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ORIGINAL ARTICLE

Prevalence of restless legs syndrome in individuals with migraine: a systematic review and meta-analysis of observational studies

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Abstract

Objective Recent studies have shown an association between migraine and restless legs syndrome (RLS), but RLS prevalence among individuals with migraine differs substantially across studies. The present work aimed to comprehensively assess available evidence to estimate RLS prevalence among individuals with migraine and non-migraine controls.

Method Web of Science, PubMed, Embase, Chinese National Knowledge Infrastructure, Wanfang, and SinoMed databases were searched for observational and case-control studies of RLS prevalence among individuals with migraine. Eligible studies were meta-analyzed using Stata 12.0 software.

Results Pooled RLS prevalence in migraine was 19%, and the prevalence was lower in Asia (16%) than outside Asia (21%). Pooled RLS prevalence was 18.8% among individuals with migraine with aura, and 18.5% among individuals with migraine without aura; the RLS prevalence in migraine with aura (MA) was higher than that of migraine without aura (MO) (OR 1.17, 95%CI 1.01–1.34; $p = 0.037$). Pooled RLS prevalence in a case-control study was significantly higher among individuals with migraine (17.9%) than among non-migraine controls (7.1%) (OR 2.65, 95%CI 2.26–3.10; $p < 0.001$).

Conclusion Our meta-analysis provides the first reliable pooled estimate of RLS prevalence among individuals with migraine, and it provides strong evidence that RLS risk is higher among individuals with migraine than among controls.

Keywords Migraine · Restless legs syndrome · Prevalence · Meta-analysis

Hui Ren and Zhong Xu are co-corresponding author to this article.

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Introduction

Migraine is a common condition of chronic headache with a prevalence of 6–20% in the general population. Migraine typically presents as recurrent headache attacks described as unilateral, pulsating, moderate, or severe, and the attacks are aggravated by routine physical activity and are associated with nausea and/or photophobia [1]. Migraine has also been associated with some sleep disorders such as prolonged rapid eye movement (REM) [2], decreased arousal index [3], periodic or restless limb movements, and restless legs syndrome (RLS) [4]. Migraine disrupts work and routine activities, amounting to disability of daily life. Migraine appears to affect women 2–3 times more often than men [5, 6]. Approximately one third of individuals with migraine have attacks of migraine with aura (MA), while the remainder suffer migraine without aura (MO).

Many clinical and epidemiological studies have reported a close relationship between migraine and RLS [7–23], which is a sensory-motor neurological disorder in which individuals experience an urge to move their legs as well as other unpleasant sensations. These symptoms occur often at rest, especially in the evening, and they decrease during motor activity. RLS prevalence in the general population is higher among US and European Caucasians (7.34–9.72%) than among Asians (4.69%) or other non-Caucasian groups [24]. RLS prevalence appears to be higher among individuals with migraine than among controls, and RLS patients seem to show higher rates of migraine than controls [25]. However, these conclusions may be unreliable because RLS prevalence among individuals with migraine has been estimated at 11.3–33.3%, making it difficult to understand the epidemiology of RLS in detail or definitively conclude whether RLS is associated with migraine.

Here, we conducted a meta-analysis of available evidence to derive a reliable estimate of RLS prevalence among individuals with migraine and compare it to the prevalence among non-migraine controls. We also examined whether RLS prevalence differs between MO and MA individuals.

Methods

Search strategy

The following six databases were systematically searched for eligible studies published up to February 2018: PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure, Wanfang, and SinoMed. Search terms were combined text words and Medical Subject Headings (MESH) terms for headache and migraine ("headache" or "headache disorders" or "migraine" or "migraine disorders") with terms for restless legs syndrome ("restless legs syndrome" or "RLS").

