Prevalence of restless legs syndrome in people with diabetes mellitus: A pooling analysis of observational studies

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Summary

Background Diabetes mellitus (DM) is associated with different clinical complications. The aim of this study was to explore the prevalence of RLS in people with diabetes mellitus and compare the risk of restless leg syndrome (RLS) between diabetic and non-diabetic population.

Methods We searched for studies of RLS prevalence in DM through PubMed, Embase, and Web of Science. Two authors independently completed the literature screening, data extraction, and bias risk assessment of eligible studies. All observational studies that assessed the prevalence or risk of RLS in DM were included, where the diagnosis of RLS was based on the International Restless Legs Syndrome Study Group (IRLSSG). Percentages, odds ratio (OR) with 95% confidence intervals (CI) were used to assess pooled estimates of RLS prevalence and risk based on random-effects models. Newcastle-Ottawa-scale (NOS) or a modified NOS were used to evaluate the quality of studies.

Findings A total of 42 studies, including 835,986 participants, met the eligibility criteria for the meta-analysis. Among them, 30 studies were included in meta-analysis to analyze the prevalence of RLS. A second meta-analysis was conducted using 31 studies to determine RLS risk between diabetes and non-diabetes. The results indicate that between 25% (95% confidence interval 21%-29%) of people with diabetes showed signs of RLS, and people with diabetes had an increased risk of developing RLS compare to people without diabetes (OR 1.98, 95%CI 1.66- 2.34, $p < 0.001$). However, the available evidence was limited due to potential risk of bias and variability between studies (I^2>75%), all of observational design.

Interpretation Our study suggests that the prevalence and risk of RLS might be higher in DM patients than in non-diabetes population. However, given limitations in the analysis and study design, the findings need to be corroborated in future studies.

Funding This work was supported by the Basic Conditions Platform Construction Project of Sichuan Science and Technology Department (2019JDPT0015), and the "1 3 5 project for disciplines of excellence, West China Hospital, Sichuan University" (ZYJC18003).

Keywords: Diabetes mellitus; Diabetes; Restless legs syndrome; Diabetic peripheral neuropathy; Meta-analysis

eClinicalMedicine 2022;46: 101357
Published online 24 March 2022
https://doi.org/10.1016/j.eclinm.2022.101357

Introduction

Diabetes mellitus (DM) remains the emerging public health problem across the world.[1,2] Restless legs syndrome (RLS) is a common neurological sensorimotor disorder characterized by uncomfortable sensations in the extremities and an overwhelming urge to move one's legs, especially in the evening and during periods of inactivity.[3,4] First mentioned in 1672 by Willis, RLS was clinically described in the early 1940s by Ekbom, who coined and published the term "restless legs syndrome".[5] As a consequence, the disease has also been called "Willis-Ekbom

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Research in context

Evidence before this study

Restless legs syndrome (RLS) is associated with several comorbidities, including diabetes. However, a deeper understanding of its prevalence and management is needed. We searched the PubMed, Embase, and Web of Science databases without language restriction. The last search was conducted on January 29, 2022 using terms "RLS", "diabetes" and related. Studies were included if they focused on describing the prevalence and risk of RLS in diabetes.

Added value of this study

Our results provide to the best of our knowledge the first pooled estimate for RLS prevalence in diabetes mellitus, strengthening previous findings related to the higher risk of RLS among people with diabetes mellitus.

Implications of all the available evidence

This meta-analysis could be useful to provide more detailed strategies for screening and clinical management of diabetic patients with RLS. Given the potential risk of bias and large heterogeneity observed, more in-depth studies are urgently needed to explore the relationship between these two diseases and the pathological mechanisms of disease.

disease". The four minimal diagnostic criteria for RLS of the International Restless Legs Study Group (IRLSSG) were[6]: 1. Desire to move the limbs usually associated with paresthesias/dysesthesias. 2. Motor restlessness. 3. Symptoms are worse or exclusively present at rest (i.e. lying, sitting) with at least partial and temporary relief by activity. 4. Symptoms are worse in evening/night.

Although the pathophysiological pathways leading to RLS are still unknown, brain iron deficiency and dysfunction of the dopaminergic system appear to play a role.[7] RLS can be secondary to various medical conditions, such iron deficiency, rheumatoid arthritis, end-stage renal disease, obesity, and some physiological states such as pregnancy.[8–11] Previous meta-analysis have shown that RLS exists in the comorbidities of a series of diseases, such as Parkinson's disease,[12] migraine,[13] and multiple sclerosis.[9] We noticed that RLS also often exists as a comorbidity in diabetic patients.[14] However, the relationship between RLS and DM has not been systematically reviewed in depth with a large sample size throughout various regions. Thereby, we performed a meta-analysis of the current observational literature in order to understand the prevalence of RLS in patients with DM.

Methods

Described as previously reported methodology,[15,16] this meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[17] This meta-analysis has been registered on the INPLASY website with the registration number of INPLASY 202,150,012.

