Restless legs syndrome is a risk factor for major depressive disorder: a systematic review and meta-analysis

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Research

Keywords: Major depressive disorder, Restless legs syndrome, Willis-Ekbom disease, Meta-analysis.

Posted Date: October 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-98096/v1

Abstract

A significant association between major depressive disorder (MDD) and restless legs syndrome (RLS), but RLS prevalence is dramatically different among MDD individuals across studies. Our present work aimed to comprehensively evaluate available evidences to determine the role of RLS in MDD. PubMed, Web of Science, Embase, Science Online, Wip Chinese Biomedical Journal, Wanfang and Chinese National Knowledge Infrastructure were searched to identify observational and case-control studies relevant to RLS and MDD. Stata 12.0 software was used for meta-analysis. RLS individuals exhibited a higher risk of MDD than non-RLS controls (OR 2.05, 95%CI 1.80–2.33; p<0.05). No significant differences were found in MDD prevalence between young RLS patients (OR 2.10, 95%CI 1.72–2.56) and older RLS patients (OR 2.02, 95%CI 1.70–2.39). In addition, no significant difference in MDD prevalence was evident between between Asian (OR 1.98, 95%CI 1.66–2.37) and European or American (OR 1.76, 95%CI 1.54–2.01) RLS patients. Our meta-analysis provides evidence that the risk for MDD is higher among RLS patients compared to non-RLS individuals suggesting that RLS may play an important role in MDD patheogenesis.

Introduction

Major depressive disorder (MDD) is one of the most common mental diseases globally that affects cognition and mood, physical health, and social and occupational functioning[1]. To date, the pathogenesis of this brain disorder is still unclear. Recent studies have shown an association between MDD and Restless legs syndrome (RLS). RLS, also known as Willis-Ekbom disease (WED), is characterized by discomforts in limbs and strong urge to move the limbs[2]. RLS patients may experience temporary improvement of movement, and their symptoms may worsen when at rest and in the evening[3]. RLS affects 2.1%-5% of general populations[4].

Epidemiological and clinical epidemiological studies have reported a close link between MDD and RLS[5], but controversy still exists. This is because MDD and RLS are both common disorders that display overlapping symptoms[6], making it difficult to study the epidemiology of MDD in detail or definitively determine whether they are mechanistically linked. Clearly, further studies are needed to address these questions.

Here, we conducted a meta-analysis on accessible studies to estimate MDD prevalence among RLS patients and non-RLS individuals. We also assessed MDD prevalence between Asian and European RLS populations.

Methods

Literature Search

We searched the databases of PubMed, Web of Science, Embase, Science Online, Wip Chinese Biomedical Journal, Wanfang and Chinese National Knowledge Infrastructure up to 13 December 2018. The search was limited to randomized controlled trials on human populations and articles written in English language. The following search strings were used: [(depression) OR (major depressive disorder) OR (depressive symptoms)] AND [(restless legs syndrome) OR (Willis-Ekbom disease) OR (RLS) OR (WED)]

Selection Criteria

Five authors (Haiwang Zhang, Changxi Zhou, Shuai Jin, Yiming Wang) reviewed all identified articles from the initial search for inclusion; Any disagreements regarding the inclusion of the articles were resolved through discussion between the authors. Inclusion criteria were established before the commencement of article reviews and contained the following aspects:

1. Being observational studies with a case-control, cross-sectional, or cohort design analyzing the role of RLS in MDD;
2. Diagnosing MDD based on the criteria of GDS, BDI, and EPDS score confirmation by clinicians;
3. RLS diagnosed according to the criteria of the international RLS study group and the data on the patients obtained through questionnaires or clinical interviews;
4. Reporting RLS prevalence or sufficient data for the prevalence calculation;
5. Being full-text articles available for the evaluation of all interested components;
6. Having available data allowing for the determination of effect size; and
7. Being articles written in English.

Exclusion criteria were as follows:

1. Failed to offer valid data or inconsistent variables;
2. Reporting no MDD prevalence among individuals with RLS or having no enough data for the prevalence calculation;
3. Having significant methodological flaws; or
4. Involving no individuals with MDD or RLS.

