

Prevalence of Restless Leg Syndrome in Iran: A Systematic Review and Meta-analysis

Reza Ghanei-Gheshlagh¹, Naser Parizad², Hossein Zahednezhad³, Mandana Sarokhani⁴,
Kourosh Sayehmiri^{5*}, Vajiheh Baghi⁶

¹ Department of Nursing, School of Nursing, Kurdistan University of Medical Sciences, Sanandaj, Iran

² Department of Nursing, School of Nursing, Tabriz University of Medical Sciences, Tabriz, Iran

³ Department of Nursing, School of Nursing, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

⁴ Research Center for Prevention of Psychosocial-Social Injuries, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran

⁵ Department of Biostatistics, Research Center for Prevention of Psychosocial-Social Injuries, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran

⁶ Saghez Shekarriz Health Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

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Abstract

Background and Objective: Restless legs syndrome (RLS) is a sensorimotor disorder that causes sleep deprivation. RLS is characterized by discomfort in the legs and severe desire to move them during sleep. Different prevalence rates about RLS are reported in Iran. This systematic review and meta-analysis was performed to estimate the prevalence of RLS in Iran.

Materials and Methods: By searching the national and international databases such as Scientific Information Database (SID), MagIran, Google Scholar, IranMedex, Science Direct, PubMed and Scopus, 30 articles published between 2005 and 2014 were found. The results of the studies were combined using the random-effects model in the meta-analysis. Heterogeneity among studies was assessed using the I² index and P value less than 0.05 were considered as statistically significant. Data were analyzed using STATA software version 11.2.

Results: In studied articles, 8459 participants were entered into meta-analysis and the prevalence of RLS was estimated as 30% (95% CI: 24%-36%). According to the meta-regression diagram, the prevalence of RLS decreased by increasing the sample size and the year of study, indicated possible rising of the prevalence, but these changes were not statistically significant. The prevalence of RLS in patients with kidney disease (45%; 95% confidence interval: 33% to 57%), patients with diabetes (35%; 95% confidence interval: 22% to 49%), and patients with neurological disease (33%; 95% confidence interval: 10% to 57%) was more than other groups.

Conclusion: Given the high estimated prevalence of RLS in this study, it is recommended to identify at-risk individuals and provide educational materials for them.

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Keywords: Iran; Restless legs syndrome; Meta-analysis; Systematic review

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Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder that disturbs sleep, and it is characterized by discomfort in the legs and severe desire to

move the legs during sleep (1). The patients resemble this unpleasant feeling similar to moving worm on the skin, flowing of water in the leg, sensing insect in bone, and sensing of electricity in the leg (2). Patients with RLS walk during the night to relieve their annoying symptoms, and they sleep in the early morning. So, they experience sleep deprivation and excessive daytime sleepiness that may interrupt their daily activities (3).

*Corresponding author: K. Sayehmiri, Research Center for Prevention of Psychosocial-Social Injuries, Medical Faculty, Ilam University of Medical Sciences, Ilam, Iran
Tel: +0989183410782, Fax: +0988413224040
Email: sayehmiri@razi.tums.ac.ir

The International Restless Legs Syndrome Study Group (IRLS) has provided four diagnostic criteria for RLS. It includes unpleasant feeling in the leg, worsening during the night by inactivity and sleep, and temporary relief by moving the leg; if a person who has had these criteria, is known as a patient with RLS (1). The cause of RLS is unknown. There is no certain biological index for RLS diagnosis; moreover, physical examinations of patients with RLS are normal and do not help with the diagnosis (4). RLS is diagnosed based on patient's history (5). Physical examinations and medical assessments help with the diagnosis only if there are co-morbidities or the cases such as end-stage renal failure, pregnancy, and iron deficiency that cause the secondary RLS (6). RLS has always been mentioned as one of the most common undetectable diseases, because it is often not diagnosed or misdiagnosed (7); sometimes, anti-depression or anti-anxiety medications are prescribed, taking these medications worsens RLS in these patients (8). All patients with this problem do not need medication, practicing proper sleep hygiene, including avoiding caffeine, nicotine, and alcohol would be helpful (9). Following RLS diagnosis, all the patients should be evaluated for iron deficiency as the most important and frequent secondary cause (10).

