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Review article

Quality of life among patients with restless legs syndrome: A systematic review and meta-analysis

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ABSTRACT

Objective: The primary aim was to estimate the pooled mean score of quality of life (QoL) (total, mental and physical health components) among patients with Restless Legs Syndrome (RLS). Secondary aims were to assess: (I) QoL differences for RLS vs. control groups, (II) heterogeneity and possible sources; and (III) moderating variables.

Methods: Studies identified in PubMed, Scopus, Web of Science, and ProQuest between January 2000 and December 2022 were included. Methodological quality was assessed with Newcastle Ottawa Scale. The protocol was pre-registered (PROSPERO, CRD42023387318).

Results: Twenty-seven studies (20121 participants, 12 countries) were included. The corrected pooled estimated mean score of QoL was 47.92 (27 studies, CI 95 %: 43.11 to 52.72, range 0–100, i.e., low–high QoL) and was marginally affected by publication year (increased 0.89 by each year, $p = 0.12$). The corrected pooled estimated mean score of the mental health component was 47.32 (17 studies, 95 % CI: 43.12 to 51.51, range 0–100) and influenced by RLS instrument (decreased with recent versions, $p = 0.05$). The corrected pooled estimated mean score of the physical health component was 39.08 (17 studies, 95 % CI: 33.05 to 45.10, range 0–100), with no statistically significant moderator. The pooled estimated QoL scores were statistically significantly lower in RLS patients compared to control groups with standardized mean difference (SMD) of −0.78, −0.57 and −0.50 respectively for overall QoL (24 studies), physical and mental health components (14 studies). Total QoL SMD was affected by proportion of women.

Conclusion: Low QoL was revealed among RLS patients, which was statistically significantly reduced compared to control groups.

1. Introduction

Restless legs syndrome (RLS) is a neurological disorder [1–3] with an estimated worldwide prevalence of 3 % in the general adult population [4]. The five diagnostic criteria presented by the International Restless Legs Syndrome Study Group [5] include (*I*) a desire to move arms and legs usually associated with discomfort, (*II*) motor restlessness, (*III*) symptoms are worse or exclusively present at rest (lying, sitting) with at least partial and temporary relief by activity, (*IV*) symptoms are worse in the evening/night and (*V*) the occurrence of the above is not only reported as symptoms primary to another medical/behavioural condition, but may be secondary to other diseases or conditions. The symptoms have been described as e.g., a burning, creeping, or drawing feeling, but also as a tingling, electrical, and painful feeling, sometimes also as

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insects crawling inside the legs [6–8]. The urge to move the legs during the night leads to sleep disturbances, which can result in significant impairment in quality of life (QoL) [5]. Insomnia, excessive daytime sleepiness, and depression are described, which might have a negative impact on social relationships and the whole life-situation [9,10]. When the diagnosis is made pharmacological treatment is usually prescribed. Dopamine agonists, L-dopa, alpha-2-delta ligands, opioids, or iron are available depending on aetiology and severity [11,12]. In the case of continuous drug therapy, a dopamine agonist is often used, but this can lead to augmentation [11–17]. Self-care has only been evaluated in a few studies making its effect difficult to assess [18]. Overall, the symptom burden, also when the diagnosis is made and treatment is initiated, makes RLS a burdensome long-term condition [19,20], which can increase the risk for decreased QoL.