Data Extraction

All studies from the systematic search were evaluated against the pre-defined inclusion criteria. Abstracts of these studies were screened and irrelevant studies were excluded. Full texts for all studies that met the inclusion criteria were obtained. Data extraction was conducted by two authors (Haiwang Zhang, Yiming Wang) and inconsistencies were resolved through discussion among four reviewers (Haiwang Zhang, Changxi Zhou, Shuai Jin Yiming Wang). The following information was extracted from the studies: the surname of the first author, year of publication, country of study cohort, diagnosis of MDD, RLS of age, and MDD prevalence in cases and/or controls (in studies with a case-control design).

Statistical analysis

Data were analyzed using Stata 12.0 (Stata Corp, USA). We evaluated MDD prevalence among individuals with RLS based on year and region. We compared MDD prevalence between individuals with and without RLS in terms of the odds ratio (OR) and associated 95% confidence interval (CI). Significance in all analyses was defined as $p < 0.05$.

I^2 was calculated to evaluate heterogeneity among studies: $I^2 < 25\%$ was considered as the absence of heterogeneity (homogeneity); $25\% \leq I^2 < 50\%$, low heterogeneity; $50\% \leq I^2 < 75\%$, moderate heterogeneity; and $I^2 \geq 75\%$, substantial heterogeneity. A fixed-effect model was used to analyze pooled data classified as

homogeneous or of low heterogeneity, whereas a random-effect model was used for the data classified as of moderate or substantial heterogeneity. Egger's tests were used to evaluate publication bias ($p > 0.05$ indicate no publication bias).

Results

Literature search and included studies

Searching the seven databases and records identified 2425 articles, and 48 of them were further examined after the removal of duplicates and clearly irrelevant articles (Fig. 1). After eliminating 29 articles based on the title and abstract, the remaining 18 were used for full-text articles assessment and eligibility, and 6 were subsequently excluded either because no data were extracted (n = 4) or variable inconsistency (n = 2)]. Therefore, 12 remaining studies were included in the present meta-analysis.

The eligible 12 studies contained 3357 individuals with RLS and 94912 non-RLS were included in the meta-analysis (Table 1). Of these studies, five were done on Asians and seven on Europeans or Americans, with five on individuals younger than 50 and seven on people older than 50. All of the 12 studies assessed MDD prevalence in patients with RLS and compared MDD between RLS and non-RLS individuals, and investigated the relationship between RLS and MDD.

Table 1
Characteristics of the 12 studies included in the meta-analysis

Study	Year	Country	Diagnosis of MDD	RLS age (M±SD)	RLS Female in Gender (%)	RLS with MDD	RLS with no MDD	No-RLS with MDD	No-RLS with no MDD
Jan Ulfberg[7]	2007	Finland	GDS	NR	NR	9	41	63	884
Lee Hochang B[8]	2008	America	GDS	58.11 ± 12.2	81	12	30	102	880
Seong Jin Cho[9]	2009	Korea	GDS	49.5 ± 12.6	75	21	51	673	5765
Ki Woong Kim[10]	2010	Korea	GDS	72.3 ± 6.2	28.8	9	50	27	628
Won-Hyoung Kim[11]	2012	Korea	GDS	72.47 ± 6.36	NR	12	190	60	1728
Yanping Li[12]	2012	America	GDS	69.6 ± 6.9	NR	44	884	1626	53845
Jan Wesström[13]	2014	Switzerland	EPDS	31.4 ± 4.7	NR	22	154	65	727
Maria Sarberg[14]	2016	Sweden	EPDS	30.1 ± 4.28	NR	14	75	15	189
Elif Deniz Safak[15]	2016	Turkey	GDS	69.9 ± 5.1	72.4	34	100	71	456
Brian B Koo[16]	2016	America	GDS	NR	NR	13	154	36	779
Chul-Hyun Cho[17]	2017	Korea	BDI	54.13 ± 8.18	56.3	64	78	853	2031
Maria Didriksen[18]	2018	Denmark	MDI	42.2 ± 12.2	58.2	73	1223	679	22730

GDS, Geriatric Depression Scale; EPDS, Edinburgh Postnatal Depression Scale; NR, not reported; MDD, major depression disorder; RLS, restless legs syndrome

Higher MDD prevalence in patients with RLS

Detailed MDD prevalence among individuals with and without RLS is listed in Table 1. Among the 12 studies, low heterogeneity was detected ($I^2 = 20.9\%$, $p < 0.001$), therefore the random-effect model was used to meta-analyze the data. Sensitivity analysis showed that none of the 12 studies significantly affected results (Fig. 2). Funnel plot was visually symmetrical, suggesting no significant publication bias (Fig. 3).