Prevalence of RLS is estimated 10% in adults, more common in women and elderly people (1). This disorder is more common in women than men and the prevalence of RLS rises with age (11). RLS is categorized into primary and secondary forms. The primary form starts at an early age and the patient has family history of this disorder; the secondary one is related to the patient's medical condition such as renal failure, Parkinson's disease, iron deficiency, pregnancy, diabetes, hypothyroidism, and rheumatoid arthritis (12, 13). RLS is more common in three groups: pregnant women, patients with end-stage renal failure and iron-deficiency anemia; iron deficiency is common among all these three mentioned groups and might cause RLS (14, 15). Nearly a quarter of women experience RLS during pregnancy; and the highest prevalence is reported in the last trimester (16).

One of the most common problems during treatment is an incident of rebound and augmentation in some patients. The rebound means that a higher dose of medication is needed over the night and developing symptoms early in the morning. Augmentation is known with the early onset of symptoms (usually two hours earlier), increasing the

severity of symptoms and involving more parts of the body. The incidence of these complications has been reported up to 20 to 30 percent in the treatment by dopaminergic agents (15). RLS increases the incidence of mental disorders, the risk of cardiovascular disease, depression, anxiety and fatigue, obesity, sleep apnea, erectile dysfunction in men, diabetes and osteoporosis, and has a negative effect on quality of life (4, 17-21). These patients hardly tolerate a long period of inactivity, such as traveling, cinema, or sleeping, as immobility worsens the symptoms. So, RLS causes public isolation, depression, and a decrease in the patients' quality of life. Sleep disorders could lead to cognitive impairment, high-risk behaviors, and impaired social relationships (1).

One of the most important goals of meta-analysis is providing a precise and reliable result by increasing the sample size, combining different studies, thereby reducing the confidence interval and solving the problems caused by the results of previous controversial studies (22). Studies conducted in Iran have reported a variety of different prevalence rates; for example, 61.5% of subjects in Molahosseini et al. study were suffering from RLS (23), while in Khazaei et al. study only 6 percent of the subjects had symptoms of RLS (24). According to numerous studies with different findings in the country, the findings in this study were reviewed systematically and data were combined to achieve a more accurate estimate of the prevalence of RLS in the region.

Materials and Methods

This systematic review and meta-analysis investigated the prevalence of RLS in Iran. All local studies published in Persian and English journals (between 2005 and 2014) were systematically reviewed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (25).

Data selection and criteria

To search conducted studies regarding the prevalence of RLS, the national and international information databases such as Scientific Information Database (SID), MagIran, Google Scholar, IranMedex, Science Direct, PubMed, and Scopus were used. A broad search strategy was performed by keywords such as sleep disorder, RLS and their combinations and the Latin equivalent of these words was used in the international databases. Furthermore, the references of the article were reviewed to access more articles. In this study,

eligibility for studies was based on inclusion and exclusion criteria. All the articles, in which the prevalence or frequency of RLS was mentioned, were entered for analysis. Exclusion criteria included being unrelated to the topic, having medical treatment, repetitive studies, and inaccessibility to the full-text articles. The methodological quality of the articles was not checked and all eligible articles were analyzed. According to the inclusion and exclusion criteria, 30 studies were

selected between the years 2005 to 2014, and more than one-third of studies were published in 2013 (Figure 1). Twenty-six out of 30 reviewed studies (86.7%) were cross-sectional studies. Based on inclusion and exclusion criteria, two authors independently screened the collected data in terms of the title and abstract and then reviewed the full-texts in the next stage. The article was reviewed by the corresponding author, in any disagreement on either stage.

