Prevalence of Restless Legs Syndrome in Iran: A Systematic Review and Meta-Analysis

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ARTICLE INFO

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ABSTRACT

Introduction: In recent years, different values of the general prevalence of restless legs syndrome (RLS) have been reported in various studies and its related factors in Iranian society are not known. The aim of this study was to evaluate the prevalence and factors associated with RLS in Iran by meta-analysis.

Methods: This study was performed based on the PRISMA checklist. There was a time limit from July 1, 2014, to November 11, 2019, for documents obtained from English and Persian databases such as MagIran, SID, MedLib, IranMedex, IranDoc, Civilica, Islamic Science Citation (ISC), Web of Science, Science Direct, Pubmed, Scopus, Springer, and Google Scholar. Comprehensive Meta-analysis (CMA-2) software was used to analyze the data by meta-analysis random- effects model.

Results: The prevalence of RLS was estimated to be 32.9% (95% CI: 22.9-44.7) in 24 studies with 26474 Iranian subjects that 65.9% of whom were women. The prevalence of this disorder was 47.6% in Iranian women (95% CI: 28.7-67.2) and 36.7% in Iranian men (95% CI: 21.4-55.3). The most and the least prevalence of RLS based on the geographical region were respectively in the east (44.3%) and north of the country (15.5%) and this difference was significant based on meta-regression (p <0.05). The prevalence of this syndrome was 50% in hemodialysis patients, 35% in other diseases, 25.7% in pregnant women, 20.2% in elderly and 13.8% in adults.

Conclusion: The prevalence of RLS in Iran is higher than in other parts of the world based on different studies. Therefore, early detection, prevention and treatment of this disorder in adults are essential.

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

Introduction

Restless legs syndrome (RLS) or Willis-Ekbom syndrome is a motor-neurological disorder that people with this syndrome tend to shake their legs during sleep and often cause insomnia (1, 2). Having an unpleasant feeling, cause people to walk during the night and fall asleep early in the morning, thereby they experience sleep deprivation and daily drowsiness that may interfere with their daily functioning (2). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), this syndrome has become a complete disorder and is one of the most common sleep disorders (3). Interestingly, most patients are undiagnosed or misdiagnosed (4). According to reports, about 80% of patients refer to a physician for their symptoms and only 6% were diagnosed with the disorder. After diagnosis, only 13% of patients are treated with appropriate medications (5). Four general criteria for the diagnosis of this syndrome have been developed by the International Restless Legs Syndrome Study Group (IRLSSG), which include 1) a strong desire to shake the legs to reduce the unpleasant feeling of the legs, 2) symptoms begin during sitting motionless, 3) the symptoms of the disease relieve by shaking the legs and 4) the onset and exacerbation of symptoms during the night (6, 7). This tendency to shake is associated with an unpleasant feeling in the legs, and patients have likened it to the feeling of an insect in the bone, the feeling of worm movement on the skin, water on the legs, and electricity in the legs (8).

The syndrome consists of two types of primary and secondary that in the first type, the disease is not caused by another disorder and often occurs with a positive family history. In contrast, secondary types occur in conditions such as pregnancy, renal failure, iron deficiency anaemia, diabetes, rheumatoid arthritis and neuropathy (9, 10). Evidence suggests that the pathologic mechanism in primary RLS is associated with dopaminergic system dysfunction and iron deficiency, whereas the secondary type mechanism is more associated with impaired blood serum phosphorus and calcium (9, 11). Recent studies have suggested the role of genetics (12) in RLS while other studies pointed to the role of infectious inflammatory factors and abnormal immune responses (13).