No significant differences in the risk of MDD between younger and older adults

Of the 12 studies, 5 focused on people younger than 50, and 7 on those older than 50. Although the results of our study were not highly heterogeneous (I^2 = 20.9%, p < 0.001), we compared these two age groups with an age of 50 as threshold for subgroup analysis. Our results showed no significant difference in MDD prevalence between these two patient groups (OR = 2.10 for patients younger than 50 and OR = 2.05 for those of 50 years or older). Sensitivity analysis showed that none of the 12 studies significantly affected the results (Fig. 4).

No significant difference in MDD risk between Asian RLS patients and European or American RLS patients

Of the 12 studies, five were done on Asian patients and seven from Europeans and Americas. Although the results of our study were not highly heterogeneous (I^2 = 20.9%, p < 0.001), we nevertheless compared the risk of MDD among Asian RLS patients with that in American or European patients, but found no significant difference between two these two groups. Sensitivity analysis showed that none of the 12 studies significantly affected the results (Fig. 5).

Discussion

In this study, we showed that the prevalence of MDD in patients with RLS was 9.74% whereas the incidence of MDD in non-RLS individuals was only 4.50%. Therefore, increased MDD is significantly linked to RLS.

Our meta-analysis included 12 case-control studies and revealed 2.05-fold higher MDD prevalence in RLS patients compared to non-RLS subjects. These results are consistent with those from a systematic review in 2014[11]. Our results appear to be robust than a study which demonstrated that MDD was more prevalent in RLS group than in non-RLS group (≥ mild depression: odds ratio (OR) = 1.95, p < 0.001; ≥moderate depression: OR = 6.15, p < 0.001; and ≥ severe depression: OR = 56.54, p < 0.001), with a predominant proportion of severe depression (97%) in RLS group[17]. A 2-to 4-fold higher risk of MDD in patients with RLS than in non-RLS subjects was also reported in epidemiological studies[9, 19–21]. Winkelman reported a positive correlation between RLS symptom frequency and depression severity[22]. Although MDD is reported frequently in RLS patients [20, 23, 24], how MDD is associated with RLS is still unclear [25, 26]. MDD risk was increased among individuals with severe RLS symptoms compared to those facing mild to moderate symptoms[27]. In addition, antidepressants can provoke or exacerbate RLS symptoms [21].

Strong association between RLS and depression could be explained by three possibilities. Firstly, RLS could cause MDD through nocturnal sleep disturbances and poor quality of life. Secondly, RLS manifestations, such as fatigue, diminished concentration and insomnia, could be misinterpreted as depressive symptoms. Thirdly, RLS and depression may share a common pathophysiology involving dopamine system. It has been reported that ropinirole, a dopamine agonist for treating RLS, improved depressive and RLS symptoms in RLS patients [28], whereas antidepressant treatment worsen RLS symptoms[26]. Although no scores related to sleep was extracted for our study, two articles were rated by EES [14, 17], and one group was rated by PSQI [10]. Several studies showed that the non-RLS group slept better than RLS group[13, 15, 16]. Our findings supported the idea that the most important cause of MDD might be chronic insomnia caused by RLS. In addition, RLS patients showed lower MMSE scores than non-RLS subjects, indicating cognitive function may be impaired in RLS cases[11]. Cognitive impairments in RLS have been reported in several previous studies[29, 30]. Cognitive

deficits in RLS patients could also result from chronic sleep disruption, comorbid MDD and a direct effect from RLS pathology itself, which requires further investigations.

Our research showed no significant difference in MDD prevalence between RLS patients under 50 years old (OR = 2.10) and those over 50 years old (OR = 2.05). Rothdach reported that men with RLS, but not women, had a higher prevalence of suffering depression[31]. Nevertheless, in a women-only Swedish study, women with RLS had an approximately double risk of self-reported depressed mood[32] although earlier reports achieved inconsistent conclusions. In our research, we did not consider the gender effect because we failed to extract useful data.

