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ARTICLE

A longitudinal study of restless legs symptoms among patients with depression

Piritta Auvinen[a], Hannu Koponen[b], Hannu Kautiainen[c,d], Katariina Korniloff[e], Tiina Ahonen[f], Mauno Vanhala[a] and Pekka Mäntyselkä[a,c]

[a]Institute of Public Health and Clinical Nutrition, General Practice, University of Eastern Finland, Kuopio, Finland; [b]Psychiatry, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [c]Primary Health Care Unit, Kuopio University Hospital, Kuopio, Finland; [d]Folkhälsan Research Center, Helsinki, Finland; [e]School of Health and Social Studies, JAMK University of Applied Sciences, Jyväskylä, Finland; [f]Primary Health Care Unit, Central Finland Central Hospital, Jyväskylä, Finland

ABSTRACT

Background: The aim of this study was to analyse the relationship between depressive symptoms and clinical depression and restless legs symptoms in a longitudinal primary care setting.

Methods: The prevalence of restless legs symptoms at baseline and after a six-year follow-up was studied in 474 patients with depressive symptoms and 333 population-based control subjects without depressive symptoms. Depressive symptoms at the baseline and after the six-year follow-up were evaluated with the Beck Depression Inventory (BDI) Second Edition. A psychiatric diagnosis was confirmed with a diagnostic interview (M.I.N.I.). Statistical comparisons between groups were made using analysis of variance (ANOVA) for continuous variables and a chi-square test or logistic models for categorical variables. Repeated measures were analysed using generalizing estimating equations (GEE) models.

Results: At baseline the prevalence of restless legs symptoms was 24.3% in control subjects, 43.8% in the patients with depressive symptoms without a depression diagnosis, and 49.3% in clinically depressed patients. During the follow-up up the prevalence of restless legs symptoms declined significantly ($p = 0.003$). In addition to baseline restless legs symptoms, the prognostic factors for restless legs symptoms among patients with clinical depression were age and BDI score. In the control subjects, moderate and high leisure time physical activity was inversely associated with restless legs symptoms at the follow-up.

Conclusions: A higher level of baseline depressive symptoms was a risk factor for restless legs symptoms in patients with clinical depression. In the prevention and treatment of restless legs symptoms among the patients with depression, the priority is the effective treatment of depression.

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Restless legs syndrome; depressive disorder; depression; primary health care

Introduction

Symptoms of restless legs syndrome are characterised by an unpleasant sensations in the legs that occurs at rest in the evening or during the night. In addition, patients suffer from an urge to move their legs, and moving or stretching their legs relieves the symptoms. The prevalence of restless legs syndrome varies greatly between 3.5% and 36.8% [1,2].

Restless legs symptoms increase the risk of self-harm and cardiovascular mortality [3,4]. They also have a negative and persistent influence on daily life [5,6]. Psychiatric disorders, especially mood and anxiety disorders, and restless legs symptoms regularly exist together [7,8]. The main theories explaining the pathophysiology of depression relate to monoamine neurotransmitters (serotonin and noradrenalin), neuroplasticity and neurogenesis [9]. Previous studies have suggested that restless legs syndrome may be related to the lack of folate, hormones (i.e. prolactin and growth hormone), deficient dopaminergic neurotransmission, depression, genetics, systemic inflammation, peripheral hypoxia and iron deficiency [7,8,10–14,17]. Knowledge of the association between mood disorders and restless legs is not well established.

The relationship between depression and restless legs symptoms is bidirectional but in previous prospective studies restless legs syndrome preceded both clinical depression and a new onset of depressive symptoms [15–17]. Depression and depressive symptoms are associated with restless legs symptoms [18]. However, there is not very much scientific knowledge about these associations based on longitudinal settings. In particular, the importance of depression or depressive symptoms in the course of restless legs symptoms is not clear.

Aims

Our previous analyses based on the baseline findings indicated that the prevalence of restless legs symptoms is different in people without depressive symptoms and those with depressive symptoms with or without clinical depression

CONTACT Piritta Auvinen pirau@student.uef.fi, University of Eastern Finland, Primary Health Care Unit, P.O.B. 1627, Kuopio, FI-70211, Finland

[19]. We hypothesised that depression and depressive symptoms may predict the persistence and worsening of restless legs symptoms. Therefore, we aimed to study the relationship between depressive symptoms, clinical depression and restless legs symptoms in a longitudinal primary care setting with a mean follow-up of six years.

