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Convergence of psychiatric symptoms and restless legs syndrome: A cross-sectional study in an elderly French population

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ABSTRACT

Objective: The objective was to evaluate the association between restless legs syndrome (RLS) with generalized anxiety disorder (GAD), major depression disorder (MDD), dysthymia, and GAD-depression comorbidity. Secondary aims were to examine the association between RLS with the cognitive-affective and somatic-vegetative disturbances experienced as part of depression and GAD.

Methods: This was a cross-sectional study of 1493 elderly participants (median age 80.6 years, 64% women) from Dijon, France. Probable RLS was assessed using the minimal diagnostic criteria of the International Restless Legs Study Group and RLS symptom frequency and treatment. Participants underwent structured interviews for MDD, dysthymia, and GAD. Participants also completed the Center for Epidemiological Studies-Depression scale (CES-D). The association between RLS and psychiatric disorders, their criterion symptoms, or symptom factors was examined using logistic regression.

Results: The point prevalence of probable RLS in this sample was 8.2%. Probable RLS was associated with isolated GAD (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.01–4.68) and comorbid GAD-any depression disorder (OR 3.26, 95% CI 1.14–9.29), but not MDD or dysthymia. Probable RLS was also associated with the GAD criterion worry most days and feeling tense, and the CES-D factors representing depressed affect, somatic symptoms, and positive affect.

Conclusions: Probable RLS was associated with GAD-depression comorbidity as well as isolated GAD. The findings challenge previous reports linking RLS solely with MDD, suggesting the association is partly driven by GAD-depression comorbidity.

1. Introduction

Restless legs syndrome (RLS) is a neurological condition characterized by unpleasant sensations in the legs and urges to move one's legs, usually at night [1–4]. RLS is associated with poor sleep quality, daytime sleepiness, and reduced quality of life [5–7]. A higher prevalence of psychiatric disorders, especially depression, has also been reported among populations with RLS [8,9]. The inclusion of RLS in the DSM-5 [10] as a sleep-wake disorder underscores the importance and topical nature of mental-wellbeing in this syndrome.

Two aspects of the depression-RLS association remain to be thoroughly investigated in the extant literature, including; 1) comorbidity between major depressive disorder (MDD) and generalized anxiety disorder (GAD), and 2) diagnostic overlap between RLS and psychiatric disorders in somatic and vegetative symptoms. With regards to the first limitation, depression-panic disorder [11] and depression-any anxiety disorder comorbidity [12] have been implicated in RLS. Otherwise, psychiatric comorbidity between depression and anxiety in RLS remains poorly understood, which might pose a barrier to understanding patient's subjective experiences of RLS and the design of clinical interventions. Specifically, guidelines for the initial treatment of RLS [13] recommend dopaminergic drugs when depression is present, but alpha 2 delta ligands when GAD is present. Indeed, among the anxiety disorders, GAD is imperative to consider because it is most commonly comorbid with MDD [14,15], shares several diagnostic criteria with MDD, and is the most prevalent anxiety disorder in geriatric

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populations [16,17].

The second limitation relates to the somatic-vegetative symptoms of MDD and GAD, which may confound or conflate the depression-RLS link. For example, common complaints among RLS sufferers, such as the urge to move, sleep-related symptoms, and fatigue [18], have direct parallels in the MDD diagnostic criteria of psychomotor agitation, sleep difficulties, and fatigability [10]. Likewise, hallmark diagnostic features of GAD include sleep difficulty (typically due to worry), tiredness, restlessness, and tenseness. However, the features of anxiety disorders have not been explored in RLS. One study reported that RLS was associated with somatic depressive symptoms measured by the Beck Depression Inventory [19], but these associations have not been extended in other depression measures, nor to MDD or GAD diagnostic criteria. An empirical investigation along these lines would help elucidate whether RLS is associated with cognitive symptoms of MDD or primarily those relating to sleep and other somatic disturbances. This is crucial because of the heterogeneity in presentations of MDD [20], and the exploration of symptom level analyses may uncover discrete associations between psychiatric disorder symptoms and RLS. For example, parallel research in other health conditions has uncovered depression symptom-specific associations with dementia [21], coronary heart disease [22], and lower urinary tract symptoms [23], among others.

The current study advances the extant literature in several ways, firstly by evaluating whether depression and GAD comorbidity modulate the association between depression and RLS. A second way this study advances beyond previous studies is by examining RLS in relation to symptoms of depression and GAD representing somatic-vegetative and cognitive-affective disturbances.

