Worldwide estimation of restless legs syndrome: a systematic review and meta-analysis of prevalence in the general adult population

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Summary
This systematic review, meta-analysis and meta-regression assessed the prevalence of restless legs syndrome (RLS) in the general adult population. Studies identified in Scopus, PubMed, Web of Science, and PsycInfo between January 2000 and February 2022 were included if they used a case–control or cross-sectional design and reported data regarding the prevalence of RLS. The protocol was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022300709). A total of 97 studies including 483,079 participants from 33 different countries met the eligibility criteria. The Newcastle Ottawa Scale was used to evaluate the methodological quality, and the fill-and-trim method was used to correct probable publication bias, while the jack-knife method was performed to assess small study effect. The corrected overall pooled prevalence of RLS was 3% (95% confidence interval [CI] 1.4%–3.8%). The pooled prevalence of RLS syndrome was affected by methodological quality (no data from non-respondents in the included studies), gender (higher among women), study design (lower prevalence in case–control versus cohort and cross-sectional studies). The figures for corrected pooled prevalence among men, women, alcohol consumers and smokers were 2.8% (95% CI 2%–3.7%); 4.7% (95% CI 3.2%–6.3%); 1.4% (95% CI 0%–4.2%); and 2.7% (95% CI 0%–5.3%), respectively. The prevalence among male and female participants was lower in community-based versus non-community-based studies. Moreover, the prevalence was higher in developed versus developing countries and among elders versus adults. In conclusion, RLS is a common disorder in the general adult population, with a higher prevalence in women; however, prevalence data are affected by study design and quality.

KEYWORDS
meta-regression, Newcastle–Ottawa Scale, prevalence, sleep, Willis Ekbom disease, Wittmaack Ekbom syndrome
1 | INTRODUCTION

Restless legs syndrome (RLS) is a sensory-motor circadian rhythm disorder (Guay et al., 2020; Koo et al., 2016) causing various sleep problems (Xu et al., 2020), cognitive deficits (Pearson et al., 2006), and depressive symptoms (Lee et al., 2008) with pronounced effects on the life situation (Harrison et al., 2021) and quality of life of the sufferer (Kushida et al., 2007). The degree of discomfort can range from mild and infrequent to severe daily discomfort. Gender (i.e., female gender) and various lifestyle factors (e.g., coffee intake, smoking, and alcohol) can increase the risk (Batool-Anwar et al., 2016) and affect the course of RLS (Mitterling et al., 2015). Clinical features and practical approach are of importance in making a correct RLS diagnosis (Wijemanne & Ondo, 2017). The five diagnostic criteria for RLS set by the International Restless Legs Syndrome Study Group (IRLSSG; Allen et al., 2014) include: (I) Desire to move the limbs, usually associated with paresthesias/dysesthesias, (II) Motor restlessness, (III) Symptoms are worse or exclusively present at rest (i.e., lying, sitting) with at least partial and temporary relief by activity, (IV) Symptoms are worse in evening/night, and (V) The occurrence of the above features is not only reported as symptoms that are primary to another medical or behavioural condition. As indicated in the criteria, RLS may be secondary to several other diseases or conditions. Meta-analyses of the prevalence of RLS in relation to specific diagnoses and conditions indicate high prevalence rates for end-stage renal disease (Huang et al., 2020), chronic liver disease (Gupta et al., 2021), multiple sclerosis (Ozdogar & Kalron, 2021), diabetes mellitus (Ning et al., 2022), peripheral neuropathy (Jiménez-Jiménez et al., 2021), migraine (Ghasemi et al., 2020), and for pregnant women in the third trimester (Darvishi et al., 2020).