Study selection criteria

To be included in the meta-analysis, studies had to [1] be observational studies with a cross-sectional, case-control, or cohort design analyzing RLS prevalence in adults with migraine; [2] diagnose migraine based on criteria of the International Classification of Headache Disorders (ICHD)-2 or -3, or confirmation by clinicians; [3] diagnose RLS based on criteria of the International Restless Legs Syndrome Study Group (IRLSSG) [26] and patient data obtained through questionnaires or clinical interviews; and [4] report RLS prevalence or sufficient data to calculate it. If more than one study evaluated the same cohort, only the study with the most complete data was included.

Studies were excluded if they [1] were editorials, reviews, case reports, letters without original data, commentaries, or critiques; [2] did not report RLS prevalence among individuals with migraine or supply enough data to calculate it; or [3] did not involve individuals with migraine or RLS.

Data extraction

Two investigators (XL Yang and Bin Liu) conducted literature searches and extracted data independently. Inconsistencies were resolved by discussion with a third reviewer (Zhong Xu). The following data were extracted from studies: surname of the first author, year of publication, country of study cohort, diagnostic criteria, age, and RLS prevalence in cases and/or controls (in studies with a case-control design).

Statistical analysis

Data were meta-analyzed using Stata 12.0 (StataCorp, USA). We evaluated RLS prevalence among individuals with migraine based on country. We compared RLS prevalence between individuals with migraine and controls in terms of the odds ratio (OR) and associated 95% confidence interval (CI). Significance in all analyses was defined as $p < 0.05$.

I^2 was calculated to evaluate the heterogeneity among studies: $I^2 < 25\%$ was considered as absence of heterogeneity (homogeneity); $25\% \le I^2 < 50\%$, low heterogeneity; $50\% \le I^2 < 75\%$, moderate heterogeneity; and $I^2 \ge 75\%$, substantial heterogeneity [27]. A fixed-effect model was used to meta-analyze pooled data classified as homogeneous or of low heterogeneity. A random-effect model was used to meta-analyze data classified as of moderate or substantial heterogeneity [28]. Egger's and/or Begg's tests were used to evaluate publication bias ($p > 0.05$ indicate no publication bias) [28, 29].

Results

Literature search and included studies

After searching the six databases and removing duplicates, 84 potentially eligible articles were identified (Fig. 1). After eliminating 55 articles based on the title and abstract, the remaining 28 were read in full and 14 were excluded because they did not provide RLS prevalence among individuals with migraine or report enough data to calculate it ($n = 7$), because they included patients of only one gender ($n = 2$), only patients with severe migraine were involved [4] ($n = 1$), the diagnosis of RLS did not follow the IRLSSG criteria [10] ($n = 1$), using the same patient cohort [15] ($n = 1$), or because they included patients under 18 ($n = 2$).

The remaining 14 studies involving 6499 individuals with migraine and 3651 controls were included in the meta-analysis (Table 1). Of all studies, six were performed in Asia and eight in Europe or the Americas. All 14 studies investigated RLS prevalence in individuals with migraine, of which nine compared these individuals with controls using a case-control design. Thirteen studies reported the RLS prevalence in migrainous including both MA and MO individuals. Twelve studies investigated RLS prevalence in MA individuals, and 11 studies investigated it in MO individuals. Eleven studies reported RLS prevalence in both MA and MO individuals.

RLS prevalence among all patients with migraine

Detailed RLS prevalence among individuals with migraine from different countries is listed in Table 1. Among the 13 studies reporting RLS prevalence among individuals with migraine, high heterogeneity was detected ($I^2 = 95.9\%$, $p < 0.001$), so a random-effect model was used to meta-analyze the data. This analysis indicated a pooled prevalence of 19% (95%CI 0.14–0.24; Fig. 2). Sensitivity analysis showed that none of the 14 studies significantly affected the results (Supplemental Fig. 1). The funnel plot was visually symmetrical, suggesting no significant publication bias (Supplemental Fig. 2). A similar conclusion was suggested by Egger's test ($p = 0.951$) and Begg's test ($p = 0.131$).

