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Restless legs syndrome is associated with increased risk of migraine

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Abstract
Migraine and restless legs syndrome (RLS) are common disorders that are associated with a high level of individual suffering and major comorbidities. The aetiologies of the disorders are largely unknown, although both migraine and RLS have been linked to disturbances in the dopaminergic system and sleep issues, suggesting a relationship between the disorders. This study examines the association between RLS and migraine in a large population of otherwise healthy adults who are not taking medication. Cross-sectional study that included 20,938 participants enrolled in the Danish Blood Donor Study from 1 May 2015 to 1 February 2017. The study included complete information on migraines, the Cambridge-Hopkins RLS questionnaire, the Major Depression Inventory Scale, sex, age, body mass index (BMI), educational level, smoking status and alcohol consumption. Associations between RLS and migraine, with and without aura, were examined using multivariable logistic regression analysis. Among the participants, 4827 were self-reported migraine sufferers and 1091 were classified as suffering from RLS. Individuals with RLS had an increased risk of migraine compared to non-RLS sufferers, with an odds ratio (OR) = 1.52 (95% confidence interval: 1.33–1.73). For the investigated subtypes of migraine, this association was found to be OR = 1.55 (1.31–1.83) for migraines with aura and OR = 1.29 (1.09–1.52) for migraines without aura. We found a significantly increased occurrence of migraine in individuals with RLS. This risk was independent of sex, age, BMI, educational level, smoking status, alcohol consumption and depressive disorder. Our findings suggest that RLS and migraine may have a common aetiology.

Keywords
migraine, restless legs syndrome, RLS, sleep disorders, the Danish Blood Donor Study, Willis–Ekbom disease

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Introduction

Migraine is a complex, primary headache disorder with recurring episodes lasting 4 to 72 hours and presenting with moderate to severe headaches, most frequently unilateral, with photophobia and phonophobia. Furthermore, many migraineurs have preceding visual or sensory symptoms called aura. Gastrointestinal symptoms such as anorexia, nausea and vomiting are also frequent. Thus, migraine is associated with a high level of individual suffering and loss of productivity in both private and work life. Moreover, migraine is considered the most disabling neurological disorder with regard to years of life lost due to disability and is the sixth most disabling of all disorders.4 Furthermore, the disorder is estimated to be the third most common neurological disorder as it affects 10–20% of the worldwide general population.4,5 Even so, the pathophysiology of migraine remains largely unknown.

Previous studies have identified a higher prevalence of restless legs syndrome (RLS) in migraine patients.5 RLS is classified as a neurological sensorimotor disorder with symptoms that include distressing or painful sensations in the legs, which are more frequent in the evenings and at night and are exacerbated when the body is at rest. Sleep disturbance is, therefore, the most significant clinical morbidity associated with RLS.6,7 RLS can worsen in combination with many other conditions, including pregnancy, iron deficiency and renal failure. In these circumstances, RLS can be considered secondary, while primary RLS is idiopathic, and more often familial.8 We have previously demonstrated that RLS affects 5.7% of Danish blood donors.9 Furthermore, we and others have reported that RLS is associated with a reduced health-related quality of life and increased depression.10–13 Despite the high prevalence of RLS and its associated comorbidities, the pathophysiology of the disorder has yet to be elucidated.14

Migraine and RLS are both disorders that are more common in women than in men. It is reported that poor sleep quality is associated with the development and severity of RLS symptoms in migraineurs.15 Further, both disorders are reported to be related to dysfunctions in the dopaminergic system,16,17 which could indicate a shared pathophysiology between them. To date, only two large-scale, population-based studies have investigated the association between migraine and RLS.18,19 These two studies included individuals with multiple medical problems, possibly linked with either migraine or RLS or both. In the current large-scale population study, we therefore investigated the association between migraine and RLS in an otherwise healthy population where no participants were undergoing medical treatments.

Methods

The current work is an observational study performed as a cross-sectional questionnaire study based on data from a population-based cohort study.

