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Increased Risk of Restless Legs Syndrome in Patients With Migraine

A Nationwide Population-Based Cohort Study

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Abstract: Previous studies suggest that an association between restless legs syndrome (RLS) and migraine exists. However, population-based data are unavailable in Asian cohorts. Our study thus aims to evaluate the association between migraine and RLS in a nationwide, population-based cohort in Taiwan and to examine the effects of age, sex, migraine subtype, and comorbidities on RLS development.

Data from the Taiwan National Health Insurance Research Database were used. Patients aged 20 years or older with newly diagnosed migraine from 2000 to 2008 were included; 23,641 patients with newly diagnosed migraine and 94,564 subjects without migraine were randomly selected and followed until RLS development, withdrawal from the National Health Insurance, or until the end of 2011. A multivariate Cox proportional hazards regression model was used to explore the risk of RLS in patients with migraine after adjustment for demographic characteristics and comorbidities.

Both cohorts were followed for a mean of 7.38 years. After adjustment for covariates, the risk of RLS was 1.42-fold higher (95% confidence interval = 1.13–1.79) in the migraine cohort than in the nonmigraine cohort (7.19 versus 3.42 years per 10,000 person-years). The increased risk was more prominent in males in the migraine cohort (1.87-fold increased risk, 95% confidence interval 1.22–2.85). Neither comorbidity status nor migraine subtype influenced the RLS risk.

This population-based study demonstrated that migraine is associated with an increased risk of RLS compared with those without migraine, particularly in male patients with migraine and regardless of the comorbidity status.

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Abbreviations: aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, LHID 2000 = Longitudinal Health Insurance Database 2000, NERD = nonerosive reflux disease, NHI = National Health Insurance, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, RLS = restless legs syndrome.

INTRODUCTION

Migraine is a prevalent primary headache disorder that affects approximately 10% to 20% of the general population, predominantly females (female:male incidence = 2–3:1).[1,2] It is characterized by recurrent headache attacks and is associated with the hypersensitivity of various central nervous functional systems.[1] Accumulating evidence suggests that multiple disorders are associated with migraine, including cardiovascular disease, anxiety and depressive disorders, epilepsy, and pain disorders.[3–6] In addition, earlier studies have suggested that sleep disorders, particularly restless legs syndrome (RLS), are possible comorbidities in patients with migraine.[7,8]

Restless legs syndrome is a sleep-related sensorimotor disorder first described in 1945 by the Swedish neurologist Ekbom. It has a prevalence of 4% to 29% in the general population, and similar to migraine, it predominantly affects females (female:male incidence = 2:1).[9–11] Restless legs syndrome is characterized by uncomfortable sensations in the legs, an overwhelming urge to move the legs, especially when at rest and during nighttime; the symptoms are relieved only upon moving the legs (eg, standing and walking).[12,13] Restless legs syndrome may be idiopathic, or, as accumulating evidence suggests, may develop secondary to a variety of medical conditions, such as diabetes, iron deficiency anemia, depression, anxiety, sleep disorder, Parkinson disease, and renal disease.[14–16] Moreover, pathophysiological mechanisms common to both migraine and RLS were proposed,[17] involving

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dopaminergic dysfunction, abnormalities of iron metabolism, the endogenous opioid system, and common genetic factors.[18,19]

Previous studies have demonstrated a higher prevalence of RLS in patients with migraine as compared with individuals without migraine.[13,20–28] Similarly, a higher prevalence of migraine in patients with RLS was also reported.[29–31] Furthermore, results from a prior systematic review suggest that migraine is associated with increased odds for RLS.[32] However, among these studies, only 2 were large-scale and population-based studies: Schürks et al[13] (Women's Health Study) and Winter et al[27] (Physicians' Health Study). These studies have their limitations; their cohorts were restricted to health-care professionals and a single sex (female and male, respectively). Furthermore, Winter et al employed a cross-sectional design rather than a longitudinal design. Nevertheless, both studies identified a higher RLS prevalence in patients with migraine compared with controls.[13,27]

To confirm these results in a broader population sample and to identify the potential confounders, such as age, migraine subtype, and comorbidities, we conducted a nationwide, large-scale, population-based study using the Taiwan National Health Insurance Research Database (NHIRD).