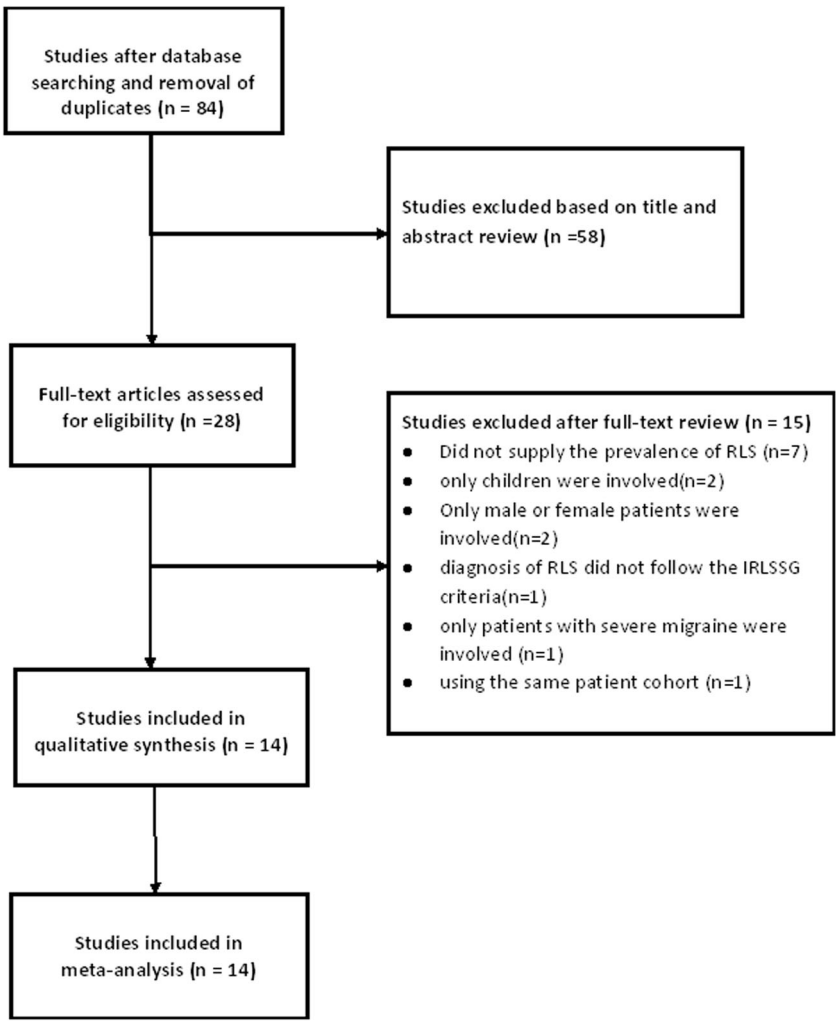

Fig. 1 Flow diagram for publication selection in the present meta-analysis

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Country/district	Diagnosis of M	Diagnosis of RLS	*n*	Age of M, (year)	Females in RLS	RLS in M, *n* (%)	RLS in MA, *n* (%)	RLS in MO, *n* (%)	RLS in controls, *n* (%)
Rhode [18]	2007	Germany	ICHD-2	IRLSSG	411	41.7 ± 12.5	47/71 (66.2)	71/411 (17.3)	11/120 (9.2)	60/321 (18.7)	23/411 (5.6)
d'Onofrio [12]	2008	Italy	ICHD-2	IRLSSG	124	NR	95/124 (76.6)	29/124 (23.4)	2/10 (20)	27/114 (23.7)	NR
Chen [8]	2010	Taiwan	ICHD-2	IRLSSG	772	42.16 ± 13.3	76 /88 (86.4%)	88/772 (11.4)	4/48 (4.5%)	29/267 (33%)	NR
Suzuki [21]	2011	Japan	ICHD-2	IRLSSG	262	38.2 ± 13.0	32/36 (88.9)	36/262 (13.7)	9/67 (13.4)	27/195 (13.8)	3/163 (1.8)
d'Onofrio [13]	2011	Italy	ICHD-2	IRLSSG	63	38.2 ± 14	3/6 (50)	NR	6/63 (9.5%)	NR	NR
Kanki [7]	2011	Japan	ICHD-2	IRLSSG	188	NR	NR	40/188 (21.3)	8/24 (33.3)	32/164 (19.5)	NR
Lucchesi [17]	2012	Italy	ICHD-2	IRLSSG	277	41.2 ± 13.5	47/63 (74.6)	63/277 (22.7)	8/34 (23.5)	55/243 (22.6)	15/200 (7.5)
De Martino [30]	2012	Italy	ICHD-2	IRLSSG	136	NR	NR	44/136 (32.4)	NR	NR	NR
Ferreira [14]	2013	Brazil	ICHD-2	IRLSSG	72	42.5	NR	18/72 (25)	8/24 (33.3)	10/48 (20.8)	6/72 (8.3)
Cho [9]	2015	South Korea	ICHD-2	IRLSSG	143	19–69	NR	13/143 (9%)	NR	NR	51/1442 (3.5)
Van Oosterhout [23]	2016	Netherlands	ICHD-IIIb	IRLSSG	2385	45.1 ± 11.6	NR	403/2384 (16.9)	170/919 (18.5)	233/1465 (15.9)	31/332 (9.3)
Lin [16]	2016	Taiwan	ICHD-IIIb	IRLSSG	372	NR	NR	24/372 (6.5)	12/111 (10.8)	12/261 (4.6)	5/133 (3.8)
Valente [22]	2017	Italy	ICHD-2	IRLSSG	180	41.0 ± 13.2	24/29 (82.8)	29/180 (16.1)	12/54 (22.2)	17/126 (13.5)	11/180 (6.1)