Data

Data were collected from the Danish Blood Donor Study (DBDS),20 an on-going, national, epidemiological cohort study with only 5% of donors declining to participate.21 Blood donors in Denmark are asked to join the study upon their second or later blood donation. Participants who joined the cohort between 1 May 2015 and 1 February 2017 completed an electronic questionnaire21 that included information on RLS, migraine, depressive disorder, body mass index (BMI), smoking status and alcohol consumption. Information on participants’ sex, age and highest educational level achieved was obtained through the National Registers. Register-based data were merged with questionnaire data at the individual level using unique Danish Civil Registration Numbers22 after which data were pseudonymized.

Migraine. The migraine variables assessed in this study were an overall binary ‘migraine’ variable and two-subgroup variables, ‘migraine without aura’ (MO) and ‘migraine with aura’ (MA). To assess the prevalence of migraine in this otherwise healthy population, the question ‘have you ever suffered from migraine?’ was used. This question was previously validated for the general population in Denmark and was found valid for identifying migraineurs.23–25

To categorize the subtypes of MA and MO, the question ‘have you ever had vision disturbances lasting 5–60 minutes followed by headache?’ was used. This question has been used in a cross-sectional study that included the general Danish population as the only aura-related question in a four-question migraine-defining scale. This particular question was, therefore, chosen for this study, although it focuses solely on visual aura and does not take other sensory aura symptoms into account. Thus, all migraine questions used in this study have been previously validated in the general Danish population. They have been reported to be the most efficient for assessing self-reported migraine experiences as these questions identified 75% of MOs and 93% of MAs (visual) with a combined sensitivity of 85% and a specificity of 81%.25 The migraine questions were validated against migraine diagnoses that were made on the basis of semi-structured telephone interviews, which lasted between 10 and 45 minutes. The interviews were conducted by one of two physicians who were specially trained in diagnosing migraine through telephone interviews. The physicians were blinded with regard to the participants’ responses to the two questions.25

Restless legs syndrome. RLS was assessed among the participants using the 10-item Cambridge-Hopkins RLS questionnaire (CH-RLSq26; with a reported diagnostic sensitivity of 87.2% and specificity of 94%).27,28 The CH-RLSq ensures the elimination of RLS mimics such as muscle cramps. Participants who reported RLS symptoms were asked to appraise the severity and frequency of them.
Both symptom frequency and severity were measured on four-point Likert-type scales, ranging from not uncomfortable/once a month to extremely uncomfortable/daily.

**Covariates.** Sex, age, depressive disorder, BMI, smoking status, alcohol consumption and educational level were considered potential covariates in the association between RLS and migraine. Information on depressive disorder was obtained using the validated Major Depression Inventory (MDI), which comprises both the ICD-10 and the DSM-IV symptoms of depressive disorder. The MDI was used to assess the presence of 10 symptoms of depression within 2 weeks prior to inclusion in this study. Depressive disorder was examined as a binary variable where participants with an MDI score of 20 or more were classified with depressive disorder. Frequent alcohol consumption was defined as alcohol intake ‘several times a week’ or ‘every day’, and low educational level was defined as high school/vocational course or less as the highest achieved educational level.

**Ethics statement.** Oral and written informed consent was obtained from all participants. The study was approved by the Scientific Ethical Committee of Central Denmark (M-20090237). Additionally, the biobank and research database have been approved by the Danish Data Protection Agency (2007-58-0015).

**Statistical analyses**

Statistical analyses were conducted using Stata/SE 14.0 (StataCorp, College Station, Texas, USA). Continuous variables were described with means and standard deviations, while the distribution of binary variables was described with percentages. Statistically significant differences between participants with and without RLS were examined by T-tests for continuous variables and by χ² tests for dichotomous data. The associations between RLS and types of migraine (any type, MA and MO) were assessed using multivariable logistic regression models and presented as odds ratios (ORs) with 95% confidence intervals (CIs) and p values. We compared three groups: (1) RLS sufferers compared to participants with no RLS, (2) RLS sufferers with frequent (symptoms occurring more than twice a week) and severe symptoms (symptom intensity categorized as moderate or severe) compared to participants without RLS and, finally, (3) participants with RLS symptoms characterized as mild or infrequent compared to individuals without RLS. Analyses differentiating between frequency and severity of RLS symptoms are presented as a supplementary. Sex, age (continuous), depressive disorder (yes/no), BMI (continuous), smoking status (yes/no), frequent alcohol consumption (yes/no) and low educational level (yes/no) were entered into the multivariable logistic regression analyses, as these were all considered possible covariates of the associations.

