

Risk of Restless Legs Syndrome Following Tension-Type Headache

A Nationwide Population-Based Cohort Study

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Abstract: Migraine and restless legs syndrome (RLS) appear to be associated, but the relationship between tension-type headache (TTH) and RLS is unknown. This nationwide, population-based, retrospective cohort study explored the potential association between TTH and RLS.

We identified 15,504 patients with newly diagnosed TTH from 2000 to 2007 and 62,016 individuals without TTH who were selected by frequency matched based on sex, age, and the index year. The study participants were followed until diagnosed with RLS, withdrawal from the NHI program, or the end of 2011. Cox proportional hazard models were used to identify risk factors for RLS in TTH patients.

After adjusting for sex, age, comorbidity, and medications, TTH was significantly associated with an increased risk of RLS (hazard ratio [HR] = 1.57, 95% confidence interval [CI] = 1.22–2.02). The risk was most prominent in patients aged 20 to 39 years in the TTH group, which

exhibited a 2.60-fold higher risk (95% confidence interval = 1.53–4.42) of RLS compared with the non-TTH group. The TTH group had a higher risk of RLS than that of the non-TTH group regardless of sex.

Tension-type headache appears to be associated with an increased risk of developing RLS. This similarity to migraines may indicate that headache and RLS have a coincident pathophysiological mechanism, a possibility requiring further study. Clinicians should be more attentive to RLS as a possible comorbidity in patients with TTH.

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Abbreviations: CIs = confidence intervals, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, RLS = restless legs syndrome, TTH = tension-type headache.

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INTRODUCTION

Tension-type headache (TTH) is one of the most common types of primary headache.¹ It typically presents as a bilateral, nonthrobbing headache with mild intensity and is generally precipitated by stress and mental tension.² In a previous review of the global prevalence of headache, TTH accounted for 46% of the cases, compared with 14% for migraine.³ Even though TTH is generally less severe than migraine, it confers a significant impact on the general population because of its much higher prevalence. Furthermore, in addition to headache pain, recent studies have suggested an association between primary headaches and sleep-related disorders.⁴ For example, data indicate that migraine is associated with sleep disorders including restless legs syndrome (RLS), parasomnia, and narcolepsy.^{5–7} Of these sleep disorders, the strongest association was determined between migraine and RLS.

First described by Ekblom in 1945, RLS is a sensorimotor disorder typically occurring at or near bedtime that is characterized by a deeply unpleasant sensation in the legs when at rest, a motor restlessness that can be relieved only by voluntary movement.⁸ The prevalence of RLS in Western countries is ~2.4% to 10% and is lower than that in Asian populations.^{9–11} The incidence of RLS increases with age and demonstrates a sex bias toward females. Restless legs syndrome can be idiopathic, or it may develop as a secondary comorbidity to a variety of medical conditions, including uremia, iron deficiency anemia (IDA), diabetes mellitus, migraine, depression, anxiety, sleep disorders, Parkinson's disease and the usage of medications such as antidepressants, antipsychotics, antihistamines, and dopamine-blocking antiemetics.¹²

Previous epidemiological studies have investigated the prevalence of RLS in patients with migraine and found it to

be higher than that of the general population.^{7,13–19} In addition, the concurrence of RLS with migraine was estimated to be 17.3% in Western⁷ and 11.4% in Asian¹³ patients. These data suggest that a common pathophysiological mechanism exists between migraine and RLS, with current hypotheses involving dopaminergic dysfunction, abnormalities of iron metabolism, the endogenous opioid system, and common genetic factors.^{20–22}

Although the relationship between migraine and RLS is somewhat well studied, that between TTH and RLS has only rarely been researched. Only 2 previous cross-sectional, clinic-based studies have investigated patients with TTH and RLS, concluding that the prevalence of concurrent TTH/RLS was 4.6%¹³ and 5.0%,²³ respectively. These studies were small-scale and lacked the longitudinal perspective required for assessing a temporal association. Therefore, we designed a nationwide, population-based cohort study to explore the possible link between TTH and RLS.

