Sleep Medicine 57 (2019) 21–29

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

The association between migraine and restless legs syndrome: an updated systematic review and meta-analysis

Jing Wang [a, b, 1], Yinghui Gao [c, d, e, 1], Lin Liu [f, 1], Weihao Xu [g], Peicheng Zhang [h], Yu Liu [h], Xiaoshun Qian [f, **], Shengyuan Yu [a, b, *]

[a] School of Medicine, Nankai University, Tianjin, 300071, China
[b] Department of Neurology, Chinese PLA General Hospital, Beijing, 100853, China
[c] Peking University People's Hospital, Beijing, 100044, China
[d] Peking University Hepatology Institute, Beijing, 100044, China
[e] Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Beijing, 100044, China
[f] Department of Respiratory Disease, Nanlou Division, Chinese PLA General Hospital, Beijing, 100853, China
[g] Department of Geriatric Cardiology, Nanlou Division, Chinese PLA General Hospital, Beijing, 100853, China
[h] Department of Retired Cadre, No. 51 Division, Beijing Military Command, Beijing, China

ARTICLE INFO

Article history:
Received 8 August 2018
Received in revised form
26 November 2018
Accepted 3 January 2019
Available online 2 February 2019

Keywords:
Migraine
Restless legs syndrome
Meta-analysis

ABSTRACT

Objective: This study aims to gain further insight into the association between migraine and restless legs syndrome (RLS).
Methods: A literature search of PubMed, Embase, and Web of Science was performed for studies investigating the association between any migraine and RLS; a meta-analysis of eligible studies was conducted to determine a pooled effect estimate for the association.
Results: Fifteen studies were included in this meta-analysis. The studies differed in methodology, but all investigated the association between migraine and RLS. Pooled RLS prevalence was 17.0% [95% confidence interval (CI) 15.0%–20.0%] among migraineurs, and 7.0% (95% CI 5.0%–8.0%) among no migraine individuals. Pooled analyses showed that migraine was associated with RLS, but effect estimates were substantially higher in case-control studies [pooled odds ratio (OR) = 3.77, 95% CI 2.73–5.21; $I^2 = 50.1\%$] than in cross-sectional studies (pooled OR = 1.25, 95% CI 1.11–1.41; $I^2 = 34.2\%$). Subgroup analyses were not conducted to find potential factors that affect this association because of too few available studies.
Conclusions: This updated meta-analysis confirms the association between migraine and RLS. Future studies should specifically investigate the potential effects of gender, age, aura status, and type (episodic or chronic) of migraine on the association between the two disorders.

1. Introduction

Migraine is a chronic, severe, and disabling brain condition, listed as the sixth most disabling disorder and the most disabling of all neurological disorders in the world [1]. Migraine affects approximately 11.7% of the general population, predominantly females [2]. It is characterized by recurrent attacks of unilateral throbbing head pain, associated vegetative symptoms, and hypersensitivity of various central nervous functional systems [3]. Accumulating evidence suggests that some diseases are associated with migraines, including cardiovascular disease, pain disorders, and psychiatric disorders [4,5]. In addition, epidemiological and clinical studies have shown that sleep disorders, particularly restless legs syndrome (RLS), are comorbid with migraine [6].

RLS is a common sleep-related sensorimotor disorder with a female predominance similar to migraine [7]. It is characterized by an overwhelming urge to move the legs, especially when at rest and during nighttime, with associated uncomfortable sensations in the legs [8]. A shared origin and pathophysiological mechanisms for migraine and RLS have been proposed, involving dopaminergic dysfunction, disturbance of iron metabolism, and common genetic factors [9–11].

* Corresponding author. No. 28, Fuxing Road, Haidian District, Beijing, 100853, China.
** Corresponding author. No. 28, Fuxing Road, Haidian District, Beijing, 100853, China.
E-mail addresses: qxspla301@126.com (X. Qian), yusy301@hotmail.com (S. Yu).
[1] These authors contributed equally to this study.

https://doi.org/10.1016/j.sleep.2019.01.027
1389-9457/

During the past two decades a number of studies have investigated the association between migraine and RLS in the general population [12–26]. A previous systematic review summarized the relevant studies and concluded that RLS was an important comorbidity of migraine [3]. As many new studies have been published since the release of the previous meta-analysis, we decided to conduct an updated systematic review and meta-analysis of all currently available evidence investigating the association between migraine and RLS to gain further insight into this association.

2. Methods

2.1. Study design

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27]. Registration of the review protocol was not undertaken. We did not apply for approval from an ethics committee since this study only used data from the published medical literature.

2.2. Data sources and searches

The PubMed, Embase, and Web of Science databases were systematically searched from their inception to 20 June 2018 for relevant studies using the following search terms: ((migraine) OR headache) AND (restless legs syndrome OR (RLS)). Additionally, a manual search of references of included studies and reviews was conducted to find more relevant articles. The literature search was conducted independently by two investigators.

2.3. Study selection

Studies were eligible for inclusion in this review if they: (a) investigated the association between migraine and RLS; (b) had a case-control, cross-sectional, or cohort design; (c) provided prevalence estimates of RLS among migraineurs or no-migraine participants or effects estimates with 95% confidence intervals (CI) for the association of the two disorders in the study population. Studies that investigated the migraine prevalence among RLS patients and control patients or no-RLS participants were excluded from this review.

Two investigators first independently assessed the eligibility of the identified literature by title and abstract reading. Potentially eligible articles were then read in full and independently by the same investigators. Discrepancies between investigators were rechecked and, if necessary, discussed with a third investigator until consensus was achieved.