The initial step in the diagnostic procedure is often taken by a general practitioner, who also might initiate treatment, while severe cases are referred to and treated at neurological clinics (Garcia-Borreguero et al., 2016). Dopamine agonists, L-dopa, Alpha-2-delta ligands, opioids, or iron are available, depending on the aetiology, symptom severity, age of the patient and presence of comorbidities (During & Winkelman, 2019; Garcia-Borreguero et al., 2018; Wijemanne & Ondo, 2017; Winkelmann et al., 2018). For a general practitioner without experience of RLS treatment, RLS might cause difficulties in the choice of treatment, but also in relation to the diagnostic procedure (Fulda et al., 2021; Umbreit et al., 2021). This can lead to under-diagnosis, especially in patients with less obvious symptomatology or lack of known comorbidities (Trenkwalder, 2007). However, there is also a risk for over-diagnosis, as many of the symptoms are non-specific and can occur in other diseases, so-called RLS mimics, which has led to a call for improved diagnostic methods and measuring instruments (Fulda et al., 2021). Trenkwalder et al. (2016) highlight that treatment of an underlying disease should be achieved as far as possible to reduce or eliminate potential RLS symptoms, which may require special skills (Garcia-Borreguero et al., 2016). Prevalence figures for the general population vary (Allen et al., 2014; Guay et al., 2020) and an improvement in the diagnostic test accuracy of screening instruments has been stressed (Fulda et al., 2021). There is a lack of recent meta-analyses of prevalence for RLS in the general population. Ohayon et al. (2012) published a synthesis of the literature 10 years ago and stated that prevalence estimates in the general adult population varied greatly (i.e., from 1.9% to 15%). The varied prevalence figures, reinforced by sometimes unclear descriptions of symptoms and signs (Allen et al., 2014; Wijemanne & Ondo, 2017) might affect the understanding of RLS as a prevalent and troublesome condition. An updated meta synthesis of the prevalence of RLS, and possible factors of importance for prevalence (e.g., gender and effects of known risk factors) can raise awareness of RLS as a potential diagnosis when a patient seeks help for sleep problems in primary care. The main purpose of this systematic review was therefore to (i) examine the prevalence of RLS in the general adult population, as well as to examine (ii) its frequency in gender subgroups, (iii) its frequency in smokers and alcohol consumers, (iv) its heterogeneity and possible sources, and (v) moderator variables for the prevalence of RLS.

2 | METHODS

2.1 | Design and registration

The present systematic review is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The protocol was registered under decree code CRD42022300709 in the International Prospective Register of Systematic Reviews (PROSPERO; Pakpour et al., 2022).

2.2 | Search strategy

Four academic databases including PubMed, Scopus, Web of Science, and PsycINFO were searched systematically between February 12 and 24, 2022. The search terms were extracted from PubMed Medical Subject Headings (MeSH), published reviews, and primary studies. The main search terms were related to RLS and included “Restless Legs syndrome”, “RLS”, “Willis Ekbom Disease”, “Wittmaack Ekbom Syndrome”. The search syntax (Appendix A) was developed using Boolean operators (AND/OR/NOT) and was implemented based on the advanced search attributes of each database. Additionally, further sources (i.e., reference lists of included studies and systematic reviews of published papers) were manually searched to increase the likelihood of retrieving relevant empirical studies.

2.3 | Eligibility criteria

Observational studies including cohort, case–control studies (i.e., both cases and controls) and cross-sectional studies were included, if relevant data regarding the prevalence of RLS in the general adult population were reported. In studies eligible for inclusion, the presence of RLS should be assessed by valid and reliable measures, clinical examination or other methods with acceptable validity and reliability. English, peer-
reviewed papers published from 2000 to February 2022 were included. There were no limitations regarding participants’ characteristics.

2.4 Study outcomes

Primary outcome

i. Estimation of RLS prevalence.

Secondary outcomes:

i. Prevalence of RLS in gender subgroups.
ii. Prevalence of RLS in subgroups of smokers, alcohol consumers, and according to region.
iii. Heterogeneity and its possible sources.
iv. Moderator variables for prevalence of RLS.

2.5 Study screening and selection

The first step was the screening of all retrieved papers based on their title and abstract. Then, in the second step, full texts of potentially relevant studies were further examined based on the inclusion criteria. In this process, relevant studies were selected. These steps were taken independently by two researchers, and then discussed and agreed upon with the other researchers.

2.6 Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality of the studies (Luchini et al., 2017). Three characteristics (i.e., selection, comparability, and outcome) are examined with the NOS checklist. The checklist has three versions for evaluating cross-sectional studies (seven items), case-control studies (eight items), and cohort studies (eight items). Despite a slight difference in the number and content of items, each item is rated with 1 point, except comparability which can have 2 points. This results in a maximum quality score of 9 points (i.e., 4 points for selection, 2 points for comparability, and 3 points for outcomes) for each study. Studies with <5 points are classified as having a high risk of bias (Luchini et al., 2017). No studies were excluded based on the quality rating. However, subgroup analysis was conducted to assess the impact on pooled effect size. The methodological quality assessment was performed independently by two reviewers. Disagreements were resolved through a consensus discussion with the other researchers.