METHODS

Data Source

This study was a population-based cohort study that used data from the Taiwan National Health Insurance Research Database (NHIRD) for the period of 1996 to 2011. The National Health Insurance (NHI) program of Taiwan is a universal insurance program established in 1995, which provides comprehensive medical coverage for ~99% of the 24 million inhabitants of Taiwan. Regarding privacy protection, any information that could potentially identify an insured person was encrypted. In this study, we used the Longitudinal Health Insurance Database 2000 (LHID2000), which contains 1 million people randomly sampled from the 2000 Registry for Beneficiaries of the NHIRD and has been demonstrated to be representative of the entire population. The National Health Research Institutes reported that there were no statistically significant differences in the distribution of sex and age between the LHID2000 and all participants in NHIRD. The LHID2000 contains the insurees' demographics, dates of clinical visits, details of prescriptions, and diagnostic codes based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Study Population

We identified patients who were 20 years of age and older with newly diagnosed tension-type headache (TTH; ICD-9-CM codes: 307.81 and 339.1) as recorded in outpatient and/or inpatient claims in the NHIRD between 2000 and 2007. The date of the first diagnosis of TTH was used as the index date. For each patient with TTH, 4 insured participants were selected from the patients without a diagnosis of TTH in the LHID2000 and frequency-matched by sex, 5-year age interval, and index year of TTH diagnosis. Both groups with restless legs syndrome (RLS; ICD-9-CM codes: 333.90 and 333.99) before the index date or with missing information regarding sex or age were excluded from this study. Overall, 15,504 patients were included in the TTH group and 62,016 participants were included in the non-TTH group.

Covariates and Outcome

The demographic factors included sex and age, for which the participants were classified into subgroups of 20 to 39, 40 to 59, and ≥60 years old. The comorbidities including migraine (ICD-9-CM code: 346), diabetes (ICD-9-CM code: 250), iron deficiency anemia (IDA; ICD-9-CM code: 280), depression (ICD-9-CM codes: 296.2, 296.3, 300.4, and 311), anxiety (ICD-9-CM code: 300.00), sleep disorder (ICD-9-CM codes: 307.4 and 780.5), Parkinson disease (ICD-9-CM code: 332), and renal disease (ICD-9-CM codes: 580–589) were defined as diseases diagnosed before the index date.

Additionally, data on concurrent medications potentially associated with “at-risk” RLS medications were extracted and classified using the World Health Organization Anatomical Therapeutic Chemical system. Medications were categorized as antidepressants, including tricyclic antidepressants (TCAs) such as imipramine; selective serotonin or norepinephrine reuptake inhibitors (SSRIs, SNRIs), such as citalopram, escitalopram, fluoxetine, sertraline, paroxetine, trazodone, venlafaxine, and mirtazapine; and antipsychotics with significant dopaminergic blockade activity such as olanzapine, risperidone, quetiapine, and lithium; and antihistamines acting on the H1 receptor such as diphenhydramine and chlorpheniramine; and dopamine-blocking antiemetics such as metoclopramide and prochlorperazine. We defined prescribed medications as those that were prescribed for at least 30 consecutive days within 1 year after the index date.

The primary outcome was restless legs syndrome (RLS; ICD-9-CM codes: 333.90 and 333.99), which was determined by records linked with the outpatient and/or inpatient claims in the NHIRD. Both groups were observed from the index date to the diagnosis date of RLS, withdrawal from the NHI program, or the end of 2011.

Statistical Analyses

The means and standard deviation (SD) were used to express the continuous variables, whereas numbers and percentages were used to express the categorical variables. The demographic factors, comorbidities, and medications of the patients with and without TTH were compared using the Pearson chi-square test. The difference in the mean age between the 2 groups was calculated using the Student *t* test. The incidence density rate (per 10 000 person-y) of RLS was calculated as the number of RLS incidents during the follow-up divided by person-years at risk for each group according to sex, age, comorbidity, and medication. We estimated the cumulative risk of RLS for both groups by using the Kaplan–Meier method, and the log-rank test was used to assess the significance of the cumulative risk curves. Multivariate Cox proportional hazards regression was used to assess the risk of RLS associated with TTH after adjustment for sex, age, comorbidities, and medications; it was also used to evaluate the effect of TTH on the risk of RLS in different subgroups according to sex, age, and comorbidity. Adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated. SAS Version 9.3 software (SAS Institute, Cary, NC) was used for the data analyses; 2-sided tests were performed, and *P* < .05 was considered statistically significant.