Material and methods

The study (Finnish Depression and Metabolic Syndrome in Adults, FDMSA) was designed to enable the comparison of the sociodemographic, lifestyle, clinical and service utilization features of subjects without depressive symptoms, patients with depressive symptoms without clinical depression, and those with clinical depression [22]. Subjects were enlisted from the primary health care services in the area of Central Finland Hospital District. The study has a catchment area of 274,000 residents. During data collection, new patients 35 years of age and older who had an appointment with a depression nurse case manager were eligible to enrol. The patients approached the nurse on their own or were referred by a general practitioner in 2008–2009 due to depressive symptoms. The study had 706 patients who had a score of least 10 on the 21-item Beck's Depression Inventory (BDI) Second Edition [12,19,20]. The follow-up was conducted in 2015–2016 approximately six years after the baseline. 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.

Random sampling was used to select a group of 426 middle-aged (> 35 years) persons as control subjects from among residents in the participating municipalities. Concurrently with the patient recruitment in 2008–2009, a random sample matched by age, gender and community representing the population in the study region was taken by the Digital and Population Data Services Agency (https://dvv.fi/en/individuals). All the subjects in the control group had a BDI score below 10 and no psychiatric diagnosis or current depressive symptoms.

At the baseline all the participants filled in a standard questionnaire form containing questions about previously diagnosed somatic disorders and use of medications, including antidepressants. Data on current smoking, years of education, use of alcohol (number of drinks per week) and leisure-time physical activity (LTPA; number of 30-min exercise sessions) were also collected. The severity of depressive symptoms was evaluated with the BDI [20]. Psychiatric diagnoses at the baseline were derived from the diagnostic interview (Mini-International Neuropsychiatric Interview; M.I.N.I., the Finnish version of M.I.N.I 5.0.0) conducted by a trained study nurse [21,22]. In the six-year follow-up, the participants filled out a standard questionnaire including the same structured questions concerning restless legs symptoms and BDI as at the baseline.

Restless legs symptoms were observed by using a structured and tested question that considered the core characteristics of restless legs syndrome discomfort: 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. The question about restless legs symptoms is answered with 'yes or no'. The questionnaire has been found to have an excellent sensitivity and specificity for restless legs syndrome among patients with neurological symptoms [23].

LTPA was determined 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?' Responses were then classified as low (0-2 sessions per month), moderate (1–2 sessions per week), or high (three or more sessions per week) [12,24].

The fasting blood sample collection procedure for total cholesterol, HDL and LDL cholesterol, triglycerides and glucose took place at the health centre's laboratories by a trained nurse in an outpatient setting. Blood samples were analysed using Modular Analytics SWA (Hitachi High-Technologies Corporation, Tokyo, Japan) [19].

Statistical analysis

Data are presented as means with standard deviation (SD) and as numbers with percentages. Statistical comparisons between groups were made using analysis of variance (ANOVA) for continuous variables and a chi-square test or logistic models for categorical variables. The significance for pairwise comparisons was corrected for multiplicity using Hommel's multiple comparison procedure (at a significance level of 0.05). Repeated measures were analysed using generalizing estimating equations (GEE) models to measure changes in the prevalence of restless legs symptoms with an unstructured covariance structure. The gender, age, smoking, body mass index (BMI), LTPA and use of selective serotonin reuptake inhibitors (SSRIs) at baseline were used as covariates in these models.

Multivariate logistic regression was used to investigate the association between baseline characteristics (restless legs symptoms, gender, age, education, BMI, smoking, LTPA, BDI score and SSRIs use at baseline) and restless legs symptoms in the follow-up. A possible nonlinear relationship between all restless legs symptoms in the follow-up and the change in BDI score was assessed by using a 3-knot-restricted cubic spline logistic model. The normality of variables was evaluated graphically and using the Shapiro–Wilk W test. Stata 16.0 (StataCorp LP, College Station, TX, USA) was used for the analysis.