According to some studies, the disorder is seen in 2% to 15% of the general population and the risk is 11% to 27% higher in women than men (14, 15). A meta-analysis of the North American population reported that the prevalence of RLS in adults ranged from 4% to 29% (16). The prevalence of RLS in adults was 4% in Brazil (17), 1.8% in Japan (18), and 1.57% in Taiwanese (19). Recent studies in Iran have reported a different prevalence of RLS and the contradictory results of the presence of symptoms and associated factors. For example, Jamalnia (20) reported the RLS rate of 50%, with a mean score of 12.02, and found no difference between men and women in this disorder. Hosseini et al. (21) reported a prevalence of 27.9% of this syndrome in cardiovascular patients and Molahosseini et al. (22) reported a prevalence of 61.5% in hemodialysis patients in Yazd. RLS has many complications and cause a decrease in the quality of life, sleep disorder, increased risk of cardiovascular disease and even death and is closely associated with depression disorder (23, 24). Although this disorder is not as life-threatening as heart disease or diabetes, it can cause chronic insomnia and drowsiness that affect patients' quality of life (8). This syndrome impedes patients' enjoyment of life and has adverse effects on their family, social and occupational activities (2). Therefore, this study aimed to determine the prevalence of RLS in Iran by meta-analysis in order to report the general prevalence of this disorder in Iranian society as well as to present factors related to this disorder.

Methods

Strategy search and study selection

The present study is a systematic review and meta-analysis that investigates the prevalence of RLS in Iranian society. Hence, to maximize the search comprehensiveness we use general English

keywords including: "Restless Legs Syndrome", "Restless Leg Syndrome", "Willis Ekbom Syndrome", "Willis-Ekbom syndrome", "Iran" which were also searched using the AND and OR operators in combination. In order to obtain relevant documentation, Persian-language articles were searched in Persian-language electronic databases including MagIran, SID, MedLib, IranMedex, IranDoc, Civilica and Islamic Science Citation (ISC). The international databases of Springer, Pubmed, Scopus, Science Direct and Web of Science were also used to collect articles published in English. Manual searching was also performed by reviewing the sources of all articles related to the topic. These sources were obtained by searching on Google Scholar.

Example of strategy search

At Pabmed, we were able to get 19 articles from April 2, 2014 to December 10, 2019. The following is the search strategy on this site.

((restless legs syndrome[MeSH Terms] OR restless legs syndrome [tiab] OR restless legs[tiab] OR Willis-Ekbom Syndrome [tiab] OR Willis Ekbom Syndrome[tiab]) AND (Iran[MeSH Terms] OR Iran[tiab]))

Eligibility criteria

All papers, theses, and conferences that evaluated the prevalence of RLS from July 1, 2014, to November 11, 2019, were included in the study. Diagnosis of RLS was determined based on the test and international criteria for RLS. The studies that discussed RLS but did not report prevalence and incidence, The studies with inadequate data, The results that could not be accessed or repeated searches were excluded from the study.

Quality assessment

After evaluating the selection of studies according to inclusion and exclusion criteria, a checklist of 22 aspects of STROBE was used to evaluate the quality of the articles. This checklist covers various aspects of the methodology, such as the objectives of the study, sample size, sampling method, type of study, definition and measurement of variables, data collection tools and statistical analysis. The rating ranges from 0 to 44, which are categorized into three types of studies of low quality (0 to 15.5), medium quality (16 to 29.5) and high quality (30 to 44) (25, 26). So, the studies those scored 16 or higher were selected for meta-analysis. Also, studies with publication bias, statistical errors, and repetitive results were identified as poor quality assessment and excluded from the study.

Data Extraction

All final articles entered into the study process were prepared to be extracted by a pre-prepared checklist. This checklist includes authors' names, year of research, place of study, type of study, type of population studied, sampling method, sample size, mean and age range, the prevalence of RLS in men and women, and the overall prevalence of legs syndrome.

Statistical analysis

Since in each article, the sample size and the number of RLS were extracted, binomial distribution was used to calculate the variance of each study and the weighted mean was used to combine the prevalence rates of different studies. Each study is weighted according to its variance. Formula Q and I^2 index were used to evaluate the heterogeneity of the studies. The rate of heterogeneity in this study was 92.1% which, while significant, was in the range of studies with severe heterogeneity (27, 28). The most crucial reason for heterogeneity in this study could be due to the large difference between prevalence rates in different studies and different populations studied. Therefore, the random-effects model was used to combine studies and reduce heterogeneity. The analyzed data which all concerned the prevalence of RLS did not need to determine the publication bias and draw funnel plot. However, the meta-regression model was used to investigate the heterogeneity of the studies and by using this model the relationship between years, sample size and gender segregation with the prevalence of RLS was investigated. Comprehensive Meta-Analysis software version 2 and significance level of 0.05 were used for data analysis.