2.4. Data extraction

Two investigators independently extracted and summarized the data of the included studies. Extracted data included the author's name, country of study origin, year of publication, study design, source population, sample size, mean age of study participants, gender distribution, migraine diagnostic criteria, study categories, RLS diagnostic criteria, and confounders adjusted in the statistical analysis. Effects estimates with 95% CIs for the association between the two disorders were extracted for further meta-analysis to calculate the pooled effect estimate of the association. If effect estimates from various models were presented, those derived from the model with the maximum number of confounders adjusted were selected. If effect estimates were not presented, the number of participants with and without migraine, and the number of participants with and without RLS among those with and without migraine were extracted to calculate the effect estimates and 95% CIs. We contacted one study's (published as an abstract) author to obtain additional data; however, we received no response.

2.5. Quality assessment

Quality assessment was performed according to the Newcastle–Ottawa Quality Assessment Scale (NOS) [28] with modified criteria for cross-sectional studies [29]. Scores ranged from 0 to 9 points for case-control and cohort studies and from 0 to 10 points for cross-sectional studies, with higher scores indicating higher study quality. We considered NOS scores of 0 to 3, 4 to 6, and $\geq$7 as low, medium, and high quality, respectively.

2.6. Statistical analysis

Included studies were pooled to gain overall RLS prevalence among migraine patients and no migraine individuals. To further investigate the association between migraine and RLS, we first calculated the odds ratios (ORs) and 95% CIs for the association between the two disorders in case-control studies not providing effect estimates. Then we pooled the ORs and 95% CIs of included studies according to study design because the ORs and 95% CIs of case-control studies adjusted for no confounders and those of cross-sectional studies were multiply adjusted; the results of differently designed studies reflected different strengths of association. Random-effects models were used to perform the pooled analyses because of moderate or substantial heterogeneity. Heterogeneity of included studies was assessed using a chi-square test and I-squared (I^2) statistic. Statistical heterogeneity was considered significant when $P < 0.10$ for the χ^2 test or $I^2 > 50\%$ [30]. Subgroup analyses by mean age of study participants and study quality were performed to explain the high heterogeneity in the meta-analysis of case-control studies. To test for publication bias, we used the statistical method described by Begg and Mazumdar [31]. Sensitivity analyses were performed by excluding one study each time and rerunning the analysis to verify the robustness of the overall results. A sensitivity analysis for meta-analysis of case-control studies was also performed by omitting studies that used self-administered questionnaires for RLS ascertainment. A two-tailed P-value < 0.05 was considered statistically significant. All analyses were carried out using STATA v.12.0 (Stata, College Station, TX, USA).

3. Results

Fig. 1 summarizes the study selection process. A total of 1717 articles were identified by the literature search. After eliminating duplicates and title and abstract reading, 47 potential articles remained for full-text screening. Of the 47 articles, 32 were excluded because they turned out not to fulfill the inclusion criteria. This left us with 15 articles for our meta-analysis, in which seven additional studies (five case-control studies and two cross-sectional studies) were identified that were not included in the previous systematic review.

3.1. Study characteristics

The characteristics of the included 15 studies are summarized in Table 1. Overall, 11 case-control studies [12–22], and four cross-sectional studies [23–26] were included in the updated meta-analysis. Two studies covered pediatric and adolescent populations [15,21], while the others involved adults. Of the 11 case-control studies, three studies provided ORs and 95% CIs [15,18,19], whereas the others provided only the numbers of individuals with and without RLS among migraineurs and controls, so we calculated the ORs and

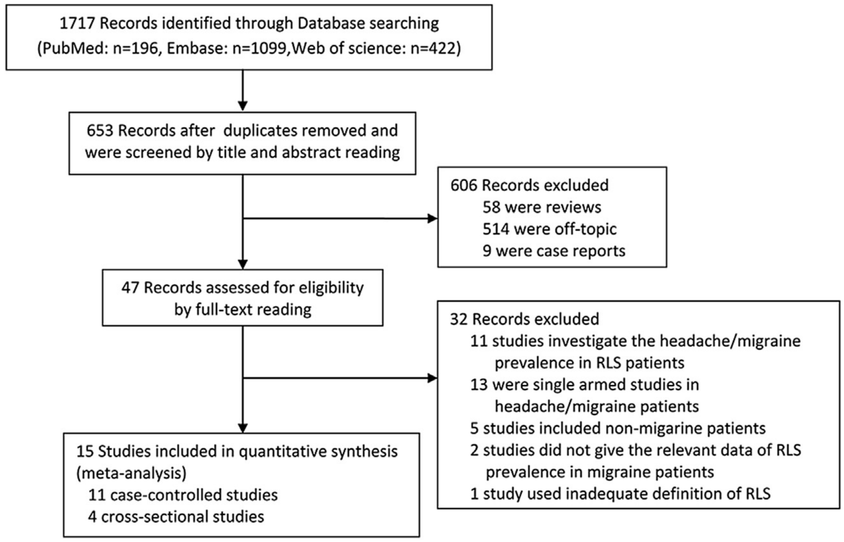

Fig. 1. Flowchart of study identification for meta-analysis.

95% CIs by ourselves. The study by Lin et al., [18] divided the migraineurs into three groups according to headache attack frequency but did not provide an overall OR and 95% CI. Therefore, we recalculated the overall effect estimate with no confounders adjusted. All cross-sectional studies provided multiple adjusted ORs and 95% CIs. The NOS qualities of the included studies are shown in Tables S1–S2.