Results

A total of 1,105 subjects, consisting of the patients and control subjects, participated in the baseline study. In all, 298 (27%) participants withdrew from the study during the follow-up: 20 because of death, 244 did not respond and 34 declined to participate. Among the patients with clinical depression, 54% of men and 69% of women participated in the follow-up ($p = 0.004$). Among the patients with depressive symptoms, the mean age of non-participating patients

was 49 years while among participating ones it was 55 years ($p < 0.001$). Otherwise, there were no significant differences between patients who dropped out and participating patients in terms of gender, BDI score and restless legs symptoms.

At the baseline, 333 subjects were control subjects with no psychiatric diagnosis (mean BDI scores = 3.1 ± 2.7 points), 192 were patients with depressive symptoms without a depression diagnosis (mean BDI scores = 17.6 ± 6.2 points) and 282 patients had received a depression diagnosis (mean BDI scores = 23.2 ± 7.8 points). The clinically depressed patients had lower LTPA, more smoking, a higher triglyceride concentration, heart rate and BMI than the control subjects. Consistently antidepressant use was more common in the patient groups. SSRIs were used by 12 (4%) of the control subjects with no psychiatric diagnosis, 60 (31%) of the patients with depressive symptoms without a depression diagnosis and 117 (41%) of the clinically depressed patients. The control subjects felt more rested and had more sufficient sleep compared to both patient groups (Table 1).

Restless legs symptoms were present in 304 (37.7%) of the study subjects at the baseline. There was a significant difference in the prevalence of restless legs symptoms between the control subjects and patient groups ($p < 0.001$; adjusted for gender, age, smoking, BMI, LTPA and SSRIs use at baseline). The control subjects had the lowest prevalence (24.3%) of restless legs symptoms. The patients with depressive symptoms without a depression diagnosis had a 43.8% prevalence of restless legs symptoms, and the highest prevalence, 49.3%, was found among the clinically depressed patients. In general, the prevalence of restless legs symptoms declined in the follow-up ($p = 0.003$; adjusted for gender, age, smoking, BMI, LTPA and SSRIs use at baseline) (Figure 1). Group-specific changes were −2% (95% CI: −7 to 3%) in the control subjects, −7% (95% CI: −14 to 1%) in the patients with depressive symptoms without clinical depression and −9%; (95% CI: −15 to −3%) in the patients with clinical depression.

In the multivariate analysis, baseline restless leg symptoms, age and BDI score predicted the presence of restless legs symptoms at the follow-up among the patients with clinical depression (Table 2). Among the patients with depressive symptoms without clinical depression, no predicting factors were found besides baseline restless leg symptoms. In the control group, the level of LTPA was inversely associated with restless legs symptoms at the follow-up.

At the follow-up, the BDI score had changed significantly in all study groups ($p < 0.001$). In the control subjects, the BDI score had increased (mean 1.1; 95% CI:0.7 to 1.6), whereas the patients with depressive symptoms without a depression diagnosis (mean −7.7; 95% CI: −9.0 to −6.5) and the clinically depressed patients (mean −10.2; 95% CI: −11.4 to −9.1) had a decreased BDI score at the follow-up compared with the baseline values.

The change in BDI score was associated with the presence of restless legs symptoms in the control group (OR 1.11 [1.04 to 1.19]; $p = 0.002$) and in the group of patients with clinical depression (OR 1.05 [1.01 to 1.08]; $p = 0.005$). The patients with depressive symptoms without clinical depression (OR 1.03 [0.98 to 1.08]; $p = 0.15$) did not reveal a significant association between the change in BDI score and restless legs symptoms at the follow-up (Figure 2).

Table 1. Demographic and clinical characteristics of the subjects at baseline.