Results

Based on these steps, 81 articles (71 through databases and 10 through manual search) were found. Of these, 23 sources were excluded because of duplication. Subsequently, the title and abstract of the remaining 58 articles were read out of which 25 articles were excluded because of lack of relevance to the topic. Next, each article or thesis was fully read, and nine were excluded due to

insufficient data and no relevance. Finally, 24 articles and theses of good quality entered the systematic review process. Based on the PRISMA checklist, all stages of the research method including search, review of articles, and extraction of required data were performed (Figure 1). A qualitative evaluation was also carried out by two completely independent researchers, and finally, the results were agreed by a third observer in a group.
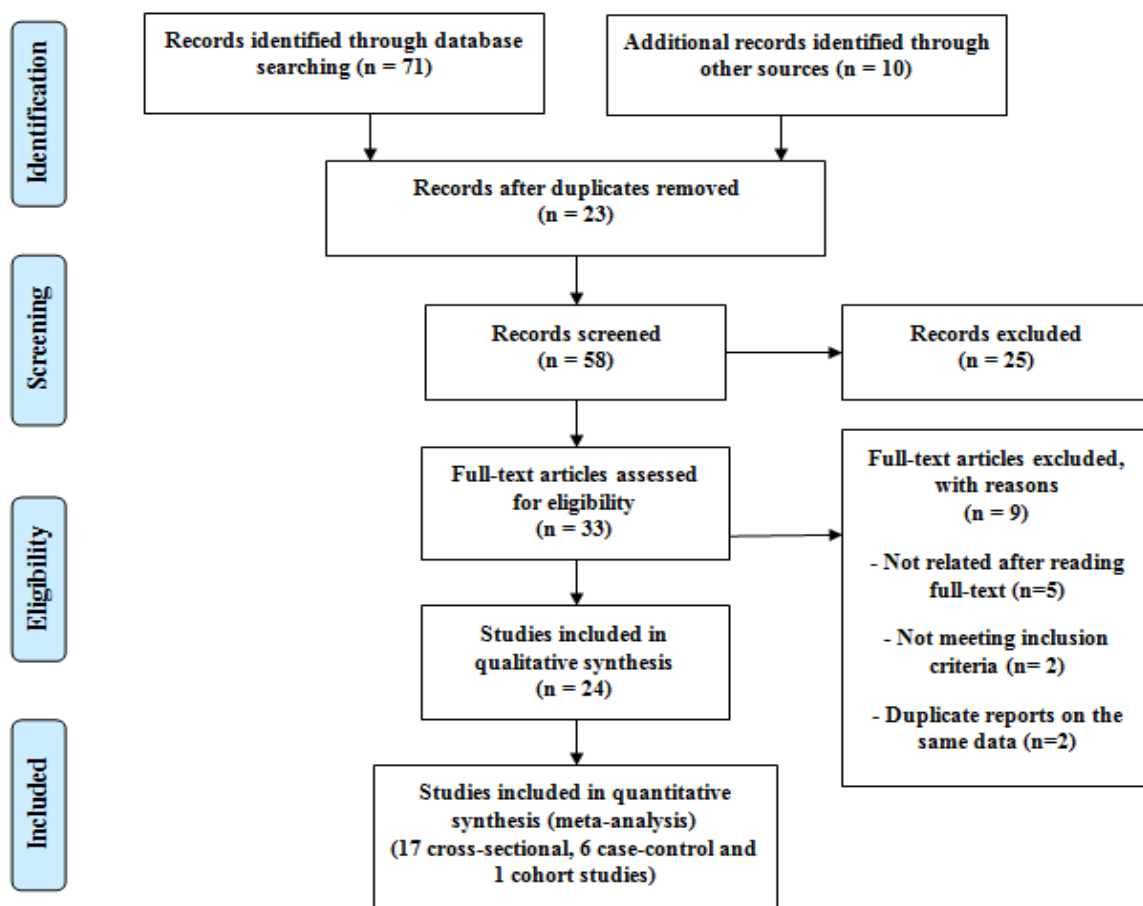
Figure 1. Flowchart Steps for Systematic Review and Meta-Analysis