3.2. Prevalence of RLS in migraineurs and non-migraineurs

All 15 studies provided information allowing calculation of RLS prevalence among migraineurs and non-migraineurs [12–26]. The prevalence of RLS among migraineurs ranged from 6.5% [18] to 33.8% [21], and that among non-migraineurs ranged from 1.8% [13] to 11.2% [23]. Since significant degrees of heterogeneity were observed across studies ($I^2 = 93.9\%$ and $I^2 = 96.2\%$ respectively, both $p < 0.001$), random-effects models were used. The pooled prevalence of RLS was 17.0% (95% CI, 15.0%–20.0%) among migraineurs and 7.0% (95% CI, 5.0%–8.0%) among non-migraineurs (Figs. 2 and 3). Subgroup analyses showed that pooled RLS prevalence among migraineurs was substantially higher in case-control studies [21.0% (95% CI, 16.0%–25.0%)] than in cross-sectional studies [12.0% (95% CI, 7.0%–16.0%)] (Fig. 2). However, the pooled RLS prevalence among non-migraineurs was slightly lower in case-control studies [6.0% (95% CI, 4.0%–8.0%)] than in cross-sectional studies [8.0% (95% CI, 5.0%–11.0%)] (Fig. 3).

3.3. Association between migraine and RLS

Data were pooled according to study design. The pooled analysis of case-control studies showed that any migraine was associated with a nearly fourfold increased odds of RLS (pooled OR = 3.77, 95% CI 2.73–5.21, $I^2 = 50.1\%$) (Fig. 4), while pooled analysis of cross-sectional studies showed that the odds of RLS among migraineurs were increased by about 25% (OR = 1.25, 95% CI 1.11–1.41, $I^2 = 34.2\%$) (Table 2, Fig. 5). No evidence of publication bias was found among the case-control and cross-sectional studies in formal investigations with Begg's tests (Table 2). Subgroup analyses of case-control studies by mean age of study participants and study quality were performed to explore the potential source of heterogeneity (Table 2, Figs. S1 and S2). Of note, subgroup analysis by age showed that the pediatric and adolescent populations had higher odds of RLS than the adult population (pooled OR = 7.46, 95% CI 3.35–16.61, $I^2 = 0.0\%$ and OR = 3.44, 95% CI 2.48–4.77, $I^2 = 48.7\%$, respectively). We also noted a significant reduction of statistical heterogeneity by age (adolescent, $I^2 = 0.0\%$) and study quality (medium, $I^2 = 1.8\%$ and high, $I^2 = 20.5\%$).

3.4. Potential factors that may affect the association between migraine and RLS

Efforts were made to find potential factors that may affect the association between migraine and RLS. However, the currently available relevant studies were too few to perform meta-analyses. Thus, we only extracted and summarized relevant results for some potential factors in Table 3.

3.5. RLS prevalence among migraineurs according to headache frequency

Three studies investigated the RLS prevalence among migraineurs according to headache frequency [18,22,26]. We did not pool the data because the three studies used different headache frequency categories. A significant increase in the prevalence of RLS was observed in Cho's study [26] in both migraineurs with 1–10 attacks per month and migraineurs with >10 attacks per month relative to migraineurs with <1 attack per month. The study by Lin et al., showed that only migraineurs with >15 attacks per month had increased prevalence of RLS compared to migraineurs with 1–8 attacks per month [18]. In Akdag's study [22], no differences in RLS prevalence were found among migraineurs with different headache frequencies (Table S3).

3.6. RLS severity in migraine patients and controls

Four studies investigated the RLS severity in migraine patients and controls [12,17,19,22]. All studies showed that the RLS patients with migraine had higher RLS severity scale scores than those without migraine. However, only one study [19] showed a statistical difference (Table S4).

3.7. Clinical characteristics of migraine according to the presence of RLS

Eight studies investigated the clinical characteristics of subjects having migraine with and without RLS [12–14,17,19–22]. We

Table 1
Characteristics of studies investigating RLS in migraine.