Search strategy

We searched the available literature in PubMed, Web of Science, and Embase databases. The search was limited to articles in English. The final search was conducted on January 29, 2022. The search string was ('restless legs syndrome', 'Willis-Ekbom disease', 'RLS') and ('diabetes mellitus', 'diabetes'). The detailed strategy for searching in databases was: (((restless legs syndrome) OR (Willis-Ekbom disease)) OR (RLS)) AND ((diabetes mellitus) OR (diabetes)).

Study selection criteria

The inclusion criteria include (1) observational studies with cross-sectional, case-control or cohort designs analyzing restless legs syndrome (RLS) in diabetes mellitus patients; (2) RLS was diagnosed according to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG)[18]; (3) reporting point prevalence of RLS or sufficient data to calculate it; (4) reporting zero prevalence among patients with DM but still meet the three inclusion criteria above.

Studies were excluded if they (1) were editorials, narrative reviews, case reports, letters, commentaries, or critiques; (2) did not report sufficient data to calculate the incidence of RLS in diabetes mellitus patients and non-diabetic population, and efforts to contact the authors were unsuccessful; (3) or did not involve patients with diabetes mellitus or RLS.

Data extraction

Two authors (NP, MX) independently assessed articles for inclusion/exclusion criteria, and discrepancies were resolved by discussion with a third reviewer (Xinglong Yang). The following data were extracted from each study: surname of the first author, publication year, country, study design, sample size, mean age, DM duration, diagnostic criteria for RLS, method of RLS evaluation, RLS prevalence in DM patients and non-diabetic population and relevant odds ratios (ORs) and 95% confidence intervals (CIs). Firstly, we gave priority to the OR value obtained through multivariate analysis, or the OR value comes from propensity score matching (PSM), which effectively adjusted for the effect of confounding factors by methods such as weighting, stratification, or regression correction. Secondly, if a separate cohort from the entire study population eliminating confounding factors artificially by the author (including age, gender, race, anemia, uremia, ferritin deficiency, peripheral neuropathy, etc.), we used the OR value calculated by a separate cohort. Finally, in the entire queue,

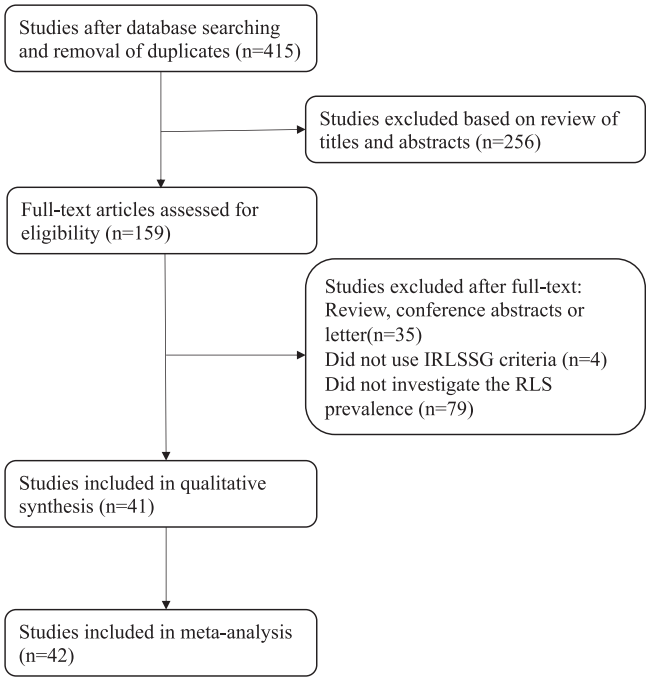

Figure 1. Flow diagram of literature search. Initially, we maintain 415 results after removing duplicates. We excluded 256 literatures based on review of titles and abstract. We excluded 117 literatures based on review of full text. Eventually, 42 studies were included in this meta-analysis. IRLSSG, International Restless Legs Syndrome Study Group.

we used the raw data to calculate the OR value based on 2 × 2 tables. If a study reported longitudinal data on RLS incidence in diabetic patients, only baseline data were extracted.

Statistical analysis

The meta-analysis was performed using STATA version 12.0 (StataCorp, College Station, TX, USA). We evaluated RLS prevalence in DM patients according to ethnicity and sex based on the DerSimonian and Laird method for random-effects meta-analysis.[19] RLS prevalence was compared between DM patients and non-diabetic individuals in terms of OR and 95% CI. $p < 0.05$ was considered statistically significant in all analyses.

Heterogeneity among the included studies was evaluated using the Q test and quantified using I^2. An I^2 value below 25% was considered as homogeneity; 25% to < 50%, low heterogeneity; 50% to < 75%, moderate heterogeneity; and at least 75%, substantial heterogeneity.[20] Publication bias was assessed using Egger's and/or Begg's tests,[21] and funnel plots were used to visually assess publication bias of included studies. Sensitivity analysis was used to assess the overall robustness of the included studies. Newcastle-Ottawa-scale (NOS) or a modified NOS[22] was used to assess the quality and risk of bias of each study (Supplementary Table 1).