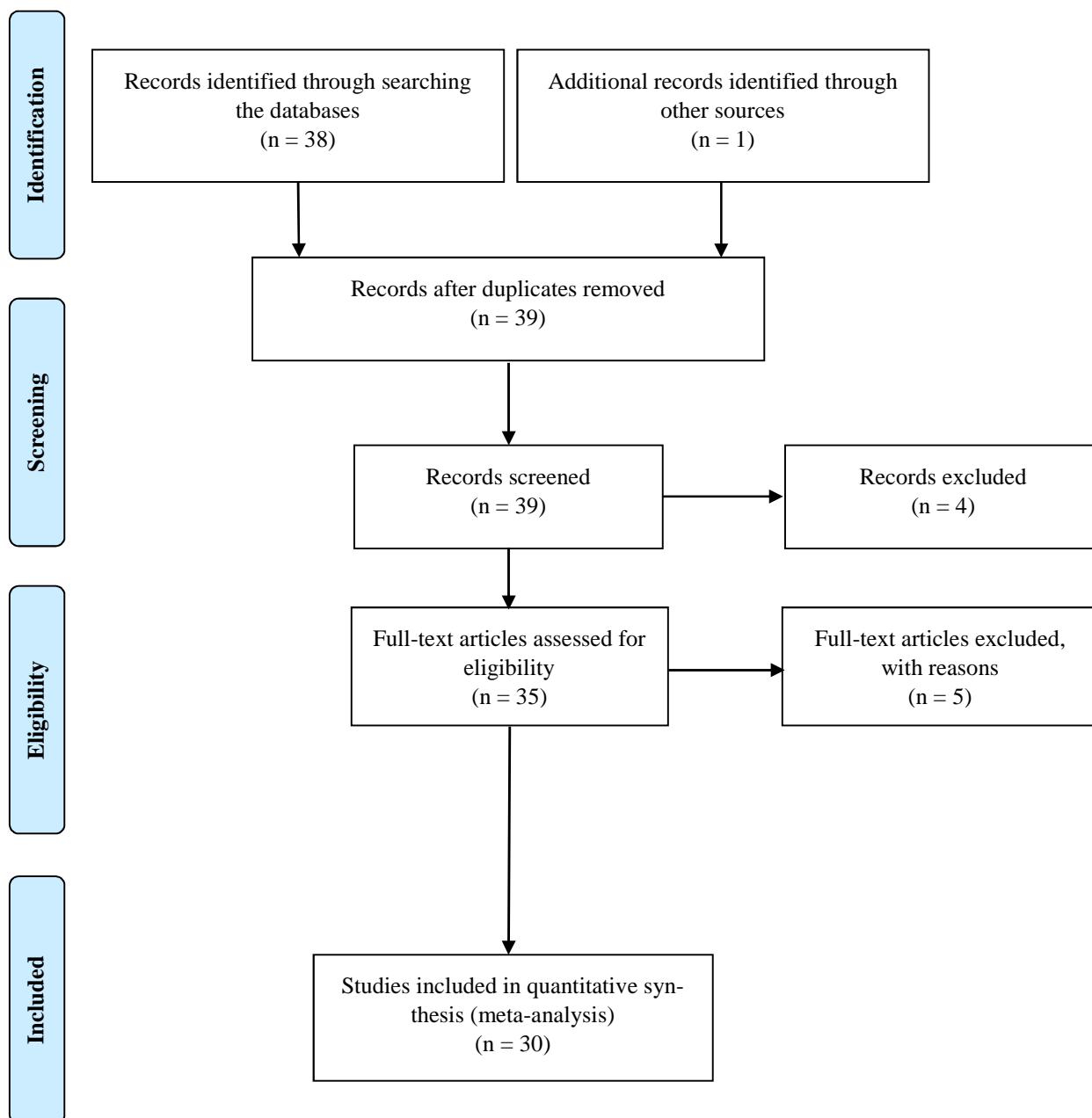


Figure 1. Entry process to systematic review and meta-analysis flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline

Data extraction

Data extraction form was used for collecting the data including variables such as first author of the article, publication year, city of performed study, sample size, sampling method, number of patients with RLS, study population, and type of the study. The study population included people with diabetes, and gynecological, renal, respiratory, digestive, neurobiological, and cardiac diseases, and the people under acute care, elderly people, healthy women, workers and students. The highest number of studies (27%) was conducted on patients on hemodialysis, and with renal disease.