Study, country	Study design	Source population	Sample size	Mean age	Gender	Migraine diagnostic criteria	Headache Categories (n,% women)	RLS diagnostic criteria	Confounder adjusted
Rhode 2007 Germany [12]	Case-control (matched by age and sex)	Migraine: patients from headache outpatient clinic and "Dortmunder Gesundheitsstudie"; controls: relatives of patients waiting in trauma outpatient clinic and from "Dortmunder Gesundheitsstudie"	822	Migraine: 41.7 ± 12.5 control: 42.1 ± 12.8	Women and men	ICHD-II	Any migraine (n = 411, 62.5%) Controls: (n = 411, 62.5%)	Interview using structured questionnaire (IRLSSG criteria) confirmed clinical diagnosis by a neurologist	NCA
Suzuki 2011 Japan [13]	Case-control (matched by age and sex)	Migraine: patients attending headache outpatient clinic; controls: recruited from hospital employees, their friends and family	425	Migraine: 38.2 ± 13.0 control: 37.3 ± 12.1	Women and men	ICHD-II	Any migraine (n = 262, 82.1%) Controls: (n = 163, 84.7%)	Face-to-face interview (IRLSSG)	NCA
Lucchesi 2012 Italy [14]	Case-control (matched by age and sex)	Migraine: patients attending the headache center at the University of Pisa; controls: NA	477	Migraine: 37.3 ± 12.1 control: 38.2 ± 13.0	Women and men	ICHD-II	Any migraine (n = 277, 68.6%) Controls: (n = 200, 68.5%)	Face-to-face interview (IRLSSG)	NCA
Seidel 2012 Austria [15]	Case-control	Cases: patients attending the Headache Unit at the Department of Child and Adolescent Psychiatry (University of Vienna); control group 1: patients from Department of Pediatrics and Adolescent Medicine after recovery; (control group 2: children and adolescents from primary and grammar schools)	292	Migraine: 13 ± 3 control 1: 13 ± 3 control 2: 13 ± 4	Girls and boys	ICHD-II (semi-structured interview)	Any migraine (n = 111, 50.5%) Control 1: (n = 73, 54.8%) Control 2: (n = 108, 54.6%)	IRLSSG questionnaire (asking about previous six months)	Age, gender, RLS family history and ESS total score
Karthik 2012 India [16]	Case-control (matched by age and sex)	Cases: neuropsychiatric patients attending a tertiary care university center; controls: participants of a study to detect the prevalence of sleep abnormalities in the general population	180	Migraine: 31.76 ± 8.2 control: 31.76 ± 8.2	Women and men	ICHD-II	MO (n = 90, 78.9%) Controls: (n = 90, 78.9%)	NA	NCA
Ferreira 2013 Brazil [17]	Case-control (matched by age, sex and employment type)	Employees of University Hospital, Sao Paulo	144	Migraine: 42.5 control: 40	Women and men	ICHD-II (face-to-face interview)	Any migraine (n = 72, 86.1%) Controls: (n = 72, 79.2%)	Questionnaire-based interview (IRLSSG)	NCA
Lin 2016 China [18]	Case-control (on a cross-sectional basis)	Migraine and controls: participants undergoing outpatient monitoring through the Department of Neurology at Tri-Service General Hospital (TSGH)	505	Migraine: 33.1 ± NA control: 35.4 ± 12.6	Women and men	ICHD-IIIβ	Any migraine (n = 372, 68.0%) Controls: (n = 133, 66.9%)	Interview diagnosis using five essential diagnostic criteria outlined by the International RLS Study Group	Gender, age, body mass index, education level, smoking status, alcohol consumption, coffee consumption, HADS anxiety, HADS depression, and PSQI score
van Oosterhout 2016 Netherlands [19]	Case-control	Migraine and controls both recruited via public announcement, advertising in the lay press and via research website and were part of the LUMINA project participants	2717	Migraine: 45.1 ± 11.6 control: 43.8 ± 15.2	Women and men	ICHD-IIIβ	Any migraine (n = 2385, 85.7%) Controls: (n = 332, 55.7%)	Self-administered questionnaire comprised four yes/no type questions based on the essential criteria proposed by the International RLS Study Group	Age, gender, body mass index (BMI), smoking (pack-years), alcohol use and lifetime depression
Valente 2017 Italy [20]	Case-control (matched by age and sex)	Migraine: outpatients clinic who both met the following inclusion/exclusion criteria and signed a written informed consent; controls: selected among	360	Migraine: 41 ± 13.2 control: 41.7 ± 14.1	Women and men	ICHD-II	Any migraine (n = 180, 79.4%) Controls: (n = 180, 71.7%)	Interview using structured questionnaire and then confirmed by a senior neurologist	NCA

Table 1 (*continued*)

Study, country	Study design	Source population	Sample size	Mean age	Gender	Migraine diagnostic criteria	Headache Categories (n,% women)	RLS diagnostic criteria	Confounder adjusted
		the patients referred to the Dermatology Clinic of the University of Udine							
Sevindik 2017 Turkey [21]	Case-control	Cases: patients referred to the two Pediatric Headache Outpatient Clinics; controls: children admitted to pediatrics clinics with complaints of upper and/or lower respiratory tract infections and gastrointestinal problems	192	Migraine: 11.36 ± 3.4 TTH: 12.8 ± 1.9 control: 7.76 ± 3.7	Girls and boys	ICHD-II	Any migraine (n = 65, 55.4%) TTH: (n = 20, 70%) Controls: (n = 97, 51.5%)	Face-to-face interview (IRLSSG)	NCA
Akdag 2018 Turkey [22]	Case-control	Migraine: patients previously or for the first time diagnosed; control: healthy volunteers including health staff or patients' companions	400	Migraine: 33.41 ± 9.2 control: 34.8 ± 7.4	Women and men	IHS classification criteria	Any migraine (n = 200, 91%) Controls: (n = 200, 90%)	Face-to-face interview (IRLSSG)	NCA
Schurks 2012 US [23]	cross-sectional analysis of a cohort study	Women's Health Study	31,370	Any migraine: 62.5 ± 6.3 no migraine: 63.9 ± 7.1 (at the time of 108-month follow-up when the RLS was diagnosed)	Women	Modified ICHD-I (questionnaire)	Any migraine (n = 6857, 100%) MA (n = 1579, 100%) MO (n = 2418, 100%) prior migraine (n = 1725, 100%) new reports of migraine (n = 1135, 100%)	Self-administered questionnaire (IRLSSG)	Age, BMI, history of diabetes, history of hypertension, history of elevated cholesterol, alcohol consumption, smoking, physical activity, parental history of myocardial infarction prior to age 60, major CVD, postmenopausal hormone use, menopausal status, history of depression, history of Parkinson's disease, number of pregnancies lasting ≥6 months, iron supplementation use, fatigue, ethnicity, and geographic location
Winter 2013 US [24]	Cross-sectional analysis of a cohort study	Physician' Health Study	22,926	63.9 ± 7.1 (at the time of RLS diagnosis)	Men	Self-report on questionnaire	Any migraine (n = 2816, 0%) no migraine (n = 20,110, 0%)	Self-administered questionnaire (IRLSSG)	Age, BMI, history of diabetes, history of hypertension, history of elevated cholesterol, alcohol consumption, smoking, physical activity, parental history of myocardial infarction before age 60, major CVD, history of depression, history of Parkinson's disease, iron supplementation use, ethnicity, and geographic location
Zanigni 2014 Italy [25]	Cross-sectional analysis of a cohort study	adult population (≥18 years old) in Val Venosta located in northern Italy	1567	46.5	Women and men	Computer-assisted interviewer-administered questionnaire based on ICHD-II	Migraine (n = 133, 84.2%) no migraine (n = 1434, 54.4%)	Self-administered questionnaire (IRLSSG)	Age, sex, sleep quality, major depression and anxiety score
Cho 2015 Korea [26]	Cross-sectional	Korean Headache-Sleep Study	2695	NA	Women and men	ICHD-II (face-to-face interview)	Migraine (n = 143, 74.8%) no migraine (n = 2552, 48.7%)	Face-to-face interview (IRLSSG)	Socio-demographic variables and sleep quality

RLS: restless legs syndrome; NA: not available; ICHD: International Classification of Headache Disorders; IRLSSG: International Restless Legs Syndrome Study Group; NCA: no confounders adjusted; ESS: Epworth sleepiness scale; MO: migraine without aura; MA: migraine with aura; IHS: International Headache Society; CVD: cardiovascular disease; HADS: The Hospital Anxiety and Depression Scale PSQI: The Pittsburgh Sleep Quality Index; TTH: tension-type headache.