2. Methods

2.1. Population

The Three-City (3C) Study is a French prospective cohort study investigating the determinants of dementia and cardiovascular diseases in persons age ≥ 65 years [24]. The current analyses use only subjects from the Dijon cohort who participated in the 5th wave of follow-up (between 2008 and 2009) when RLS was first assessed. For the purposes of this study, from 2283 eligible persons, participants were excluded for; Parkinson's disease (n = 37), dementia (n = 135), missed the psychiatric interview (n = 2), and missed an item on the RLS assessment (n = 614), leaving 1493 participants for analysis. The study protocol has been approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre, and each participant provided signed and informed consent.

2.2. Restless legs syndrome assessment

At face-to-face interview, participants were asked the 4 minimal diagnostic criteria of the International Restless Legs Study Group. The minimal diagnostic criteria have been used in previous epidemiological studies [25,26], including the current sample [27]. The first question was: “Have you ever felt unpleasant sensation in the legs (restlessness, tingling, tension, annoyances, contractions, twitching, numbness, electricity, etc.) with the irresistible need or want to move?” Response options were “yes” or “no.” If the participant responded “yes,” he or she was asked further: “Do these unpleasant sensations occur solely or mainly at rest (when you are sitting or lying down, without moving your legs) and do they improve with movement?” and “Are these unpleasant sensations more intense in the evening or at night than in the morning?” Response options for these questions were “yes” or “no.” If the participant responded “yes” to all 3 questions, he or she was considered as meeting minimal criteria for probable RLS. For those respondents who experienced any RLS symptoms, they were also asked about the frequency of symptoms. Possible response options were: at least once a year but less than once a month, once a month, 2 to 4 times per month, 2 to 3 times per week, 4 to 5 times per week, and 6 to 7 times per week. Consistent with Silva et al. [28], RLS was considered probable (binary coded = 1) if symptoms were reported ≥5 days per month and considered negative if symptoms were reported ≤4 times per month in order to identify participants with significant RLS symptoms.

2.3. Assessment of anxiety and depression

Participants underwent a structured clinical interview with trained psychologists using the French translation of the MINI International Neuropsychiatric Interview (MINI) [29]. The interview was performed blinded to RLS status and other self-reported data. The MINI has established psychometric validity for affective disorders, including inter-rater agreement and concurrent validity with other structured clinical interviews [30,31]. For brevity, only the GAD, major depression, and dysthymia modules were administered. No hierarchical exclusion rules were adopted, thus permitting depression and GAD comorbidity. Psychiatric disorders were arranged in several ways, firstly as discrete disorders (GAD, MDD, dysthymia). Secondly, persons were stratified based on comorbidity between GAD and any depression (MDD or dysthymia) and created four distinct groups: comorbid GAD-any depression, isolated GAD, isolated any depression, and no anxiety or depression. Stratification was also created using MDD (omitting dysthymia) to create the groups: comorbid GAD-MDD, isolated GAD, isolated MDD, and no anxiety or MDD. Likewise, a GAD and dysthymia model was created (omitting MDD): comorbid GAD- dysthymia, isolated GAD, isolated dysthymia, and no anxiety or depression. In a subset of respondents to all questions of the MDD and GAD MINI modules, each criterion was arranged into cognitive-affective and somatic-vegetative symptoms based on previous research [32].

Depressive symptoms were assessed by a self-report questionnaire with the Centre for Epidemiological Studies-Depression scale (CES-D) [33]. The CES-D lists 20 different depression symptoms, and respondents endorse each question based on the previous week using a Likert scale from “rarely or none” to “most or all of the time.” The CES-D scale is best represented by 4 factors measuring somatic complaints (7 items), depressed affect (7 items), positive affect (4 items, reverse keyed and reverse scored), and interpersonal problems (2 items) [34]. Participant responses to the CESD were arranged accordingly in this study, confirmed by factor analysis, and converted to z scores with a mean of 0 and SD = 1 as reported elsewhere [21].