In the present study, out of the 24 studies that referred to RLS, a sample size of 26474 ranged from 15 to 75 years was obtained from Yazd, Tehran, Qazvin, Mashhad, Zabol, Kermanshah, Ilam, Saghez, Ardabil and Ahwaz. Of these, 65.9% were women (N= 17450) (Table 1). The overall prevalence of RLS in Iran was estimated to be 32.9% (95% CI: 22.9-44.7) by meta-analysis

(Figure 2). The mean age of the participants was 52.34 years with a 95% confidence interval (46.1-58.53). Also prevalence of RLS in hemodialysis patients was 50% (95% CI: 35.3-64.7), other diseases 35% (95% CI: 21.6-51.2), pregnant women 25.7% (95% CI: 13.3-44), 20.2% of the elderly (95% CI: 10.5-35.4) and adults 13.8% (95% CI: 4.2-37.1).
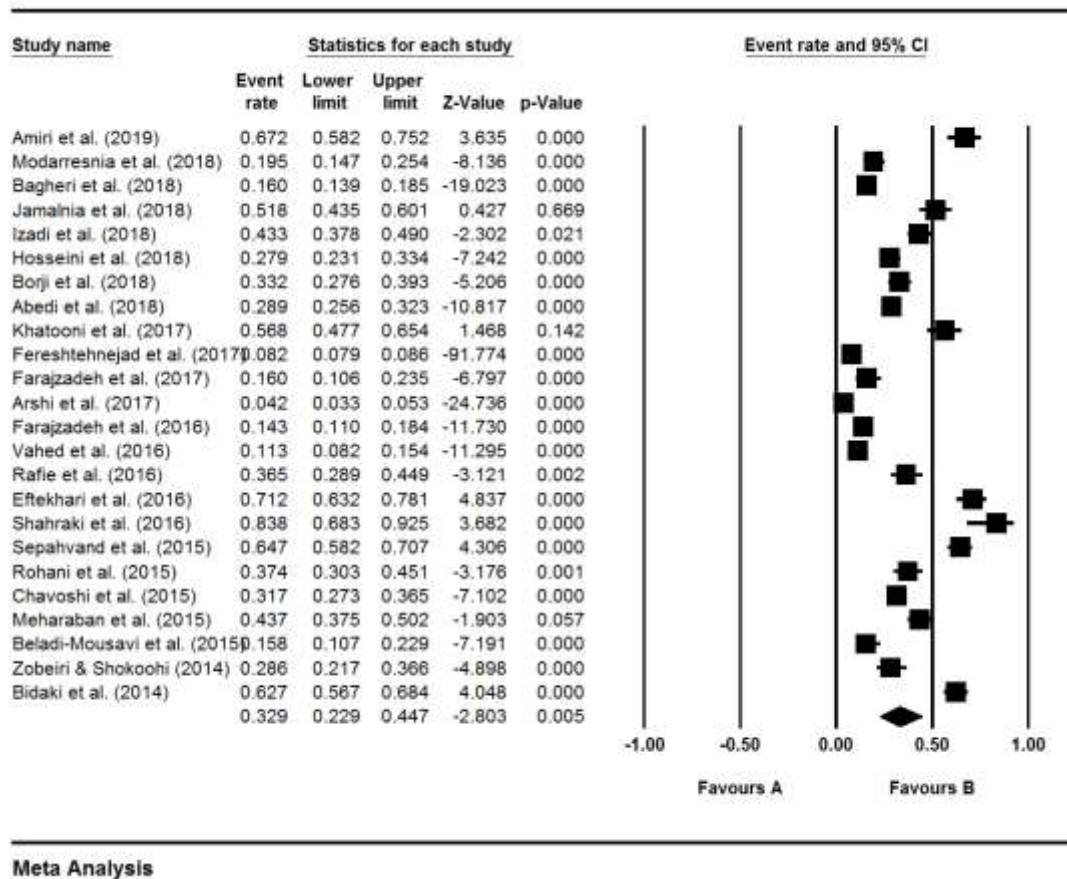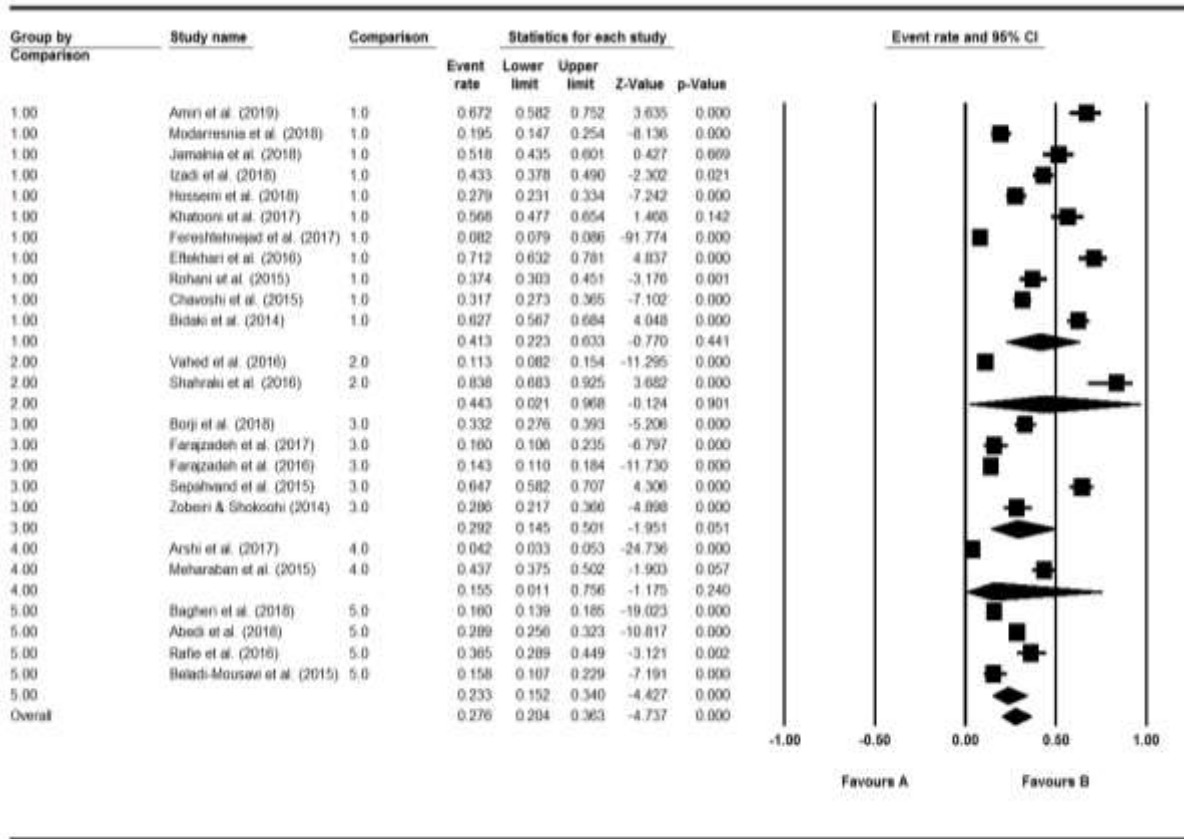
Figure 2. Forest plot about prevalence of RLS based on random model; the middle square of each segment represents the percentage and length of segments estimated with 95% confidence interval in each study. The rhombic sign is the prevalence of RLS for the entire study.