RESULTS

We identified 15,504 patients with TTH from 2000 to 2007 as the TTH group and frequency-matched 62,016 participants without TTH by sex, age, and year of index date as the non-TTH group (Table 1). The distributions of sex and age at entry were

TABLE 1. Baseline Demographic Factors and Comorbidity of Study Participants According to Tension-Type Headache Status

Characteristics	Non-TTH Group N = 62,016		TTH Group N = 15,504		P Value
	n	%	n	%	
Sex					0.99
Women	41,264	66.54	10,316	66.54	
Men	20,752	33.46	5188	33.46	
Age, years					0.99
20–39	18,600	29.99	4650	29.99	
40–59	27,036	43.60	6759	43.60	
≥ 60	16,380	26.41	4095	26.41	
Mean (SD) [†]	49.11	(15.78)	49.41	(15.54)	0.03
Comorbidity					
Migraine	1419	2.29	1769	11.41	<0.001
Diabetes	5633	9.08	1618	10.44	<0.001
IDA	1260	2.03	460	2.97	<0.001
Depression	2398	3.87	1839	11.86	<0.001
Anxiety	3203	5.16	2534	16.34	<0.001
Sleep disorder	9227	14.88	5190	33.48	<0.001
Parkinson’s disease	466	0.75	157	1.01	0.001
Renal disease	4847	7.82	1865	12.03	<0.001
Medications					
Antidepression	1510	2.43	1594	10.28	<0.001
Antipsychotic	1209	1.95	851	5.49	<0.001
Antihistamines	3264	5.26	1585	10.22	<0.001
Antiemetics	945	1.52	575	3.71	<0.001

IDA = iron deficiency anemia, SD = standard deviation, TTH = tension-type headache.

[†] Student’s *t* test.

the same in both groups. Females accounted for 66.54% of the patients in both groups. The mean ages of the TTH and non-TTH groups were 49.41 (SD = 15.54) years and 49.11 (SD = 15.78) years, respectively. Compared with participants without TTH, patients with TTH had a higher prevalence of comorbidities and medication usage, including comorbidities of migraine, diabetes, IDA, depression, anxiety, sleep disorder, Parkinson disease, and renal disease and use of medications such as antidepressants, antipsychotics, antihistamines, and antiemetics.

The results of the log-rank test and the cumulative incidence curve of RLS, as shown in Figure 1, indicated that a significantly higher incidence rate of RLS was exhibited by the patients with TTH than by those without TTH ($P < .001$).

During an average 7.83 years of follow-up period, 118 patients in the TTH group and 182 patients in the non-TTH group developed RLS (Table 2). The incidence density rates of RLS for the TTH and non-TTH groups were 9.61 and 3.76 per 10 000 person-years, respectively. After adjustment for sex, age, comorbidity, and medications, the TTH group exhibited a 1.57-fold (95 % CI = 1.22–2.02) higher risk of developing RLS than the non-TTH group did. Multivariate analysis showed that patients with IDA, depression, anxiety, sleep disorder, and Parkinson disease were associated with a significantly higher risk of RLS compared with patients without these conditions (adjusted HR = 1.77, 95% CI = 1.03–3.05; 1.64, 1.18–2.30; 1.64, 1.20–2.25; 1.56, 1.18–2.05; and 4.37, 2.74–6.96, respectively). In addition, patients using anti-psychotics had a significantly higher risk of RLS than those not using anti-psychotics (adjusted HR = 9.95, 95% CI = 7.18–13.78).