2.4. Assessment of covariates

At each follow-up, participants underwent a clinical assessment with physicians, underwent anthropometry measures, and a blood draw to determine cardiometabolic risk factors (e.g., blood pressure, dyslipidemia). Comorbidities were classified according to the International Classification of Disease criteria and included cardiovascular disease (myocardial infarction, coronary artery bypass or percutaneous intervention, peripheral vascular disease, and stroke). Hypertension was defined as systolic blood pressure ≥ 140/90 mmHg or current antihypertensive treatment. Diabetes was defined as medication use for diabetes or fasting plasma glucose ≥7.0 mmol/L. Hypercholesterolemia was defined as total cholesterol level ≥ 6.2 mmol/L or treatment with lipid-lowering agents. Face-to-face interviews were conducted using a standardized questionnaire with trained interviewers covering demographic characteristics, daily life habits, and medical history, and these were validated against medical records. Assessment of alcohol and tobacco consumption was collected by a designated nutrition survey. Other maladies, including thyroid disorders and cancer, were obtained by self-report only.

Global cognitive function was assessed by the Mini-Mental State Examination (MMSE) [35]. Mobility was assessed with a French translation of the Rosow and Breslau scale, which evaluates the ability

to do heavy work around the house, walk half a mile, and climb stairs [36]. Medication use during the preceding month was determined at interview, and the medications themselves were seen by the interviewer. The name of the medication was recorded, and all drugs were subsequently coded according to the French translation of the World Health Organization Anatomical Therapeutic Chemical classification system [37]. Psychotropic medication was recorded and included antidepressants (serotonin reuptake inhibitor, tri- and tetra-cyclic, monoamine oxidase inhibitor, atypical), anxiolytics/benzodiazepines, neuroleptics, and Parkinson's disease medication. Patient self-reports of anti-inflammatory drug use for pain were also recorded.

2.5. Statistical analyses

The characteristics of participants were compared according to RLS status with chi-square, independent samples *t*-tests, and Wilcoxon-Mann-Whitney tests depending on the variable distribution. The association between psychiatric disorders with a positive classification for probable RLS was analyzed with logistic regression showing the odds ratio (OR) and 95% confidence interval (95% CI).

The first model analyzed the odds for probable RLS attributable to a discrete MINI diagnosis of MDD, GAD, or dysthymia in a single model. For comparative purposes, the analysis was repeated by stratifying respondents based on comorbidity between GAD-any depression (encompassing MDD and dysthymia), or caseness for isolated GAD, isolated depression, or neither (reference category). The analysis was repeated omitting dysthymia, arranging disorders based on comorbidity between GAD-MDD, or caseness for isolated GAD, isolated MDD, or neither (reference category). Then the analysis was repeated omitting MDD, arranging disorders based on comorbidity between GAD- dysthymia, or caseness for isolated GAD, isolated dysthymia, or neither (reference category).

The next set of analyses concerned the subset of persons asked MINI screener questions for GAD and MDD, which were arranged into two groups of cognitive-affective and somatic-vegetative symptoms, respectively. Analysis of MDD cognitive-affective and somatic-vegetative symptoms simultaneously entered GAD as a covariate. A corresponding analysis was run with GAD cognitive-affective and somatic-vegetative symptoms divided in a similar manner, entering MDD as a covariate. Finally, in the total sample, each of the 4 CES-D factors were regressed against a probable RLS diagnosis. Four separate CES-D models were run to eliminate multicollinearity between the CES-D factors z-sores.

All analyses were adjusted for age and sex in the first step. Fully adjusted models additionally entered education, smoking, alcohol use, mobility, body mass index, hypertension, hypercholesterolemia, diabetes, cardiovascular disease, cancer, thyroid disease, antidepressant/psycholeptic, anxiolytic/ benzodiazepine, and anti-inflammatory drugs. The use of antidepressants and anxiolytics was adjusted for because these are closely related to psychiatric disorders, may indicate higher affective disorder severity, and their use may worsen RLS [9,38]. Fully adjusted models were performed when the ratio of predictor variables to binary outcomes did not overfit the logistic model, based on the recommendations by Babyak [39]. There was an insufficient number of probable RLS outcomes for fully adjusted analysis according to MDD and GAD criterion symptoms. In these analyses, we entered only age and sex as adjustment variables, and opted not to pursue covariate selection strategies [40]. All analyses were performed with IBM SPSS 24.0, a two sided p value of $p < .05$ was considered as statistically significant for the independent variables. No adjustment was made for multiple comparisons [41].

3. Results

The sample included 1493 participants with a median age of 80.6 years and was comprised of 64.1% women. There were 122 (8.2% of total) persons who met criteria for probable RLS, and a comparison of participants by probable RLS status on demographics and comorbidities is shown in Table 1. There were differences between RLS groups in the proportion of females, mobility, thyroid disease, and use of anti-inflammatory drugs.