Statistical analysis

The prevalence has a binomial distribution. The variance of every article was calculated through the binomial distribution variance. Inverse the variance weighting was allocated to each study. I^2 index was used to assess the heterogeneity of the data. The heterogeneity was divided into three classes of less than 25% (low heterogeneity), 25% to 75% (moderate heterogeneity) and more than 75% (high heterogeneity). The random effects model was used because of heterogeneity of the data. There was no need for assessing publication bias, while quality control stages variable was done precisely. Data were analyzed using STATA software version 11.2 (StataCorp LP., College Station, TX, United States).

Results

Concluding studies were conducted between the years 2005 to 2014 and total sample size of the studies was 8459 persons with the mean of 282 people in each study. Table 1 shows the characteristics of included studies.

The lowest prevalence was reported in hospital personnel (6.1%) in Khazaei et al. study (24), and the highest prevalence was reported in hemodialysis patients in the Arab Baniasad et al. study (51). Estimation of RLS prevalence was performed with a random effects model in the entire country. Prevalence of RLS in 30 articles with the sample size of 8459 persons was 30% (95%CI: 24% to 36%). In the current study, heterogeneity was 98.4% that considered as one of the highest heterogeneity studies. So, the random effects model was used for subsequent reviews. Based on the random effects model, authors assumed that the observed differences are because of the various sampling and the difference in RLS prevalence

rates in different studies. Moreover, 10 studies (33.3%) were conducted in Tehran (Table 1).

In 20 studies (66.7%), convenience sampling method, 4 studies (13.3%) random sampling, and 4 studies (13.3%) census sampling method were performed. Sampling method was not mentioned in two studies (6.7%).

The prevalence of RLS was 34% (95% CI: 3-66%) with census sampling, 32% (95% CI: 24-41%) with convenience sampling and 13% (95% CI: 12-15%) with random sampling. The highest prevalence was reported with census sampling and the lowest with random sampling. According to the random effect models, prevalence of RLS was estimated as 30% (95% CI: 24-36%) in Iran.

The studies were separated based on the target population. Most of the studies were conducted among patients with renal disease and patients on hemodialysis. The prevalence of RLS in patients with renal disease (45%; 95% CI, 33-57%), patients with diabetes (35%; 95% CI, 22-49%), and patients with neurological disease (33%; 95% CI, 10-57%) was more than other groups, respectively.

Based on Meta-regression diagram, the RLS frequency was decreased by increasing the year of the study ($P = 0.899$) (Figure 2).

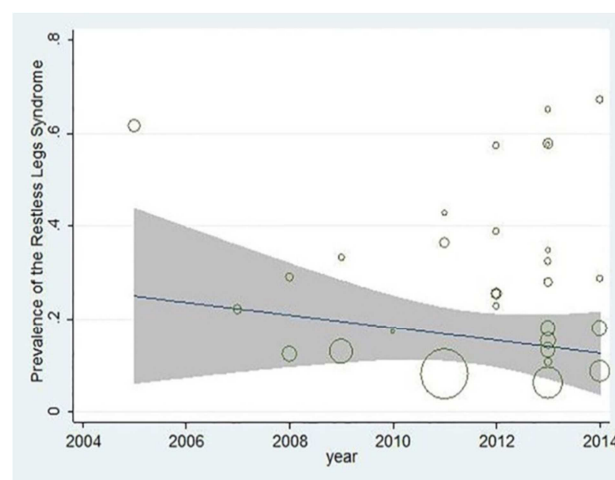


Figure 2. The meta-regression diagram of the prevalence of restless legs syndrome (RLS) based on the year of study. The greater circle shows the greater sample size number.