Muayqil [31]	2018	Saudi Arabia	ICHD-III	IRLSSG	1115	30.99 ± 10.76	NR	389/1115 (34.9)	154/410 (37.6)	235/699 (33.6)	129/718 (18.0)

Values separated by a solidus mark refer to "RLS/patients with migraine or controls." *ICHD*, International Classification of Headache Disorders; *IRLSSG*, International Restless Legs Syndrome Study Group; *M*, migraine (with or without aura); *MA*, migraine with aura; *MO*, migraine without aura; *NR*, not reported; *RLS*, restless legs syndrome

Random-effect meta-analysis further revealed lower RLS prevalence among individuals with migraine in Asia (16%, 95%CI 0.07–0.26) than outside Asia (21%, 95%CI 0.17–0.24; Fig. 2).

RLS prevalence among MA or MO individuals

Twelve studies investigated RLS prevalence in individuals with MA, and prevalence ranged from 8.3 to 37.6%. High heterogeneity ($I^2 = 89.3\%$) was found across the studies, so random-effect meta-analysis was performed. This analysis indicated a pooled prevalence of 18.8% among MA individuals (95%CI 0.125–0.251, Supplemental Fig. 3). Eleven studies were meta-analyzed using a random-effect model because of moderate heterogeneity ($I^2 = 71.5\%$), giving a pooled prevalence of 18.5% (95%CI 0.126–0.244) among MO individuals (Supplemental Fig. 4).

Eleven studies reported RLS prevalence in both MA and MO individuals, and low heterogeneity ($I^2 = 36.5\%$) was found among these studies. Fixed-effect meta-analysis shows the RLS prevalence in MA was higher than that of MO (OR 1.17, 95%CI 1.01–1.34; $p = 0.037$, Fig. 3). The funnel plot was visually symmetrical, suggesting no significant publication bias (Supplemental Fig. 5). A similar conclusion was suggested by Egger's ($p = 0.938$) and Begg's tests ($p = 0.973$).