Table 1
Comparisons between probable RLS and non-RLS participants on demographics and comorbidities (N = 1493).

Variable	No RLS (n = 1371)	Probable RLS (n = 122)	P
Female sex	869 (63.4)	88 (72.1)	0.054
Age in years, median (IQR)	80 (77–85)	79 (77–84)	0.30
Education			0.11
Primary < 5 years	271 (19.8)	30 (24.6)	
Short secondary 5–9 years	594 (43.3)	52 (42.6)	
Full secondary 10–12 years	268 (19.5)	26 (21.3)	
Higher education/degree > 12 years	238 (17.4)	14 (11.5)	
Tobacco smoking			0.16
Never	845 (61.7)	82 (67.2)	
Former	478 (34.9)	38 (31.1)	
Current	47 (3.4)	2 (1.6)	
Alcohol consumption (g/per day), median (IQR)	2.74 (0–10.97)	4.11 (0–10.97)	0.33
Incapacity in mobility	892 (65.1)	90 (73.8)	0.052
Body mass index in kg/m^2			0.26
< 25	634 (46.2)	52 (42.6)	
25–29	553 (40.3)	49 (40.2)	
> 30	184 (13.4)	21 (17.2)	
Hypertension	1012 (73.8)	86 (70.5)	0.43
Hypercholesterolemia	501 (36.5)	44 (36.1)	0.92
Diabetes	163 (11.9)	10 (8.2)	0.22
Cardiovascular disease	179 (13.1)	16 (13.1)	0.99
Cancer	156 (11.4)	13 (10.7)	0.81
Thyroid disease	164 (12.0)	26 (21.3)	0.003
Anti-inflammatory drugs	103 (7.5)	17 (13.9)	0.012

IQR, interquartile range; RLS, restless legs syndrome.

The proportion of depression, anxiety disorders, and psychosocial variables according to RLS status is shown in Table 2. The prevalence of major depression and comorbid GAD-depression was higher in the probable RLS group.

3.1. Depression disorder and comorbidity models

The discrete disorder model showed that GAD was associated with increased odds of probable RLS. Both MDD and dysthymia were not associated with probable RLS (age-sex adjusted results e-Table 1). Adjustment for covariates did not alter the significant association between probable RLS with GAD (adjusted models in Fig. 1). In the next model considering comorbidity, RLS remained associated with GAD but was also associated with comorbid GAD-any depression. The comorbid GAD-MDD and GAD-dysthymia models implicated only isolated GAD with probable RLS, but these models were limited to few cases in each disorder group.

Table 2
Comparisons between probable RLS and non-RLS participants on sleep and psychosocial comorbidities (N = 1493).

Variable	No RLS (n = 1371)	Probable RLS (n = 122)	P
Generalized anxiety disorder	63 (4.8)	13 (11.2)	0.003
Major depression	78 (5.9)	11 (9.5)	0.13
Dysthymia	32 (2.4)	4 (3.4)	0.53
Comorbid GAD-any depression	19 (1.4)	5 (4.1)	0.041
MMSE score, Median (IQR)	27 (26–28)	27 (25–28)	0.77
Antidepressant or psycholeptic	306 (23.2)	36 (31.0)	0.06
Anxiolytic or benzodiazepine	257 (19.5)	31 (26.7)	0.06

GAD, generalized anxiety disorder; IQR, interquartile range; MMSE, Mini Mental State Examination; RLS, restless legs syndrome

Discrete Disorders and Comorbidity Models	OR (95% CI)	P
Model 1: Discrete disorders (without comorbidity)		
Generalized anxiety disorder	2.34 (1.23 – 4.43)	0.010
Major depression	1.33 (0.67 - 2.61)	0.41
Dysthymia	0.91 (0.30 - 2.72)	0.86
Model 2: Comorbid and isolated GAD, any depression		
Generalized anxiety disorder	2.17 (1.01 - 4.68)	0.048
Any depression disorder	1.20 (0.60 – 2.42)	0.61
Comorbid GAD-any depression disorder	3.26 (1.14 – 9.29)	0.027
Model 3: Comorbid and isolated GAD, major depression		
Generalized anxiety disorder	2.45 (1.21 – 4.97)	0.013
Major Depression	1.41 (0.66 – 3.01)	0.38
Comorbid GAD-Major depression	2.63 (0.71 – 9.74)	0.15
Model 4: Comorbid and isolated GAD, dysthymia		
Generalized anxiety disorder	2.09 (1.03—4.22)	0.04
Dysthymia	0.69 (0.15—3.09)	0.63
Comorbid GAD-dysthymia	5.05 (0.89—28.67)	0.68