METHODS

Data Source

The National Health Insurance (NHI) program, implemented in 1995, is a compulsory single-payer healthcare system covering 99.9% of Taiwan's population at the end of 2014. The NHIRD is managed by the Taiwanese National Health Research Institutes and published by the Bureau of NHI of Taiwan. In this study, we used the Longitudinal Health Insurance Database 2000 (LHID 2000), a subset of the NHIRD. The LHID 2000 includes the 1996 to 2011 medical claims of 1 million beneficiaries randomly selected from the 23.75 million NHI beneficiaries. The LHID 2000 contains comprehensive outpatient and inpatient information, including demographic data, clinical visit details, prescription details, and the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes. To ensure patient confidentiality, the National Health Research Institutes scrambled the patient identification number, which is necessary to link the data with a patient identity. Our study was approved by the Ethics Review Board of China Medical University (CMU-REC-101–012).

Study Population

We conducted a population-based retrospective cohort study by selecting participants aged 20 years and older who were newly diagnosed with migraine (ICD-9-CM 346) and without a previous diagnosis of RLS (ICD-9-CM 333.90 and 333.99) during 2000 to 2008, as the migraine cohort. Migraine diagnoses were identified according to the *International Classification of Headache Disorders, Second Edition* criteria.[33] The date of the first migraine diagnosis was used as the index date. In addition, we divided the migraine cohort into 4 subcohorts: migraine with aura (ICD-9-CM 346.0), migraine without aura (ICD-9-CM 346.1), unspecified migraine (ICD-9-CM 346.9), and other migraine (ICD-9-CM 346.2 and 346.8) cohorts. For each patient with migraine, 4 insured individuals without migraine were randomly selected from the NHIRD, and frequency-matched for sex, age (5-year span), and the index year using the same inclusion criteria as that of the migraine cohort.

Outcome and Comorbidities

The primary outcome was RLS (ICD-9-CM 333.90 and 333.99). Restless legs syndrome diagnoses complied with the recommendations of the International RLS Study Group.[12] All participants were followed up from the index date to RLS onset, withdrawal from the NHI, or December 31, 2011. The medical comorbidities, including diabetes (ICD-9-CM 250), iron deficiency anemia ([IDA], ICD-9-CM 280), depression (ICD-9-CM 296.2, 296.3, 300.4, and 311), anxiety (ICD-9-CM 300.00), sleep disorder (ICD-9-CM 307.4 and 780.5), Parkinson disease (ICD-9-CM 332), and renal disease (ICD-9-CM 580–589), were defined as diseases diagnosed before the index date.

Statistical Analyses

The distributions of the baseline characteristics (sex, age group, and comorbidities) were compared between the migraine and nonmigraine cohorts. A χ^2 test was used to examine the categorical variables, and a Student t test was used to examine the continuous variables. The incidence density rates (per 10,000 person-years) of RLS stratified by sex, age, and comorbidity were calculated for the migraine and nonmigraine cohorts. We assessed the cumulative RLS incidences in the migraine and nonmigraine cohorts by using the Kaplan–Meier method, and tested the differences by using a log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to assess the risk of RLS and the RLS-associated risk factors. The multivariate Cox proportional hazards regression model was adjusted for sex, age, and comorbidities of diabetes, IDA, depression, anxiety, sleep disorder, Parkinson disease, and renal disease. We also used Cox proportional hazards regression models to calculate the risk of RLS and migraine stratified by sex, age, and comorbidities. We used SAS 9.4 software (SAS Institute, Cary, NC) to manage and analyze the data. Two-sided $P < 0.05$ was considered significant.

RESULTS

We included 23,641 patients with migraine and 94,564 subjects without migraine. In the migraine cohort, 81.64% were younger than 60 years and 72.09% were females. The mean ages in the migraine and nonmigraine cohorts were 45.21 (standard deviation = 15.30) and 44.98 years (standard deviation = 15.60), respectively. Compared with the nonmigraine cohort, the comorbidities of diabetes (7.96% versus 7.17%), IDA (3.47% versus 2.06%), depression (9.93% versus 3.51%), anxiety (14.79% versus 5.01%), sleep disorder (33.95% versus 14.07%), Parkinson disease (0.95% versus 0.55%), and renal disease (10.38% versus 6.38%) were more prevalent in the migraine cohort (Table 1).