2.7 Data extraction

A pre-designed form was prepared to extract data. The data included the first author’s name, publication year, data collection date, study design, country, number of participants, gender, mean age, scales used to assess RLS, numerical results regarding the frequency of RLS, moderator variables, and quality assessment result. The data extraction was performed independently by two reviewers. Disagreements were resolved through a consensus discussion with the other reviewers.

2.8 Data synthesis

A quantitative synthesis using STATA software version 14 was conducted. Meta-analysis was carried out using a random-effect model because the included studies were taken from different populations, and both within- and between-study variances should be accounted for (Hox & Leeuw, 2003). The random-effects model was applied based on the assumption that there were different real effects due to differences in the study groups or differences in the measurement methods between the study groups. These differences cause two types of variances, within and between studies, which should be considered in the meta-analysis. Meta-analysis with the random-effects model considers both variances in the calculation of effect size and degree of heterogeneity. Also, in the random-effects model, the relative weights of each study are more balanced than the weights assigned in the fixed-effects model, because standard random-effect methods add a common variance component to each study weight to account for between-study variation in summary effects. Consequently, this dual source of variability (within and between studies) will result in a wider variance, standard error (SE), and confidence interval (CI) for the summary effect (Bailli et al., 2018).

The Q Cochrane statistic was used to assess heterogeneity. Also, the severity of heterogeneity was estimated using the I² index (Huedo-Medina et al., 2006). The I² index is interpreted as mild (I² < 25%), moderate (25 < I² < 50%), severe (50 < I² < 75%), or highly severe (I² > 75%) (Huedo-Medina et al., 2006). As the primary outcome for the present study is the prevalence of RLS, the pooled prevalence and its 95% CI are analysed with the use of the METAPROP module in STATA. To assess moderator effects, subgroup analysis (analysed using the METAPROP module based on grouping variables in STATA) or meta-regression (analysed using the METAREG module considering individuals’ study effect size and their SE besides the variable of interest) was carried out based on different variables. Subgroup analysis and meta-regression should be conducted to find possible sources of heterogeneity and differences of pooled effect size based on different variables (Morton et al., 2010). Meta-regression is a fixed- or random-effects model considering one or more study features as covariates. It is used to create a model describing the linear relationship between (both continuous and categorical) study-level covariates and the effect size (Winters-Miner et al., 2015).

A funnel plot (i.e., a scatterplot of the estimate of effect from each study included in the meta-analysis against a measure of its precision, usually 1/SE) and Begg’s test (i.e., an assessment of whether there is a significant correlation between the ranks of the effect estimates and the ranks of their variances) were used to assess publication bias (Rothstein et al., 2005). We used pseudo 95% CI to...
demonstrate the effect sizes derived from each study (logit event rate) against their corresponding SEs. Publication bias is underreported in systematic reviews (Onishi & Furukawa, 2014; Shi & Lin, 2019), and can be caused by multiple issues (Rothstein et al., 2005) leading to incorrect conclusions, as the synthesised effect estimates may be exaggerated in a false direction (e.g., an over- or under-estimation of prevalence) in studies with less significant results, or smaller sample sizes (Nissen et al., 2016; Shi & Lin, 2019). Therefore, methods to adjust and produce unbiased findings were used (Sterne et al., 2011). The best approach is to recover related unpublished results using the fill-and-trim method, a non-parametric approach based on examining the funnel plot's asymmetry method (Herrmann et al., 2017). In the present study, we used the fill-and-trim method to adjust probable publication bias (conducted using the METATRIM module in STATA).

The jack-knife method was used for sensitivity analysis (Hedges & Olkin, 2014). It assesses the bias of an estimator through cross-validation in an iterative process. Initially, an approximation is done on the whole sample. Secondly, each element that creates problems is dropped from the whole sample and the variable in focus is assessed in this new smaller sample (Salkind, 2010).