Our results also showed that the prevalence of MDD in RLS Asians (OR = 2.10) was not significantly different from that in Europe and American cases (OR = 2.05). No significant difference appeared in MDD rates either, between the first (8.3%)[11] and second (9.5%)[11] studies on RLS in Koreans. Comparing our results with those from other western studies on older adults, the prevalence rate was slightly lower in our analysis than in the study by Hogl for the group of 50–89 years (10.6%)[33], and slightly higher than in study by Ohayon for the group over 70 years old (8.7%) [34].

Some limitations in this study should be noted. The risk of publication bias might exist, though we did complete a relatively comprehensive searching in various international and Chinese databases, and Egger's tests detected no significant bias. Our selected samples, RLS 3357 individuals and 94912 non-RLS ones, might still be subjected to random errors. Since our meta-analysis covered ethnically different populations in multiple countries, heterogeneity might also affect our findings.

Despite those limitations, the present meta-analysis for the first time reliably estimated MDD prevalence among individuals with RLS, which was higher than that among non-RLS ones. Such findings should be replicated in larger, multi-sites observational studies. Our results may inspire clinicians to pay more attention to MDD in RLS and to explore effective treatments for both diseases based on their potential links in pathophysiology.

Abbreviations

MDD: Major depressive disorder; RLS: Restless legs syndrome; WED: Willis-Ekbom disease; GDS: Geriatric Depression Scale; BDI: Beck Depression Inventory; EPDS: Edinburgh Postnatal Depression Scale; CI: Confidence interval; NR: Not reported.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Haiwang Zhang and Yiming Wang designed the study. Haiwang Zhang, Changxi Zhou, Shuai Jin and Song Li collected the data and conducted the initial data analysis. Haiwang Zhang, Youssif Ben Zablah and Neil Merovitch drafted the manuscript; Xingde Liu, Kaide Xia, Peng Li, Guangyuan Xia, Junwen Wang, Xiaohong Kang helped to analysis the data, interpret the results and comment to the manuscript. All authors confirmed to review the final version for submission.