Sex stratification showed that both women and men with TTH had a greater risk of developing RLS than those without TTH (adjusted HR = 1.49, 95 % CI = 1.10–2.01 and adjusted HR = 1.81, 95 % CI = 1.14–2.89, respectively) (Table 3). Age

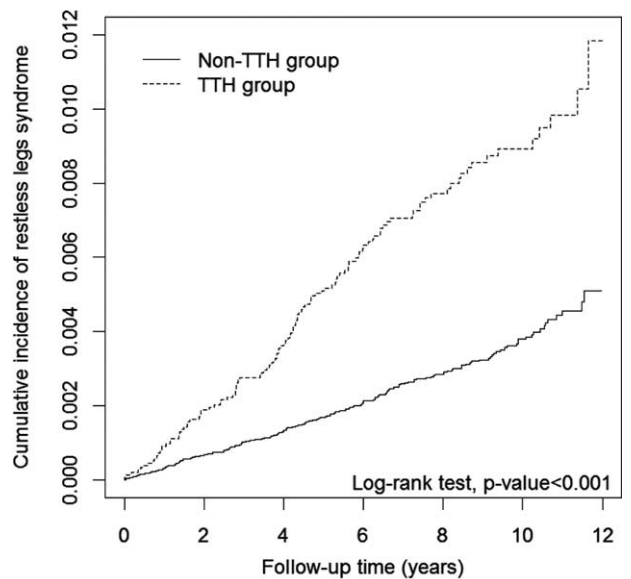


FIGURE 1. Cumulative incidence curves of restless legs syndrome for groups with and without tension-type headache. TTH = tension-type headache.

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

Characteristics	Event No.	Person-Years	IR	HR (95% CI)	
				Univariate	Multivariate [†]
TTH					
No	182	484,383	3.76	1.00	1.00
Yes	118	122,808	9.61	2.55 (2.02–3.22) ^{***}	1.57 (1.22–2.02) ^{***}
Sex					
Women	209	410,841	5.09	1.00	1.00
Men	91	196,350	4.63	0.92 (0.72–1.17)	0.96 (0.75–1.23)
Age, years					
20–39	75	187,721	4.00	1.00	1.00
40–59	115	271,236	4.24	1.06 (0.79–1.42)	0.94 (0.70–1.26)
≥ 60	110	148,234	7.42	1.87 (1.39–2.51) ^{***}	1.21 (0.88–1.67)
Comorbidity					
Migraine					
No	277	583,710	4.75	1.00	1.00
Yes	23	23,480	9.80	2.08 (1.36–3.18) ^{***}	0.80 (0.51–1.24)
Diabetes					
No	263	555,659	4.73	1.00	1.00
Yes	37	51,531	7.18	1.53 (1.08–2.15) [*]	0.99 (0.69–1.42)
IDA					
No	286	595,448	4.80	1.00	1.00
Yes	14	11,742	11.92	2.51 (1.47–4.30) ^{***}	1.77 (1.03–3.05) [*]
Depression					
No	233	576,890	4.04	1.00	1.00
Yes	67	30,301	22.11	5.54 (4.22–7.27) ^{***}	1.64 (1.18–2.30) ^{**}
Anxiety					
No	231	567,468	4.07	1.00	1.00
Yes	69	39,723	17.37	4.36 (3.33–5.71) ^{***}	1.64 (1.20–2.25) ^{**}
Sleep disorder					
No	182	505,917	3.60	1.00	1.00
Yes	118	101,274	11.65	3.31 (2.62–4.18) ^{***}	1.56 (1.18–2.05) ^{**}
Parkinson’s disease					
No	278	603,545	4.61	1.00	1.00
Yes	22	3645	60.35	13.35 (8.65–20.63) ^{***}	4.37 (2.74–6.96) ^{***}
Renal disease					
No	264	559,284	4.72	1.00	1.00
Yes	36	47,906	7.51	1.60 (1.13–2.27) ^{**}	0.94 (0.65–1.35)
Medications					
Antidepressant					
No	239	584,676	4.09	1.00	1.00
Yes	61	22,514	27.1	6.68 (5.04–8.84) ^{***}	0.81 (0.56–1.18)
Antipsychotic					
No	212	593,112	3.57	1.00	1.00
Yes	88	14,078	62.5	17.59 (13.72–22.56) ^{***}	9.95 (7.18–13.78) ^{***}
Antihistamines					
No	261	571,105	4.57	1.00	1.00
Yes	39	36,085	10.8	2.38 (1.70–3.33) ^{***}	1.39 (0.98–1.97)
Antiemetics					
No	282	596,360	4.73	1.00	1.00
Yes	18	10,830	16.6	3.53 (2.19–5.68) ^{***}	1.07 (0.64–1.76)