The cumulative incidence curves of RLS for migraine status are illustrated in Figure 1. We used the log-rank test to examine the cumulative incidence of RLS in the migraine and nonmigraine cohorts and discovered that the cumulative incidence of RLS was significantly higher in the patients with migraine than in the participants without migraine ($P < 0.001$). During an average follow-up period of 7.38 years, we observed a higher incidence density rate of RLS in the migraine cohort than in the nonmigraine cohort (7.19 versus 3.42 years per 10,000 person-years). After adjustment for sex, age, and comorbidities of diabetes, IDA, depression, anxiety, sleep disorder, Parkinson disease, and renal disease, the adjusted hazard ratio (aHR) of RLS was 1.42-fold higher (95% confidence interval [CI] = 1.13–1.79) for the migraine cohort than for the nonmigraine cohort (Table 2). Compared with younger patients, the

TABLE 1. Baseline Demographic Factors and Comorbidity of Study Participants According to Migraine Status

	Nonmigraine N = 94,564		Migraine N = 23,641		
Characteristics	**n**	**%**	**n**	**%**	***P* Value**
Sex					0.99
Female	68,168	72.09	17,042	72.09	
Male	26,396	27.91	6599	27.91	
Age, y					0.99
20–39	38,556	40.77	9639	40.77	
40–59	38,648	40.87	9662	40.87	
≥60	17,360	18.36	4340	18.36	
Mean (SD)†	44.98	15.60	45.21	15.30	0.04
Comorbidity					
Diabetes	6777	7.17	1881	7.96	<0.001
IDA	1944	2.06	820	3.47	<0.001
Depression	3316	3.51	2348	9.93	<0.001
Anxiety	4739	5.01	3494	14.79	<0.001
Sleep disorder	13,309	14.07	8027	33.95	<0.001
Parkinson disease	524	0.55	224	0.95	<0.001
Renal disease	6035	6.38	2454	10.38	<0.001

IDA = iron deficiency anemia, SD = standard deviation.
† Student *t* test.

risk of RLS was 1.62-fold higher (95% CI = 1.21–2.17) in patients >60 years, suggesting that RLS risk increases with age. In the multivariable model, the risk of RLS was higher for the patients with comorbidities of IDA (aHR = 2.01, 95% CI = 1.28–3.18), depression (aHR = 3.6, 95% CI = 2.7–4.83), anxiety (aHR = 1.73, 95% CI = 1.29–2.32), sleep disorder (aHR = 1.60, 95% CI = 1.2–2.06), and Parkinson disease (aHR = 5.25, 95% CI = 3.3–8.25).

The sex-specific analysis showed that the incidence density rates of RLS in females and males with migraine were 6.77 and 8.31 years per 10,000 person-years, respectively; higher than those in the nonmigraine cohort (3.49 and 3.23 years per 10,000 person-years, respectively). In addition, male patients with migraine exhibited a significantly higher risk of RLS (aHR = 1.87, 95% CI = 1.22–2.85) than did the male patients without migraine. The incidence density rate of RLS increased with the age in both cohorts; however, patients with migraine were not associated with the risk of RLS compared with individuals without migraine in all age groups. The migraine cohort exhibited a higher risk of RLS than did the nonmigraine cohort both for patients without any comorbidity (aHR = 1.59, 95% CI = 1.07–2.36) and with comorbidity (aHR = 1.59, 95% CI = 1.22–2.08) (Table 3). Among patients with migraine, the risks of RLS in the migraine without aura, unspecified migraine, and other migraine cohorts were not significantly higher than that for the migraine with aura cohort (Table 4).

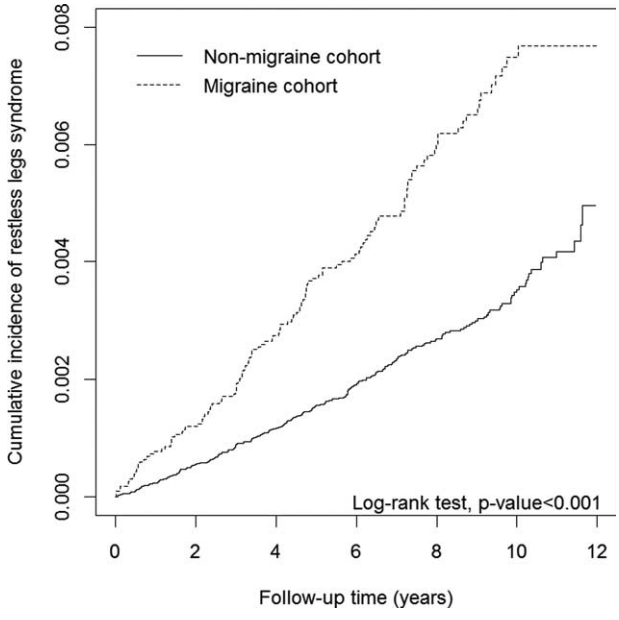

FIGURE 1. Cumulative incidence curves of restless legs syndrome for cohorts with and without migraine.