3 | RESULTS

3.1 | Study screening and selection process

The initial search in four databases resulted in 11,144 studies: ISI Web of Knowledge (n = 3,224), Scopus (n = 6,210), PubMed (n = 1,710), PsycINFO and reference lists of included studies (n = 54). After removing duplicated papers, 10,789 papers were screened based on title and abstract. Then, 282 papers appeared to be potentially eligible, and their full texts were reviewed. Finally, 97 studies met the eligibility criteria and were pooled in the meta-analysis. Figure 1 shows the search process based on the PRISMA flowchart.
3.2 | Study description

The 97 studies comprised 483,079 participants from 33 different countries (Argentina, Australia, Brazil, Canada, China, Colombia, Denmark, Eastern Africa, Egypt, Finland, France, Germany, Greece, Iceland, India, Iran, Iraq, Italy, Japan, Korea, Mexico, the Netherlands, Norway, Pakistan, Portugal, Saudi Arabia, Spain, Sweden, Turkey, Taiwan, UK, USA). The country with the most eligible studies (n = 12) was the USA. The smallest sample size was 78 (Haggstram et al., 2009) and the largest sample size was 88,673 (Gao et al., 2009). The mean (SD, range) age of participants was 51.16 (16.02, 15–109) years. More than half of the overall participants were female (56.34%), 17.50% were smokers, and 26.30% were alcohol consumers. The most frequently used study design was cross-sectional (n = 78). In all, 17 studies were cohort type and two were case–control studies. In the case–control studies, data regarding controls were also included if relevant for the prevalence of RLS. Data were collected with various measures to assess RLS, with the IRLSSG 2003 (n = 33) being the most frequently used scale, followed by IRLSSG 1995 (n = 11). Table S1 provides the summary characteristics of all included studies.

3.3 | Quality assessment

Based on NOS, 92 studies were categorised as being high quality. The impacts of study quality were further assessed and reported in subgroup analysis. The most common problems were in sample size being not estimated or justified (81.82%), and non-representativeness of the sample due to no description of the response rate or the characteristics of the responders and the non-responders (95.96%). The results of the quality assessment are provided in Table S1 and Figure 2.

3.4 | Outcome measures

3.4.1 | Overall RLS prevalence estimates

The pooled estimated RLS was 11% (97 studies; 95% CI 10%–13%, \( I^2:99.8\%\), \( \tau^2 < 0.001 \)). Figure 3 provides the Forest plot showing the pooled prevalence of RLS. Based on Begg’s test (\( p = 0.19 \)) and a funnel plot (Figure 4), the probability of publication bias was confirmed. In the following fill-and-trim analysis 47 studies were imputed and the corrected results showed that the pooled prevalence of RLS was 3% (95% CI 1.4%–3.8%; between studies variance = 0.005). The funnel plot after trimming is provided in Figure 5. Also, sensitivity analysis showed that the pooled effect size was not affected by a single study effect.

Subgroup analysis (Table 1) showed that the pooled prevalence of RLS syndrome was affected by methodological quality (6%[95% CI 4%–8%] low quality versus 12%[95% CI 11%–13%] high quality; \( p = 0.30 \)), gender (7%[95% CI 6%–7%] men versus 11%[95% CI 9%–12%] women; \( p = 0.19 \)), study design (case–control: 8%[95% CI 6%–9%] versus cohort: 12%[95% CI 8%–15%] and cross-sectional: 12%[95% CI 10%–13%]; \( p = 0.79 \)), but not significantly according to the meta-regression (Table 2). The variables investigated in subgroup analysis and meta-regression had no significant effect on the estimated effect size or heterogeneity.

As methodological quality affected the pooled prevalence, further investigation was conducted to explore the most influential methodological item. Based on uni- and multivariable meta-regression, there was a selection bias as non-respondents were not dealt with. In this item of the NOS checklist, the score is acquired when comparability between respondents and non-respondents’ characteristics is established, and the response rate is satisfactory. No score is given if the response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory, or no description of the response rate or the characteristics of the responders and the non-
FIGURE 3  Forest plot displaying the estimated pooled prevalence of restless legs syndrome. CI, confidence interval; ES, effect size.
3.4.2 | Gender-specific outcome measures