The least prevalence of RLS was observed in a study by Arshi et al. (36) in Ardabil (4.2%) and the most prevalence of RLS was in Shahraki-Moghaddam et al. (40) in Zabol (83.8%). The results of the meta-analysis of the prevalence of RLS in the reviewed articles are presented in Figure 3 based on geographical regions and since the confidence intervals intersect, the relationship is not statistically significant (p <0.05). The most prevalence of RLS based on the geographical region was observed in the east of Iran (44.3%) and the least prevalence was related to the north of the country (15.5%). Meta-regression showed a significant difference between the geographical regions and the prevalence of RLS (P= 0.001, β= 0.185).

Table 1. Overview of the papers that met the eligibility criteria

Papers	Publication year	Place	Sample size	Population	Type of Study	Sampling method	Age range	Mean ± SD age	Prevalence (%)		Total Prevalence (%)
									Male	Female	
Amiri et al. (9)	2019	Yazd	116	Hemodialysis	Cross-sectional	Convenience	15-85	60.1 ± 14.4	61.8	75	67.2
Modarresnia et al. (29)	2018	Tehran	210	Diabetic	Cross-sectional	Convenience	30-70	54.9 ± 7.8	-	-	19.5
Bagheri et al. (30)	2018	Ahvaz	980	Postmenopausal women	Cross-sectional	Cluster	30-70	57.3 ± 8.5	-	-	16
Jamalnia (20)	2018	Tehran	137	Students	Cross-sectional	Convenience	≥ 18	-	41.5	56.3	51.8
Izadi et al. (10)	2018	Tehran	300	Multiple Sclerosis	Cross-sectional	Random	14-70	35.9 ± 8.4	49.3	41.5	43.3
Hosseini et al. (21)	2018	Tehran	290	Cardiovascular	Cross-sectional	Convenience	22-79	56.1 ± 12.3	24.8	29.8	27.9
Borji et al. (31)	2018	Ilam	250	Elderly	Case-control	Two-stage cluster	≥ 65	71.6 ± 7.9	-	-	33.2
Abedi et al. (32)	2018	Ahvaz	700	Pregnant women	Case-control	Convenience	≥ 15	27.5 ± 6.3	-	-	28.9
Khatooni et al. (33)	2017	Qazvin	118	Multiple Sclerosis	Cross-sectional	Convenience	≥ 17	25.5 ± 5.7	60.5	55	56.8
Fereshtehnejad et al. (34)	2017	Tehran	19176	Adults	Cross-sectional	Multistage random	≥ 30	56.5 ± 10.2	7.5	8.6	8.2
Farajzadeh et al. (35)	2017	Saqqez	125	Elderly	Case-control	Convenience	≥ 60	73.1 ± 6.9	-	-	16
Arshi et al. (36)	2017	Ardebil	1558	Adults	Cross-sectional	Convenience	18-30	36.6 ± 12.1	-	-	4.2
Farajzadeh et al. (23)	2016	Saqqez	350	Elderly	Case-control	Cluster	≥ 60	68.8 ± 7.7	9.4	20.1	14.3
Vahed et al. (37)	2016	Mashhad	300	Pregnant women	Case-control	Convenience	18-35	-	-	-	11.3
Rafie et al. (38)	2016	Ahvaz	137	Hemodialysis	Cross-sectional	Convenience	17-84	53.8 ± 12.1	32.9	40.6	36.5
Eftekhari et al. (39)	2016	Yazd	139	Hemodialysis	Cross-sectional	Convenience	15- >60	58.2	61.2	87	71.2
Shahraki et al. (40)	2015	Zabol	37	Hemodialysis	Cross-sectional	Convenience	≥ 18	45.1 ± 18.1	82.6	85.7	83.8
Sepahvand et al. (41)	2015	Kermanshah	221	Acute coronary syndrome	Cross-sectional	Random	≥ 18	61.3	56.6	77.6	65
Rohani et al. (42)	2015	Tehran	163	Hemodialysis	Cross-sectional	Convenience	18-82	61.3 ± 13.3	35.9	40	37.4
Chavoshi et al. (43)	2015	Tehran	397	Hemodialysis	Cross-sectional	Convenience	≥ 20	57.6 ± 15.4	23.7	47.4	31.7
Meharaban et al. (44)	2015	Ardabil	231	Pregnant women	Cohort	Random	18-45	38.1 ± 1.5	-	-	43.7
Beladi-Mousavi et al. (45)	2015	Ahvaz	139	Hemodialysis	Cross-sectional	Convenience	≥ 25	51.8 ± 13.3	13.9	18.3	15.8
Zobeiri & Shokoohi (46)	2014	Kermanshah	140	Diabetic	Case-control	Convenience	≥ 30	46.3 ± 13.9	-	-	28.6
Bidaki et al. (47)	2014	Yazd	260	Hemodialysis	Cross-sectional	Convenience	40-60	-	-	-	62.7

Meta Analysis

Figure 3. Forest plot about prevalence of RLS based on geographical regions by random model; Number 1: Central region (Yazd, Tehran, Qazvin), number 2: East (Mashhad and Zabol), number 3: West (Kermanshah, Ilam, Saqez), number 4: North (Ardebil) and number 5: South (Ahvaz).

