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SCIENTIFIC INVESTIGATIONS

The seasonal pattern of restless legs syndrome in a sample from the Korean Health Insurance Review and Assessment Service national database

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Study Objectives: To assess the seasonality of restless legs syndrome (RLS) using data from the Korean national health insurance database.

Methods: We retrospectively reviewed a randomly selected sample representing 3% of the national health insurance claims database in South Korea. From this sample, we obtained the monthly numbers of patients with RLS and diagnoses from 2009 to 2016, along with prescriptions for monthly dopamine agonists and clonazepam for patients with RLS from 2009 to 2013. Total dopamine agonist and clonazepam doses were converted to levodopa-equivalent doses, and the monthly cumulative prescription dose was calculated. Cosinor analysis was used to evaluate the seasonal pattern of each variable.

Results: This study included 11,466 patients with RLS and their diagnoses and 4,887 prescriptions for dopamine agonists and clonazepam. There were significant seasonal patterns in the numbers of patients with RLS ($P < .001$) and diagnoses ($P < .001$), both of which peaked in August. The magnitude of the greatest difference in the number of patients with RLS between August (highest) and February (lowest) was 29.96% (95% confidence interval, 24.03–100.80), and that of the number of RLS diagnoses was 39.56% (95% confidence interval, 31.24–47.89). The cumulative prescription dose of medication showed no significant seasonality.

Conclusions: Our findings suggest that the prevalence of RLS is seasonally affected, with an increase during summer.

Keywords: restless legs syndrome, Willis-Ekbom disease, seasonality, South Korea, national health insurance

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BRIEF SUMMARY

Current Knowledge/Study Rationale: A seasonal pattern of restless legs syndrome has been suggested in previous studies but has not been validated in a large clinical population. In this study, we sought to evaluate the seasonal pattern of restless legs syndrome in a randomly selected cohort of patients from the Korean national health insurance database.

Study Impact: The number of patients diagnosed with restless legs syndrome showed significant seasonality, peaking in August. This result suggests that the prevalence of restless legs syndrome is seasonal and may be associated with the pathophysiology of the disease.

INTRODUCTION

Restless legs syndrome (RLS) is a disease characterized by an urge to move the legs, often accompanied by uncomfortable sensations. These sensations worsen in the evening, at night, or during rest and are partially or completely relieved by movement.[1] The clinical course of RLS varies from remission to continuous progression, and in many patients, the severity of the symptoms fluctuates throughout life.[2] Various medical and psychiatric conditions and substances such as alcohol affect RLS symptoms, but they may wax and wane for no apparent reason.

A seasonal variation in RLS symptoms has been suggested.[3] Previous studies have reported patients with RLS that worsens in summer[4,5] or in hot environments.[6] Using Internet search query data, Ingram and Plante[7] concluded that RLS symptoms show seasonality, with a peak during summer, in both Northern and Southern Hemisphere countries. A retrospective observational study by Liguori et al[8] strongly supported these observations, with the authors reporting significant increases in RLS severity during the summer. However, no study has examined any seasonal difference in the prevalence or severity of RLS in a large clinical population.

In the present study, we examined the number of patients with RLS, their diagnoses, and the cumulative doses of various dopamine agonists and clonazepam prescribed for RLS in a random sample of 3% of the Health Insurance Review and Assessment Service (HIRA) database of South Korea to determine whether the number of diagnoses or symptom severity of RLS has a seasonal pattern. We hypothesized that both of these factors have a seasonal pattern, with a peak during summer.