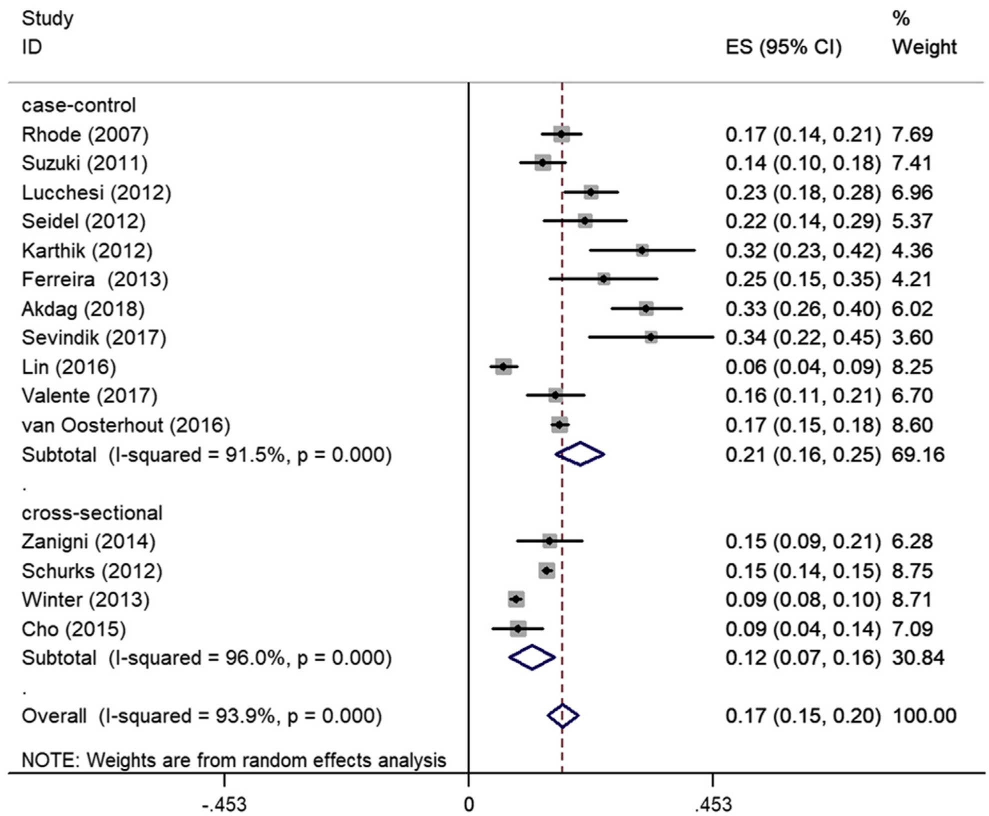

Fig. 2. Forest plots of RLS prevalence among migraineurs.

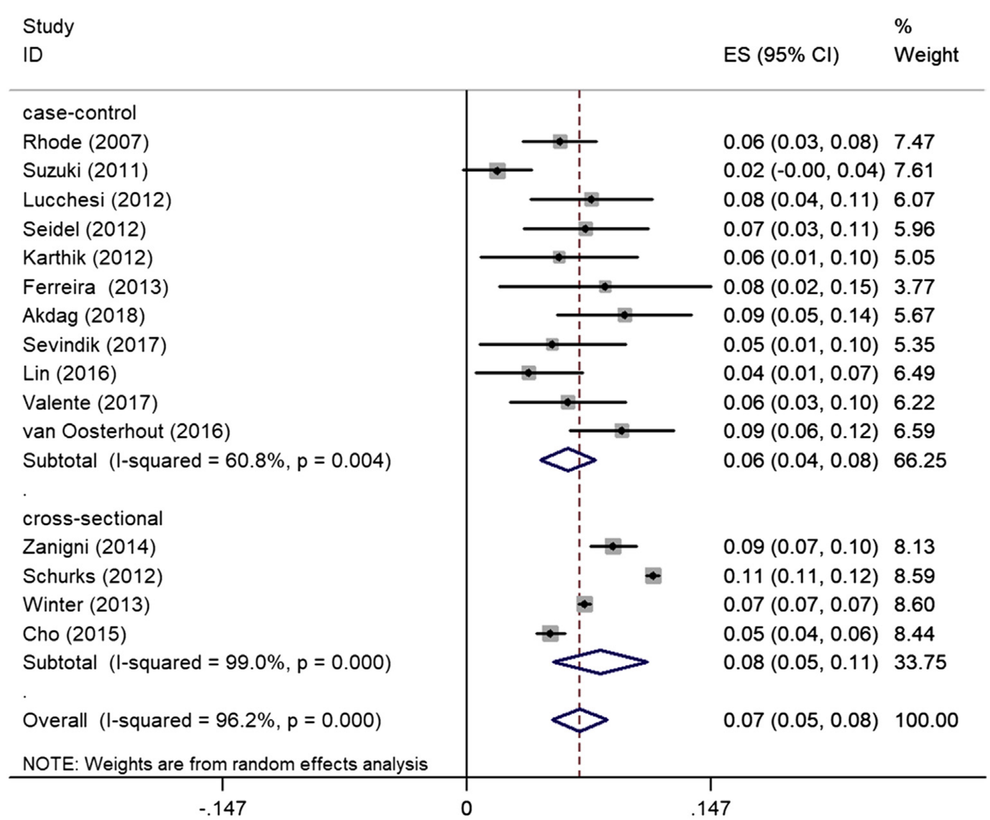

Fig. 3. Forest plots of RLS prevalence among non-migraineurs.