The prevalence of RLS was studied by gender segregation in 14 studies, with a sample size of 21720 and 64.3% of whom were women (N= 13965). The results of Figure 4 showed that the prevalence of RLS in Iranian women was 47.6% (95% CI: 28.7-67.2) and in Iranian men was 36.7% (95% c CI: 21.4-55.3%). As can be seen, the prevalence of RLS is higher in women than in men. Significant differences were found between the two sexes by meta-regression (β= -0.10, P= 0.037). Other results of meta-regression showed that there was a significant negative relationship between the prevalence of RLS and sample size (β= -0.0001, P= 0.001), year of publication (P= 0.001, -0.28) and mean age of the subjects (β= -0.03, P= 0.001). On the other hand, based on the results of the sensitivity analysis, none of the studies alone had a significant effect on the outcome of the study.
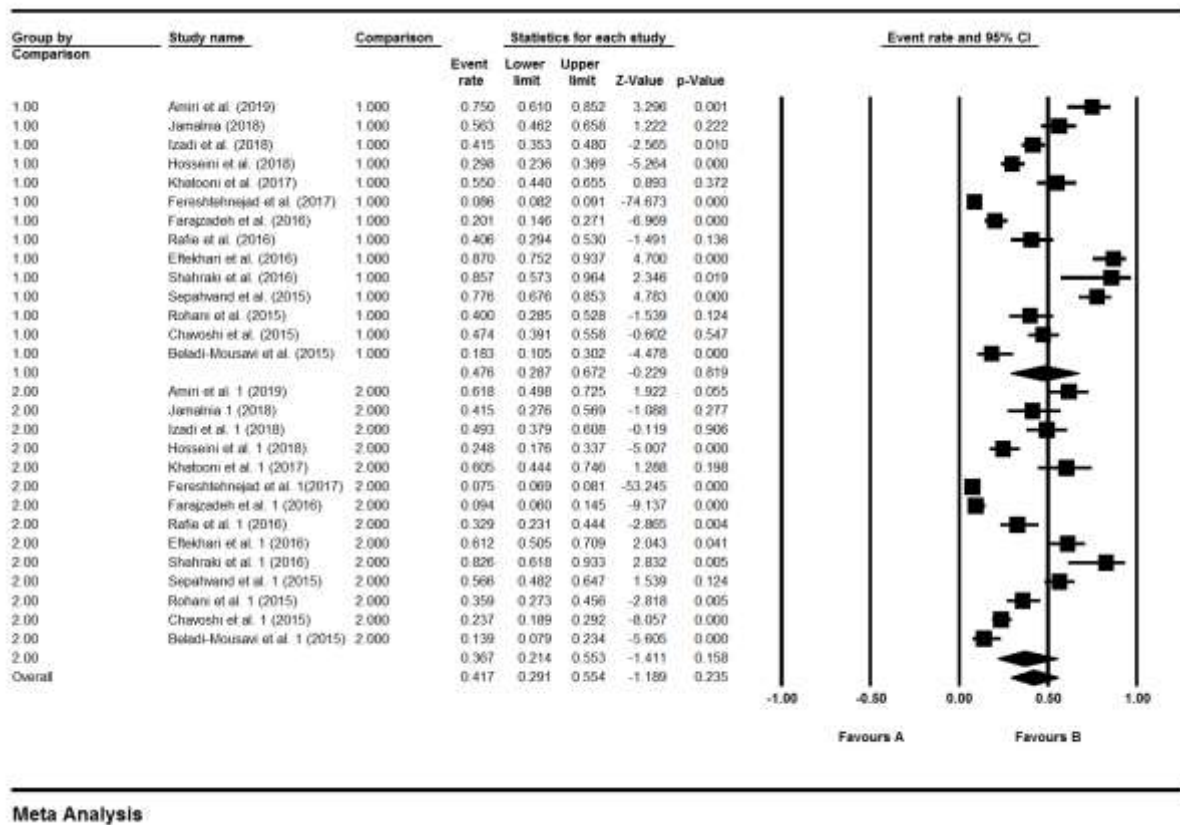
Figure 4. Forest plot about prevalence of RLS based on gender segregation by random model; (women=1 and men=2)