METHODS

Data source

The national health insurance system of South Korea covers 98% of the national population.[9] This system includes the HIRA, from which researchers can access a database covering

the diseases and prescribed medications of 90% of South Korean patients.[10] In this study, we collected an annual random sample of data representing 3% of the database for national in- and outpatients in South Korea from 2009 to 2016 via the HIRA. Each year's sample was extracted independently and was not contiguous. No personal information was collected except age (by 5-year groups) and sex, and consent was not required from the patients. Patients treated with Korean traditional medicines were excluded, and the remaining patients diagnosed with RLS were extracted and analyzed. Analyses of the whole population were repeated on a subset of patients with early-onset RLS aged < 45 years.[11] Data were also analyzed by sex to determine any sex differences. The study was approved by the institutional review board of Dongguk University Ilsan Hospital (institutional review board number 2019-08-001).

Data acquisition

To determine the seasonal pattern of RLS prevalence, the numbers of patients with RLS and diagnoses during each month were extracted. The prescribed dose of dopamine agonists, the first-line treatment for RLS, and clonazepam was extracted as an indicator of RLS severity. When extracting the prescription data for the dopamine agonists and clonazepam, we limited the study period from 2009 to 2013 because alpha2delta ligands emerged as a second first-line treatment option for RLS in 2014, when they were found to be as effective as dopamine agonists for RLS.[12] Because dopamine agonists are also prescribed for Parkinson disease, patients who were additionally diagnosed with Parkinson disease were excluded. We calculated the monthly cumulative prescription doses of dopamine agonists, clonazepam, and dopamine agonists plus clonazepam based on the daily prescription dose and prescription duration. In the case of dopamine agonists, the prescription data for ropinirole and pramipexole, both of which are covered by insurance in South Korea, were collected, and the levodopa-equivalent doses (20 and 100 times the ropinirole and pramipexole doses, respectively) were calculated.[13] In calculating the prescription dose of dopamine agonists plus clonazepam, the clonazepam dose was first converted to the pramipexole-equivalent dose, with the ratio of clonazepam to pramipexole in patients with RLS being 4:1.[14] Next, the levodopa-equivalent dose was calculated for ropinirole, pramipexole, and clonazepam.[13]

Statistical analysis

Descriptive statistics on sex and the year of RLS diagnosis were generated. Cosinor analysis was used to evaluate the seasonal patterns of the number of patients with RLS and diagnoses and the cumulative prescription doses of the medications. This analysis enabled us to determine whether the data exhibited a sinusoidal pattern over time, and we assessed the amplitude, phase, and length of the pattern along with the significance of its seasonality. The unequal number of days in each month was adjusted in the analysis. The magnitude of the monthly peak (the ratio of the highest to lowest values) was calculated as well. P values < .05 were considered to indicate statistical significance. All statistical analyses were performed in R version 3.6.3 software (R Foundation for Statistical Computing, Vienna, Austria),[15] using the package "season" version 0.3.11.[16]

RESULTS

Clinical and demographic data

The 3% annual random sample collected from the HIRA from 2009 to 2016 consisted of 1,469,466 patients. We excluded 78 patients treated with Korean traditional medicine. Of the remaining 1,469,388 patients, 11,466 patients who had been diagnosed with RLS were analyzed (**Figure 1**). Approximately 60% of the patients were female, and early-onset RLS accounted for approximately 16% of all patients. The number of patients with RLS tended to increase each year (**Table 1**).

In the analysis of the prescribed doses of medications for RLS, a total of 1,431,442 patients collected from 2009 to 2013 were included in our initial cohort, of whom 49 were excluded because they were treated with Korean traditional medicine. Of the remaining 1,431,393 patients, 5,567 had been diagnosed with RLS, among whom 680 were excluded because of a prior diagnosis of Parkinson disease, leaving 4,887 patients analyzed to determine the cumulative dose of dopamine agonists and clonazepam prescribed for RLS (**Figure S1** in the supplemental material). The demographic characteristics of this patient population were similar to those of the population in the analysis of RLS diagnosis (**Table S1**).