CI = confidence interval, HR = hazard ratio, IDA = iron deficiency anemia, IR = incidence density rate, per 10000 person-years, TTH = tension-type headache.

[†] Adjusted for tension-type headache, sex, age (categorical), comorbidity, and medications in Cox proportional hazards regression.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

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

Characteristics	Tension-Type Headache						Compared to Non-TTH Group	
	No			Yes			HR (95% CI)	
	Event No.	Person-Years	IR	Event No.	Person-Years	IR	Crude	Adjusted [‡]
Sex								
Women	131	327,782	4.00	78	83,058	9.39	2.34 (1.77–3.10) ^{***}	1.49 (1.10–2.01) ^{**}
Men	51	156,600	3.26	40	39,750	10.06	3.09 (2.04–4.67) ^{***}	1.81 (1.14–2.89) [*]
Age, years								
20–39	31	149,831	2.07	44	37,889	11.61	5.61 (3.55–8.89) ^{***}	2.60 (1.53–4.42) ^{***}
40–59	76	216,677	3.51	39	54,559	7.15	2.03 (1.38–2.99) ^{***}	1.18 (0.77–1.80)
≥ 60	75	117,875	6.36	35	30,359	11.53	1.81 (1.21–2.70) ^{**}	1.31 (0.86–2.00)
Comorbidity status [†]								
No	75	349,075	2.15	35	58,871	5.95	2.74 (1.83–4.09) ^{***}	2.32 (1.54–3.50) ^{***}
Yes	107	135,308	7.91	83	63,936	12.98	1.64 (1.23–2.18) ^{***}	1.26 (0.93–1.69)

CI = confidence interval, HR = hazard ratio, IR = incidence density rate, per 10,000 person-years, TTH = tension-type headache.

[†] Patients with any one of migraine, diabetes, iron deficiency anemia, depression, anxiety, sleep disorder, Parkinson’s disease, and renal disease were classified as the comorbidity group.

[‡] Mutually adjusted for sex, age (continuous), comorbidity, and medications in Cox proportional hazards regression.

^{*} $P < 0.05$.

^{**} $P < 0.01$.

^{***} $P < 0.001$.

stratification showed a higher risk of developing RLS in the 20- to 39-year-old subgroup of patients with TTH than in those without TTH (adjusted HR = 2.60, 95% CI = 1.53–4.42). Comorbidity stratification showed a significantly higher risk of developing RLS in patients with TTH than in those without TTH in patients with no comorbidities (adjusted HR = 2.32, 95% CI = 1.54–3.50).

DISCUSSION

To the best of our knowledge, this study is the first nationwide, large-scale, population-based, longitudinal study to demonstrate an increased (1.57-fold higher) subsequent risk of RLS in the TTH group versus the non-TTH group, after adjustment for age, sex, comorbidities, and medications. We found that patients with TTH in the 20- to 39-year-old subgroup showed the greatest magnitude of risk (2.60-fold) of developing RLS. Finally, regardless of the participants’ sex, the TTH group had a higher risk of RLS than that of the non-TTH group.

Our results are consistent with 2 previous studies analyzing the association between TTH and RLS.^{13,23} However, those studies were clinic-based, cross-sectional studies, whereas our study is a large-scale, nationwide, population-based study with a longitudinal design and a broad age range (20–60 years old), which makes our study more generalizable to the general population. Moreover, our study was designed specifically to consider possible confounding factors of RLS.