Comparison of RLS prevalence between individuals with migraine and controls

Nine studies with a case-control design comparing individuals with migraine and controls were meta-analyzed using a fixed-effect model because of the absence of heterogeneity ($I^2 =$ 19%; Table 1). Pooled RLS prevalence was significantly higher in the presence of migraine (17.6%) than in the controls (7.1%) (OR 2.65, 95%CI 2.26–3.10; $p < 0.001$; Fig. 4). The funnel plot was visually symmetrical (Supplemental Fig. 6), and Egger's and Begg's tests ($p = 0.211$) were associated with $p > 0.05$ ($p = 0.140$), suggesting no significant risk of publication bias.

Discussion

The present study shows the pooled prevalence of RLS in migraine was 19% (16% among Asians and 21% among non-Asians). The RLS prevalence was higher in MA than in MO. Meta-analysis of case-control studies showed that RLS prevalence was much higher among individuals with migraine than among controls.

Our meta-analysis of 11 case-control studies indicates 2.65-fold higher RLS prevalence in individuals with migraine than in controls. These results are consistent with the conclusions of a systematic review in 2014 [32] and much robust

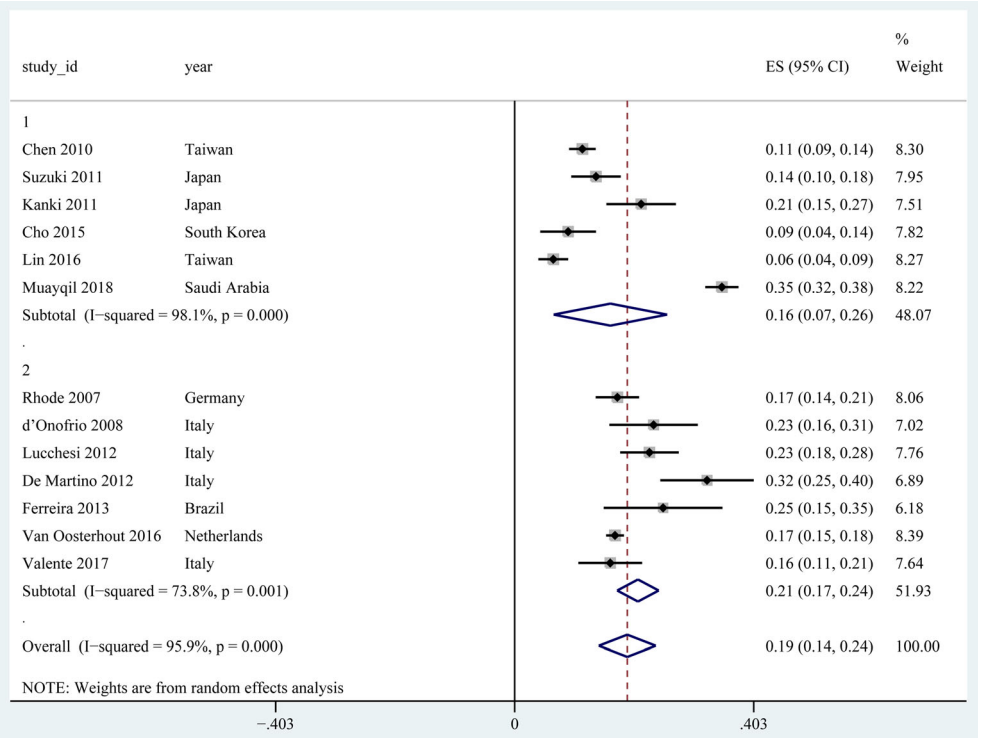

Fig. 2 Forest plot of RLS prevalence among individuals with migraine in the entire study set (19%), in Asia (16%), or outside Asia (21%). The *x*-axis indicates the 95% confidence interval. ES, effect size