Discussion

The results of the meta-analysis in the present study obtained from 24 studies between 2014 and 2019 with a sample size of 26474, of which 65.9% were women showed that the prevalence of RLS in Iran was 32.9% (95% CI: 22.9-44.7). The age range of the samples ranged from 15 to 75 years with a mean age of 52.34 years (95% CI: 46.09-53.53). On the other hand, the prevalence of this disorder was 50% in hemodialysis patients, 35% in other patients, 25.7% in pregnant women, 20.2% in elderly and 13.8% in adults. In a meta-analysis study that investigated the prevalence of RLS in Iran between 2005 and 2015, Ghanei-Gheshlagh et al. (6) reported 30% of the total prevalence of RLS in 30 studies (95% CI: 23 -37) which is a high rate in a community and this result is in line with the results of the present study. However, in their study, Fereshtehnejad et al. (34) reported an average prevalence of RLS at 6% and reported that 6 out of every 1,000 Iranians have RLS. Compared to the World Report, the prevalence of the syndrome in North America and Europe is estimated to be between 5.5% and 11.6% and in the Asian population between 1% and 7.5% (48). Compared to results reported from similar studies elsewhere in the world, it should be noted that the prevalence of RLS in Iran is higher than in the rest of the world and it is severe.

Meta-regression results showed that there was a significant negative relationship between the prevalence of RLS and the sample size, year of publication, and mean age of the subjects. This means that the smaller the sample size, mean age, and publication of articles, the higher the prevalence of RLS in Iranian society. Abdi et al. (49) reported an 18.5% prevalence (95% CI: 16.05-12.02) of RLS in Asian pregnant women and also found that there is no significant relationship between the prevalence of RLS in patients with the year of publication (p= 0.939), sample size (p= 0.161) and mean age of the samples (p= 0.105). In European and American

societies, it has been reported that the prevalence of RLS in the general population increase with ageing but in Asian countries, there have been no changes in the prevalence of this disorder with ageing (49, 50).

The prevalence of RLS in Iranian women, in 14 studies with a sample size of 21720 that 64.3% of whom were women, was 47.6% (95% CI: 28.7-67.2) and was 36.7% in Iranian men (95% CI: 21.4-55.3). As can be seen, the prevalence of RLS was higher in women than in men and based on meta-regression, the difference between the two sexes was statistically significant. That is, the prevalence of RLS has more to do with the female gender. Consistent with the data obtained, two significant studies in the world reported a higher prevalence of RLS in women than in men (16, 49). However, some studies have not reported a gender difference in the prevalence of this disorder (20, 51). On the other hand, the results of the prevalence of RLS by geographical regions show that the most prevalence of RLS was related to the East of Iran with 44.3% and the least prevalence of this disease related to the North of Iran with 15.5% and there was a significant difference between regions. The presence of racial differences, predisposing factors, environmental factors such as geographical location and sample size can lead to vast differences in the prevalence of RLS in various studies (52, 53), However, so far, no information has been obtained comparing the prevalence of RLS in different regions of Iran.

Conclusion

The aim of this study was to determine the prevalence and factors associated with RLS in Iran by meta-analysis. The results showed that the prevalence of RLS in Iran was 32.9%. That means out of every 100 Iranians, about 33 have RLS and the prevalence of this disorder in women is higher than in Iranian men. Therefore, early detection of the disorder, providing appropriate prevention and treatment strategies to reduce it in Iranian adults, especially women, is required.

Author contribution

M.H.S. conceived of the presented idea. A.I. developed the theory and performed the computations. M.H.S. and E.S. verified the analytical methods. M.H.S encouraged H.M. to investigate [a specific aspect] and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

Conflict of Interest

The authors declared no conflicts of interest.

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