We found that potential comorbidities of RLS, such as migraine, diabetes, IDA, depression, sleep disorder, anxiety, and renal disease, were more prevalent in the TTH group than in the non-TTH group. Although previous studies have found that TTH may be comorbid with several psychiatric and medical conditions including major depression, generalized anxiety disorder, sleep disorders, panic disorder, and diabetes,²⁴ our result is consistent with the more robust evidence surrounding RLS and migraine. Furthermore, previous studies have shown

that, in the general population, 94% of patients with migraine have TTH and that 56% of these patients have frequent episodic TTH.²⁵ Although the patients with TTH in this study exhibited a higher prevalence of the aforementioned comorbidities with RLS than did the comparison cohort, multivariate Cox analyses demonstrated that TTH was still an independent factor for predicting the subsequent RLS risk.

Previous population-based studies on the incidence of RLS in the general population are scant.^{26,27} In our study, the annual incidence rate of RLS in our non-TTH group (3.76/10 000 person-y) was lower than that previously reported in a German cohort (14–43/1000 person-years).²⁶ This result may relate to the overall lower prevalence of RLS reported for Asian populations versus European and North American (non-Asian) populations.^{9,28} Restless legs syndrome showed no obvious sex-based predisposition in our study cohort (Table 2), which is unusual because many studies have reported a higher prevalence of RLS in females.^{10,29} Therefore, our study cohort results should be interpreted cautiously, acknowledging the effects of ethnic differences, methodological differences, and clinical settings. Nevertheless, in this study, our findings of a higher adjusted hazard ratio of RLS with the comorbidities of IDA, depression, anxiety, sleep disorder, or Parkinson disease, as well as the usage of antipsychotics (Table 2), are in agreement with earlier documentation of these conditions as potential risk factors for RLS.^{12,27,30}

Notably, the TTH subgroup analysis showed a significantly higher risk of RLS in the 20- to 39-year-old subgroup of patients with TTH than in the patients without TTH, even relative to the other subgroups. Furthermore, although the higher risk of RLS in the TTH group was not influenced by a patient’s sex after adjustment for multivariable effects, this result is different from the results of a previous Turkish study,²³ which demonstrated that RLS is biased toward female and older-age patients with TTH. However, interpretation of these differences warrants using the same caution as described above,

acknowledging possible ethnic differences, methodological differences, and differing clinical settings. For example, the Turkish study was a clinic-based study with a small sample size that enrolled patients with TTH and anemia. In our results, the risk of RLS in the TTH group was higher in participants without comorbidities (Table 3). We interpret this as reinforcing our finding that TTH is an independent potential risk factor associated with RLS.

Several mechanisms may potentially underlie the pathophysiological connection between TTH and RLS. First, previous studies have suggested that TTH pathophysiology stems from serotonin and other neurotransmitters.³¹ Serum serotonin levels were associated with pain thresholds in patients with chronic pain³² and were altered in TTH patients.^{33,34} However, RLS has previously been linked to disturbances of the A11 (dorsal-posterior hypothalamic) dopaminergic system.³⁵ However, using SPECT imaging, Jho et al found that decreased pontine and medullary serotonin transporter availability correlated with the increased severity of RLS, suggesting that RLS may entail brainstem serotonergic tone.³⁶ Collectively, these data suggest that a relationship between TTH and RLS may be associated with dysfunctional dopaminergic/serotonergic interactions in the deep brain and brainstem. Second, deficient antinociceptive activity in supraspinal structures of the central nervous system (ie, decreased descending pain inhibition) may contribute to the increased pain sensitivity in patients with chronic TTH.³⁷ Moreover, the pathophysiology of RLS could also include disturbed supraspinal pain modulation areas or descending dopaminergic pathways.³⁸ Therefore, because of the potential shared mechanism of impaired supraspinal pain modulation, RLS may modulate or influence the central pain threshold to precipitate or worsen TTH-related pain. Furthermore, the converse could be true. However, further study is necessary to explore these hypotheses.