Role of funding sources

The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Study selection

A total of 415 potentially eligible articles were identified after searching the three databases and removing duplicates (Figure 1). After eliminating 256 articles based on the title and abstract, the remaining 159 were read in full and 118 were excluded because they did not use IRLSSG diagnostic criteria ($n = 4$), they did not investigate RLS prevalence ($n = 79$), or they were conference abstracts or letters ($n = 35$). In the end, 41 publications containing 42 studies met all the eligibility criteria and were included in the meta-analysis.[14,23–62]

Study characteristics

The characteristics of the 42 included studies, involving 835,986 DM patients, are summarized in Table 1. All studies were observational and were published between 2001 and 2020. Sample sizes ranged from

Study	Year	Country	Study design	Age (years)	RLS assessment method	IRLSSG criteria	Sample size			RLS in DM (%)	RLS in ND (%)	OR (95%CI)
							DM (M/F)	RLS (+)/ RLS (-)	Males with RLS			
Skomro	2001	Canada	Case-control	57.5 ± 14.85	NA	Yes	58 (29/29)	14/44	8/29	24.1	12.5	2.227 (0.783−6.337)
Happe	2005	Germany	Cross-sectional	12.0 ± 3.7	Questionnaire and interview	Yes	46 (21/25)	1/45	NA	22.0	NA	NA
Lopes	2005	Brazil	Cross-sectional	58.3 ± 12.3	NA	Yes	100	27/73	NA	27.0	NA	NA
Gemignani	2007	Italy	Cross-sectional	65.4 ± 10.5	NA	Yes	82	26/56	NA	31.7	NA	NA
Merlino	2007	Italy	Case-control	65.1 ± 8.6	Interview	Yes	124	22/102	NA	17.7	5.70	4.65 (1.07−20.17)
Minai	2007	USA	Cross-sectional	46.62 ± 15.36	Questionnaire	Yes	19	11/8	NA	57.9	39.1	2.139 (0.621−7.37)
Ulfberg	2007	Sweden	Cross-sectional	NA	Questionnaire	Yes	52	6/46	NA	11.5	4.6	2.677 (1.085−6.603)
Wesstrom	2008	Sweden	Cross-sectional	NA	Questionnaire	Yes	79	16/63	NA	20.2	15.6	1.37 (0.786−2.391)
Winkelman	2008	USA	Cross-sectional	67.9 ± 10.2	Questionnaire	Yes	443	26/417	NA	5.9	5.1	1.156 (0.753−1.774)
Al-Jahdli	2009	Saudi Arabia	Cross-sectional	55.7 ± 17.2	Questionnaire	Yes	119	68/51	NA	57.1	42.6	1.797 (1.061−3.043)
Juuti	2009	Finland	Cross-sectional	NA	Questionnaire	Yes	88	42/46	NA	47.7	48.7	0.67 (0.31−1.47)
Tasdemir	2009	Turkey	Cross-sectional	38.57 ± 15.42	Questionnaire	Yes	61	10/51	NA	16.4	3.0	6.278 (3.05−12.961)
Merlino	2010	Italy	Cross-sectional	65.1 ± 8.6	Interview	Yes	124	22/102	NA	17.7	NA	NA
Li	2011	China	Cross-sectional	39.0 ± 14.8	Questionnaire	Yes	51	21/30	NA	41.2	6.4	10.254 (5.712−18.407)
Plantinga	2012	USA	Cross-sectional	58.9 (57.7−60.1)	Questionnaire	No	1424	NA	NA	NA	NA	1.40 (1.12−1.78)
Cho	2013	South Korea	Case-control	62.91 ± 10.95	Interview	Yes	199 (92/107)	16/183	7/92	8.0	3.6	2.56 (1.030−6.363)
Giannini	2013	Italy	Cross-sectional	46.27 ± 16.25	Interview	Yes	45	6/39	NA	13.3	9.9	1.407 (0.587−3.374)
Lin	2013	China	Cross-sectional	61.9 ± 12.6	Questionnaire	Yes	394	128/226	NA	32.5	21.5	3.61 (2.27−5.77)
Medeiros	2013	Brazil	Cross-sectional	57.59 ± 11.04	Questionnaire	Yes	110 (38/72)	16/94	NA	14.5	NA	NA
Szentkiralyi (DHS)	2013	Germany	Cohort	52.1 ± 13.8	Interview	Yes	101	NA	NA	NA	NA	1.57 (0.75−3.30)
Szentkiralyi (HSP)	2013	Germany	Cohort	50.3 ± 16.4	Interview	Yes	349	NA	NA	NA	NA	1.89 (1.18−3.03)
Winter (W)	2013	France	Cross-sectional	63.6 ± 6.9	Questionnaire	Yes	2230	340/1890	NA	15.2	11.7	1.19 (1.04−1.35)
Winter (M)	2013	France	Cross-sectional	68.4 ± 9.05	Questionnaire	Yes	1970	217/1753	NA	11.0	7.2	1.41 (1.21−1.65)
Harashima	2014	Japan	Cross-sectional	65.0 ± 11.2	Questionnaire	Yes	100	8/92	NA	8.0	NA	NA
Rohani	2014	Iran	Cross-sectional	61.3 ± 13.3	Interview	Yes	85	34/51	NA	40.0	34.6	1.259 (0.666−2.381)
Zobeiri	2014	Iran	Case-control	46.3 ± 13.93	Questionnaire	Yes	140 (80/60)	40/100	NA	28.6	7.1	5.20 (2.48−10.90)
Innes	2015	USA	Cross-sectional	56.96 ± 0.49	Questionnaire	Yes	103	37/66	NA	35.9	21.5	2.045 (1.28−3.267)
Metta	2015	India	Cross-sectional	51.6 ± 11.9	NA	Yes	100	17/83	NA	17.0	NA	NA
Yildiz	2015	Turkey	Case-control	50.6 ± 14.1	Questionnaire	Yes	27	15/12	NA	55.6	30.2	4.1 (1.2−13.7)
Sabic	2016	Bosnia and Herzegovina	Case-control	48.43 ± 15.37	Questionnaire	Yes	30 (9/21)	7/23	NA	23.3	13.3	1.978 (0.513−7.635)
Safak	2016	Turkey	Cross-sectional	71.59 ± 5.68	Interview	Yes	160	44/116	NA	27.5	12.0	2.68 (1.612−4.454)
Molnar	2016	USA	Cohort	59.8 ± 14.3	Interview	Yes	825,442	NA	NA	NA	NA	1.22 (1.13−1.32)

