless legs symptoms as pain, or a pathomechanism of restless legs symptoms had caused an onset of widespread pain.

Pain and depression usually interrelate with each other. Depression predicts pain or a pain-related disability more probably than vice versa [37], and predisposes one to obesity and low physical activity [38, 39]. Metabolic features, such as a higher triglyceride and glucose levels, have been found to be associated with an increased level of specific musculoskeletal pain, such as tendon and back pain [40, 41].

Inflammatory markers, such as C-reactive protein and interleukin-6, increase in depression and have an influence on monoamines [42]. Furthermore, inflammation markers such as interleukin-6 are linked to chronic widespread musculoskeletal pain [43]. The main occasion for depression to be determined is the monoamine hypothesis, including serotonin, dopamine and noradrenaline insufficiency, which additionally has an impact on the chronic pain mechanism [44]. The patients with diagnosed depression had the most continuous widespread musculoskeletal pain and restless legs symptoms did not

exacerbate the occasion. The comorbidity of pain and depression is well known and explicated e.g. a function of indoleamine 2,3-dioxygenase (IDO) or anti- and pro-inflammatory cytokines [45]. Dysregulation of the hypothalamus-pituitary-adrenal axis and hypercortisolism was associated with depression but patients with widespread pain or restless legs syndrome had an insignificant affiliation [46–48]. Besides the depression and pain, systemic inflammation might play a role in restless legs symptoms [16, 49].

The subjects with depression symptoms or diagnosed depression used pain medication, such as paracetamol, anti-inflammatory drugs and opioids, more often than the controls. Opioids, gabapentin and pregabalin are potential treatments for restless legs symptoms and severe pain but there was no evidence of the effects of paracetamol or nonsteroidal anti-inflammatory drugs on restless legs symptoms.

The strengths of our investigation included a geographically representative sample of middle-aged and elderly subjects. Moreover, we used a diagnostic interview in addition to a self-rating of depressive symptoms. The question assessing the restless legs symptoms has been validated in a clinical setting [31] but not particularly in the present setting. Therefore because clinical differential diagnostics were not conducted in the present study, we regarded participants with a positive result in this screening as having restless legs symptoms instead of having the restless legs syndrome. We had no data on how long the symptoms of depression or restless legs had been present, which was a limitation. Another limitation was the cross-sectional design of our study, which does not justify making inferences of causality. Additionally, only persons aged 35 or older were enrolled in the study, so the results could not be generalised to younger age groups [6, 16].

6 Implications

When treating patients with pain, physicians should be conscious of the role of restless legs symptoms, depressive symptoms and depression in ensuring high-quality sleep and a life that is could be as pain-free as possible. Notably restless legs symptoms had an association with frequent continuous widespread musculoskeletal pain in the controls and patients with depressive symptoms without a depression diagnosis.

This finding indicates that there may be an opportunity for intervention and may prompt clinicians to screen for restless leg symptoms in subjects with pain, and vice

versa. Restless legs symptoms exacerbated the intensity of pain in all study groups. This grievous condition stipulates apposite treatment from physicians, either medical or non-medical, while the pathophysiology is studied.

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Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The study protocol was approved on the 17th of April 2007 by the Ethics Committee of Central Finland Central Hospital.

References

- [1] Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, Whiteford HA. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013;10:e1001547.
- [2] Stubbs B, Vancampfort D, Veronese N, Thompson T, Fornaro M, Schofield P, Solmi M, Mugisha J, Carvalho AF, Koyanagi A. Depression and pain: primary data and meta-analysis among 237 952 people across 47 low- and middle-income countries. *Psychol Med* 2017;47:2906–17.
- [3] Uchida S, Yamagata H, Seki T, Watanabe Y. Epigenetic mechanisms of major depression: targeting neuronal plasticity. *Psychiatry Clin Neurosci* 2018;72:212–27.
- [4] 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.
- [5] Cho CH, Kim L, Lee HJ. Individuals with restless legs syndrome tend to have severe depressive symptoms: findings from a community-based cohort study. *Psychiatry Investig* 2017;14:887–93.
- [6] Auvinen P, Mäntyselkä P, Koponen H, Kautiainen H, Korniloff K, Ahonen T, Vanhala M. Prevalence of restless legs symptoms according to depressive symptoms and depression type: a cross-sectional study. *Nord J Psychiatry* 2018;72:51–6.