Seasonal pattern of patients with RLS and diagnoses

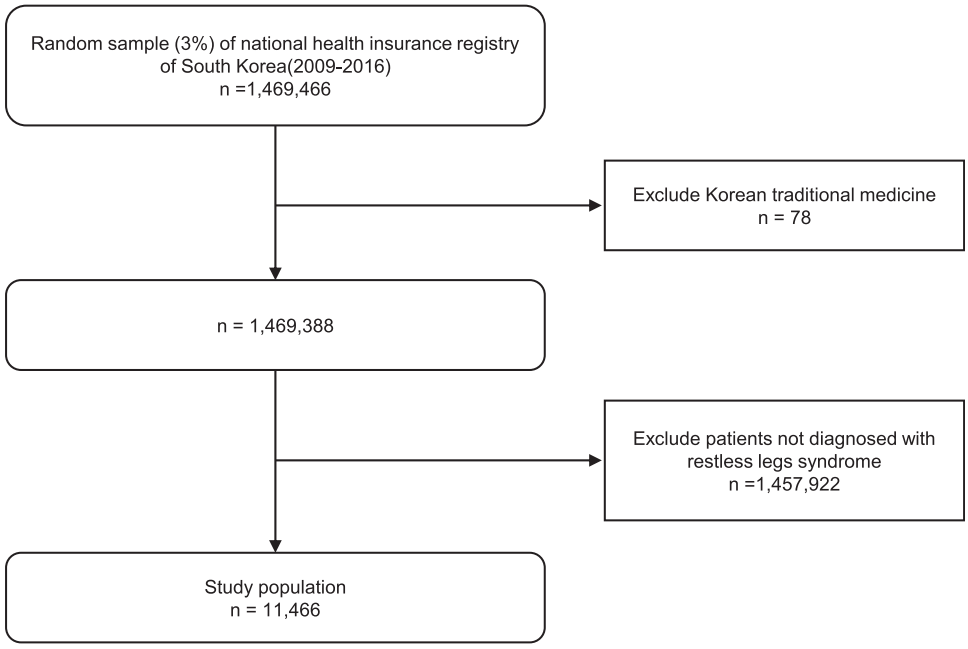
The number of patients with RLS showed significant seasonality that peaked in August, July, and August for all patients (amplitude 24.93; phase 8.1; P < .001), men (amplitude 9.43; phase 7.9; P < .001), and women (amplitude 15.57; phase 8.2; P < .001), respectively. The magnitude of the greatest difference in the number of patients with RLS between the highest and lowest months was 29.96% (95% confidence interval [CI], 24.03–100.80) in all patients, 28.80% (95% CI, 15.49–42.11) in male patients, and 31.61% (95% CI, 23.77–39.44) in female patients (**Figure 2**).

The number of RLS diagnoses also showed significant seasonality that peaked in August, July, and August for all patients (amplitude 124.08; phase 8.0; P < .001), men (amplitude 45.42; phase 7.9; P < .001), and women (amplitude 78.69; phase 8.0; P < .001), respectively. The magnitude of the greatest difference in the number of RLS diagnoses between the highest and lowest months was 39.56% (95% CI, 31.24–47.89) in all patients, 36.44% (95% CI, 24.19–48.70) in male patients, and 42.14% (95% CI, 28.91–55.37) in female patients (**Figure 3**).

In the analysis of early-onset RLS (ages < 45 years), the number of patients with this diagnosis showed seasonality, with peaks in August regardless of sex (all patients: amplitude 6.68, phase 8.4, P < .001; men: amplitude 2.66, phase 8.8, P = .002; women: amplitude 4.11, phase 8.2, P < .001). The magnitude of the greatest difference in the number of patients with RLS between August, the highest month, and February, the lowest month, was 51.53% (95% CI, 20.64–82.41), 62.41% (95% CI, 24.03–100.80), and 49.15% (95% CI, 20.64–82.41) in all patients, male patients, and female patients, respectively (**Figure S2**).

The number of RLS diagnoses in patients with early-onset RLS also peaked in July, August, and July for all patients

Figure 1—Flow diagram of patient selection for analysis of number of patients with RLS diagnoses.