An often-used model to describe QoL [21] is the one provided by Wilson and Cleary [22] which includes physiological variables, symptom status, functional health, general health perceptions, and overall QoL. There are generic measurements (i.e., to be used in the general population). Disease specific measurements, where health and function are assessed in relation to specific symptoms and issues related to the diagnosis can also be used [23]. Differences in RLS-symptom profiles have been reported between men and women [16] why gender-specific analyses of QoL may be warranted. Moreover, conditions with long-term and burdensome symptoms require validated instruments. Walters et al., [24] found both generic and disease specific instruments to be used in RLS, but validity aspects varied. During the past 20 years the diagnostic criteria, as well as recommended first-line treatment has changed [3], which may affect QoL outcomes. Thirdly, the current knowledge gap contains lack of understanding for differences in QoL compared to patients with other diagnoses, and to healthy populations, but also for how heterogeneity may be affected by clinical- and/or research-based aspects. Surprisingly, there is, despite the mentioned arguments, no recent meta-analysis that summarizes QoL in patients with RLS. Therefore, the primary aim of the present study was to estimate the pooled mean score of QoL (total, mental and physical health components) among patients with RLS. Secondary aims were to assess: (*I*) QoL score differences for patients with RLS vs. control groups, (*II*) heterogeneity and possible sources; as well as (III) moderating variables (i.e., publication year, methodological quality, community-based survey, development status of the country, income status of the country, gender, participant group, RLS scale, QoL measure type, and control group).

2. Method

2.1. Study design

This systematic review is set up and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. The protocol was prospectively registered under decree code of CRD42023387318 in the PROSPERO International prospective register of systematic reviews [26].

2.2. Inclusion criteria

Observational studies (e.g., cross-sectional, cohort and case-control studies) were included if relevant data regarding diagnosis of RLS and QoL were reported. The presence of RLS had to be assessed using valid and reliable measures, a clinical examination, or other methods with acceptable validity and reliability according to accepted diagnostic criteria for RLS, as presented in international guidelines at the time of the data collection for the respective studies. The assessment of QoL had to be done using a validated measure. English-language, peer-reviewed papers published from 2000 to December 2022 were included. There were no limitations regarding participants' characteristics. Studies with the following conditions were excluded. Those that: 1) did not report mean (SD) score for QoL; 2) carried out a review study.

2.3. Information sources

Four academic databases; PubMed, Scopus, Web of Science, and ProQuest were searched systematically between January 8th to 11th 2023.

2.4. Search strategy and selection process

PubMed Medical Subject Headings (MeSH), published reviews, and primary studies were used to define search terms. Restless legs syndrome and its synonyms including RLS, Willis Ekbom Disease, Wittmaack Ekbom Syndrome, and "Quality of life" were main search terms. Boolean operators (AND/OR/NOT) were used to develop the search syntax, which was customized for each database based on their advanced search characteristics (Appendix 1). Additionally, reference lists of all included studies and previously published systematic reviews in RLS were hand searched to increase the probability to find and include all appropriate papers. The selection process was done independently by two researchers. First, title and abstract of all retrieved papers were assessed. Then, full texts of potentially relevant studies were further examined based on the above-mentioned inclusion criteria. Relevant studies were selected via this two-step process. Disagreements between the two researchers in the selection process were resolved via discussions in the research group.

2.5. Data collection process

Data collection was performed independently by two researchers. An Excel sheet specifically designed for the current study was used to pull data. Data including first author's name, publication year, study design, country, number of participants (total and in subgroups), participants' gender (and percent of female participants), and mean age were collected. Scales used to assess RLS and QoL, as well as their version and scoring attributes, including numerical results regarding the mean scores of QoL (i.e., total, mental, and physical health components were available) among RLS and control groups, numerical results regarding association of QoL and RLS severity were accumulated. Some studies reported median and interquartile range [27,28] which was converted to mean and SD using the following website https://vassarstats.net/median_range.html. In two studies [29,30], required data were reported as bar plots which were extracted as numerical reports using the following website https://apps.automeris.io/wpd/. Disagreements in the data collection procedure were resolved through a discussion in the research group.