- [7] Ondo W, Jankovic J. Restless legs syndrome: clinicoetiologic correlates. *Neurology* 1996;47:1435–41.
- [8] Hornyak M, Sohr M, Busse M, 604 and 615 Study Groups. Evaluation of painful sensory symptoms in restless legs syndrome: experience from two clinical trials. *Sleep Med* 2011;12:186–9.
- [9] Chung PW, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK. Restless legs syndrome and tension-type headache: a population-based study. *J Headache Pain* 2017;18:47.
- [10] Schurks M, Winter A, Berger K, Kurth T. Migraine and restless legs syndrome: a systematic review. *Cephalalgia* 2014;34:777–94.
- [11] Viola-Saltzman M, Watson NF, Bogart A, Goldberg J, Buchwald D. High prevalence of restless legs syndrome among patients with fibromyalgia: a controlled cross-sectional study. *J Clin Sleep Med* 2010;6:423–7.
- [12] Ding Z, Stehlik R, Hedner J, Ulfberg J, Grote L. Chronic pulmonary disease is associated with pain spreading and restless legs syndrome in middle-aged women—a population-based study. *Sleep Breath* 2019;23:135–142.
- [13] van Oosterhout WP, van Someren EJ, Louter MA, Schoonman GG, Lammers GJ, Rijsman RM, Ferrari MD, Terwindt GM. Restless legs syndrome in migraine patients: prevalence and severity. *Eur J Neurol* 2016;23:1110–6.
- [14] Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. *J Womens Health Gend Based Med* 2001;10:335–41.
- [15] Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelmann JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB, International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria—history, rationale, description, and significance. *Sleep Med* 2014;15:860–73.
- [16] Auvinen P, Mäntyselkä P, Koponen H, Kautiainen H, Korniloff K, Ahonen T, Vanhala M. Elevation of tumor necrosis factor alpha levels is associated with restless legs symptoms in clinically depressed patients. *J Psychosom Res* 2018;115:1–5.
- [17] Salminen AV, Rimpila V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). *Neurology* 2014;82:1856–61.
- [18] Khan FH, Ahlberg CD, Chow CA, Shah DR, Koo BB. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. *J Neurol* 2017;264:1634–41.
- [19] Rizzo G, Li X, Galantucci S, Filippi M, Cho YW. Brain imaging and networks in restless legs syndrome. *Sleep Med* 2017;31:39–48.
- [20] Byrne KA, Norris DD, Worthy DA. Dopamine, depressive symptoms, and decision-making: the relationship between spontaneous eye blink rate and depressive symptoms predicts Iowa Gambling Task performance. *Cogn Affect Behav Neurosci* 2016;16:23–36.
- [21] de Oliveira CO, Carvalho LB, Carlos K, Conti C, de Oliveira MM, Prado LB, Prado GF. Opioids for restless legs syndrome. *Cochrane Database Syst Rev* 2016:CD006941.
- [22] Trenkwalder C, Winkelmann J, Inoue Y, Paulus W. Restless legs syndrome—current therapies and management of augmentation. *Nat Rev Neurol* 2015;11:434–45.
- [23] Scholz H, Trenkwalder C, Kohonen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. *Cochrane Database Syst Rev* 2011:CD006009.
- [24] Beck AT. A systematic investigation of depression. *Compr Psychiatry* 1961;2:163–70.
- [25] Raatikainen I, Vanhala M, Mäntyselkä P, Heinonen A, Koponen H, Kautiainen H, Korniloff K. Does level of leisure time physical activity, in a sample of patients with depression, predict health care utilization over a subsequent 5-year period? Findings from a Finnish cohort study. *Ment Health Phys Act* 2018;15:40–4.
- [26] Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. *J Clin Psychol* 1984;40:1365–7.
- [27] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(Suppl 20):22–57.
- [28] Koponen H, Kautiainen H, Leppanen E, Mäntyselkä P, Vanhala M. Cardiometabolic risk factors in patients referred to depression nurse case managers. *Nord J Psychiatry* 2015;69:262–7.
- [29] Sheehan DV, Lecrubier Y, Janavs J. Mini-International Neuropsychiatric Interview (MINI). Tampa, FL: University of South Florida, Institute for Research in Psychiatry; Paris: INSERM-Hopital de la Salpetriere, 1994.
- [30] Korniloff K, Kotiaho S, Vanhala M, Kautiainen H, Koponen H, Mäntyselkä P. Musculoskeletal pain in melancholic and atypical depression. *Pain Med* 2017;18:341–7.
- [31] Ferri R, Lanuzza B, Cosentino FII, Iero I, Tripodi M, Spada RS, Toscano G, Marelli S, Aricò D, Bella R, Hening WA, Zucconi M. A single question for the rapid screening of restless legs syndrome in the neurological clinical practice. *Eur J Neurol* 2007;14:1016–21.
- [32] Kim JB, Koo YS, Eun MY, Park KW, Jung KY. Psychosomatic symptom profiles in patients with restless legs syndrome. *Sleep Breath* 2013;17:1055–61.
- [33] Hoogwout SJ, Paananen MV, Smith AJ, Beales DJ, O'Sullivan PB, Straker LM, Eastwood PR, McArdle N, Champion D. Musculoskeletal pain is associated with restless legs syndrome in young adults. *BMC Musculoskelet Disord* 2015;16:294.
- [34] Bachmann CG, Rolke R, Scheidt U, Stadelmann C, Sommer M, Pavlakovic G, Happe S, Treede RD, Paulus W. Thermal hypoaesthesia differentiates secondary restless legs syndrome associated with small fibre neuropathy from primary restless legs syndrome. *Brain* 2010;133(Pt 3):762–70.
- [35] Rana AQ, Qureshi AR, Rahman L, Jesudasan A, Hafez KK, Rana MA. Association of restless legs syndrome, pain, and mood disorders in Parkinson's disease. *Int J Neurosci* 2016;126:116–20.
- [36] Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. *Sleep Med Rev* 2013;17:173–83.
- [37] Lerman SF, Rudich Z, Brill S, Shalev H, Shahar G. Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. *Psychosom Med* 2015;77:333–41.
- [38] Brunet A, Augestad LB, Gudmundsdottir SL. Personality, physical activity, and symptoms of anxiety and depression: the HUNT study. *Soc Psychiatry Psychiatr Epidemiol* 2013;48:745–56.
- [39] Olvera RL, Williamson DE, Fisher-Hoch SP, Vatcheva KP, McCormick JB. Depression, obesity, and metabolic syndrome: prevalence and risks of comorbidity in a population-based