RLS = restless legs syndrome.

Table 1—Characteristics of patients with RLS from the 3% sample of the HIRA database during 2009–2016.

Characteristics	All RLS (n = 11,466)	Early-Onset RLS[a] (n = 1,882)
Female sex	7,001 (61.1)	1,091 (58.0)
Year		
2009	657 (5.7)	129 (6.9)
2010	780 (6.8)	132 (7.0)
2011	1,105 (9.6)	147 (7.8)
2012	1,491 (13.0)	258 (13.7)
2013	1,534 (13.4)	243 (12.9)
2014	1,817 (15.9)	306 (16.3)
2015	1,912 (16.7)	332 (17.6)
2016	2,170 (18.9)	335 (17.8)

Data are presented as n (%). [a]Early-onset RLS = ages < 45 years. HIRA = Health Insurance Review and Assessment Service, RLS = restless legs syndrome.

(amplitude 30.40; phase 7.8; $P < .001$), men (amplitude 13.29; phase 8.1; $P = .002$), and women (amplitude 17.41; phase 7.6; $P < .001$), respectively. The magnitude of the greatest difference in the number of RLS diagnoses between the highest and lowest months was 49.31% in all patients (95% CI, 22.49–76.14), 59.94% in male patients (95% CI, 22.68–97.20), and 46.94% in female patients (95% CI, 17.24–76.63; **Figure S3**).

Seasonality of medications prescribed for patients with RLS

The monthly cumulative dose of dopamine agonists prescribed for RLS (converted to the levodopa-equivalent dose) exhibited no significant seasonality. The dose peaked in June in all patients (amplitude 819.68; phase 6.0; $P > .50$), in September in the male patients (amplitude 1,710.35; phase 9.1; $P = .444$), and in March in the female patients (amplitude 1,930.55; phase 3.9; $P = .271$), but none of these increases were statistically significant. No consistent tendency was observed among the groups (**Figure S4**). When we analyzed the medications prescribed for early-onset RLS, we found that the number of patients was not sufficient to achieve statistical significance.