DISCUSSION

To the best of our knowledge, this is the first nationwide, population-based longitudinal study that demonstrates an increased risk of RLS in patients with migraine. We demonstrated that the risk of subsequent development of RLS in patients with migraine was 1.42-fold higher than in the nonmigraine cohort, after adjustment for age, sex, and medical comorbidities. We discovered that male patients with migraine had a high risk (1.87-fold) of RLS. Moreover, regardless of the comorbidity status or migraine subtype, the migraine cohort exhibited a higher risk of RLS than did the nonmigraine cohort.

Our results were consistent with those of the previous 2 large-scale, population-based studies, although some methodological dissimilarities must be considered.[13,27] Our study included participants of diverse age (20–60-year old) and the cohorts were of mixed sex. In addition, we considered a longitudinal study design, unlike that of Winter et al.[27] The longitudinal study design enables the consideration of possible

TABLE 2. Cox Model Measured Hazard Ratios and 95% Confidence Interval of Restless Legs Syndrome Associated With Migraine and Covariates

				HR (95% CI)	
Characteristics	**Event Number**	**Person-years**	**IR**	**Univariate**	**Multivariate†**
Migraine					
No	238	695,567	3.42	1.00	1.00
Yes	127	176741	7.19	2.10 (1.69–2.60)***	1.42 (1.13–1.79)**
Sex					
Female	264	635,023	4.16	1.00	1.00
Male	101	237,285	4.26	1.03 (0.82–1.29)	1.09 (0.86–1.38)
Age, y					
20–39	105	360,309	2.91	1.00	1.00
40–59	153	362,951	4.22	1.44 (1.13–1.85)**	1.20 (0.93–1.55)
≥60	107	149,049	7.18	2.48 (1.89–3.24)***	1.62 (1.21–2.17)**
Comorbidity					
Diabetes					
No	320	813,869	3.93	1.00	1.00
Yes	45	58,440	7.7	1.98 (1.45–2.70)***	1.24 (0.89–1.72)
IDA					
No	345	854,479	4.04	1.00	1.00
Yes	20	17,830	11.22	2.84 (1.81–4.46)***	2.01 (1.28–3.18)**
Depression					
No	278	834,619	3.33	1.00	1.00
Yes	87	37,689	23.08	7.07 (5.56–9.00)***	3.64 (2.74–4.83)***
Anxiety					
No	289	819,855	3.53	1.00	1.00
Yes	76	52,454	14.49	4.25 (3.30–5.48)***	1.73 (1.29–2.32)***
Sleep disorder					
No	230	733,585	3.14	1.00	1.00
Yes	135	138,724	9.73	3.21 (2.59–3.98)***	1.60 (1.24–2.06)***
Parkinson disease					
No	342	868,043	3.94	1.00	1.00
Yes	23	4265	53.93	14.09 (9.23–21.51)***	5.25 (3.34–8.25)***
Renal disease					
No	327	813,954	4.02	1.00	1.00
Yes	38	58,354	6.51	1.63 (1.17–2.29)***	0.89 (0.63–1.27)

CI = confidence interval, HR = hazard ratio, IDA = iron deficiency anemia, IR = incidence density rate, per 10,000 person-years.
** $P < 0.01$.
*** $P < 0.001$.
† Adjusted for migraine, sex, age (categorical), and comorbidity.

confounders (risk factors) for the development of RLS and is more generalizable.

In the current study, consistent with previous observations,[3–6] the possible comorbidities of migraine, such as diabetes, IDA, depression, anxiety, sleep disorders, Parkinson disease, and renal disease were more prevalent in the migraine cohort than in the comparison cohort. Although the patients with migraine in this study exhibited a different prevalence of comorbidities associated with the RLS development compared with the nonmigraine cohort, multivariate Cox analyses demonstrated that migraine was an independent factor for predicting the RLS risk.