Table 1 (Continued)

Study	Year	Country	Study design	Age (years)	RLS assessment method	IRLSSG criteria	Sample size			RLS in DM (%)	RLS in ND (%)	OR (95%CI)
							DM (M/F)	RLS (+)/ RLS (-)	Males with RLS			
Coronel	2017	Ecuador	Cross-sectional	64.08 (51.99–76.17)	Questionnaire	Yes	290 (207/83)	134/156	NA	46.2	NA	NA
Castillo-Torres	2018	Mexico	Cross-sectional	47.85 ± 16.55	Interview	Yes	59	11/48	NA	18.6	17.4	1.089 (0.398–2.975)
Cuellar	2018	USA	Cross-sectional	59.5 ± 11.6	NA	Yes	121	54/67	NA	44.6	NA	NA
Modarresnia	2018	Iran	Cross-sectional	54.89 ± 7.81	Questionnaire	Yes	210 (83/127)	41/169	NA	19.5	NA	NA
Tuo	2018	China	Case-control	65.0 ± 19.0	Questionnaire	Yes	90	9/81	NA	10.0	3.1	3.611 (1.077–12.11)
Akin	2018	Turkey	Cross-sectional	60.9 ± 10.3	Interview	Yes	318 (126/192)	90/228	26/126	28.3	NA	NA
Bhagawati	2019	India	Cross-sectional	46.55 ± 15.38	Questionnaire	Yes	72	21/51	NA	29.2	17.1	1.995 (1.08–3.687)
Rafie	2019	Iran	Cross-sectional	53.8 ± 12.19	Interview	Yes	44	22/22	NA	50.0	30.1	2.321 (1.109–4.859)
Sunwoo	2019	South Korea	Cross-sectional	44.5 ± 15.0	Questionnaire	Yes	135	7/128	NA	5.2	2.3	2.281 (1.023–5.086)
Pinheiro	2020	India	Cross-sectional	56 ± 13.5	NA	Yes	210 (139/71)	17/193	13	NA	NA	NA

Table 1: **Characteristics of the studies included in the meta-analysis.**
Abbreviations: IRLSSG, International Restless Legs Syndrome Study Group; DM, diabetes mellitus; M, males; F, females; RLS, restless legs syndrome; OR, odds ratio; CI, confidence interval; NA, not available; ND, non-diabetic population.

19 to 825,442. Of the 42 studies, 18 were from Asia[14,23–25,28,36,37,43,46,47,50,51,53,55,56,60–62] and 24 were from Europe and the Americas.[26,27,29–35,38–42,44,45,48,49,52,54,57–59,63] Seven studies had a case-control design,[28,40,48,50,52,56,62,63] 32 had a cross-sectional design,[14,23–27,29–39,41–43,45–47,49,51,53,55,57–61] and three had a cohort design.[44,54]

Risk of bias

Each study was given a Newcastle-Ottawa Scale quality score.[64] The detailed scoring of each domain is in the Supplementary Table 1, and the quality score of "fair" or "good" is displayed. (Supplementary Table 1)

Overall analysis

Because of the high heterogeneity observed across thirty-one studies including RLS frequency in diabetes (I^2 = 95.6%, P < 0.001), the random-effect DerSimonian and Laird method was applied to analyze the prevalence of RLS among DM patients. The pooled prevalence of RLS among DM patients was 25% (95% CI 21%–29%; p < 0.001) (Table 2; Figure 2A).

For the comparison of RLS prevalence between DM patients and non-diabetic population, the random-effects model was again adopted because of the significant heterogeneity (I^2 = 79.3%, P < 0.001). The pooled data revealed that patients with diabetes had a higher risk of RLS (OR 1.98, 95% CI 1.66–2.34; p < 0.001) than non-diabetic population (Table 2; Figure 2B).