2.6. Assessment of methodological quality and risk of bias

Methodological quality was assessed independently by two researchers with the use of the Newcastle Ottawa Scale (NOS) [31]. Selection, comparability, and outcome are three methodological domains assessed using the NOS. Based on three different methodologies for observational studies, three NOS versions have been defined for evaluating cross-sectional studies (seven items), case-control studies (eight items), and cohort studies (eight items). Despite a slight difference in number and content of items, each item is rated with a point, except comparability which can have two points. This gives a maximum quality score of 9 (i.e., 4 points for selection, 2 points for comparability, and 3 points for outcomes) for each study. Studies with less than 5 points are classified as having a high risk of bias [31]. In the present meta-analysis, no studies were excluded based on the quality rating. However, subgroup analysis was conducted to assess the impact of quality on pooled effect size. Disagreements were resolved by consensus discussion in the research group.

2.7. Effect measures

The following effects measures based on objectives and content in the included studies were used:

(I) Mean scores of QoL among patients with RLS (i.e., including total score, as well as mental and physical health components' score) were analysed with the Metan module (STATA statistical software package). The pooled estimate of mean QoL score with 95 % Confidence Interval (CI) was reported. To have comparable scores (i.e., 0–100) for the meta-analysis, scores obtained from studies not reporting QoL scores this way (n = 3) were converted to the 0–100 scale. For this purpose, the following conversion formula was used: Adjusted score = [(acquired raw score- minimum possible score) /(maximum - minimum possible score)] * 100 [32]. Most of the studies used measures of QoL where higher scores indicated better QoL. However, some studies (n = 4) used disease specific measures of QoL where higher scores indicated worse QoL. To be consistent, QoL scores in these four studies were reversed. Mean standard error (SE) was calculated by dividing the standard deviation to the square root of the sample size for the group.

(II) Standardized mean difference (SMD) was used to compare the mean scores of QoL (i.e., including total score, as well as mental and physical health component scores) among patients with RLS vs. various control groups. The pooled SMD with its 95 % CI was reported. The SMD effect size of 0.2–0.5 is considered as a small effect size; 0.5–0.8 is considered as a medium effect size; and greater than 0.8 is interpreted as a large effect size [33].

2.8. Synthesis methods

A quantitative synthesis using STATA software version 14 was conducted. Meta-analysis was run using a random effect model because included studies were taken from different populations, and both within-study and between-study variances should be accounted for [34]. The Q Cochrane statistic was used to assess heterogeneity. Also, the severity of heterogeneity was estimated using the I2 index [35].

2.9. Additional analyses

To assess moderator effects (i.e., publication year, methodological quality, community-based survey, development status of the country, income status of the country, gender, participant group, RLS scale, QoL measure type, and control group), subgroup analysis or meta-regression was carried out based on the number of studies in each group. The decision threshold for considering a variable as significant in the meta-regression depends on the number of studies included. When below 10 studies are included, the threshold is 0.20, between 10 and 20 studies, the threshold is 0.15, and above 20 studies, the threshold is 0.10 [36,37]. Variables with mentioned p-values and positive adjusted R square were entered in a multivariable meta-regression.

2.10. Reporting bias assessment

Funnel plot, Begg's Test and The fill-and-trim method were used to assess and adjust for publication bias [38].The jack-knife method was used to assess small study effect [39].

3. Results

3.1. Study screening and selection process

The initial search in four databases resulted in 3100 studies: PubMed (n = 823), ISI Web of Science (n = 1314), Scopus (n = 875) and ProQuest (n = 88). No study was added by hand search in reference lists of the included studies. After removing duplicated papers (n = 1201), a further 1899 papers were screened based on title and abstract. Then, 146 papers appeared to be potentially eligible, and their full texts were reviewed. Finally, 27 studies met the eligibility criteria and were pooled in the meta-analysis (i.e., 27 studies reported mean QoL scores in patients with RLS, and 25 studies reported QoL scores among patients with RLS compared with different control groups). Fig. 1 shows the search process based on the PRISMA flowchart.