than a study reporting 1.42-fold higher risk of RLS among individuals with migraine in a population-based cohort study in Taiwan [33]. However, how RLS might be associated with migraine is unclear, especially since the two disorders appear to be neurologically distinct. It is possible, however, that both involve dysfunction of the dopaminergic system. RLS is thought to involve the A11 dopaminergic nucleus of the dorsal-posterior hypothalamus, which is the sole source of spinal dopamine [34]. Consistent with the RLS phenotype in humans, A11-lesioned rats show hyperactive behavior, increased wakefulness across the rest-activity cycle, and a reduced sensory threshold. Abnormal firing of A11/A13 neurons during premonitory symptoms contributes to the development of migraine headache and the associated nausea and vomiting [35]. In addition, both RLS and migraine may involve iron deficiency [36], although more studies are needed

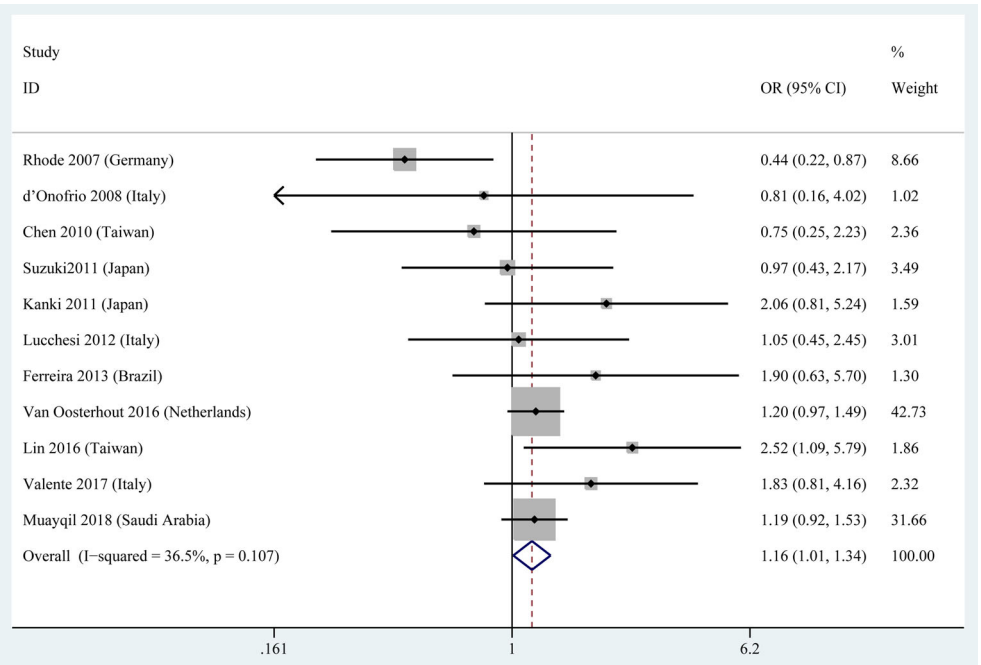

Fig. 3 Forest plot of RLS prevalence among MA or MO individuals, based on data from 11 studies that compared the two types of individuals in parallel. The RLS prevalence in MA was higher than that in MO ($p > 0.05$). The *x*-axis indicates the 95% confidence interval. ES, effect size