Subgroup analysis

Prevalence of RLS among DM patients. In subgroups divided by ethnicity, 14 studies included Asian patients and 17 studies included non-Asian patients. The pooled estimates showed that the prevalence of RLS among diabetic patients was higher in Asia (26%, 95% CI 19%–34%; P < 0.001; I^2 = 95.2%, p < 0.001) than outside Asia (23%, 95% CI 18%–28%; P < 0.001; I^2 = 95.7%, p < 0.001). (Table 2, Supplementary Figure 1)

Two studies evaluated the prevalence of RLS in both male and female diabetes patients. The prevalence of RLS was higher in male patients (49%, 95% CI 0%–103%; P < 0.001; I^2 = 99.2%, p < 0.001) than in female patients (29%, 95% CI 20%–39%; P = 0.001; I^2 = 60.7%, p = 0.004) (Table 2, Supplementary Figure 2).

Comparison of RLS prevalence between DM patients and non-diabetic population. In subgroups classified by populations, 13 studies were performed in Asians[23,25,28,36,37,46,47,50,51,53,55,56,62] and 17 in non-Asians.[26,27,32,34,35,40,42,44,45,48,49,52,54,57–59] Risk of RLS was higher among diabetic patients than in non-diabetic population, and the risk was higher in Asian

Outcome measures	Number of studies	Sample size	Heterogeneity (I^2, P)	Model	Estimates with 95%CI	*p*-value	Conclusion
Overall analyses							
Prevalence of RLS in DM	31	8020	I^2 = 95.6%, P < 0.001	Random	25% (21%−29%)	< 0.001	Significant
Comparison of RLS prevalence between DM patients and non-diabetic population	30	834,193	I^2 = 79.3%, P < 0.001	Random	1.98 (1.66−2.34)	< 0.001	Significant
Subgroup analyses of the prevalence of RLS in DM							
Subgroups stratified by ethnicity							
Asian	14	2059	I^2 = 95.2%, P < 0.001	Random	26% (19−34%)	< 0.001	Significant
non-Asian	17	5961	I^2 = 95.7%, P < 0.001	Random	23% (18%−28%)		
Subgroups stratified by sex							
Male	2	528	I^2 = 99.2%, P < 0.001	Random	49% (0%−103%)	0.004	Significant
Female	2	528	I^2 = 60.7%, P = 0.111	Random	29% (20%−39%)		
Subgroup analyses of the comparison of RLS prevalence between DM patients and non-diabetic population							
Subgroups stratified by population							
Asian	13	1577	I^2 = 68.2%, P < 0.001	Random	3.10 (2.21−4.35)	< 0.001	Significant
non-Asian	17	832, 616	I^2 = 28.0%, P = 0.136	Random	1.34 (1.21−1.48)		
Subgroups stratified by methods							
Interview	10	826, 608	I^2 = 55.7%, P = 0.016	Random	1.71 (1.30−2.25)	< 0.001	Significant
Questionnaire	19	7527	I^2 = 83.7%, P < 0.001	Random	2.16 (1.68−2.78)		
Subgroups stratified by OR extraction						<0.001	Significant
Reported	12	832,850	I^2 = 76.1%, P < 0.001	Random	1.59 (1.33−1.90)		
DDE	18	1685	I^2 = 71.1%, P < 0.001	Random	2.31 (1.68−3.16)		
Subgroups stratified according to whether the sample size is greater than ten thousand							
More than ten thousand	1	825,442		Random	1.22 (1.13−1.32)	< 0.001	Significant
Less than ten thousand	29	8751	I^2 = 77.1%, P < 0.001	Random	2.07 (1.70−2.53)		

***Table 2*: Meta-analysis of the prevalence of restless legs syndrome (RLS) in diabetes mellitus (DM) and the risk of RLS in patients with DM.**
Abbreviations: CI, confidence interval; RLS, restless legs syndrome; DM, diabetes mellitus; DDE, demographic data extrapolated.