**RLS prevalence estimates among male subgroups**

The pooled estimated RLS prevalence among male participants was 7% (55 studies; 95% CI 6%–7%, $I^2$:98.30%, $\tau^2 < 0.001$). Figure 6 provides a Forest plot showing the pooled prevalence of RLS among male participants. Based on Begg's test ($p = 0.002$) and a funnel plot (Figure 7), the probability of publication bias was confirmed. In the following fill-and-trim analysis, 22 studies were imputed, and the corrected results showed that the pooled prevalence of RLS was 2.8% (95% CI 2%–3.7%; between studies variance = 0.001). The funnel plot after trimming is provided in Figure 8. Also, sensitivity analysis showed that the pooled effect size was not affected by a single study effect. The prevalence of RLS among male participants was reported to be lower in community-based versus non-community-based studies (6% versus 10%), which was borderline significant ($p = 0.06$). Other variables investigated in subgroup analysis and meta-regression had no significant effect on the estimated effect size or heterogeneity (Table 1, Table 2).

**RLS prevalence estimates among female subgroups**

The pooled estimated RLS prevalence among female participants was 11% (58 studies; 95% CI 9%–12%, $I^2$:99.52%, $\tau^2 < 0.001$). Figure 9 provides a Forest plot showing the pooled prevalence of RLS among the female participants. Based on Begg's test ($p < 0.001$) and the funnel plot (Figure 10), the probability of publication bias was confirmed. In the following fill-and-trim analysis, 23 studies were imputed, and the corrected results showed that the pooled prevalence of RLS was 4.7% (95% CI 3.2%–6.3%; between studies variance = 0.005). The funnel plot after trimming is provided in Figure 11. Also, a sensitivity analysis showed that the pooled effect size was not affected by a single study effect. The prevalence of RLS among female participants was reported to be significantly lower in community-based versus non-community-based studies (9% vs. 16%; $p = 0.02$). Other variables investigated in subgroup analysis and meta-regression had no significant effect on the estimated effect size or heterogeneity (Table 1, Table 2).

3.4.3 | RLS prevalence estimates among alcohol consumers

The pooled estimated RLS prevalence among alcohol consumers was 8% (10 studies; 95% CI 5%–10%, $I^2$:98.24%, $\tau^2 < 0.001$). The probability of publication bias was confirmed (Begg's test $p = 0.15$) and the pooled prevalence of RLS was 1.4% (95% CI 0%–4.2%; between studies variance = 0.002). The prevalence of RLS among alcohol consumers was significantly higher among elders versus adults (18% versus 3%). Other variables investigated in subgroup analysis and meta-regression had no significant effect on the estimated effect size or heterogeneity (Table 1, Table 2).

3.4.4 | RLS prevalence estimates among smokers

The pooled estimated RLS prevalence among smokers was 12% (22 studies; 95% CI 9%–14%, $I^2$:98.74%, $\tau^2 < 0.001$). The probability of publication bias was confirmed (Begg's test $p = 0.45$) and the pooled prevalence of RLS was 2.7% (95% CI 0%–5.3%; between studies variance = 0.005). Other variables investigated in subgroup analysis...
## Table 1: Results of subgroup analysis regarding estimated pooled prevalence of RLS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Male participants</th>
<th>Female participants</th>
<th>Alcohol consumers</th>
<th>Smokers</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Studies, n</td>
<td>Pooled prevalence (95% CI)</td>
<td>I²</td>
<td>Studies, n</td>
<td>Pooled prevalence (95% CI)</td>
</tr>
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<td>Quality</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low quality</td>
<td>7</td>
<td>6 (4; 8)</td>
<td>98.15</td>
<td>4</td>
<td>5 (3; 7)</td>
</tr>
<tr>
<td>High quality</td>
<td>90</td>
<td>12 (11; 13)</td>
<td>99.82</td>
<td>51</td>
<td>7 (6; 7)</td>
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<tr>
<td>Community based survey</td>
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<tr>
<td>Yes</td>
<td>66</td>
<td>10 (9; 11)</td>
<td>99.81</td>
<td>42</td>
<td>6 (5; 7)</td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>14 (11; 18)</td>
<td>99.69</td>
<td>13</td>
<td>10 (7; 12)</td>
</tr>
<tr>
<td>Development status of country</td>
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<td></td>
<td></td>
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<tr>
<td>Developed</td>
<td>74</td>
<td>12 (10; 13)</td>
<td>99.79</td>
<td>45</td>
<td>7 (6; 8)</td>
</tr>
<tr>
<td>Developing</td>
<td>23</td>
<td>11 (8; 14)</td>
<td>99.76</td>
<td>10</td>
<td>6 (4; 9)</td>
</tr>
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<td>Study design</td>
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<td></td>
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<tr>
<td>Cross-sectional</td>
<td>78</td>
<td>12 (10; 13)</td>
<td>99.77</td>
<td>45</td>
<td>6 (5; 7)</td>
</tr>
<tr>
<td>Cohort</td>
<td>17</td>
<td>12 (8; 15)</td>
<td>99.83</td>
<td>10</td>
<td>9 (6; 11)</td>
</tr>
<tr>
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<td>8 (6; 9)</td>
<td></td>
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<td>IRLSS 2003</td>
<td>32</td>
<td>12 (8; 15)</td>
<td>99.80</td>
<td>20</td>
<td>7 (5; 9)</td>
</tr>
<tr>
<td>IRLSS 1995</td>
<td>11</td>
<td>14 (9; 19)</td>
<td>99.72</td>
<td>5</td>
<td>5 (2; 8)</td>
</tr>
<tr>
<td>Other</td>
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<td>11 (10; 12)</td>
<td>99.75</td>
<td>30</td>
<td>6 (5; 7)</td>
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<td>Age group of participants</td>
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<tr>
<td>Adults</td>
<td>67</td>
<td>10 (9; 12)</td>
<td>99.81</td>
<td>36</td>
<td>6 (5; 7)</td>
</tr>
<tr>
<td>Elderly</td>
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<td>15 (11; 18)</td>
<td>99.79</td>
<td>19</td>
<td>8 (6; 10)</td>
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<tr>
<td>Overall Estimated Prevalence</td>
<td>97</td>
<td>11 (10; 13)</td>
<td>99.80</td>
<td>55</td>
<td>7 (6; 7)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; I², Heterogeneity Index.
3.4.5 | RLS prevalence estimates according to region