**Results**

**Response rates and demographics**

In total, 22,586 otherwise healthy blood donors were asked to fill in a questionnaire comprising information for the current study. Among these donors, migraine was reported by 5240 (23.2%), with 10.9% reporting MA and 12.3% reporting MO. Subsequently, 676 participants were excluded due to missing information on at least one item on the CH-RLSq. A further 394 participants with missing data on one or more items on the MDI scale were excluded (RLS cases, n = 18), as were 572 participants with missing data on age, BMI, smoking status, alcohol consumption or highest achieved educational level (RLS cases, n = 22). Finally, six RLS cases were excluded due to missing information on the frequency or severity of RLS symptoms. Thus, the study population was defined as the 20,938 participants (9572 women and 11,366 men) for whom complete and relevant data were available (Figure 1).

**Migraine and RLS**

Of the 20,938 participants in the study population, 4827 participants were classified as suffering from any type of migraine (2253 with MA and 2574 with MO; Table 1) and 1091 (5.2%) were classified as RLS sufferers (632 women and 459 men). We observed a higher prevalence of both types of migraine, MA and MO, among RLS cases compared to non-RLS sufferers (Table 1). Participants with RLS were more likely to suffer from any type of migraine (OR = 1.52, 95% CI: 1.33–1.73), MA (OR = 1.55, 95% CI: 1.31–1.83) and MO (OR = 1.29, 95% CI: 1.09–1.52) compared to participants without RLS. The statistical significance of the associations was unchanged, and ORs were increased slightly when information on BMI, educational level and depressive disorder were included in the regression analyses.
level, smoking status, alcohol consumption and depressive disorder was included in the model (Table 2).

### RLS frequency and severity

We stratified the participants according to their reported frequency and severity of RLS symptoms. In total, 524 participants reported moderate to severe RLS symptoms (2.7%), while 345 reported frequent experiences of RLS symptoms (1.8%; symptoms occurring twice a week or more). Combined, 197 reported both severe and frequent symptoms (1.0%). We found an increased susceptibility to migraine in all RLS cases, even when the symptoms were categorized as infrequent or mild (Online Supplementary Table S1). In particular, a high migraine risk was observed in RLS cases with frequent and severe symptoms (1.8 CI: 1.25–2.26). Similarly, RLS cases with frequent or severe symptoms had the highest OR for MO (OR = 1.94, 95% CI: 1.36–2.75). The odds for MO in women with RLS did not vary significantly by RLS symptom intensity (Online Supplementary Table S1).

### Discussion

Our study showed that the prevalence of migraine, MA and MO, was higher among participants with RLS compared to participants without RLS. Moreover, we found that RLS cases with frequent or severe symptoms had the highest risk of migraine and MA. Thus, our findings suggest that RLS and migraine (both MA and MO) are comorbid disorders. The results from previous studies with significantly smaller sample sizes are conflicting and the effect of aura status appears unclear. Only two other large-scale population-based studies have been conducted. One study included 31,370 participants from the Women’s Health Study, which reported that RLS was associated with migraine and that the association did not vary by migraine aura status (OR of RLS for MO sufferers = 1.24, 95% CI: 1.09–1.40; for MA sufferers = 1.27, 95% CI: 1.10–1.48). The other study included 22,926 participants from the Physician’s Health Study, which reported similar results (OR for RLS in all migraineurs = 1.20, 95% CI: 1.04–1.38). Thus, our findings support and add to these results as we included only otherwise healthy adults who, in general, were not undergoing any medical treatment or suffering from differential diagnoses. There are several potential explanations for the associations observed in this study. Migraine and RLS are central nervous system disorders and severe sleep disturbance is reported as the primary clinical comorbidity of RLS. As it is presumed that poor sleep quality triggers migraine attacks, it is plausible that sleep quality is the shared link or causal factor. In support of this hypothesis, a Dutch study reported that poor quality of sleep was independently associated with prevalence and severity of RLS in migraine patients.