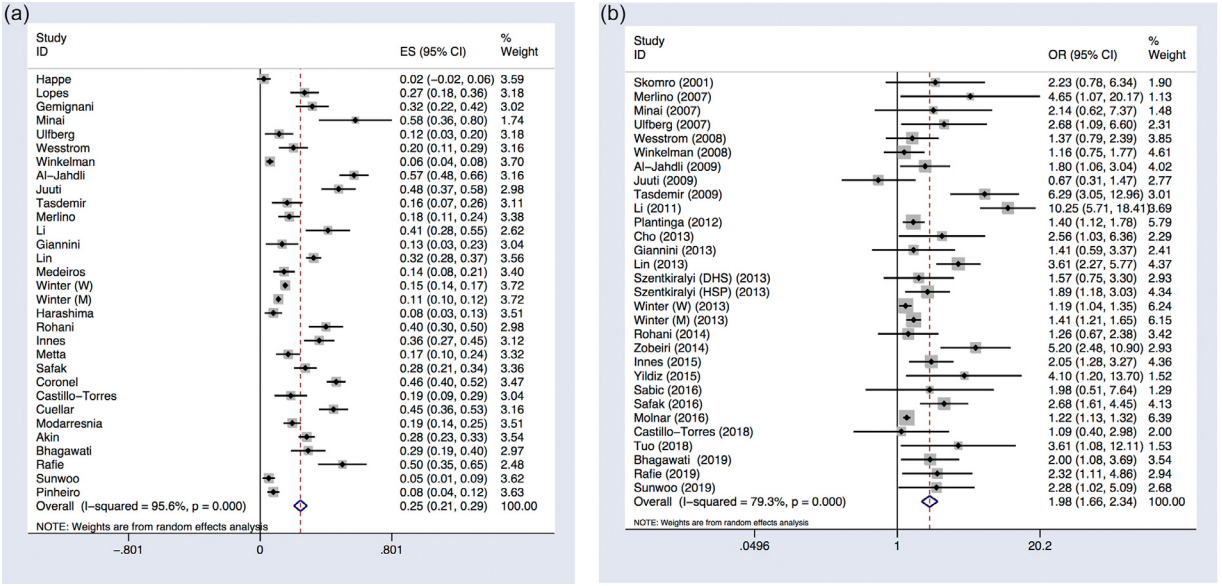

Figure 2. Forest plots of overall analysis. (A) Forest plot of the prevalence of restless leg syndrome (RLS) among patients with diabetes mellitus (DM). (B) Forest plot comparing the prevalence of restless leg syndrome (RLS) between diabetes mellitus (DM) patients and non-diabetic population. Each study corresponds to a line segment parallel to the X-axis; the black dots represent the estimated value of the effect of each study; the square represents the weight of each research, the larger the weight, the larger the area of the square; the line segment represents the 95% confidence interval of the effect size of each study; the diamond represents the summary results of the Meta-analysis synthesis of each study; the center of the diamond represents the point estimate of the summary result effect size, and is marked with a dashed line perpendicular to the X axis; the width of the diamond represents the summary result effect size 95%CI. $X = 0$ is invalid line, which means no statistical significance if 95% CI intersect it.

populations (OR 3.10, 95% CI 2.21 - 4.35; $P < 0.001$; $I^2 = 68.2\%$, $p < 0.001$) than in non-Asian populations (OR 1.34, 95% CI 1.22 − 1.48; $P = 0.136$; $I^2 = 28\%$, $p < 0.001$) (Table 2, Supplementary Figure 3).

Next we stratified the studies based on the method of RLS assessment. There are two common methods for RLS assessment. One is to issue questionnaires to participants, and they conduct self-assessment. The other is that doctors conduct face-to-face interviews with participants.[65,66] Except for six studies that cannot obtain RLS evaluation methods from the text. Ten studies based on interviews[27,28,32,40,44,46,47,51,54] showed that the risk of RLS was higher in diabetic patients than in non-diabetic population (OR 1.71, 95% CI 1.30−2.25; $P = 0.016$; $I^2 = 55.7\%$, $p < 0.001$). Similarly, 19 studies based on questionnaires[23,25,26,34−37,42,45,48-50,53,55−59,62] also showed that higher risk of RLS in diabetic patients than in non-diabetic population (OR 2.16, 95% CI 1.68 −2.78; $P < 0.001$; $I^2 = 83.7\%$, $p < 0.001$). (Table 2, Supplementary Figure 4)

We conduct subgroup analysis according to the extraction method of OR value. Whether it is a statistical analysis of OR values reported in the direct literature (OR 1.59, 95% CI 1.33−1.90; $P < 0.001$; $I^2 = 76.1\%$, $p < 0.001$) or a statistical analysis of OR values that we extrapolated from demographic data (OR 2.31, 95% CI 1.68−3.16; $P < 0.001$; $I^2 = 71.1\%$, $p < 0.001$), they are consistent with the overall results. (Table 2, Supplementary Figure 5)

We also conduct subgroup analysis of the study based on whether the sample size is greater than 10,000. The results show that the results of the sample size greater than 10,000 (OR 1.22, 95% CI 1.13−1.32; $p < 0.001$) and the results of the sample size less than 10,000 (OR 2.07, 95% CI 1.65−2.4; $P < 0.001$; $I^2 = 77.1\%$, $p < 0.001$) are consistent with the overall research results (Table 2, Supplementary Figure 6).

Sensitivity analysis

We performed a sensitivity analysis by omitting the individual studies one at a time to test the robustness of our findings. We found that the sequential removal of each study did not alter the results of primary overall analyses (Figure 3A and B).

Publication bias

Begg's funnel plots estimating the publication bias in the included studies analyzing risk of RLS in DM patients (Figure 4A) and in included studies comparing RLS risk between patients and the non-diabetic population (Figure 4B) appeared symmetrical with respective P values of 0.007 and 0.276. Egger's test showed that the P values are 0.834 and 0.049, respectively. The funnel plots seen by the naked eye showed that a potential publication bias exists in our research.