The pooled estimated RLS prevalence according to region was highest in South America 16% (seven studies; 95% CI 8%–24%, $\tau^2$: 99.69%, $\chi^2$: 0.01) and Europe 16% (40 studies; 95% CI 12%–19%, $\tau^2$: 99.79%, $\chi^2$: 0.01) followed by Africa 12% (three studies; 95% CI 0%–24%, $\tau^2$: -), North America 9% (13 studies; 95% CI 7%–12%, $\tau^2$: 99.84%, $\chi^2$: < 0.001), Oceanic 7% (two studies; 95% CI 6%–7%, $\tau^2$: -) and Asia 6% (31 studies; 95% CI 5%–7%, $\tau^2$: 98.99%, $\chi^2$: < 0.001), respectively.

Publication bias was assessed for each region and no publication bias was found for South America (Begg’s test, $p = 0.94$). Probable publication bias was found for Europe (Begg’s test $p = 0.001$) with a corrected pooled prevalence of 5.9% (18 studies imputed; 95% CI 2%–9.7%, $\tau^2$: 0.02), Asia (Begg’s test, $p = 0.001$) with a corrected pooled prevalence of 2.3% (12 studies imputed; 95% CI 1.2%–3.3%,$\tau^2$: 0.001) and for North America (Begg’s test, $p = 0.01$) with a corrected pooled prevalence of 2% (seven studies imputed; 95% CI 0%–4%, $\tau^2$: 0.002). Publication bias was not checked for Africa and Oceanic due to low number of studies.

4 | DISCUSSION

The present systematic review and meta-analysis aimed to examine the prevalence of RLS in the general adult population, its prevalence in subgroups (i.e., by gender, smokers, and alcohol consumers), its heterogeneity, possible sources, as well as moderator variables for prevalence. After employing a rigorous selection method, using the PRISMA guidelines, full texts of 282 papers from 2000 to 2022 were reviewed to ensure we included all evidence in this field to quantify the prevalence of RLS in the general population. A total of 97 studies, the majority being cross-sectional ($n = 78$), comprising 483,079 participants from 33 different countries, were included. The results indicated a pooled RLS prevalence of 11% (95% CI 10%–13%, $\tau^2$: 99.80%, $\chi^2$: < 0.001). Ohayon et al. (2012) published a synthesis of the literature 10 years ago and found that if only “symptoms” was applied to evaluate the occurrence of RLS, prevalence, estimates ranged from 9.4% to 15%. If a set of symptoms that met the then existing minimal diagnostic criteria of the IRLSSG, the prevalence in the literature ranged from 3.9% to 14.3%. When frequency/severity was added, prevalence ranged from 2.2% to 7.9%, and when differential diagnosis was applied, prevalence estimates were between 1.9% and 4.6%. The results of Ohayon et al. (2012), especially those that used the then existing minimal diagnostic criteria, are comparable to our pooled prevalence.