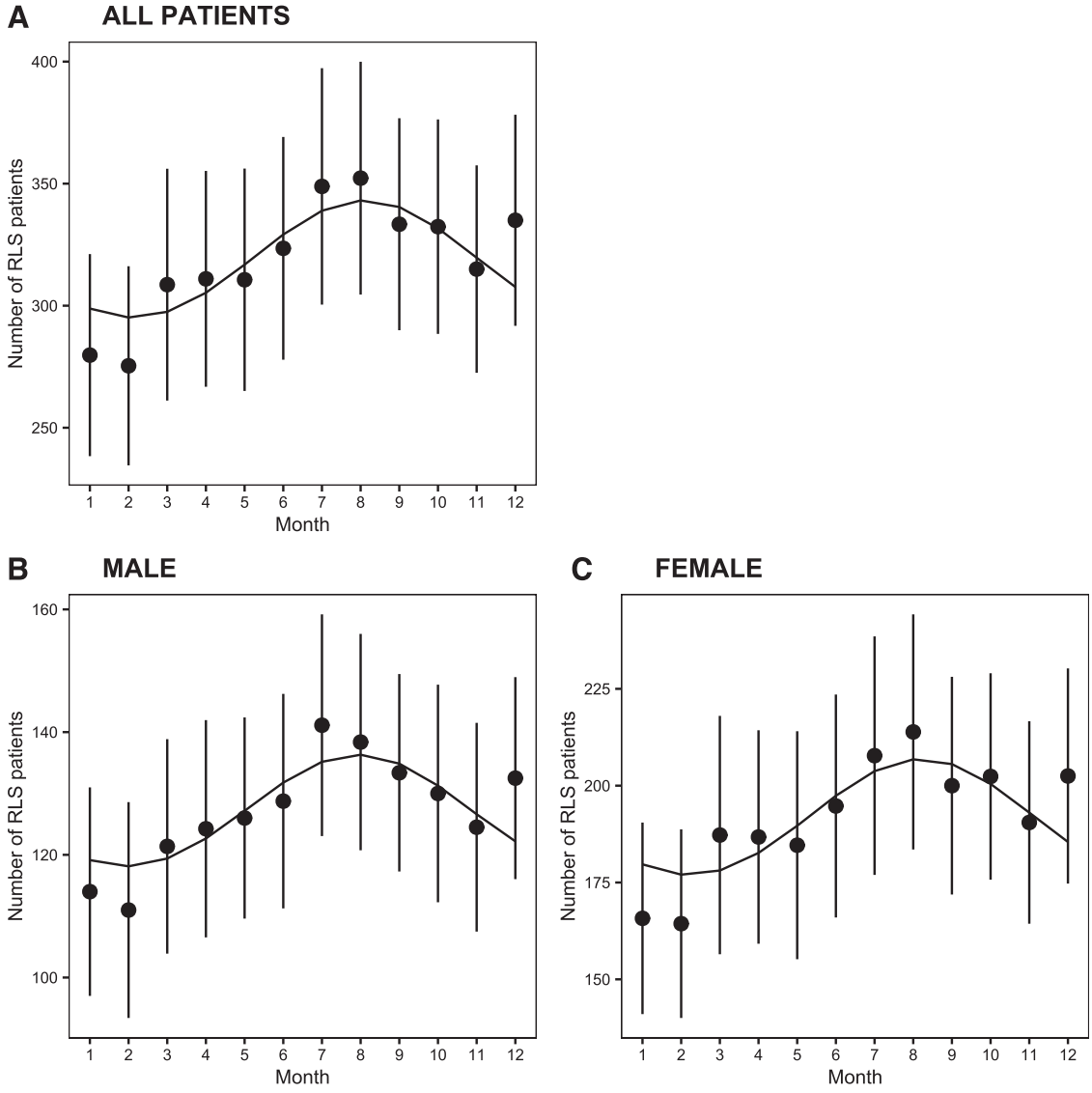
Similar results were seen for clonazepam, with the monthly cumulative prescription dose peaking in September in all patients (amplitude 22.41; phase 9.7; $P > .50$), in August in male patients (amplitude 10.96; phase 8.5; $P > .5$), and in October in female patients (amplitude 14.96; phase 10.6; $P = .481$). Although the number of clonazepam prescriptions increased in late summer to fall regardless of sex, the difference was not statistically significant.

The monthly cumulative prescription dose of dopamine agonists plus clonazepam (converted to the levodopa-equivalent dose) peaked in May in all patients (amplitude 1,223.35; phase 5.7; $P > .5$), in August in male patients (amplitude 1,529.29; phase 8.8; $P > .5$), and in April in female patients (amplitude 2,018.27; phase 4.0; $P = .238$). As with other treatments, these differences were not statistically significant.

DISCUSSION

This study showed that the monthly prevalence of RLS exhibits a seasonal pattern, peaking in late summer. In particular, the increase in prevalence of RLS during the summer seems to be more pronounced for early-onset RLS (ages < 45 years). This is the first big data study to show the seasonality of RLS.

Figure 2—Seasonal pattern of the normalized number of patients with RLS in South Korea.