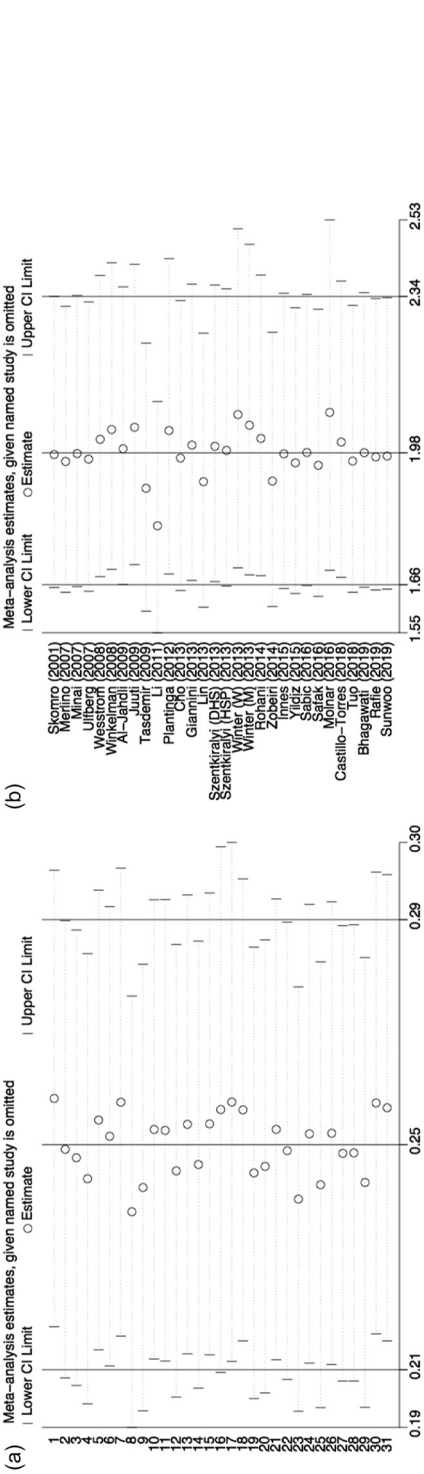

Figure 3. Sensitivity analysis. (A) Sensitivity analysis of the overall prevalence of restless leg syndrome (RLS) in diabetes mellitus (DM). (B) Sensitivity analysis of the risk of RLS in patients with DM. The sphere represents the combined estimate of the meta-analysis after omitting a particular study. It can be roughly seen that the balls fall in the middle of the two short vertical lines, which means that the overall stability is good.

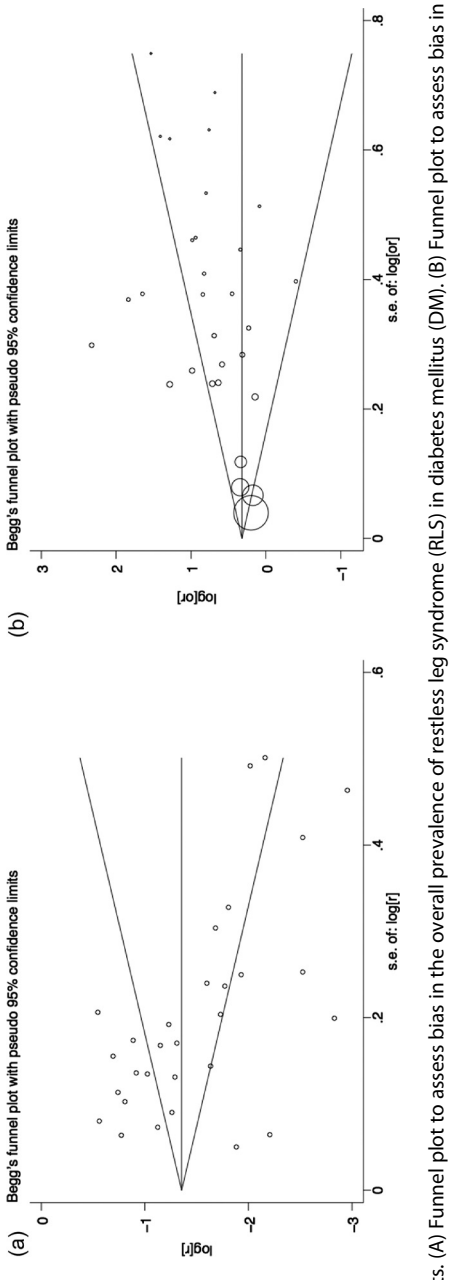

Figure 4. Funnel plots. (A) Funnel plot to assess bias in the overall prevalence of restless leg syndrome (RLS) in diabetes mellitus (DM). (B) Funnel plot to assess bias in the comparison of RLS prevalence between DM patients and non-diabetic population. The naked eye can see that not all the balls fall in the middle of the funnel, suggesting that there may be potential bias.

Discussion

Conclusion was reached from our analysis of 31 studies involving 8020 individuals, namely, a pooled RLS prevalence (based on IRLSSG diagnostic criteria) of 25% among DM patients, much higher than the prevalence of 5–10% reported in the general population.[67] The prevalence appears to be slightly whereas significantly higher in Asian countries (26%) than non-Asian countries (23%). Moreover, the prevalence of RLS in male patients was higher than in female patients (49% vs. 29%). In addition, results were found that nearly twofold higher risk of RLS in diabetic patients than in non-diabetic population (OR 1.98, 95% CI 1.66–2.34; $p < 0.001$). This increased risk was stable across ethnic subgroup, OR extraction subgroup, and sample size subgroup.