A matched case-control study showed that migraine and MA were more prevalent among patients with primary or idiopathic RLS. Primary RLS is hereditary and believed to be related to brain iron deficiency. Secondary RLS can be caused by iron deficiency with anaemia. Fuh et al. demonstrated that variants of the MEIS1 gene, involved in iron metabolism, were associated with RLS in migraine patients. This finding supports the analyses conducted by Earley et al. (2014), which suggested that disruption of iron transport in the brain causes dysfunction in the

### Table 1. Demographic and clinical features of the study population.

| Characteristic          | Non-RLS sufferers | RLS sufferers | p Value |
|-------------------------|-------------------|--------------|---------|
| Female sex (%)          | 659 (60.4)        | 632 (57.9)   | <0.001  |
| Age (mean ± SD)         | 42.0 (12.7)       | 43.0 (12.1)  | 0.014   |
| Migraine (%)            | 4471 (22.5)       | 356 (32.6)   | <0.001  |
| MO (%)                  | 2397 (12.1)       | 177 (16.2)   | <0.001  |
| MA (%)                  | 2074 (10.5)       | 179 (16.4)   | <0.001  |
| Depressive disorder (%) | 549 (2.8)         | 71 (6.5)     | <0.001  |
| BMI (mean ± SD)         | 25.8 (4.1)        | 25.9 (4.4)   | 0.404   |
| Current smoker (%)      | 2536 (12.8)       | 153 (14.0)   | 0.231   |
| Low educational level (%)| 11,475 (57.8)    | 659 (60.4)   | 0.092   |

RLS: restless legs syndrome; SD: standard deviation; MO: migraine without aura; MA: migraine with aura; BMI: body mass index.

*Age was log-transformed in order to obtain normal distribution before examining statistically significant difference between groups.

### Table 2. Multivariable logistic regression analyses with migraine as dependent variable and restless legs syndrome (RLS) as the independent variable.

| Characteristic | Comparison groups | Model 1<sup>a</sup> | Model 2<sup>b</sup> |
|----------------|-------------------|----------------------|----------------------|
| Migraine       | RLS: yes versus no| 1.52 (1.33–1.73)     | 1.64 (1.43–1.87)     |
| MO             | RLS: yes versus no| 1.29 (1.09–1.52)     | 1.39 (1.17–1.64)     |
| MA             | RLS: yes versus no| 1.55 (1.31–1.83)     | 1.65 (1.40–1.95)     |

RLS: restless legs syndrome; OR: odds ratio; CI: confidence interval; MO: migraine without aura; MA: migraine with aura; BMI: body mass index.

<sup>a</sup>Adjusted for sex and age.

<sup>b</sup>Adjusted for sex, age, BMI, educational level, smoking status, alcohol consumption and depressive disorder (yes/no).
striatal dopaminergic system subsequently causing RLS.\textsuperscript{37} Moreover, accumulation of brain iron has been observed in migraine patients under 50 years of age, and it was reported that this causes dysregulation in the dopaminergic system.\textsuperscript{38,39} These findings, together with other previous studies reporting that both RLS and migraine are linked by fluctuations in dopamine and serotonin levels in the brain,\textsuperscript{16,40} offer a potential explanation for the observed associations between RLS and the different types of migraine.