- representative sample of Mexican Americans. *J Clin Psychiatry* 2015;76:e1300-5.
- [40] Rinaldo L, McCutcheon BA, Gilder H, Kerezoudis P, Murphy M, Maloney P, Hassoon A, Bydon M. Diabetes and back pain: markers of diabetes disease progression are associated with chronic back pain. *Clin Diabetes* 2017; 35:126–31.
- [41] Tilley BJ, Cook JL, Docking SI, Gaida JE. Is higher serum cholesterol associated with altered tendon structure or tendon pain? A systematic review. *Br J Sports Med* 2015;49:1504–9.
- [42] Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord* 2013;150:736–44.
- [43] Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience* 2016;338:114–29.
- [44] Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* 2014;CD007115.
- [45] Walker AK, Kavelaars A, Heijnen CJ, Dantzer R. Neuroinflammation and comorbidity of pain and depression. *Pharmacol Rev* 2013;66:80–101.
- [46] Aggarwal VR, Macfarlane GJ, Tajar A, Mulvey MR, Power A, Ray D, McBeth J. Functioning of the hypothalamic-pituitary-adrenal and growth hormone axes in frequently unexplained disorders: results of a population study. *Eur J Pain* 2014;18:447–54.
- [47] Staufienbiel SM, Penninx BW, Spijker AT, Elzinga BM, van Rossum EF. Hair cortisol, stress exposure, and mental health in humans: a systematic review. *Psychoneuroendocrinology* 2013;38:1220–35.
- [48] Wetter TC, Collado-Seidel V, Oertel H, Uhr M, Yassouridis A, Trenkwalder C. Endocrine rhythms in patients with restless legs syndrome. *J Neurol* 2002;249:146–51.
- [49] Trotti LM, Rye DB, De Staercke C, Hooper WC, Quyyumi A, Bliwise DL. Elevated C-reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. *Brain Behav Immun* 2012;26:1239–43.