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Effect of physical activity interventions on symptom severity for Restless Legs Syndrome : A systematic review and meta-analysis of randomized controlled trials

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 September 2024 and was last updated on 18 September 2024.

INTRODUCTION

Review question / Objective To find practical evidence that nonpharmacological treatments can also improve the symptom severity of restless legs syndrome, a meta-analysis was used to demonstrate the effect of physical activity interventions on symptom severity for Restless Legs Syndrome (RLS).

Condition being studied Restless Legs Syndrome (RLS), also known as Willis-Ekbom disease, is a common neurological sensorimotor disorder characterized by an uncontrollable urge to move the legs. This impulse is often accompanied by uncomfortable or unpleasant sensations in the legs. Symptoms occur during rest and inactivity, are partially or totally relieved by movement, and worsen in the evening or night compared with during the day.1 The occurrence of the above features is not associated with as symptoms that are primary to other medical or behavioral conditions (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).2 According to the cause of onset, restless legs syndrome can be divided into primary (idiopathic) and secondary disorders, which are secondary conditions that are often related to iron deficiency, pregnancy or end-stage renal disease,3 and are also associated with diabetes, obesity, and peripheral neuropathy.4 The prevalence of restless legs syndrome in different populations is as follows: the prevalence of RLS is 2.0% to 10.8% in European and American adults;5 older population-based studies have suggested that the prevalence of RLS may range from 5% to 15%;6 and the prevalence of RLS across all three trimesters is 21% in pregnant women;7 the prevalence of RLS can reach approximately 30% in hemodialysis patients with chronic kidney disease.8,9 Previous studies have shown that the prevalence of Restless Legs Syndrome is relatively high. Pharmacological therapies are usually used for RLS, but medications for RLS can have significant side effects. Studies indicate that

levodopa or dopamine agonist treated patients experience more adverse events than placebo treated patients do.10,11 Therefore, many patients with RLS are eager for nonpharmacological treatments. In recent years, some researchers have conducted physical activity interventions in experiments to explore the therapeutic effects of physical activity interventions on RLS. To evaluate the effectiveness and consistency of physical activity interventions for RLS in experimental studies in greater detail, this paper adopted a systematic review and meta-analysis for the screened and included studies. The results of this study will contribute to providing options for nonpharmacological treatment for patients with RLS and clinicians.

METHODS

Search strategy The researchers in this study searched six electronic databases (Scopus, Cochrane Library, PubMed, Web of Science, Embase, CNKI) from the databases' inception to April 19, 2024. Keywords: Restless Legs Syndrome, Willis Ekbom Disease, physical exercise, physical training, physical activity; retrieved from (such as PubMed): (AF= (Restless Legs Syndrome or Willis Ekbom Disease) AND AF= (physical exercise or physical training or physical activity).

Participant or population The participants were definitively diagnosed with restless leg syndrome (primary or secondary), and there was no age limit.

Intervention Physical activity intervention programs involve cycling exercise, walking exercise, strength and stretching exercise, muscle relaxation exercise.

Comparator The nonpharmacological routine intervention group or the blank intervention.

Study designs to be included The randomized controlled trials.

Eligibility criteria The following inclusion criteria were applied: (1) the subjects were definitively diagnosed with restless leg syndrome (primary or secondary), and there was no age limit; (2) the RCT design, in which the experimental group received only physical activity intervention, there were no restrictions on sports events, and the control group received routine intervention or blank intervention; (3) the English or Chinese literature was published publicly in peer-reviewed journals; (4) the research results must be measured by using proven tools; (5) the studies had at least two data points (pre- and post-measures).

The exclusion criteria were as follows: (1) non-RCTs; (2) studies were republished; (3) full text was not available; (4) valid data, such as the mean value, standard deviation, and number of participants could not be extracted; (5) baseline of demographic characteristics for the groups were missing; (6) pre-test datas were expressed by mean ± SD, and post-test datas were expressed by mean ± SE; (7) outcome indicators were not related to symptom severity of RLS.

Information sources Six electronic databases from Scopus, Cochrane Library, PubMed, Web of Science, Embase, and CNKI were searched for randomized controlled trials on the effect of physical activity interventions on symptom severity for RLS from the database inception to April 19, 2024.