	Control	BDI ≥10		
	A $N = 333$	B Without depression $N = 192$	C Depression $N = 282$	p Value [Multiple comparison]
Female, *n* (%)	197 (59)	143 (74)	211 (75)	<0.001 [A/B, A/C]
Age, mean (SD)	53 (10)	55 (10)	52 (10)	0.002 [B/C]
Education years, mean (SD)	12.2 (3.4)	10.9 (3.3)	11.1 (3.0)	<0.001 [A/B, A/C]
Body mass index (kg/m^2), mean (SD)	26.6 (4.4)	27.8 (5.9)	28.1 (5.7)	<0.001 [A/B, A/C]
Currently smoking, *n* (%)	57 (17)	39 (20)	88 (31)	<0.001 [A/C, B/C]
Alcohol use, doses, *n* (%)				0.038 [A/B]
0	47 (14)	46 (24)	61 (22)	
1–9	241 (72)	125 (65)	182 (65)	
≥10	45 (14)	21 (11)	39 (14)	
Leisure time physical activity, *n* (%)				0.003 [A/C, B/C]
Low	40 (12)	34 (18)	64 (23)	
Moderate	145 (44)	92 (48)	119 (42)	
High	148 (44)	65 (34)	98 (35)	
Heart rate (beats/min), mean (SD)	66.4 (9.2)	67.0 (8.8)	69.0 (10.0)	0.002 [A/C,]
BP, (mmHg), mean (SD)				
Systolic	128.8 (15.1)	130.8 (16.9)	130.7 (15.1)	0.23
Diastolic	80.4 (9.5)	81.3 (9.5)	81.4 (10.5)	0.41
Plasma glucose (mmol/l), mean (SD)	5.70 (1.06)	5.61 (0.90)	5.71 (1.03)	0.54
Serum cholesterol (mmol/l), mean (SD)	5.05 (0.89)	5.14 (0.93)	5.12 (0.99)	0.49
Serum LDL cholesterol (mmol/l), mean (SD	3.12 (0.82)	3.10 (0.83)	3.09 (0.89)	0.91
Serum HDL cholesterol (mmol/l), mean (SD)	1.57 (0.42)	1.60 (0.46)	1.56 (0.44)	0.75
Serum triglycerides (mmol/l), mean (SD)	1.18 (0.62)	1.40 (1.83)	1.34 (0.76)	0.013 [A/C]
Antidepressants, n (%)	23 (7)	87 (45)	194 (69)	<0.001 [A/B, A/C, B/C]
SSRIs	12 (4)	60 (31)	117 (41)	<0.001 [A/B, A/C, B/C]

P values (at a significance level of 0.05) for pairwise group comparisons adjusted for multiplicity using the Hommel's multiple comparison procedure. The results in the table are shown as numbers (percentage) and means (standard deviation).

SD: standard deviation; BDI: 21-Item Beck Depression Inventory; BMI: body mass index; alcohol dose: 12 grams of pure alcohol; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NSAID: nonsteroidal anti-inflammatory drugs; SSRIs: Selective serotonin reuptake inhibitors.