The majority of the studies were conducted in Tehran. The highest prevalence was reported in Yazd (67%; 95%CI: 60-74%) and the lowest prevalence in Qazvin (12%; 95% CI: 9-16%). The total prevalence of RLS was estimated as 30% (95% CI: 24-36%) in different cities. Studies were strongly heterogeneous ($I^2 = 98.4\%$; $P > 0.001$).

Table 1. Characteristics of included studies

Article	Place	Time	The sample size	The study population	Type of study	Sampling method	Prevalence (%)	95%CI (%)	
								Upper	Lower
Molahosseini et al. (23)	Tehran	2005	504	Hemodialysis	Cross-sectional	Convenience	61.5	66	57
Aslani et al. (26)	Shahrekordeh	2007	205	Heart failure	Cross-sectional	Convenience	22.0	28	16
Ansarin et al. (27)	Tabriz	2008	194	Renal failure	Cross-sectional	Uncertain	28.9	35	23
Javadzade et al. (28)	Qazvin	2008	300	Students	Cross-sectional	Random	12.3	16	9
Samilipour et al. (29)	Bushehr	2009	130	Hemodialysis	Cross-sectional	Uncertain	33.1	41	25
Sharifian et al. (30)	Tehran	2009	780	Workers	Cross-sectional	Random	12.8	15	10
Shahidi et al. (31)	Torbat Heydariyeh	2010	41	Hemodialysis	Cross-sectional	Census	17.1	29	6
Habibzadeh et al. (2)	Urmia	2011	300	ICU	Cross-sectional	Convenience	36.3	42	31
Ghanei et al. (32)	Saghez	2011	108	Diabetes	Cross-sectional	Convenience	42.6	52	33
Najafi et al. (33)	Isfahan	2011	2099	Neurology	Cross-sectional	Convenience	8.0	9	7
Alidosti et al. (34)	Chaharmahal Bakhtiari	2013	171	Hemodialysis	Cross-sectional	Census	57.3	65	50
Dehghan Nayeri et al. (3)	Saghez	2012	110	Pregnant women	Cross-sectional	Convenience	22.7	31	15
Habibzadeh et al. (35)	Urmia	2012	168	Hemodialysis	Cross-sectional	Convenience	38.7	46	31
Khaledi Paveh et al. (36)	Kermanshah	2013	300	PMS	Cross-sectional	Convenience	25.4	30	20
Bojji et al. (37)	Tehran	2012	225	IBS	Comparative	Convenience	25.3	31	20
Yazdi et al. (38)	Tehran	2013	400	Workers	Case-control	Random	15.2	19	12
Torabi et al. (39)	Jahrom	2013	360	Elderly people	Cross-sectional	Convenience	57.7	63	53
Vahdat et al. (40)	Tehran	2013	443	Pregnant women	Cross-sectional	Convenience	17.8	21	14
Yazdi et al. (41)	Tehran	2013	152	Epilepsy	Cross-sectional	Convenience	32.3	40	25
Shaygannejad et al. (42)	Isfahan	2013	126	MS	Case-control	Convenience	65.1	73	57
Khazaei et al. (24)	Kermanshah	2013	653	Shift workers	Cross-sectional	Census	6.1	8	4
Chehri et al. (43)	Kermanshah	2013	95	Asthma	Cross-sectional	Convenience	34.7	44	25
Miri et al. (44)	Tehran	2013	205	MS	Cross-sectional	Convenience	27.8	34	22
Gholamrezaei et al. (45)	Tehran	2013	90	Cardiac patients	Cross-sectional	Convenience	10.5	17	4
Sharifi et al. (46)	Bandar Abbas	2013	80	Hemodialysis	Cross-sectional	Census	57.5	68	47
Khazaie et al. (47)	Kermanshah	2013	311	Women	Cross-sectional	Random	13.1	17	9
Zobeiri and Shokoohi (48)	Kermanshah	2014	140	Diabetes	Case-control	Convenience	28.6	36	21
Yazdi et al. (49)	Tehran	2014	414	Workers	Cross-sectional	Convenience	8.6	11	6
Miri et al. (50)	Tehran	2014	443	Pregnant women	Cross-sectional	Convenience	17.8	21	14
Arab Baniasad et al. (51)	Yazd	2014	160	Hemodialysis	Cross-sectional	Convenience	67.2	74	60