Our cohort study results should be interpreted cautiously and with recognition of its inherent ethnic and methodological differences. For example, our control cohort's annual RLS incidence rate (3.42/10,000 person-years) was lower than that of a German cohort (9–22/1,000 person-years).[34] Moreover, studies have reported that Asian controls show a lower RLS prevalence than the European and North American (ie, non-Asian) controls.[23,35] Furthermore, in our study cohorts, the RLS occurrence showed no clear sex-dependent predisposition (Table 2), unlike the many studies where a higher RLS prevalence was reported in females than in males.[9–11] Therefore, our results should be interpreted cautiously, and consideration should be given to the effects of differences in cohort ethnicities, methodologies, and clinical settings. Notably, our data showed a high aHR for RLS in elderly patients (>60 years) and patients with the comorbidity of IDA, depression, anxiety, sleep disorders, or Parkinson disease (Table 2). This result is in agreement with earlier reports of these conditions as potential risk factors for RLS.[14,15,36]

The migraine subcohort analysis revealed that the male patients with migraine exhibited a significantly higher risk of RLS than did the patients without migraine, which is

TABLE 3. Incidence Density Rates and Hazard Ratios of Restless Legs Syndrome According to Migraine Status Stratified by Sex, Age, and Comorbidity

	Migraine						Compared With Nonmigraine Cohort	
	No			Yes			HR (95% CI)	
Characteristics	Event Number	Person-years	IR	Event Number	Person-years	IR	Crude	Adjusted‡
Sex								
Female	177	506,441	3.49	87	128,583	6.77	1.93 (1.49–2.50)***	1.29 (0.98–1.69)
Male	61	189,127	3.23	40	48,158	8.31	2.57 (1.73–3.83)***	1.87 (1.22–2.85)**
Age, y								
20–39	63	287,223	2.19	42	73,086	5.75	2.61 (1.77–3.86)***	1.46 (0.96–2.24)
40–59	103	289,694	3.56	50	73,256	6.83	1.91 (1.37–2.68)***	1.29 (0.90–1.84)
≥60	72	118,650	6.07	35	30,398	11.51	1.90 (1.27–2.84)**	1.44 (0.94–2.20)
Comorbidity status†								
No	114	526,250	2.17	32	94,712	3.38	1.54 (1.04–2.28)*	1.59 (1.07–2.36)*
Yes	124	169,318	7.32	95	82,029	11.58	1.57 (1.20–2.05)**	1.59 (1.22–2.08)***

CI = confidence interval, HR = hazard ratio, IR = incidence density rates, per 10,000 person-years.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.
† Patients with any one of diabetes, iron deficiency anemia, depression, anxiety, sleep disorder, Parkinson disease, and renal disease were classified as the comorbidity group.
‡ Mutually adjusted for sex, age (continuous), and comorbidity.

inconsistent with the results of previous population-based studies.[13,27] However, interpretation of the discrepancy warrants caution because of the limited number of population-based studies and possible ethnic differences. We identified that the higher risk of RLS in the patients from the migraine cohort was not influenced by the age after adjustment for multivariable effects; this risk was high regardless of the comorbidity status. These results reinforce our finding that migraine is independently associated with RLS. Finally, no differences were observed in RLS occurrence among the patients with different migraine subtypes (ie, migraine with or without aura). This finding is consistent with that of the previous studies demonstrating that the odds of RLS in patients with migraine did not differ in the presence or absence of auras.[13,28]

Two key mechanisms linking migraine and RLS are currently being explored. First, the neurotransmitter dopamine is suspected in the migraine pathophysiology because dopamine-mediated behaviors appear before the migraine attacks (eg, yawning, food craving, and gastrointestinal disorders).[1] In addition, dopamine agonists can aggravate the symptoms, whereas dopamine antagonists are effective in treatment regimens.[37] Studies on rats have shown that dopamine directly inhibits nociception in the trigeminocervical complex.[38,39] The association of dopamine and RLS is more tenuous, although central dopaminergic hypofunction of hypothalamic neurons (A11) targeting the spinal cord have been implicated in the RLS pathophysiology.[19] This hypothesis is supported by the substantial improvement in RLS symptoms seen following the initiation of dopamine agonist treatment.[40] Moreover, the dopamine link between migraine and RLS is supported by Cologno et al,[41] who observed a higher prevalence of premonitory symptoms in patients with migraine and RLS than in patients with migraine and no RLS.