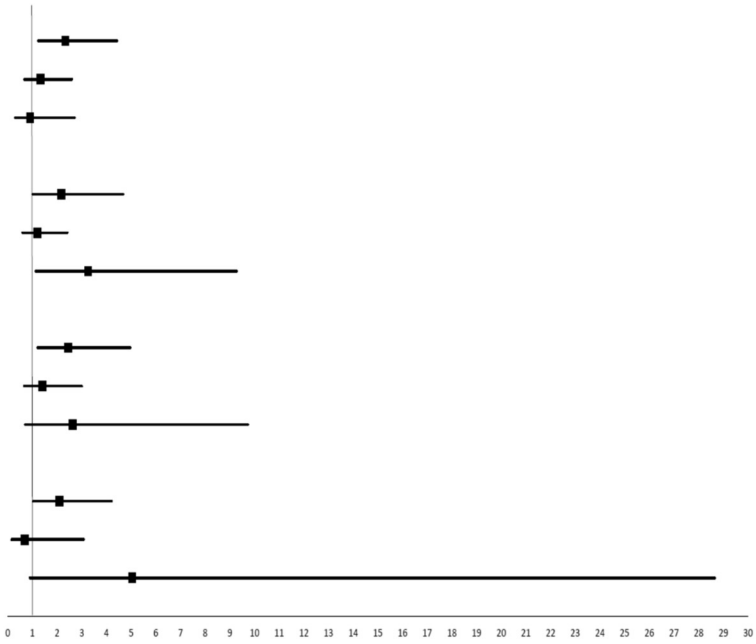

Fig. 1. Forest plot showing the adjusted odds ratio for probable restless legs syndrome stratified by depression, generalized anxiety disorder, and disorder comorbidity.

3.2. Cognitive and somatic symptom models

The cognitive-affective and somatic-vegetative models for MDD and GAD are reported in e-Table 2 and e-Table 3, respectively. None of the MDD symptoms were significantly associated with probable RLS however marginal associations were evident for appetite/weight change (OR 1.97; 95% CI 0.99–3.94, $p = .054$) and anhedonia (OR 2.21; 95% CI 0.99–4.94, $p = .054$). In the GAD models, the cognitive-affective symptom "worry most days" was associated with probable RLS (OR 2.19; 95% CI 1.26–3.79, $p = .005$). Also, the somatic-vegetative symptom "feeling tense" was associated with probable RLS (OR 3.90; 95% CI 1.01–15.07, $p = .048$).

The findings relating to depression factors measured by the CES-D are reported in e-Supplement 4 (age and sex-adjusted), and fully adjusted models are reported in Fig. 2. Probable RLS was associated with depressed affect (OR 1.23; 95% CI 1.04–1.46, $p = .016$), somatic symptoms (OR 1.27; 95% CI 1.07–1.52, $p = .007$) and positive affect (OR 1.21; 95% CI 1.00–1.45, $p = .048$) but not interpersonal problems.

4. Discussion

This cross-sectional study among 1493 participants showed that probable RLS was significantly associated with GAD and also comorbid GAD-depression. In terms of discrete psychiatric criterion symptoms, the hallmark feature of GAD (worry) was also associated with probable RLS, while anhedonia in MDD was marginal. Moreover, a mix of somatic-vegetative and cognitive-affective symptoms was significantly associated with probable RLS. Collectively, the findings suggest that the putative risk for probable RLS attributable to GAD and depression is not entirely explained by somatic-vegetative symptomatology or disturbances in the sleep-wake cycle. Furthermore, the association between RLS and depression disorders here was partly explained by GAD-depression comorbidity.