There are several aspects to consider when examining the prevalence in the general population (e.g., differences in subgroups, with description of heterogeneity and possible sources). Our subgroup
analyses (Table 1) showed differences for pooled RLS prevalence according to gender, methodological quality, setting, development status of country, study design, use of RLS measure used for data collection and participant groups, but none were significant according to the meta-regression (Table 2), except for the prevalence among women, which was reported to be significantly lower in community-based versus non-community-based studies (9% versus 16%; p = 0.02). Interestingly, we found a higher prevalence of RLS among alcohol consumers in developed versus developing countries, but also a higher prevalence of RLS among elders versus adults in these subgroups, which was not significant in other subgroups (Table 1). South America and Europe were the regions with the highest pooled prevalence, while Asia and North America were the two with the lowest. Prevalence data according to region should be evaluated with caution due to a low number of studies in some regions. However, some of these differences were anticipated and in line with previous research, e.g., a higher prevalence for women, and a lower prevalence for community-based samples and low-quality studies. Use of relevant updated diagnostic criteria, and how data were collected, and symptoms evaluated (e.g., through clinical assessments, or self-reported

FIGURE 6 Forest plot displaying the estimated pooled prevalence of restless legs syndrome among male participants. CI, confidence interval; ES, effect size
data using validated instruments), could also be anticipated to impact prevalence, but rather surprisingly none of these variables did so.

Unfortunately, there is no biological diagnostic test available for RLS, meaning that a diagnosis is based on an assessment of the patient's description of symptoms. Importantly, all five IRLSSG diagnostic criteria must be satisfied (Fulda et al., 2021; Garcia-Borreguero et al., 2018). In this systematic review, all included studies used relevant diagnostic criteria. However, as our meta-analysis is based on studies from 2000 to 2022, and small changes have been made during this period regarding the diagnostic definition (i.e., 2003 and 2012; Allen et al., 2014), this means different sets of diagnostic criteria have been used in the included studies. When looking at the year of data collection in comparison to when new diagnostic criteria were introduced, a total of 26 studies, out of the studies providing information on time for data collection, collected data before 2003; 33 between 2004 and 2012, and 17 between 2013 and 2022. Studies that have collected data based on either the pre-2003, or 2003 diagnostic criteria, might present a higher proportion of false positives and consequently an exaggerated prevalence, as the 2012 criteria were modified to include an additional fifth criterion emphasising differential diagnosis to lower the false positives and improve specificity. The fifth criterion implies a greater emphasis on differentiating other conditions that mimic RLS (e.g., leg cramps or arthritic pain in lower limbs), which decreases the risk of misdiagnosis. Several comorbidities or conditions, such as end-stage renal disease, chronic liver disease, multiple sclerosis, diabetes mellitus, iron deficiency, and polyneuropathy (e.g., linked to alcohol abuse, and vitamin B12 deficiency) have been associated with high prevalence rates of RLS (Gupta et al., 2021; Huang et al., 2020; Jiménez-Jiménez et al., 2021; Ning et al., 2022; Ozdogar & Kalron, 2021). Furthermore, side-effects of specific pharmacotherapy (e.g., neuroleptics, antidepressants, anti-epileptics, lithium, and antihistamines) can induce or worsen RLS symptoms (Allen et al., 2014). Therefore, even if procedures were adherent to diagnostic criteria, with the fifth criterion in use, difficulties in adequately assessing diagnostic criteria during the data collection could have affected the occurrence of RLS in the included studies. The 10-item IRLSSG 2003 (Group, 2003) was the most frequently used RLS-specific instrument (n = 32). According to the meta-regression, the use of a data collection tool did not significantly affect the prevalence, nor did the time when the data collection was performed or the data collection procedure (Table 2).