ICU: Intensive care unit; PMS: Premenstrual syndrome; IBS: Irritable bowel syndrome; MS: Multiple sclerosis

Discussion

To our best knowledge, present study is the first systematic review investigated the frequency of RLS in different regions of Iran. The total sample size of 30 reviewed studies was 8459 persons from 2005 to 2014. The lowest and the highest sample sizes were related to the study of Shahidi et al. with 41 persons (31) and Najafi et al. with 2099 persons (34). In this study, the total prevalence of RLS was 30%. Different prevalence rates are reported in various studies. For example, Kim et al. found the prevalence of RLS in patients with renal disease as 28.0% in Korea, 12.2% in Japan, 62.0% in China, and 6.6% in India (52).

In this study, frequency of RLS in the elderly population (58%) and patients with renal disease (45%) was more than other target populations. Leschziner and Gringras believed that the prevalence of RLS in elderly people is more than other age groups and its prevalence rises by rising the age (4).

RLS has a high prevalence in patients with renal disease and patients on hemodialysis. Different frequencies were reported in the conducted local studies on these patients. The highest frequency (67.2%) was reported in the study of Arab Baniasad et al (51).

Unpleasant symptoms of RLS start or intensify in the sunset and subside in the early morning, leading to sleeping disorder in patients. In Holmes et al., almost 80% of the patients reported severe sleep attack and insomnia. This high prevalence figures the importance of stresses on sleeping disorder as a characteristic of RLS (7). Moreover, many of the problems are not diagnosed correctly in these patients, and the symptoms sometimes are attributed to anxiety and depression (8). Unfamiliarity of medical staff with the symptoms of RLS and lack of proper diagnosis of this disease may cause that many patients do not seek medical treatment. Thus, not referring to the physician because of imagining the disease simple, wrong diagnosis, subjective symptoms, lack of biological index for the diagnosis, and failures to diagnosis with clinical examination and self-treatment of the patients are the main barriers of reporting the real statistics about RLS in society. Four criteria presented by IRLS are used for the diagnosis and if a patient has all the four criteria, the diagnosis will be confirmed (1).

RLS intensity tools are used for investigating the severity of RLS. These tools are often mis-

used, and this is one of the reasons behind the difference of the reported prevalence rate. Some reviewed studies about sleep disorder reported only the prevalence or frequency of RLS without pointing to screening and assessment tools. Since, symptoms of RLS are subjective, people may be unable to report their symptoms precisely, or they may exaggerate them.

In the present study, the meta-regression diagram showed that the frequency of the RLS was decreased by increasing the sample size, and increasing the year of study, indicated the rising of the frequency; though these changes were not statistically significant. In other words, the prevalence of RLS is not dependent on the passage of time and sample.

One of the main limitations of this study was the lack of methodological quality assessment of included articles. High sample size population-based studies are recommended to evaluate the prevalence of RLS (53).

Conclusion

Different prevalence rates of RLS are reported around the world. This difference may be because of racial differences, predisposing and environmental factors like geographical location and methodological limitations (such as low sample size and contradictory interpretation of diagnostic criteria). Regarding the high estimated prevalence of RLS in current study, it seems essential to provide educational programs for health staff and patients for obtaining further information and proper management of the disease.

Conflict of Interests

Authors have no conflict of interests.

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