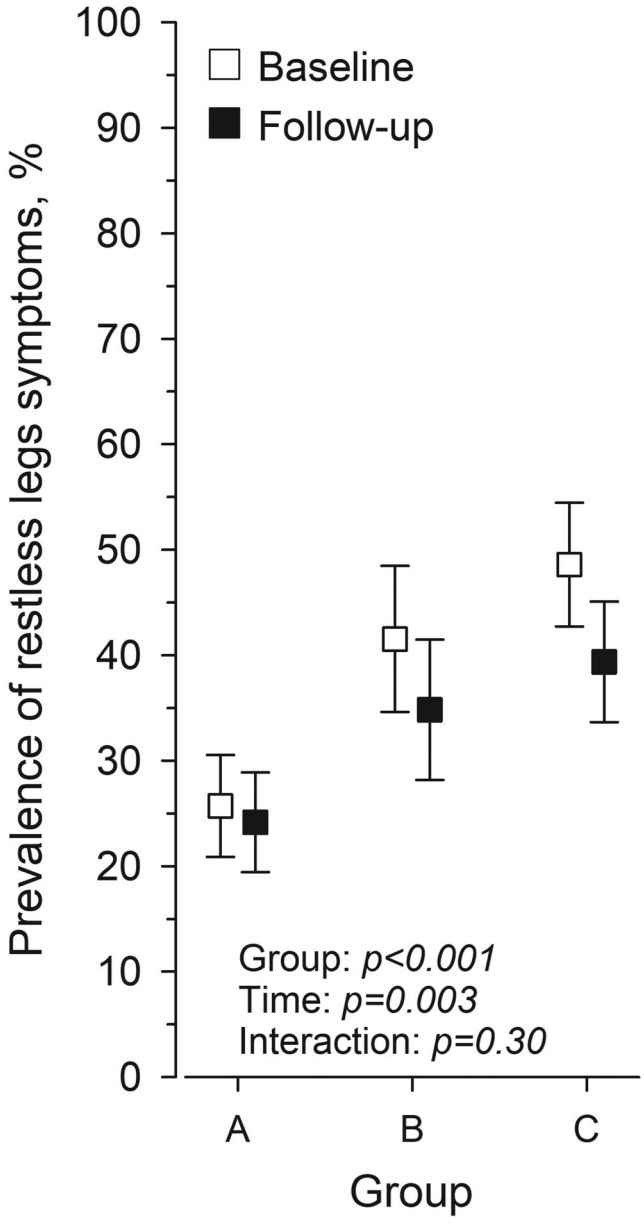

Figure 1. Prevalence of restless legs symptoms in control subjects (A), patients with depressive symptoms without a depression diagnosis (B) and clinically depressed patients (C) at baseline and follow-up. The results are adjusted for gender, age, smoking, body mass index, physical activity and selective serotonin reuptake inhibitors at baseline.

Discussion

The main findings of this study indicated the differences in the longitudinal relationship between mood disorders and restless legs symptoms among control subjects, patients with depressive symptoms without clinical depression, and those with clinical depression. The baseline level of depressive symptoms predicted restless legs symptoms only in the patients with clinical depression. A change in depressive symptoms between the baseline and the follow-up was associated with restless legs symptoms at the follow-up in the non-depressive population and in the patients with clinical depression.

The baseline level of restless legs symptoms predicted restless symptoms in the follow-up although they decreased moderately but significantly in all groups. However, the course of restless legs symptoms in our study seemed to be quite stable, as was also found in a hospital-based study and a questionnaire study of patients with restless legs syndromes [25,26]. In previous prospective studies, restless legs syndrome preceded both clinical depression and a new onset of depressive symptoms [15,16]. In the present study, the baseline level of depressive symptoms predicted restless legs symptoms in the follow-up with those participants who had clinical depression at the baseline. An increasing level of depressive symptoms during the follow-up period increased the odds of having restless legs symptoms at the follow-up. This finding is in line with a previous study based on subjects with restless legs syndrome that suggests that a change in depressive score is associated with a change in restless legs symptoms [25].

Recent studies have shown that drug treatment of restless legs symptoms improves mood, which is plausible as dopamine agonists may also alleviate depressive symptoms [27]. In the present study, a decreasing level of depressive symptoms was associated with decreasing odds of having restless legs symptoms in the follow-up. Therefore, it can be assumed that effective treatment of depression probably relieves restless legs symptoms. About seven out of 10 clinically depressed patients in our study used antidepressants at the baseline. Among them, the follow-up BDI-score was markedly lower (10 points) in the follow-up compared with baseline, suggesting a treatment response. There are also

Table 2. Association between baseline characteristics and restless legs symptoms in the follow-up according to a logistic regression model.