### 4.1 Clinical implications

A wide range of data collection tools can be used to screen for RLS. RLS-specific questionnaires or specific questions based on diagnostic criteria for RLS are preferable, but questionnaires that screen for multiple sleep disorders (e.g., Global Sleep Assessment Questionnaire; Roth et al., 2002 or SLEEP-50; Spoormaker et al., 2005) can also be used. However, RLS is primarily a subjective disorder, and using a short, validated patient-completed single-condition measure created by specialists could, based on its brevity, comprehensiveness, specificity, as well as psychometric soundness, be desirable in a study focusing on RLS prevalence. The high prevalence of sleep disorders in the general population presents introduces a need for extensive questionnaires to screen for various symptoms and multiple sleep disorders in a primary care context, but an extensive questionnaire might blur the patient's perception of RLS symptoms.

### 4.2 Strengths and limitations

Despite a comprehensive search of the literature, using four major databases, and rigorous methodology (i.e., including quality assessment with NOS, meta-regression, and sensitivity testing), there are
limitations to consider in this meta-analysis. First, our results are partly limited with respect to methodology and design. The dataset included observational studies, which means cohort, case-control studies (i.e., both cases and controls), and cross-sectional studies were used, which might have affected prevalence estimates (Rothstein et al., 2005). An RLS diagnosis is based on the patient’s perception or description of symptoms. All but two of our studies relied on data from face-to-face interviews, telephone interviews, self-reports, or postal questionnaires, although based on relevant diagnostic criteria and validated tools, the use of patient’s self-assessments in the results can be seen as doubtful. The two studies that used clinical assessments (Erer et al., 2009; Ishaq et al., 2020), which might have included a more thorough examination both showed lower prevalence. Second, the retrospective nature of the study, including data from 2000 until 2022, meant that half of the included studies relied upon data from the IRLSSG four essential diagnostic criteria for RLS. Third, most of the analysed studies (78 of 97) used a cross-sectional design, which only offers weak evidence of causality. Fourth, only articles in English were included, which may have caused some selection bias. Fifth, publication bias can lead to incorrect conclusions (e.g., an over- or under-estimation of RLS prevalence), but fill-and-trim, a non-parametric approach based on examining the funnel plot’s asymmetry

![Forest plot displaying the estimated pooled prevalence of restless legs syndrome among female participants. CI, confidence interval; ES, effect size](https://onlinelibrary.wiley.com/doi/10.1111/jsr.13783)
was used. Finally, the patient populations included in these studies were derived from 33 countries, but data on ethnicity was not collected, and even though analyses regarding country development status were performed in the whole sample, as well as in the subgroups, the prevalence among ethnic minority individuals could not be calculated in the analysis.

4.3 | Future research

Future studies on RLS prevalence in the general adult population should include studies with high methodological quality (e.g., relevant assessment methods, meaning that all five IRLSSG diagnostic criteria must be satisfied, and validated tools must be used) that explore both gender and age aspects in different regions, with a focus on heterogeneity and its possible sources, including publication bias. Sociodemographic characteristics and potential factors that might limit RLS symptom burden, such as social supports and coping could also be explored. This would allow for testing of causal pathways in various groups and design and content of potential preventive self-care interventions. The RLS association with periodic limb movement disorder is well known, but it is unknown to diagnoses such as obstructive sleep apnea and insomnia. This potential association could be of clinical interest, and should be explored in future studies, as the occurrence of severe RLS symptoms might affect use of continuous positive airway pressure (CPAP) treatment (e.g., lower CPAP adherence among patients with RLS based on recurrent need to leave the bed during the night). Moreover, an updated meta synthesis of quality of life and psychological distress in patients with RLS, and possible moderator variables are needed.

5 | CONCLUSIONS

The findings of this review suggest that the pooled estimate for RLS prevalence in the general population, when publication bias is considered, strengthens previous suggestions that RLS is a common disorder with a higher prevalence in women. However, prevalence data are affected by study design and quality.

AUTHOR CONTRIBUTIONS

Anders Broström devised the research question together with Amir Pakpour. Zainab Alimoradi and Amir Pakpour performed the searches and completed the analyses together with Anders Broström. Jonas Lind, Martin Ulander and Fredrik Lundin contributed to the analysis and conducted cross-checks. Anders Broström and Amir Pakpour wrote the initial draft of the manuscript in consultation with Jonas Lind, Martin Ulander, and Fredrik Lundin. All authors provided critical feedback and assisted in shaping the manuscript. All authors approved the final version of the manuscript before submission.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study is available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.
## APPENDIX A

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