Previous studies have consistently demonstrated an association

Depressive Symptoms	OR (95% CI)	P
Depressed Affect	1.31 (1.10-1.57)	0.003
Somatic symptoms	1.34 (1.11-1.62)	0.002
Positive Affect	1.26 (1.03-1.52)	0.022
Interpersonal Problems	1.09 (0.92-1.30)	0.32

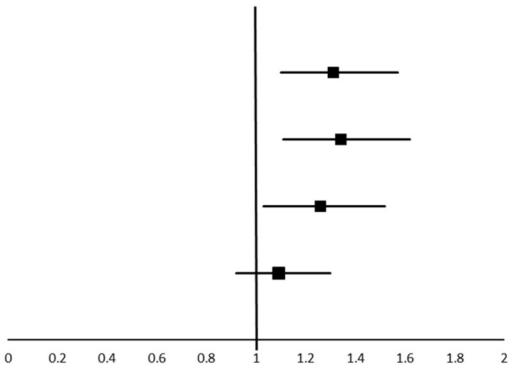

Fig. 2. Forest plot showing the adjusted odds ratio for probable restless legs syndrome symptoms according to depression factors measured by the CES-D.

between RLS and depression. Our findings did not support a significant association between isolated depression or MDD with probable RLS, which contrasts to previous studies evaluating diagnosed depression in primary care [18] and population studies [11]. Here, MDD and dysthymia disorders were combined in some analyses, and it is possible that only more severe MDD episodes are associated with RLS, though lifetime and 12-month estimates tend to be similar in RLS studies [8]. There are few prospective studies that have compared MDD and dysthymia in relation to RLS [12] and none were reported in previous literature reviews [8,9]. Less is reported on the association between RLS with dysthymic states, and these states may fall in between MDD and subclinical depression. Thus, further investigations might extend our findings by investigating depression subtypes in relation to RLS, taking into consideration their chronicity and age of onset, given that late-onset depression is characterized by distinct neurological profiles [42].

Few population studies of RLS have assessed depression-anxiety comorbidity [11,12] and somatic symptoms [19], and no prior studies have investigated these diagnostic aspects in the same sample. Our findings indicate that GAD and GAD-depression comorbidity portends higher risk for probable RLS. Generally, our findings are in line with earlier reports that RLS and anxiety disorder risk estimates, including GAD and panic disorder, tend to be higher by comparison to MDD [11,12]. Similar to the current findings, prior studies had wide confidence intervals [7,11] encouraging further investigation in larger samples and those utilizing validated clinical assessments for RLS.

Here it was also evident that a combination of somatic-vegetative and cognitive-affective symptoms was associated with probable RLS. Our finding contrasts with a report that showed RLS is associated with depressive symptoms representing sleep-wake disturbances such as reduced sleep and loss of energy [19]. Though the direction of this association is unclear, one study showed that RLS is associated with incident depression even after controlling for sleep duration, suggesting that sleep duration alone cannot explain the depression-RLS link [43]. Curiously, the individual sleep and fatigue items in the MDD and GAD MINI modules were unrelated to probable RLS. However, the criterion worry most days was significantly associated with probable RLS, and this ruminative process commonly affects sleep duration and quality [43,44], which might explain the association with probable RLS here. It is possible that measures of GAD-specific symptoms, such as worry and intolerance of uncertainty, as well as somatic domains such as anxiety sensitivity, may uncover discrete associations between RLS and GAD or other anxiety disorder symptomatology in future studies.

The consistent association between RLS and psychiatric disorders and poorer prognosis [9,45] encourage clinical intervention among elderly persons with RLS and comorbid GAD or depression. Common treatments might include cognitive-behavioral therapy and pharmacological management [45]. With regards to the latter, selective serotonin reuptake inhibitors are frontline pharmacological agents for MDD and GAD. However, these may worsen RLS and periodic limb movements [9,38]. Moreover, international RLS guidelines recommend the elimination or correction of exacerbating factors, including antidepressants, when using dopaminergic drugs [13]. These RLS guidelines also recommend dopamine receptor agonists as initial RLS treatment choice when comorbid depression is present, but recommend alpha 2 delta ligands when comorbid GAD is present [13]. The optimal treatment for comorbid MDD-GAD in RLS has not been explored. Recent updated RLS guidelines indicate that the dopamine receptor agonist pramipexole is beneficial to depression and anxiety symptoms and there was insufficient evidence for the antidepressant bupropion [46]. One caveat of dopamine receptor agonists is the potential to induce impulse control disorders such as pathological gambling, hypersexuality, and compulsive shopping [47]. Otherwise, the alpha 2 delta ligand pregabalin has demonstrated efficacy in populations with either MDD, GAD, comorbid MDD-GAD, or RLS. Specifically, pregabalin has Level A evidence for the treatment of RLS by the International Restless Legs Syndrome Study Group [48]. This classification was largely based on a randomized, double-blind study comparing pregabalin (300 mg/d) with pramipexole (0.25 or 0.5 mg/d) in 719 patients over 52 weeks [49]. Likewise, a number of studies have supported the efficacy of pregabalin to treat GAD [50], comorbid GAD-depression [51], and the efficacy has extended to sleep symptoms in GAD [52]. There are some limitations, including limited therapeutic approvals for alpha 2 delta ligands in the treatment of RLS in Europe [53]. Also, and importantly, suicidal ideation is a reported adverse effect of pregabalin [54], and is common in RLS [55], underscoring the need for close monitoring in RLS patients. The convergence in potential pharmacological treatments for RLS and GAD might also encourage examination of common neurotransmitter pathways, considering that the nexus of psychiatric disorders and RLS is poorly understood [9].