Main outcome(s) Seven studies with randomized controlled trials were ultimately included, with a total of 263 patients with RLS. (1) The effect size analysis showed that in the physical activity intervention group, compared with the nonpharmacological routine intervention group or the blank intervention group, the physical activity intervention effectively improved the symptom severity of RLS (WMD=-5.61, 95% CI: -7.18 ? -4.04, $p < 0.00001$). (2) Subgroup analysis showed that: ① sample size that more than or equal to 30 subjects (WMD=-6.303, 95% CI: -7.900 ? -4.706, P=0.000) had a greater positive effect on the improvement of symptom severity for RLS by physical activity interventions than sample size that less than 30 subjects (WMD=-1.994, 95% CI: -7.181 ? 3.192, P=0.008); ② physical activity greater than or equal to 45 minutes (WMD=-6.122, 95% CI: -9.514 ? -2.731, P=0.003) had a more positive effect on the improvement of symptom severity for RLS than physical activity intervention less than 45 minutes (WMD=-2.796, 95% CI: -7.699 ? 2.107, P=0.004); ③ physical activity more than or equal to 12 weeks (WMD=-5.361, 95% CI: -6.649 ? -4.074, P=0.001) had a higher positive effect on the improvement of symptom severity for RLS than physical activity intervention less than 12 weeks (WMD=-2.399, 95% CI: -10.448 ? 5.650, P=0.000). (3) Sensitivity analysis indicated that the study results were stable. (4) Publication bias assessment revealed that the P-values of Egger's test (P=0.4243) and Begg's test (P=0.7545) are both significantly greater than 0.05, and the safety-loss coefficient of 9 studies is 212, which is significantly greater than (5K+10)(55),

confirming that there is no publication bias for the studies included in thispaper.

Quality assessment / Risk of bias analysis Methodological quality was evaluated via the Physiotherapy Evidence Database (PEDro). Randomized controlled trials with a score of 5 or above (total score of 10) were of moderate to high quality on the PEDro scale.13 Some authors have also suggested that scores of ? 4 are considered 'poor', scores of 4--5 are considered 'fair', scores of 6--8 are considered 'good' and scores of 9--10 are considered 'excellent'.14 On the basis of the above, the quality of the studies included in this study is medium or higher.

Strategy of data synthesis The contents of the extracted data are as follows: (1) basic information, including research title, author, and publication time, is included in each study. (2) basic information of the subjects: average age of patients/participants, sex composition, sample sizes of the experimental group and control group, and so forth. (3) Intervention measures: sporting events, frequency, time, duration. (4) Control measures: control measures taken, frequency, duration, time. (5) The pre-test and the post-test in the experimental group: means and standard deviations of symptom severity scores for RLS. (6) The pre-test and the post-test in the control group: means and standard deviations of symptom severity scores for RLS. (7) Symptom severity scores for RLS were measured via the International Restless Legs Syndrome Study Group Rating Scale in the experimental group and control group.
RevMan 5.4 software was used for the analysis of the effect size in the included studies, and a forest plot was drawn. Stata 17.0 software was used for the assessment of subgroup analysis, sensitivity analysis, and publication bias in the included studies, and a funnel plot was drawn. CMA V3 software was used to calculate the classic fail-safe N.
Owing to the high level of heterogeneity in the included studies (I2=82%, p < 0.00001), a random-effects model was used for analysis. In addition, since the same tools were used for measuring indicators, the weighted mean difference(WMD) was adopted as the effect size**.**

Subgroup analysis A sample size that was more than or equal to 30 subjects (WMD=-6.303, 95% CI: -7.900 ? -4.706, P=0.000) had a greater positive effect on the improvement of symptom severity for RLS by physical activity interventions than a sample size that was less than 30 subjects, owing to confidence interval of a sample size subgroup that was less than 30 subjects includes the null line (WMD=-1.994, 95% CI: -7.181 ? 3.192, P=0.008), there was no significant difference in the effect of physical activity intervention and nonpharmacological routine intervention or blank intervention on symptom severity for RLS. A single intervention duration showed that physical activity greater than or equal to 45 minutes (WMD=-6.122, 95% CI: -9.514 ? -2.731, P=0.003) had a greater positive effect on the improvement of symptom severity for RLS than did a physical activity intervention less than 45 minutes, as the confidence interval of a single intervention duration subgroup that was less than 45 minutes includes the null line (WMD=-2.796, 95% CI: -7.699 ? 2.107, P=0.004), there was no significant difference in the effect of physical activity intervention and nonpharmacological routine intervention or blank intervention on symptom severity for RLS. A duration exhibited that physical activity greater than or equal to 12 weeks (WMD=-5.361, 95%CI: -6.649 ? -4.074, P=0.001) had a greater positive effect on the improvement of symptom severity for RLS than did a physical activity intervention of less than 12 weeks, since confidence interval of the total duration subgroup that less than 12 weeks includes null line (WMD=-2.399, 95% CI: -10.448 ? 5.650, P=0.000), there was no significant difference in the effect of physical activity intervention and nonpharmacological routine intervention or blank intervention on symptom severity for RLS. As seen above, sample size, single intervention duration and total duration as grouping factors were not significant factors for heterogeneity, which may be caused by otherfactors.

Sensitivity analysis The source of heterogeneity in the included studies was further explored by using the sensitivity one by one elimination method. if any one study is omitted, the combined effect size of the remaining eight studies is basically consistent with the original effect size, indicating that this study results are stable andreliable.

Country(ies) involved Poland, China.

Keywords Restless Legs Syndrome, symptom severity, physical activity, meta-analysis, systematic review.

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