Acknowledgements

Not applicable

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Figures

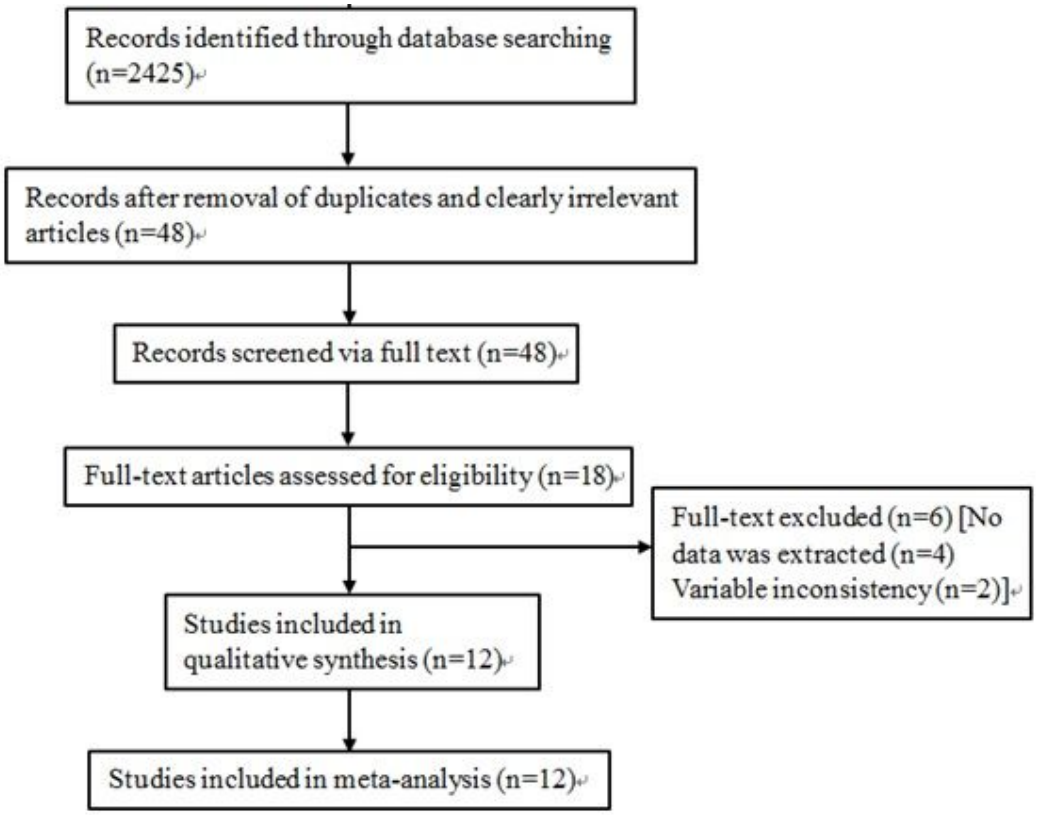

Figure 1

Summary of the study selection

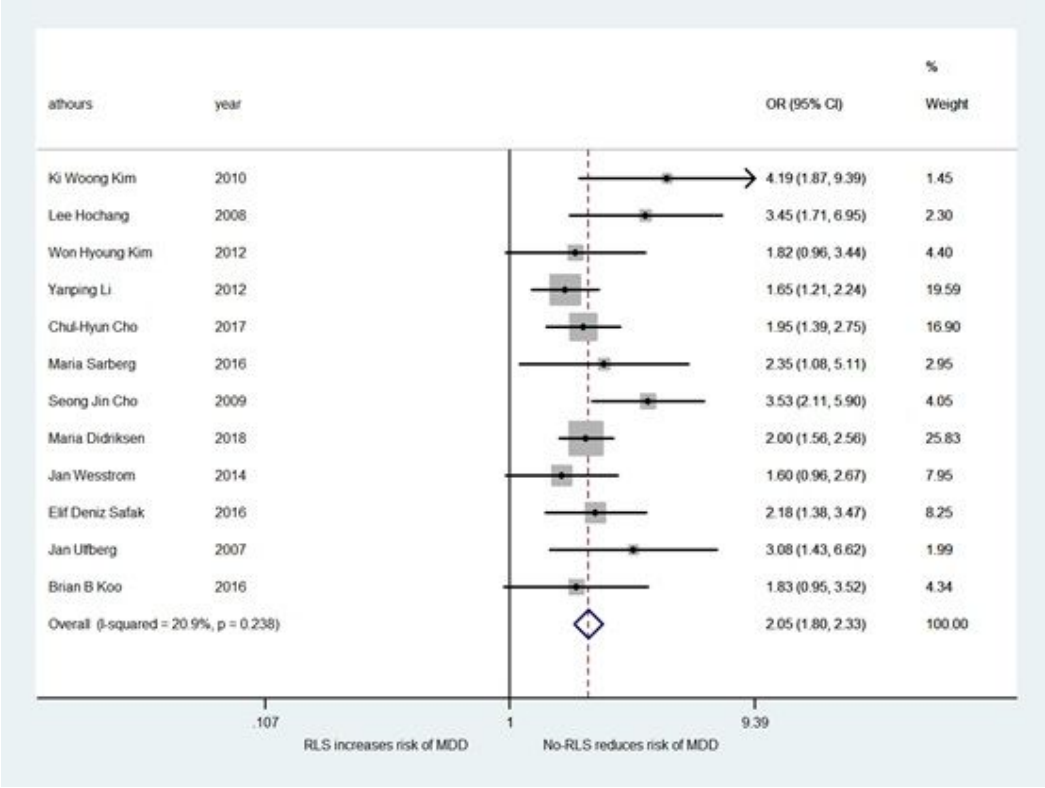

Figure 2

Forest plot of MDD prevalence in individuals with and without RLS based on case-control studies. The prevalence was significantly higher among individuals with RLS ($p<0.005$). The x-axis indicates 95% confidence interval.