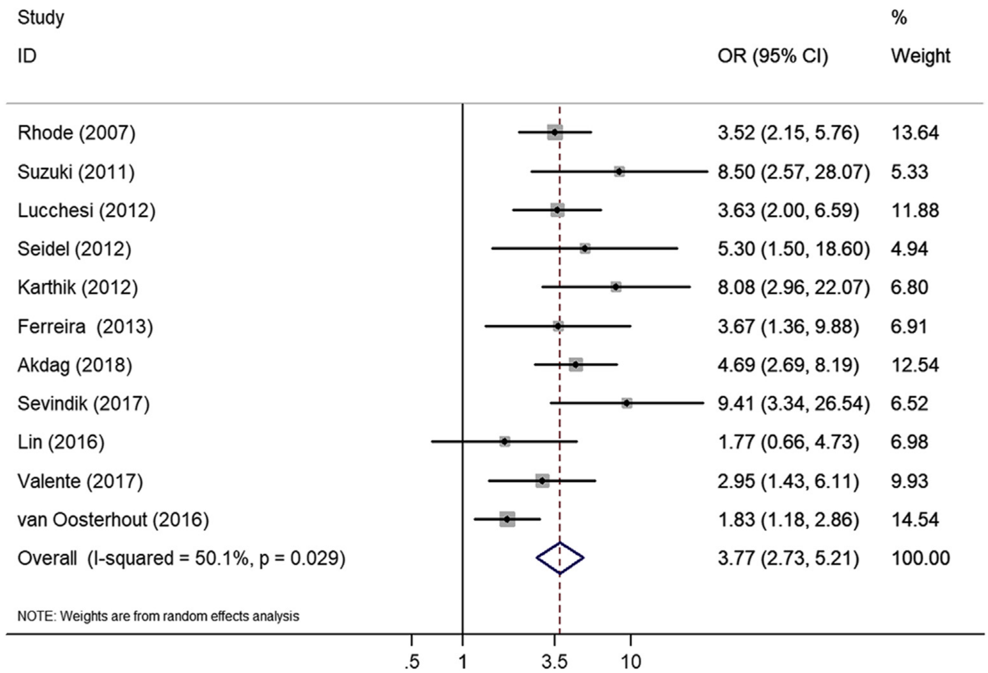

Fig. 4. Forest plots of association between migraine and RLS from the case-control studies.

Table 2
Association between any migraine and RLS, heterogeneity, and publication bias.

	No. of studies	Pooled OR (95% CI)[a]	Heterogeneity		Publication bias
			I^2 in %	*p*-value	Begg's test
Case-control studies	11	3.77 (2.73–5.21)	50.1%	0.03	0.07
Age subgroup					
Adult population	9	3.44 (2.48–4.77)	48.7%	0.05	
Adolescent population	2	7.46 (3.35–16.61)	0.0%	0.49	
Study quality subgroup					
Medium	8	4.29 (3.32–5.54)	1.8%	0.42	
High	3	2.11 (1.28–3.48)	20.5%	0.28	
Cross-sectional studies	4	1.25 (1.11–1.41)	34.2%	0.21	0.17

RLS: restless legs syndrome; OR: odds ratio; CI: confidence interval.
[a] From random-effects model.

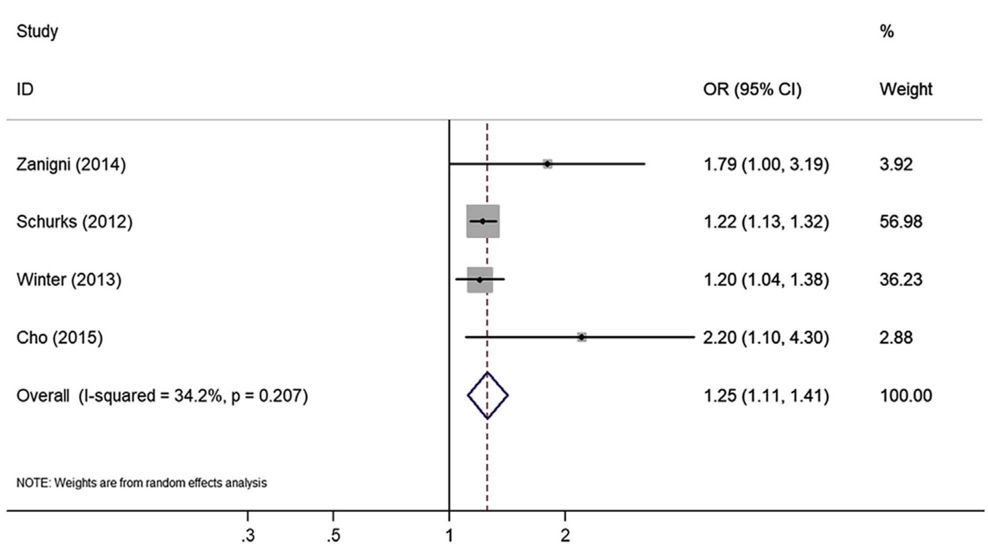

Fig. 5. Forest plots of association between migraine and RLS from the cross-sectional studies.

Table 3
Association between any migraine and RLS according to gender, aura status, episodic or chronic type, and age.