There are several clinical implications to be considered. First, TTH should be viewed as a potential risk factor for RLS, in addition to migraine and other risk factors that are better known. Therefore, patients with TTH should be evaluated for RLS both initially and at follow-up. Second, our data indicate that clinicians should consider the RLS risk in patients with TTH regardless of their sex or comorbidity status, thus facilitating the early detection of RLS. Third, though RLS may begin at any age, most individuals with RLS are >40 years old.³⁹ However, our results showed that the 20- to 39-year-old subgroup of TTH patients had a greater risk of developing RLS. Thus, we believe that the influence of age on the TTH–RLS relationship requires further study, but clinicians should still be aware of the potential risk of subsequent RLS development in younger patients with TTH. Finally, previous studies have pointed to a possible common genetic origin for migraine and RLS, located on chromosome 14q21;⁴⁰ however, the involvement of genes in the etiology of TTH and RLS has not yet been fully understood. Future studies for finding a common genetic locus between these 2 conditions are warranted.

The major strength of this study is its design, which allows a large sample size and sufficient statistical power to explore the TTH–RLS relationship and a variety of covariates. In addition, the diagnostic aspects of the study were extremely rigorous; headache diagnoses were identified according to the International Classification of Headache Disorders, 2nd Edition (ICHD-II) criteria, and RLS was diagnosed by neurologists, rather than through self-reports or questionnaires. The criteria for diagnosis of RLS in this study complied with the

recommendations of the International RLS Study Group (IRLSSG),⁸ that is, when all 4 essential criteria were met. The 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 of Taiwan. All insurance claims should be scrutinized and coded by medical reimbursement specialists and peer reviewed according to the criteria for diagnosis of RLS in this study. If these doctors or hospitals commit errors in diagnoses or coding, they will be punished with a lot of penalties. Therefore, the diagnoses and coding of restless legs syndrome in this study were highly reliable. Inclusion in the TTH group required diagnosis by a neurologist, minimizing the likelihood of mistaken diagnoses. A prior study determined that neurologists' diagnoses of headache disorder according to the ICHD-II criteria in Taiwan were >91% accurate.⁴¹ Furthermore, the National Health Insurance Administration in Taiwan routinely audits samples of medical charts, assessing their accuracy in detail; the reliability and validity of the NHI research database for epidemiologic investigations have been reported.⁴² We believe that these diagnostic selection criteria are more precise than patient recall assessed using a questionnaire. Finally, our longitudinal design facilitated assessing the potential temporal relationship between TTH and RLS.

This study had some limitations. First, our TTH cohort comprised only active TTH patients seeking medical treatment throughout the study period. However, the clinical symptoms of TTH can be mild or infrequent; therefore, some control participants with TTH who did not seek medical assistance may have been misclassified. Consequently, the risk of developing RLS in patients with TTH may have been underestimated. Second, although the diagnoses did rely on data from practicing neurologists, we could not verify diagnoses through face-to-face interviews with patients, which also made additional clinical information for RLS or TTH (such as duration and frequency of TTH or prognoses) unavailable to us. Thus, we could not differentiate chronic from episodic TTH or determine whether the severity of RLS was associated with TTH frequency, duration, or other headache characteristics. Third, the NHIRD dataset is derived from an administrative database that lacks detailed clinical data, such as RLS severity, neuroimaging, or other laboratory results. Therefore, the precise diagnosis of idiopathic or secondary RLS was not available in this database. Furthermore, the aforementioned medications may induce or exacerbate the symptoms of RLS.⁴³ In our study, the medication records were based on the NHIRD databases, which did not include information on over-the-counter medications or treatment compliance. Thus, it is difficult to determine whether the RLS symptoms in these patients were secondary to medication use. Finally, our study demonstrated only a temporal association between TTH and the risk of subsequently developing RLS; the causal relationship between these 2 disorders warrants further investigations.

In conclusion, this study demonstrated a temporal association between TTH and the risk of subsequently developing RLS, particularly in patients with TTH aged 20 to 39 years, regardless of the participants' sex. Although the pathophysiological mechanism linking TTH and RLS remains unclear, this finding may provide further insight for clinicians encountering a difficult diagnosis. These findings suggest that in addition to migraine patients, screening TTH patients for RLS is also necessary. Additional studies are necessary to examine both the mechanism and causality of this relationship.

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