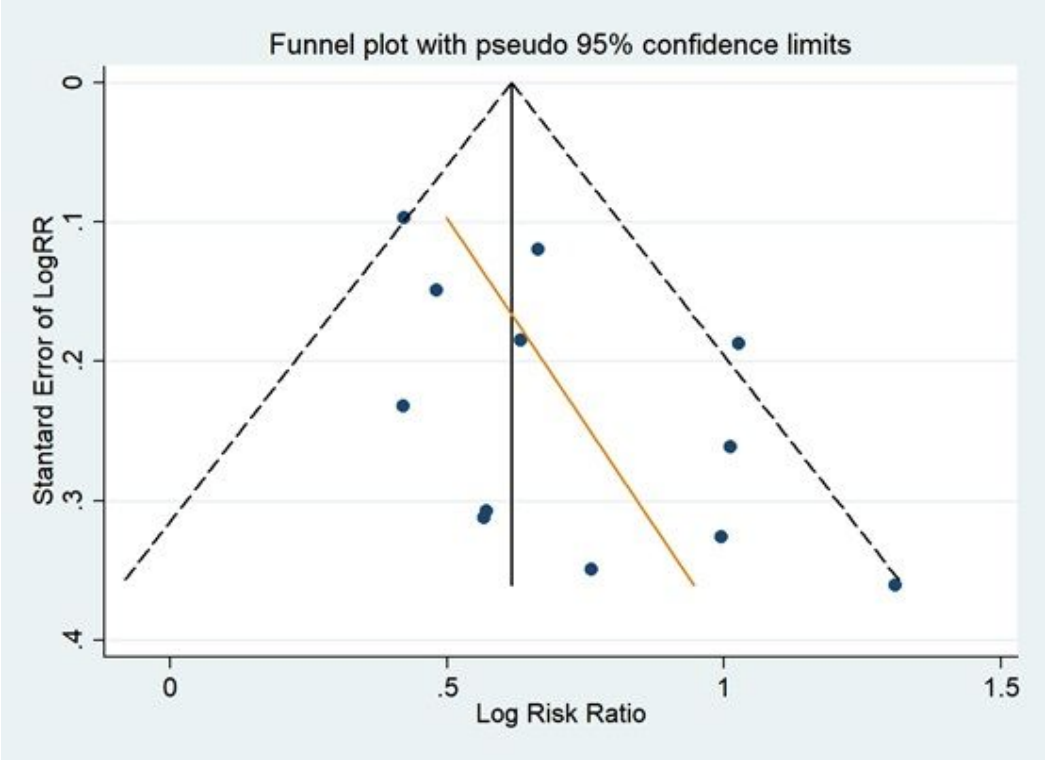

Figure 3

Funnel plot showing no significant publication bias.