Potential factors	Study	Studies design	Categories	Results [OR (95% CI)]
Gender	Lucchesi	Case-control	Men	3.32 (1.05–10.49)
			Women	3.77 (1.87–7.57)
	Winter	Cross-sectional	Men	1.20 (1.04–1.38)
	Schurks	Cross-sectional	Women	1.22 (1.13–1.32)
Aura status	Lucchesi	Case-control	MA	3.80 (1.47–9.82)
			MO	3.61 (1.97–6.61)
	Karthik	Case-control	MO	8.08 (2.96–22.07)
	van Oosterhout	Case-control	MA	1.99 (1.24–3.20)
			MO	1.74 (1.08–2.79)
	Lin	Case-control	MA	3.10 (1.06–9.10)
			MO	1.23 (0.43–3.58)
	Schurks	Cross-sectional	MA	1.27 (1.10–1.48)
			MO	1.24 (1.09–1.40)
	Zanigni	Cross-sectional	MA	2.48 (1.12–5.53)
			MO	1.35 (0.72–2.53)
Migraine type	Lucchesi	Case-control	EM	2.35 (1.21–4.56)
			CM	6.44 (3.31–12.54)
	Lin	Case-control	EM	1.38 (0.50–3.82)
			CM	3.58 (1.09–11.82)
Age	Cho	Cross-sectional	≤50	3.90 (2.10–7.40)
			>50	1.50 (0.90–2.40)

RLS: restless legs syndrome; OR: odds ratio; CI: confidence interval; MA: migraine with aura; MO: migraine without aura; EM: episodic migraine; CM: chronic migraine.

summarized the main results of these studies in Table S5. A family history of RLS, self-reported poor sleep quality and depression symptoms were more common in individuals with migraine and RLS than in those without RLS. Furthermore, the Pittsburgh Sleep Quality Index (PSQI) global score, most of the PSQI component score, and the Beck's Depression Inventory (BDI) score were significantly higher in migraine patients with RLS than in those without RLS.

3.8. Sensitivity analyses

Sensitivity analyses of case-control studies and cross-sectional studies showed that the OR and 95% CI did not change substantially after removing any one study (Figs. S3 and S4), which further verified the robustness of the pooled results. Further sensitivity analysis of case-control studies was performed by omitting studies with an RLS diagnosis based on a questionnaire; these pooled results did not change much either (Fig. S5).

4. Discussion

In this updated systematic review and meta-analysis of studies investigating the association between migraine and RLS, findings were pooled from >60,000 subjects. The main results suggest that RLS prevalence among migraineurs is significantly higher than that among non-migraineurs (17.0% vs. 7.0%), and migraine is associated with significantly increased odds for RLS (OR = 3.77, and 1.25 for pooled analyses of case-control, and cross-sectional studies, respectively).

4.1. Comparison with a previous systematic review

Our results are in line with those of a previously published review by Schurks and colleagues [3]. Both reviews pooled the available data according to study design and demonstrated the existence of the association between migraine and RLS. However, there are some notable differences between this updated analysis and the previous review.

First, our meta-analysis of case-control studies shower lower increased odds of RLS as compared to the previous one (OR = 3.77 vs. OR = 4.19). However, our pooled analysis of cross-sectional studies (including the previous two ‘cohort studies’ and two additional studies) showed higher increased odds of RLS (25% vs. 22%).

Second, the previous review suggested that gender and aura status might have potential modifying effects on the association between migraine and RLS [3]. Since the release of the last review, there was new evidence indicating that age might influence the association between the two disorders. A cross-sectional study by Cho et al., showed that migraine and RLS are only associated in adults under age 50 but not in those over 50 [26]. Subgroup analysis of case-control studies in our review showed that adolescent migraineurs had higher odds of RLS than adult migraineurs (OR = 7.46 vs. OR = 3.44). However, the result for adolescent migraineurs was from pooled analyses of two case-control studies. As such, the result is likely to be imprecise. Furthermore, there was also evidence suggesting the association might be affected by type (episodic or chronic) of migraine [18]. In sum, our review found that age and type of migraine might be the other two potential modifying factors. The currently available data was scarce and unsatisfactory, and there was insufficient evidence to draw any firm conclusions about the gender, age, aura status, and migraine type issues.

Third, our meta-analysis analyzed current studies not included in the previous review and summarized new investigations on RLS prevalence among migraineurs according to headache frequency. However, given that the relevant studies used different frequency categories, we did not attempt to pool the data for meta-analysis. The results of two studies showed that migraineurs with high headache attack frequency had increased odds of RLS compared to those with low headache attack frequency [18,26]. However, this result was not supported by the third study [22]. These inconsistent results might be due to different study designs, headache frequency categories, and participant populations. Thus, we could not figure out whether migraineurs with high headache attack frequency had increased odds of RLS based on the current evidence. We believe this issue is worth further investigation in the future.

Fourth, compared with the previous review, we specifically did an additional analysis of RLS severity in patients comorbid with or without migraine. Moreover, we found that current studies all suggested that patients had severer RLS symptoms when they comorbid with migraine.

Finally, based on new evidence from current studies, we summarized and analyzed the clinical characteristics of subjects having migraine with and without RLS. The current evidence suggested that migraineurs with RLS were more likely to have sleep problems and experience depression than those without RLS. These findings indicate that it is important to identify and treat depression and sleep problems in migraineurs, especially those with RLS.