3.2. Study characteristics

Overall, 27 studies that comprised 20,121 participants (1979 with RLS and 18,144 counterparts without RLS) from 12 different countries (i.e., Canada, India, Italy, Germany, Greece, Japan, Turkey, Slovakia, South Korea, Sweden, UK, and USA) were included (Table 1). Almost all studies were conducted in developed (n = 26) and high income (n = 20) countries based on the World Bank. The country with the highest number of eligible studies were South Korea (n = 6) and Turkey (n = 5). The smallest sample size was 16 [40], and the largest sample size was 6900 [41]. The mean (SD) age of participants was 50.79 (11.77) years with an age range of 28 to 72. More than half of overall participants were females (63.16 %). All studies were cross-sectional. As displayed in Table 1, the most frequently used instrument to assess RLS was the IRLSSG 2003 (n = 17). QoL was assessed using generic (n = 19) and disease specific (n = 8) instruments. The most frequently used QoL instrument was the Medical Outcomes Study 36-item short-form health survey (SF-36) (n = 11). In studies with a case-control group, eight

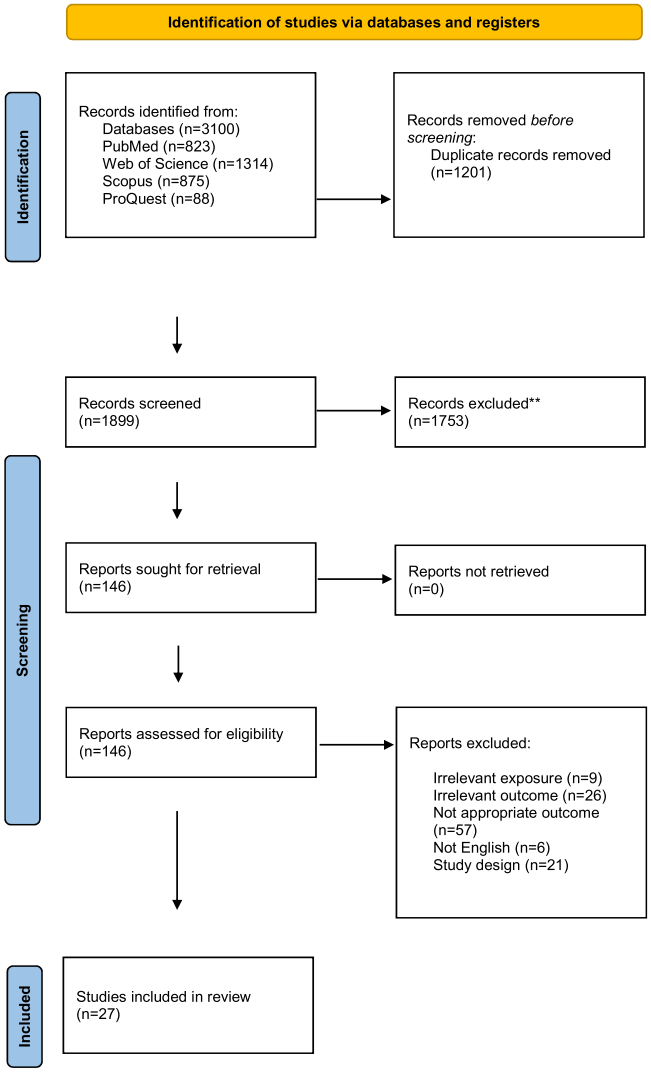

Fig. 1. Search process based on the PRISMA flowchart.

Table 1
Summary of characteristics of the included studies (N = 27).