While the reasons behind an association between DM and RLS remain unclear, we speculate that the association may be explained by one or more of the following pathophysiological mechanisms. Up to 96% of patients with RLS and type 2 diabetes have diabetic neuropathy,[68] and type 2 diabetic patients are at 7.9-fold higher risk of RLS if they also have diabetic neuropathy.[40] Abnormal peripheral inputs due to small-fiber neuropathy associated with diabetes can trigger spinal generators underlying RLS phenomena.[31] Indeed, results from rats were found that show reduced dopamine content in the striatum and midbrain, which are important parts of RLS circuitry.[69] Additionally, individuals with diabetes are at increased risk of sleep disorders, particularly excessive daytime sleepiness,[29] and RLS patients are with significantly higher levels of hemoglobin A1C and fasting plasma glucose than healthy controls.[70]

Results were gotten that the prevalence of RLS was higher in Asian diabetic patients than in non-Asian patients, which is contrary to the previous higher risk of RLS in multiple sclerosis patients and Parkinson's disease in non-Asian populations. This change may reflect the difference in RLS assessment methods, that is, the threshold used to determine whether symptoms occur frequently to ensure the diagnosis of RLS.[71] The differences in patient's age, disease severity and peripheral nerve involvement also contribute to the difference. In addition, results were also reported that differential expression of genes related to DM risk among various ethnic groups.[72] Asians may be less sensitive to insulin than non-Asians, potentially leaving them more susceptible to complications related to DM.[73] Results from our work were found namely, RLS prevalence was higher among male patients than among female patients, according to two of 31 studies that reported sex information. This contrasts with the higher frequency of women with RLS in other comorbidities, such as Parkinson's disease and multiple sclerosis. This may be related to the different comorbidities of the patients and the limited sample size we included. The underlying mechanism needs further study.

RLS is often accompanied by many diseases, such as neurological diseases, sleep-related diseases and so on. Because many patients have mild symptoms, it is difficult to identify.

Our meta-analysis presents several limitations. First, the retrospective nature of the study meant that data on several potentially important variables were missing. Second, moderate statistical heterogeneity and potential bias was showed. This might be explained by differences in demographic characteristics and study designs. Indeed, studies differed in the method of RLS assessment, the threshold of symptom frequency for diagnosing RLS, the age of patients, as well as the severity and duration of DM, all of which may have confounded our analyses. Nevertheless, our sensitivity analysis suggested robust overall findings. Third, most studies includes both type 1 DM (T1DM) and type 2 DM (T2DM), which caused the difficulty to analyze the diabetes mellitus type. Fourth, only articles in English were included, which may cause some selection bias. Additional eligible studies may be identified by including other languages. Fifth, although we performed some subgroups analysis and showed stable results. Our research will still be affected by some untreated confounding factors. Sixth, the 825,442 subjects came from one study among the 835,986 subjects included in the meta-analysis, whereas the process of inclusion/exclusion is in conformity with the specification of Cochrane Collaboration. Thereby, final number of included studies are adhered to statistical methodology and we have added discussion in related parts. However, it needs to be considered that this paper may have a disproportionate weight during the analysis process, which may affect the results. In addition, although the studies we included are based on the criteria of the International Restless Legs Syndrome Research Study Group (IRLSSG), the significance of polysomnography for restless legs syndrome (RLS) should still be considered. Our results need to be verified in future large prospective studies due to the lack of sleep physiology examination. Also, the impact of diabetes treatment on the prevalence of restless legs syndrome should also be considered in future studies.

In conclusion, to the best of our knowledge this is the first pooled estimate for RLS prevalence in DM, strengthening previous suggestions that RLS risk is higher among DM patients than among non-diabetic population. However, more studies are needed to determine whether this is true for both types of diabetes. The available evidence justifies further exploration of the potential link between RLS and DM and efforts to develop effective treatments against both disorders.

Data sharing statement

This meta-analysis of secondary analysis of raw data from published original articles. All the data used for the study are included in the manuscript and supplementary material.

Author contributions

Conceptualization: NP, MX, YXL, XYM, LT; Date curation: NP, MX, YXL; Formal analysis: NPP, MX, YX; Funding acquisition: XY; Investigation: MX, YXL; Methodology: NP; Project administration: XY, LT; Resources: NP; Software: NP; Xin Mu; YXL; Supervision: XY; Validation: XY; Visualization: NP; XY; Writing-original draft preparation: NP, MX; Writing-review and editing: YXL, XYM, LT.

Funding

This work was supported by the Basic Conditions Platform Construction Project of Sichuan Science and Technology Department (2019JDPT0015), and the "1 3 5 project for disciplines of excellence, West China Hospital, Sichuan University" (ZYJC18003).

Declaration of interests

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

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101357.

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