This study is presented with several strengths, including the well-defined elderly cohort and the use of structured interviews to determine GAD and depression status. Also, study participants underwent extensive neurological examination every 2 years to diagnose disorders such as dementia, mild cognitive impairment, and Parkinson's disease. A main limitation of our study is the possibility for misclassification of RLS based on only self-report questions for epidemiological studies, and these precede updated criteria [56]. Other studies have utilized case-control matching of persons with RLS determined by neurologists or physicians [12,57]. Also, this study cannot rule out that RLS “mimics” such as attention deficit hyperactivity disorder [58], cramps, neuropathy, radiculopathy, arthritis, positional discomfort, and unconscious leg movements [59,60]. With regards to the latter, anxiety and depression might mimic RLS symptoms through psychomotor restlessness or agitation and spuriously conflate the association between RLS and GAD. Along these lines, we cannot rule out that we inadvertently adjusted for potential ‘colliders’, which could lead to different effect estimates [61]. Interestingly, the MDD criterion psychomotor agitation trended towards lower odds for probable RLS. Nonetheless, it was possible that anxiety and depression are secondary features of RLS, as bidirectional links have been reported [4], and cognitive-affective disturbances are common in persons with sleep disorders [9]. It is also plausible that more severe and chronic psychiatric disorders are especially associated with RLS [2]. As a result of utilizing only the 5th wave of follow-up, our study is limited by few participants with depression and anxiety disorders and RLS. There is also a possibility for other biases in our study, such as residual confounding, selection biases, and attrition. Given the cross-sectional design, this study cannot determine the longitudinal association or causality between depression, anxiety, and RLS symptoms. Another limitation concerns the generalizability of these findings, which would not extend to specific sub-populations prone to RLS, such as Parkinson's disease [62].

In conclusion, GAD, either comorbid with depression or in isolation, was associated with probable RLS. The findings further indicated that probable RLS is associated with cognitive and somatic criterions of GAD and depressive symptom factors. Somatic-vegetative symptoms and disturbances in the sleep-wake cycle did not fully explain the association between affective disorders and RLS. The findings challenge previous reports linking RLS solely with MDD, suggesting the association is partly driven by GAD-depression comorbidity.

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interpretation of the data or in preparation, review, or approval of the manuscript. The 3C Study supports are listed on the Study website (www.three-city-study.com).

Odds ratios (OR) with 95% confidence intervals (CI) that exceed 1 (vertical line) indicate an increased risk for probable restless legs syndrome. Models are adjusted for; age, sex, education, smoking, alcohol use, mobility, body mass index, hypertension, hypercholesterolemia, diabetes, cardiovascular disease, cancer, thyroid disease, anti-inflammatory drugs, mini-mental state examination, antidepressant/ psycholeptic, anxiolytic/ benzodiazepine.GAD, generalized anxiety disorder.

Odds ratios (OR) with 95% confidence intervals (CI) that exceed 1 (vertical line) indicate an increased risk for probable restless legs syndrome per 1 SD increase in z score. Positive Affect scores are reverse scored, and thus higher scores denote lower positive affect. Models are adjusted for; age, sex, education, smoking, alcohol use, mobility, body mass index, hypertension, hypercholesterolemia, diabetes, cardiovascular disease, cancer, thyroid disease, anti-inflammatory drugs, mini-mental state examination, antidepressant/ psycholeptic, anxiolytic/ benzodiazepine, and generalized anxiety disorder. CES-D, Center for Epidemiology Studies Depression Scale.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2019.109884.

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