			BDI ≥10			
	Control		Without depression		Depression	
	OR (95% CI)	*p* Value[a]	OR (95% CI)	*p* Value[a]	OR (95% CI)	*p* Value[a]
Restless legs symptoms at baseline	7.40 (3.99 to 13.70)	<0.001	5.72 (2.88 to 11.37)	<0.001	9.02 (4.98 to 16.36)	<0.001
Gender (Male)	0.57 (0.31 to 1.05)	0.071	1.25 (0.59 to 2.68)	0.56	1.30 (0.68 to 2.50)	0.43
Age	1.01 (0.97 to 1.04)	0.74	1.03 (0.99 to 1.06)	0.18	1.04 (1.00 to 1.07)	0.025
Education years	1.03 (0.94 to 1.13)	0.50	0.93 (0.83 to 1.04)	0.23	1.07 (0.96 to 1.19)	0.21
BMI	0.99 (0.93 to 1.05)	0.72	0.97 (0.91 to 1.03)	0.28	1.02 (0.97 to 1.07)	0.48
Currently smoking	0.59 (0.25 to 1.37)	0.22	1.79 (0.76 to 4.20)	0.18	1.23 (0.63 to 2.39)	0.54
LTPA		0.008		0.97		0.095
Low	1 (Reference)		1 (Reference)		1 (Reference)	
Moderate	0.82 (0.33 to 2.02)		0.52 (0.21 to 1.31)		1.37 (0.64 to 2.92)	
High	0.36 (0.14 to 0.94)		0.85 (0.32 to 2.23)		1.95 (0.88 to 4.33)	
BDI	1.06 (0.95 to 1.19)	0.27	0.99 (0.94 to 1.05)	0.75	1.06 (1.02 to 1.10)	0.007
SSRIs	0.47 (0.08 to 2.75)	0.40	0.86 (0.41 to 1.78)	0.68	0.98 (0.54 to 1.77)	0.95

[a]p for linearity.
BDI: 21-Item Beck Depression Inventory; BMI: body mass index; LTPA: Leisure time physical activity; SSRIs: Selective serotonin reuptake inhibitors.

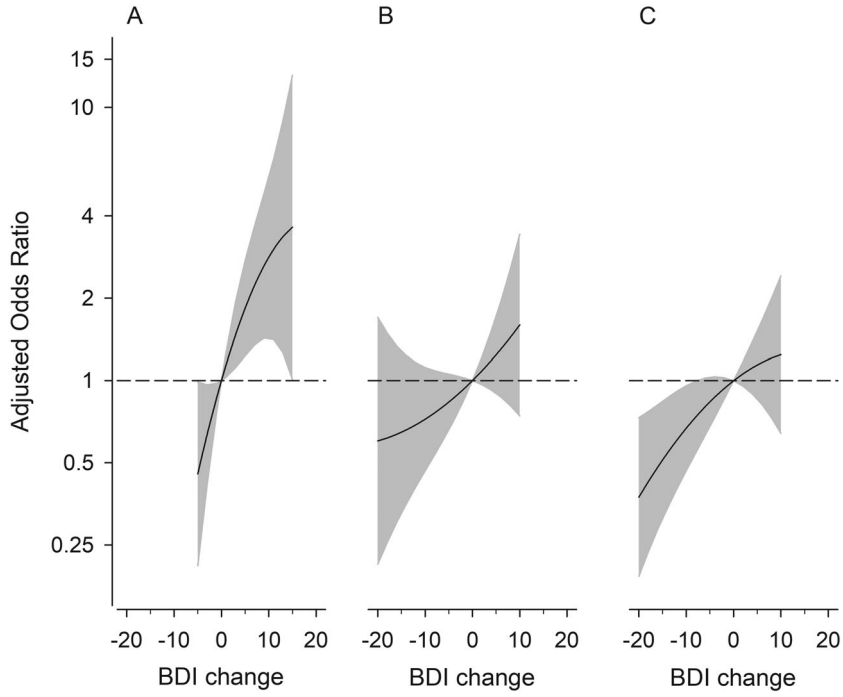

Figure 2. Odds ratios of restless legs symptoms in the follow-up in control subjects (A), patients with depressive symptoms without a depression diagnosis (B) and clinically depressed patients (C) according to a change in the Beck's Depression Inventory score. The results are adjusted for restless legs symptoms at baseline, gender, age, education years, smoking, body mass index, physical activity, Beck's Depression Inventory score and selective serotonin reuptake inhibitors at baseline. The graphs were derived from a 3-knot restricted cubic spline regression models. No change in BDI as the reference values. The grey area represents 95% confidence intervals.

studies in which antidepressant use has been linked to restless legs symptoms [28,29] though recent results have strongly questioned the relationship [30,31]. It is known that SSRI medications can be used for diseases other than depression alone. In this study, 31% of patients with depressive symptoms without diagnosed depression received SSRI medication and it may be possible that patients with SSRIs no longer suffered equally from depressive symptoms. On the other hand, the majority of the patients in the group did not use medication. In this study, the potential effect of antidepressant use on restless legs symptoms has been considered, and no association between symptoms and antidepressant or SSRIs use has been identified. In the future, it would be necessary to explore this particular role of antidepressants in the course of restless legs symptoms based on a prospective setting.