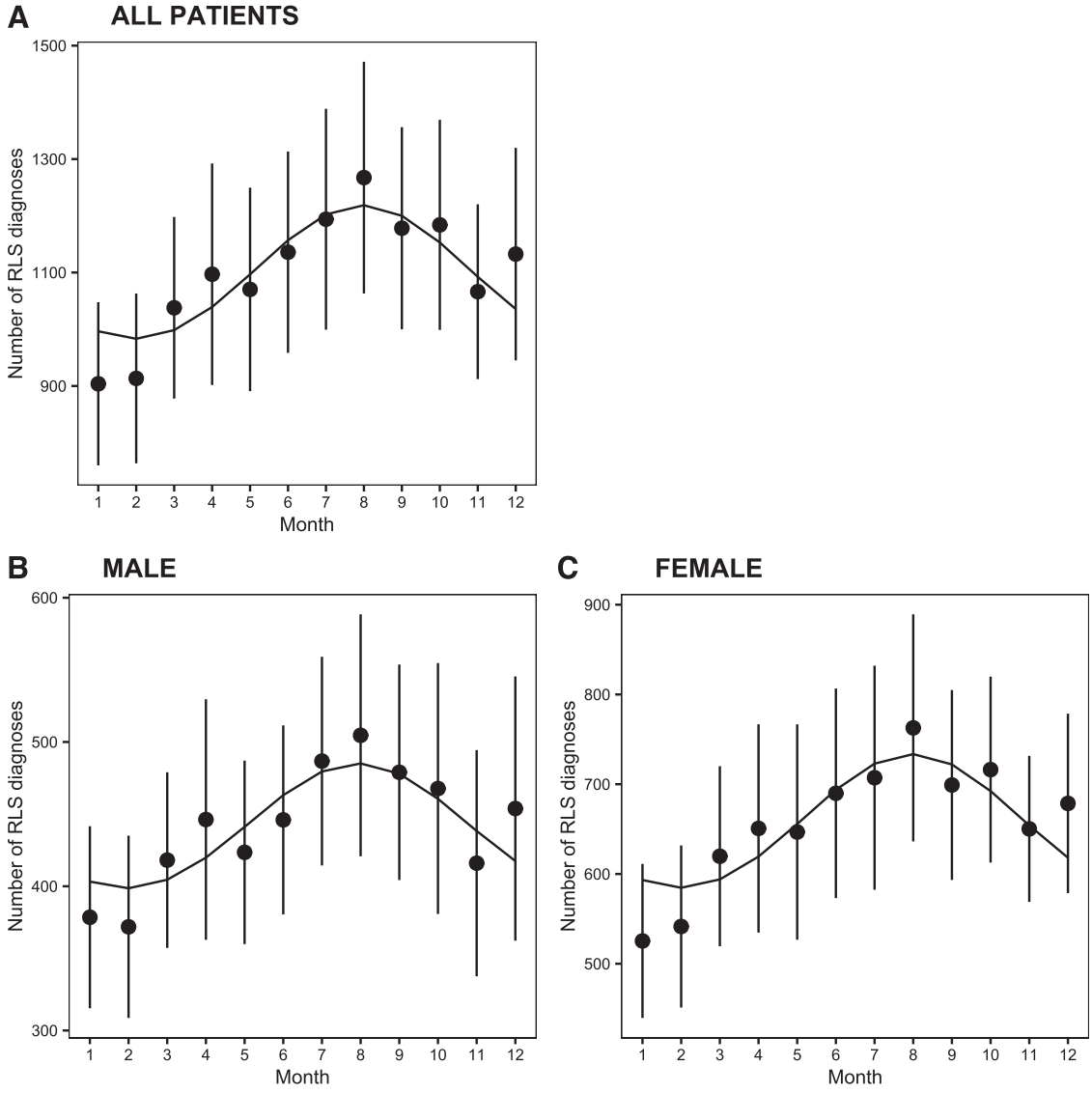
Lines indicate fitted cosinor analysis model. Points with bars are monthly means ± SE. Patients with RLS showed significant seasonality with peaks **(A)** in August for all (men and women: n = 11,466, amplitude 24.93, phase 8.1, $P < .001$), **(B)** in July for men (n = 4,465, amplitude 9.43, phase 7.9, $P < .001$), and **(C)** in August for women (n = 7,001, amplitude 15.57, phase 8.2, $P < .001$). RLS = restless legs syndrome, SE = standard error.