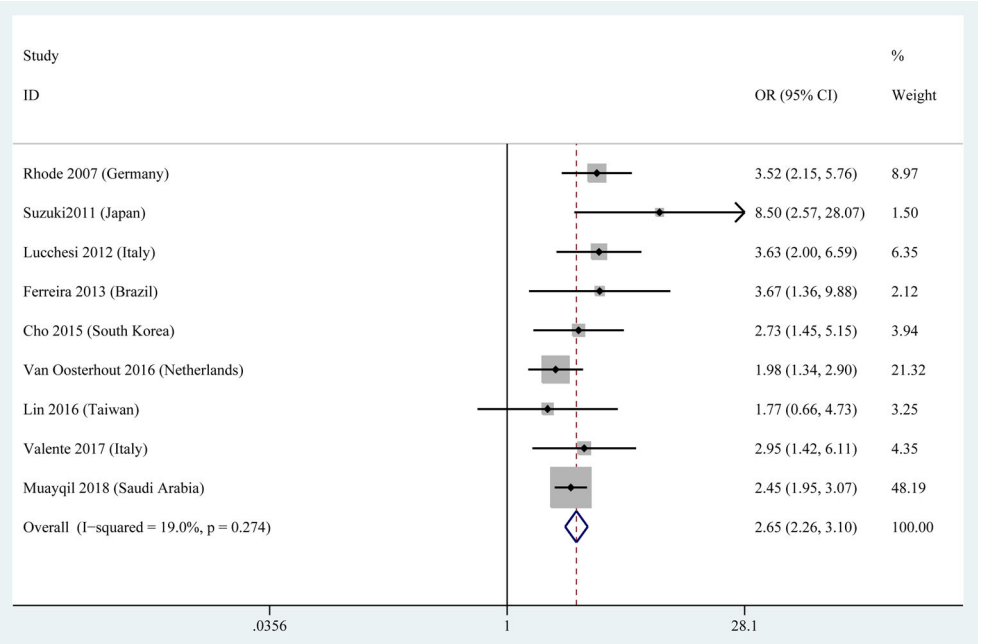

Fig. 4 Forest plot of RLS prevalence in individuals with migraine or in controls, based on case-control studies. The prevalence was significantly higher among individuals with migraine ($p < 0.001$). The *x*-axis indicates the 95% confidence interval. ES, effect size

to verify this. Moreover, the prodromal symptomatology (mood changes, yawning, drowsiness, food craving), accompanying symptoms (nausea, vomiting, hypotension), and postdromal symptoms (mood changes, drowsiness, tiredness) of migraine may be related to dopaminergic activation [37]. Interestingly, dopaminergic agonist was effective to prodromal symptomatology of migraine. RLS symptoms disappear after treatment with dopaminergic agonist, and treating patients with concomitant RLS and migraine with immediate-release pramipexole improves not only RLS symptoms but also headache frequency and RLS symptoms [38]. These various studies point to common elements in the pathophysiology of RLS and migraine.

Our results also show the RLS prevalence in patient with migraine was lower in Asian (16%) countries than in non-Asian countries (21%). Actually, the RLS prevalence in general population also shows a similar geographic discrepancy [24]. Discrepancies in study design and cultural barriers may account for these differences; however, the RLS prevalence was higher in North American and European populations than in those of African descent [39]. Thus, the ethnic or genetic discrepancies may be the foremost reason.

The available evidence seems to indicate significant difference in RLS prevalence between MA and MO individuals. Pooled RLS prevalence was 18.8% in MA individuals and 18.5% in MO individuals. Meta-analysis of 11 studies reporting RLS prevalence was higher in MA group than in MO group ($p = 0.037$). What are the detailed reasons for this phenomenon still to be elusived.

There were some limitations in our study. The risk of publication bias always exists, although we did search a range of international and Chinese databases without language constraints, and Egger's and Begg's tests suggested no significant risk of publication bias. Although large, our total sample of 6499 individuals with migraine and 3651 controls may still be subject to random error. Since our meta-analysis examined ethnically different populations from various countries, heterogeneity may affect our results. In addition, all the studies in our meta-analysis applied the older four-item IRLSSG diagnostic criteria, without the new fifth item, which stipulates that an individual cannot be diagnosed with RLS unless he or she presents typical symptoms. Future work should apply this new criterion.

Despite these limitations, the present meta-analysis provides the first relatively reliable estimate of RLS prevalence among individuals with migraine, which is higher than the prevalence among controls. These findings should be extended in large, multi-site observational studies. The results may inspire clinicians to pay more attention to RLS in migraine and to explore effective treatments for both diseases based on potential links in their pathophysiology.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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