There is little research on the nature of the causation between depression and restless legs symptoms and the possible underlying mechanisms. Cardiometabolic risk factors related to lifestyle can be one connection between depression and restless legs symptoms. A high BMI and low physical activity have been found to increase the risk for developing restless legs syndrome [32]. The relation between a high BMI and level of depressive symptoms may not be straightforward and the association may be influenced by gender and race [33,34]. In our study, the control subjects had a lower BMI than the patients with depressive symptoms or with clinical depression and a lower prevalence of restless legs symptoms.

Moderate or high LTPA protected control subjects against restless legs symptoms in the present study. This finding is concordant with a previous finding indicating that the presence of restless legs symptoms is longitudinally associated with lower physical function [32]. In another previous study, exercise was associated with beneficial anti-inflammatory effects e.g. inhibiting the production of tumour necrosis factor and stimulating the occurrence of anti-inflammatory cytokines [35]. Patients with depression probably have more severe pathophysiology related to restless legs symptoms, which may have resulted in the finding that, for them, exercise did not have the protective effective found in the non-depressed control subjects.

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 self-rating of depressive symptoms. Furthermore, we could assess the same subjects at the baseline and at the follow-up with the same measures of depressive symptoms, depression diagnostics and restless legs symptoms. However, because clinical differential diagnostics for restless legs 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 restless legs syndrome. The question about restless legs symptoms is answered "yes or no", thus it is not possible to determine the severity of the symptoms. We had no data on how long the symptoms of depression or restless legs had been present.

Only persons aged 35 or older were enrolled in the study, so the results cannot be generalised to younger age groups [19]. A prospective study design based on voluntary participation almost always has incomplete and interrupted follow-up of subjects, which can bias association estimates [36]. In

the present study, a quarter of the original baseline sample was lost in the follow-up. It is possible that those who did not respond represented a more severe progression of depressive symptoms. However, the participating subjects represented, in a fairly balanced way, all the groups of the original sample, indicating no evidence of serious bias.

Our study indicates that the course and prognostic factors are different for non-depressive subjects, patients with depressive symptoms without fulfilling the diagnostic criteria of depression, and for patients with clinical depression. This finding highlights the importance of a proper assessment of depressive symptoms and diagnosis of depression for patients needing treatment for restless legs symptoms. However, prospective studies focusing on these issues are needed. The results of the present study indicate a longitudinal association between depression and restless legs symptoms. These findings suggest that in the prevention and treatment of restless legs symptoms among patients with depression, the priority is the effective treatment of depression. In addition, our findings suggest that among the population without depressive symptoms, promoting physical activity and mental health should be included in a preferred strategy.

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Ethical approval

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

Disclosure statement

The authors declare that they have no competing interests

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Notes on contributors

Piritta Auvinen Ph.D. has studied restless legs symptoms and depression in the Institute of Public Health and Clinical Nutrition in the University of Eastern Finland. The dissertation 'Restless legs symptoms in primary health care patients with depression.' was completed in 2021.

Hannu Koponen Ph.D. is a researcher and a professor in the Department of Psychiatry in the University of Helsinki.

Hannu Kautiainen is a professional statistical analyst in several research groups.

Katariina Korniloff Ph.D. is a researcher in the Institute of Rehabilitation in the JAMK University of Applied Sciences in Jyväskylä.

Tiina Ahonen Ph.D. is a researcher in the Primary Health Care Unit in the Central Finland Central Hospital in Jyväskylä.

Mauno Vanhala Ph.D. is a researcher and a former professor in the Institute of Public Health and Clinical Nutrition in the University of Eastern Finland.

Pekka Mäntyselkä Ph.D. is a researcher and a professor in the Institute of Public Health and Clinical Nutrition in the University of Eastern Finland.

ORCID

Piritta Auvinen http://orcid.org/0000-0003-2002-159X

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