In contrast, the prescribed dose of medications, used as a marker of RLS severity, showed no evidence of seasonality. During the study period, the number of people diagnosed with RLS in South Korea gradually increased. RLS is not well recognized and has therefore been underdiagnosed in South Korea compared to North America and Western Europe.[17] The increase in the diagnosis of RLS may result from an increase in awareness of the disease.

Although the mechanism by which the prevalence of RLS increases during summer is beyond the scope of this study, several hypotheses can be suggested. First, RLS occurrence and the seasonality of dopamine levels in the central nervous system may be related. Dopamine synthesis in the putamen and caudate nucleus and dopamine metabolites in the cerebrospinal fluid are reported to decrease during summer.[18–20] Because RLS symptoms are thought to occur when dopamine activity is low,[21] evidence of decreased levels of dopamine in the central nervous system during summer in South Korea may be associated with RLS symptoms. Second, decreased central nervous system iron levels in summer may also contribute to RLS symptoms. Previous studies have shown that RLS may be related to iron deficiency in the central nervous system,[22] with Maes et al[23] reporting higher ferritin levels from November to May than from June to October.

In contrast to RLS diagnoses, the prescribed doses of dopamine agonists and clonazepam showed no significant seasonal pattern, which suggests that the seasonal variation in RLS severity is not clear. This observation is in direct contrast to previous studies showing that RLS severity worsens in summer,[8] highlighting the potential limit to inferring the severity of RLS based on the prescription dose of medications. In particular, clonazepam is used for a variety of medical and

Figure 3—Seasonal pattern of the normalized number of RLS diagnoses in South Korea.



Lines indicate fitted cosinor analysis model. Points with bars are monthly means ± SE. RLS diagnoses showed significant seasonality with peaks **(A)** in August for all (men and women: n = 11,466, amplitude 124.08, phase 8.0, $P < .001$), **(B)** in July for men (n = 4,465, amplitude 45.42, phase 7.9, $P < .001$), and **(C)** in August for women (n = 7,001, amplitude 45.42, phase 7.9, $P < .001$). RLS = restless legs syndrome, SE = standard error.

psychiatric disorders, so its prescription may not accurately represent the severity of RLS symptoms. Moreover, frequent visits to a doctor to diagnose RLS may be because of increasing symptom severity. A further prospective study measuring self-reported symptoms of RLS will be needed to accurately evaluate the seasonal variation in RLS severity.

Our study has a notable strength in that it is the first big data study to confirm the seasonal pattern of RLS occurrence. However, it has several limitations as well. First, this study was conducted on only a 3% sampling of the South Korean population. As a random sample, the selection bias was minimized but not eliminated. A follow-up study examining the entire population of South Korea may therefore be warranted. Second, we randomly sampled 3% of the HIRA database, which contains information on diagnoses and treatment but lacks other clinical information such as disease onset and RLS severity via which the incidence and severity of the disease could be measured directly. A clinical visit is an indirect measure and can be influenced by other factors, such as vacations and holidays. Third, because of the nature of retrospective studies, we were unable to evaluate augmentation in patients with RLS. The prescribed dose of medication may be related not only to disease severity but also to the augmentation of the disease. Fourth, the seasonal pattern of iron supplementation in patients with RLS was not assessed because iron supplementation is not routinely covered by the national health insurance system of South Korea.

CONCLUSIONS

Our results suggest that there is a seasonal effect in RLS prevalence in South Korea that peaks during summer. This finding will help

clinicians understand the clinical course of RLS and manage it more appropriately.

ABBREVIATIONS

CI, confidence interval
HIRA, Health Insurance Review and Assessment Service
RLS, restless legs syndrome

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed in the Department of Psychiatry, Dongguk University Ilsan Hospital, Goyang, Republic of Korea. The authors report no conflicts of interest.