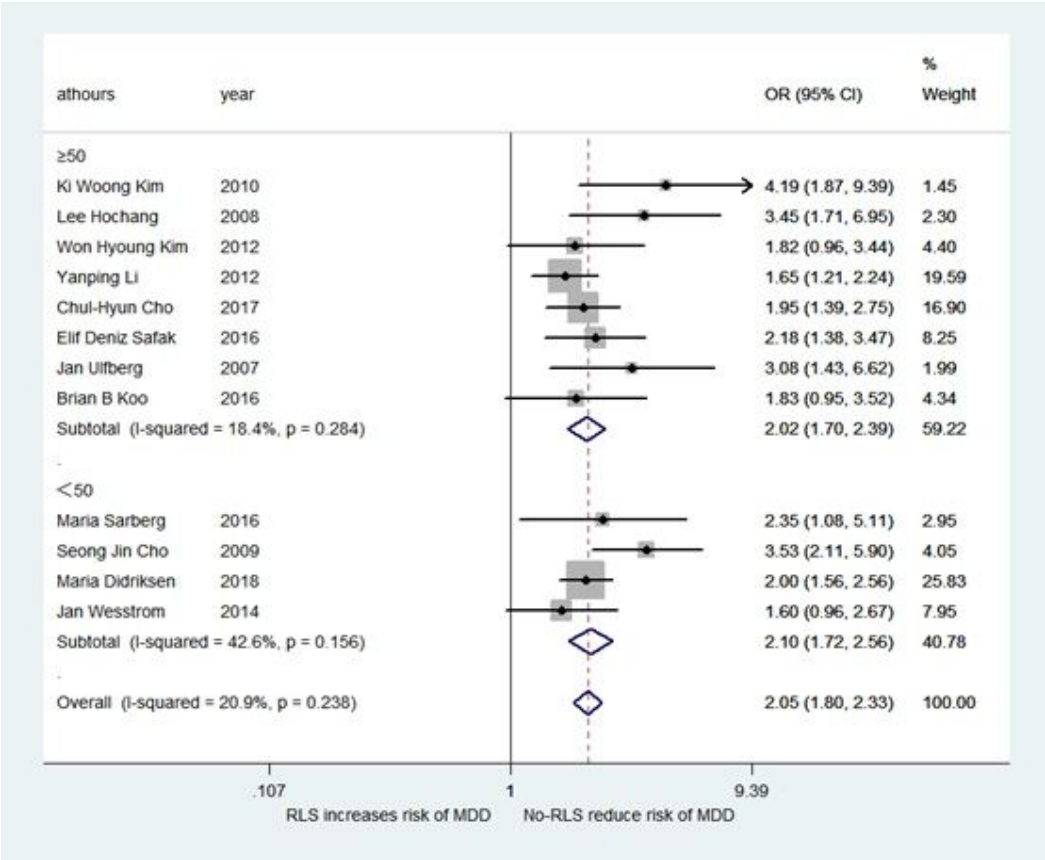

Figure 4

No significant difference in MDD prevalence between RLS patients under 50 years old and those of 50 or olders. The x-axis indicates 95% confidence interval.

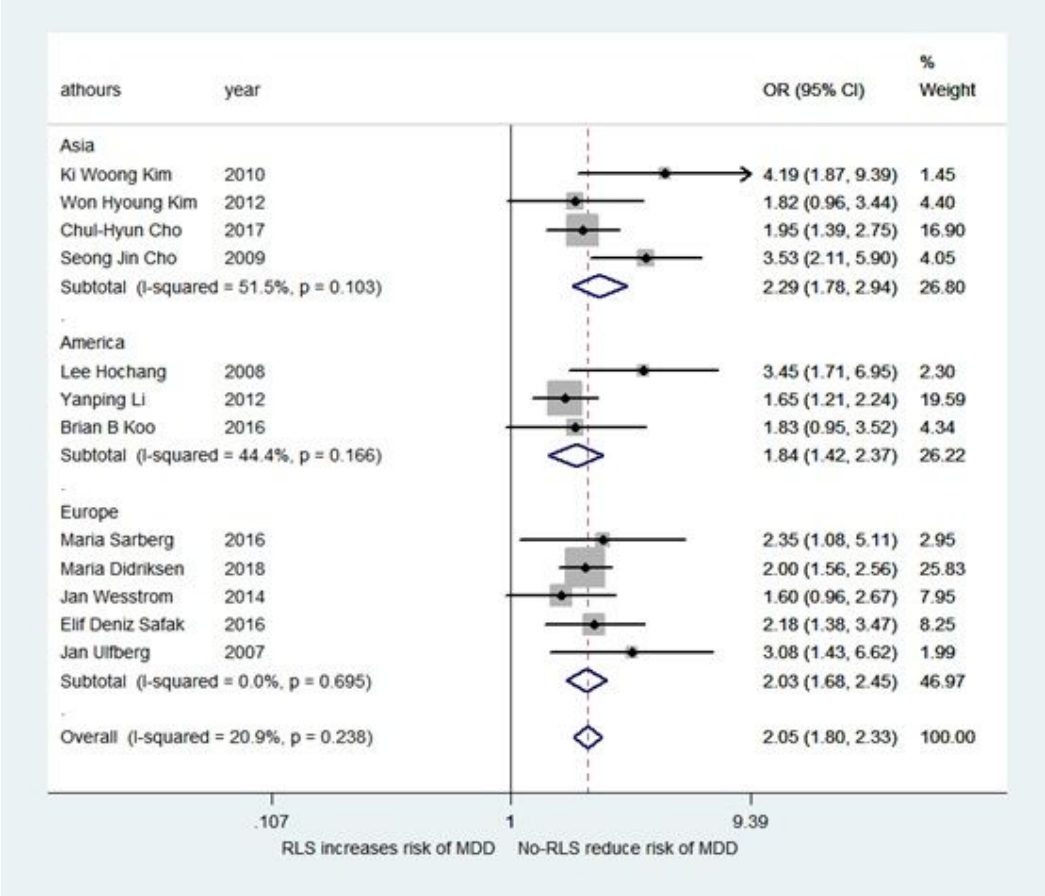

Figure 5

No significant difference in MDD prevalence between Asian RLS patients and European or American RLS patients. The x-axis indicates 95% confidence interval.