4.2. Limitations

While this review is systematic and comprehensive, there are three limitations. First, the pooled analysis of case-control studies might overestimate the association between migraine and RLS, because most case-control studies did not adjust for the potential effects of confounders. Although confounders were taken into account in the cross-sectional studies, the low number of included studies (four cross-sectional studies) might lead to an inaccurate estimation of pooled analyses. Second, the analyses of potential effects by gender, aura status, migraine type, and age on the association between migraine and RLS were based on only a few studies. Thus, we could not draw certain conclusions whether the modifying effect by those factors truly exists. Third, most of the included case-control studies were assessed as medium-quality, and this should be taken into account when interpreting the findings of this review.

4.3. Implications for further research

The limited number of studies investigating the potential effects of gender, aura status, age, and episodic or chronic type on the association between migraine and RLS and the limited number of studies with different headache attack categories, highlight the need for more well-designed comparative research in this area to provide further insight into the association between migraine and RLS.

5. Conclusions

Despite the limitations mentioned above, this systematic review and meta-analysis indicate that RLS is an important comorbidity in migraine. The currently available data is still too scarce to figure out whether the modifying effects of gender, age, aura status, and type of migraine truly exist. Also, the degree of association between migraine and RLS may be determined by the severity of migraine. Given the heavy burden of migraine and RLS in the general population, future research is urgently needed to address these unresolved questions.

Funding

This work was supported by the Healthcare Fund of the Chinese PLA Logistics Security Ministry (16BJZ25).

Acknowledgments

We would like to thank LetPub (www.letpub.com) for providing linguistic assistance during the preparation of this manuscript.

Conflicts of interest

The authors have declared no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.027.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.01.027.

References

[1] Goadsby PJ, Holland PR, Martins-Oliveira M, et al. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev 2017;97(2):553–622.
[2] Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(9995): 743–800.
[3] Schürks M, Winter A, Berger K, et al. Migraine and restless legs syndrome: a systematic review. Cephalalgia 2014;34(10):777–94.
[4] Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. Headache 2006;46:1327–33.
[5] Diener HC, Kuper M, Kurth T. Migraine-associated risks and comorbidity. J Neurol 2008;255:1290–301.
[6] Cannon PR, Larner AJ. Migraine and restless legs syndrome: is there an association? J Headache Pain 2011;12:405–9.
[7] Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165: 1286–92.
[8] Venkateshiah SB, Ioachimescu OC. Restless legs syndrome. Crit Care Clin 2015;31(3):459–72.
[9] Sabayan B, Bagheri M, Borhani Haghighi A. Possible joint origin of restless leg syndrome (RLS) and migraine. Med Hypotheses 2007;69:64–6.
[10] Akerman S, Goadsby PJ. Dopamine and migraine: biology and clinical implications. Cephalalgia 2007;27:1308–14.
[11] Paulus W, Dowling P, Rijsman R, et al. Pathophysiological concepts of restless legs syndrome. Mov Disord 2007;22:1451–6.
[12] Rhode AM, Hösing VG, Happe S, et al. Comorbidity of migraine and restless legs syndrome-a case-control study. Cephalalgia 2007;27(11):1255–60.
[13] Suzuki S1, Suzuki K, Miyamoto M, et al. Evaluation of contributing factors to restless legs syndrome in migraine patients. J Neurol 2011;258(11): 2026–35.
[14] Lucchesi C, Bonanni E, Maestri M, et al. Evidence of increased restless legs syndrome occurrence in chronic and highly disabling migraine. Funct Neurol 2012;27(2):91–4.
[15] Seidel S, Böck A, Schlegel W, et al. Increased RLS prevalence in children and adolescents with migraine: a case-control study. Cephalalgia 2012;32(9): 693–9.
[16] Karthik N, Kulkarni GB, Taly AB, et al. Sleep disturbances in 'migraine without aura'-a questionnaire based study. J Neurol Sci 2012;321(1–2):73–6.
[17] Ferreira KS, Eckeli A, Dach F, et al. Comorbidities, medications and depressive symptoms in patients with restless legs syndrome and migraine. Arq Neuropsiquiatr 2013;71(2):87–91.
[18] Lin GY, Lin YK, Lee JT, et al. Prevalence of restless legs syndrome in migraine patients with and without aura: a cross-sectional, case-controlled study. J Headache Pain 2016;17(1):97.
[19] van Oosterhout WP, van Someren EJ, Louter MA, et al. Restless legs syndrome in migraine patients: prevalence and severity. Eur J Neurol 2016;23(6): 1110–6.
[20] Valente M, Janes F, Russo V, et al. Prevalence of restless legs syndrome in migraine patients: a case-control study. Analysis of risk factors for restless legs syndrome in migraine patients. Headache 2017;57(7):1088–95.
[21] Sevindik MS, Demirci S, Göksan B, et al. Accompanying migrainous features in pediatric migraine patients with restless legs syndrome. Neurol Sci 2017;38(9):1677–81.
[22] Akdag Uzun Z, Kurt S, Karaer Unaldi H. The relationship with restless legs syndrome, fibromyalgia, and depressive symptoms in migraine patients. Neurol Sci 2018;39(8):1409–14.
[23] Schürks M, Winter AC, Berger K, et al. Migraine and restless legs syndrome in women. Cephalalgia 2012;32(5):382–9.
[24] Winter AC, Schürks M, Berger K, et al. Migraine and restless legs syndrome in men. Cephalalgia 2013;33(2):130–5.
[25] Zanigni S, Giannini G, Melotti R, et al. Association between restless legs syndrome and migraine: a population-based study. Eur J Neurol 2014;21(9): 1205–10.
[26] Cho SJ, Chung YK, Kim JM, et al. Migraine and restless legs syndrome are associated in adults under age fifty but not in adults over fifty: a population-based study. J Headache Pain 2015;16:554.
[27] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9. W64.
[28] Wells GS, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available at: www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed 20 June 2018].
[29] Herzog R, Álvarez-Pasquin MJ, Díaz C, et al. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health 2013;13:154.
[30] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[31] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.