Another possible explanation for the associations found in this study could be related to cardiovascular dysfunction. There is an on-going debate concerning whether migraine is a vascular disorder or a neuronal dysfunction.\textsuperscript{3,41} In a recently published meta-analysis of 375,000 individuals, 38 susceptibility loci for migraine were identified.\textsuperscript{4} This study demonstrated that the genes associated with migraine were enriched for genes expressed in the cardiovascular and digestive system, which supports the hypothesis of migraine being a vascular disorder.\textsuperscript{4} The debate over cardiovascular origins also applies to RLS as several studies have reported associations between cardiovascular risk factors and RLS.\textsuperscript{9,40–44} Moreover, RLS has been suggested as a potential predictor of future cardiovascular disorders.\textsuperscript{45} Another point worth considering is that the associations found in this study could be the consequence of common effects or symptom overlap of migraine and RLS. For example, it has previously been found that both migraine and RLS are comorbid with depressive disorder.\textsuperscript{10,46} However, the associations remained when we introduced information on depressive disorder into our statistical models.

Methodologically, it should be mentioned that the migraine questions in our survey were not synonymous with a clinical diagnosis of migraine, which should be kept in mind when interpreting the results from this study. However, all clinical diagnostics on migraine include a self-reported description of headache and related symptoms such as pain severity and photophobia and phonophobia. The two questions used to identify migraineurs in this study are demonstrated to have sensitivities of 93 and 75\% (test sensitivity and specificity combined: 85 and 81\%, respectively\textsuperscript{25}), and the main migraine screening question that we used has been validated for use as a single question.\textsuperscript{23,24} The large study population in this study, with prevalence being similar to what has been reported in other population-based studies from Western countries,\textsuperscript{3} indicates that the questions are reliable for assessing the experience of migraine and its subtypes. In support of this, the Women’s Health Study, which applied similar migraine questions as used in this study, reported good agreement of self-reported migraine with the diagnostic criteria of the International Headache Society.\textsuperscript{18,46} Second, even though the CH-RLSq is considered one of the most accurate scales for identifying RLS cases, the scale may have underestimated the number of RLS cases in our study population because of a known RLS-misclassification risk caused by a possible misinterpretation of one of the items (item 8) in the CH-RLSq. The effect of this potential misclassification bias has previously been examined in a subgroup of our study population and is described in more detail elsewhere.\textsuperscript{9} Overall, this study is susceptible to misclassification bias due to the self-reported nature of some of the included data, with recall bias being an implicit risk. However, because validated questions and scoring systems were used, we expect the potential misclassifications would be random and not bias the results.

The population included in this study is methodologically strong, as there is a predominance of studies conducted on patient populations rather than general populations. A population-based study including otherwise healthy individuals, such as the present one, is a reliable way to establish concurrence between disorders, as this assures that the links observed between RLS and migraine disorders cannot be attributed to the use of medications or to unknown comorbidities. Blood donors comprise a selected population group, as they are required to be generally healthy and not requiring medication. A previous study of the socioeconomic composition of Danish blood donors showed that middle- to high-income groups had a four-fold higher donor prevalence than the lowest income group (6.7\% compared to 1.7\%).\textsuperscript{47} These findings suggest that the DBDS population is more homogenous in terms of socioeconomic status compared to the general Danish population, which, in turn, has a low degree of family income inequality with an OECD estimated Gini-index of 0.254. Thus, generalizations should be made with the above assumptions in mind.

Finally, as this is a cross-sectional study, we were not able to make any causal conclusions about the directions of the associations. Chen et al. investigated the temporal relationship between RLS symptoms and migraine attacks using 2-week diary records from 30 migraine patients (28 women and 2 men). These records contained information on the experience of RLS symptoms and migraine attacks. The study found the association to be bidirectional. The authors reported that nocturnal RLS symptoms were associated with migraine attacks the following day (OR = 1.97, \( p = 0.001 \)) and that daytime migraine attacks were associated with subsequent nocturnal RLS symptoms (OR = 6.94, \( p < 0.001 \)).\textsuperscript{39} This dual association supports a close but complex pathogenic link between migraine and RLS.

In conclusion, we have shown that RLS is associated with MA and MO migraines, even when the RLS symptoms are characterized as mild or infrequent, in a large, otherwise healthy population as opposed to a patient-based population. Findings from this study may hopefully help lead to a better understanding of the underlying mechanisms of two complex and severely burdensome disorders.
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Supplemental material
Supplementary material for this article is available online.

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