The second hypothesis relates to iron metabolism. Iron deposition in the brain is considered to be involved in migraine pathogenesis, and increased iron accumulation appears to be associated with repeated migraine attacks.[42] Iron deficiency also appears to play a role in the etiology and pathogenesis of RLS.[43] Therefore, deregulated iron metabolism (eg, inappropriate deposition leading to reduced bioavailable iron) may contribute to the pathophysiology of (and a link between) these disorders. Furthermore, since iron is a cofactor of tyrosine

TABLE 4. Incidence Density Rates and Hazard Ratios of Restless Legs Syndrome Among Different Type of Migraine Patients

Migraine Cohort	Number	Event Number	Person-years	IR	Crude HR (95% CI)	aHR† (95% CI)
Migraine with aura	1812	12	12,569	9.55	1.00	1.00
Migraine without aura	7380	28	58,227	4.81	0.50 (0.25–0.98)*	0.60 (0.31–1.19)
Unspecified migraine	13,504	84	99,049	8.48	0.87 (0.48–1.62)	1.01 (0.55–1.86)
Other migraine diagnoses	945	3	6896	4.35	0.45 (0.13–1.61)	0.50 (0.14–1.76)

ICD-9-CM: migraine with aura, 364.0; migraine without aura, 346.1; unspecified migraine, 346.9; and other migraine diagnoses, 346.2 and 346.8.
CI = confidence interval, aHR = adjusted hazard ratio, IR = incidence density rates, per 10,000 person-years.
* $P < 0.05$.
† Adjusting for sex, age, and comorbidity.

hydroxylase, an enzyme required for dopamine synthesis, evidence suggesting that disruptions in brain iron trafficking lead to disturbances in striatal dopamine neurotransmission, which may be related to RLS pathophysiology, is mounting.[44] Therefore, the link between iron deficiency and dopamine metabolic theories may be considered in conjunction with dopamine deregulation. Finally, previous studies have pointed to a common genetic origin for RLS and migraine located on chromosome 14q21.[45,46] It has also been reported that families with several members of successive generations are affected by migraine with aura and RLS.[47] Furthermore, a recent study demonstrated that the Meis homeobox 1 gene was associated with a significantly higher susceptibility to RLS in patients with migraine.[48] These findings support the hypothesis of a shared genetic etiology of RLS and migraine. Collectively, these evidences suggest that the relationship between migraine and RLS may be one of common pathogenetic substrates.

Our findings have several clinical implications. Migraine should be regarded a potential risk factor for RLS, and patients with migraine should be evaluated for RLS both initially and at follow-up. In addition, given the differences between our study and previous studies,[27,41] additional research is required to evaluate the influence of sex or hormones on the migraine–RLS relationship.

The major strengths of this study lie in its large (nationwide) sample size and longitudinal design, which provide sufficient power to delineate the differences between the 2 study cohorts and across various covariates. Moreover, in this study, the diagnoses of ''migraine'' and ''RLS'' were based on the ICD-9 codes determined by qualified clinical physicians (not always neurologists) for the strictly audited reimbursement process. Migraine diagnoses were identified according to the *International Classification of Headache Disorders, Second Edition* criteria,[33] and RLS diagnoses complied with the recommendations of the International RLS Study Group.[12] In addition, NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single buyer, the government in Taiwan. All insurance claims should be scrutinized and coded by medical reimbursement specialists and peer reviewed according to the standard criteria for diagnoses of migraine and RLS in the study. Therefore, the diagnoses and coding in this study were highly reliable. Finally, our longitudinal study afforded an assessment of the temporal relation between RLS and migraine, which helps comprehend the direction of the association between these 2 disorders to provide a potential bidirectional relationship suggesting comorbidity.

The study had several limitations. First, the NHIRD dataset is derived from an administrative database that lacks detailed clinical data, such as duration and frequency of migraine occurrences, RLS severity, neuroimaging, polysomnograms, suggested immobilization tests, and other laboratory results. Therefore, the precise diagnosis of idiopathic or secondary RLS was not available in this database. Second, the NHIRD-based cohort only included patients with migraine seeking medical treatment throughout the study period. Patients with migraine who did not seek medical attention may have been grouped incorrectly into the control cohort, leading to the underestimation of the RLS risk in patients with migraine. Finally, we could not establish an association with the causalities in this study, an aspect that can be considered in further research.

In conclusion, this large-scale, cohort, nationwide population-based longitudinal study demonstrated an association between migraine and the risk of RLS, particularly in male patients with migraine, regardless of comorbidities or migraine subtype. These findings lay the foundation for deeper understanding of the underlying mechanisms for both disorders and provide direction to clinicians to improve their diagnoses and therapies.

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