Author Year Reference #	Country Income Development	Population based study	Mean age Female %	Target population with RLS/ Comparison group	QoL scale	Type of QoL measure	RLS scale	N (RLS, control)	NOS category/ total NOS score
Abetz L, 2004 [42]	UK High Developed	No	62.4 63.5	RLS patients/No control	SF36	Generic	IRLS-PV	85 (85, -)	Low risk of bias/6
Kushida C, 2007 [41]	USA High Developed	No	53.2 63	RLS patients/Healthy control	SF36	Generic	RLS screening criteria by answering	6900 (158, 6742)	Low risk of bias/6
Kim KW, 2009 [43]	South Korea High Developed	No	71.9 57.8	Elder people/Healthy control	SF36	Generic	IRLSSG 2003	714 (59, 655)	Low risk of bias/6
Benediktsdottir B, 2009 [44]	Sweden and Iceland High Developed	Yes	40 -	General population/ Healthy control	SF-12	Generic	IRLSSG 2003	1344 (205, 1139)	Low risk of bias/6
Cho SJ, 2009 [45]	South Korea High Developed	Yes	41 54.3	General population/ Healthy control	European Quality of Life–5 Dimensions (EQ-5D)	Generic	IRLSSG 2003	6509 (72, 6437)	Low risk of bias/6
Ostacoli L, 2010 [46]	Italy High Developed	No	46.5 54.1	Cancer patients undergoing chemotherapy/Same disease RLS free	Functional assessment of Cancer Therapy (FACT-G)	Disease Specific	IRLSSG 2003	257 (47, 210)	Low risk of bias/6
Cannavo S, 2011 [40]	Italy High Developed	No	54 64.3	Acromegalic patients/Same disease RLS free	Acro-QoL	Disease Specific	IRLSSG 2003	16 (7, 9)	High risk of bias/4
Giannaki CD, 2011 [29]	Greece High Developed	No	54.1 27.1	Haemodialysis patients/Same condition RLS free	SF36	Generic	IRLSSG 2003	70 (30, 40)	Low risk of bias/7
Cho YW, 2012 [47]	South Korea High Developed	No	51.7 60.7	RLS patients/No control	SF36	Generic	IRLSSG 2003	107 (107, -)	Low risk of bias/6
Cho YW, 2012 [48]	South Korea High Developed	No	53.1 65.6	RLS patients/Healthy control	SF36	Generic	IRLSSG 2003	429 (215, 214)	Low risk of bias/6
Walia HK, 2013 [30]	USA High Developed	No	51 61	Palliative care patients/Same condition RLS free	SF-12	Generic	IRLSSG 2003	76 (31, 45)	Low risk of bias/7
Fereshtehnejad SM, 2014 [49]	Sweden High Developed	No	60.9 71.3	Parkinson's disease/ Same disease RLS free	Parkinson's disease Quality of Life Questionnaire	Disease Specific	IRLSSG 2003	108 (16, 92)	Low risk of bias/6
Civelek GM, 2014 [50]	Turkey Upper middle Developed	No	49 100	Fibromyalgia syndrome/Same disease RLS free	Fibromyalgia Impact Questionnaire	Disease Specific	IRLSSG 2003	115 (49, 66)	Low risk of bias/6
Demirci S, 2015 [28]	Turkey Upper middle Developed	No	44 38.5	Ankylosing spondylitis/Same disease RLS free	Ankylosing Spondylitis quality of life questionnaire	Disease Specific	IRLSSG 2014	108 (39, 69)	Low risk of bias/6
Cho YW, 2015 [51]	South Korea High Developed	No	52.9 68.1	RLS patients/No control	SF36	Generic	IRLSSG 2003	160 (160, -)	Low risk of bias/6
Chatterjee SS, 2015 [52]	India Lower middle Developing	No	31.2 55.7	Somatoform pain disorder/Same disease RLS free	QLES-Q	Generic	IRLSSG 2003	192 (56, 136)	Low risk of bias/6
Song ML, 2015 [53]	South Korea High Developed	No	–	RLS patients/Healthy Control	SF36	Generic	IRLSSG 2014	263 (148, 117)	Low risk of bias/6
Schindlbeck KA, 2016 [54]	Germany High Developed	No	50.3 86.4	Inflammatory bowel disease/Same disease RLS free	European Quality of Life–5 Dimensions (EQ-5D)	Generic	IRLSSG 2003	43 (22, 21)	Low risk of bias/6
Kubo K, 2016 [55]	Japan High Developed	Yes	54.8 61.9	General population/ Healthy Control	SF36	Generic	IRLSSG 2003	985 (36, 949)	Low risk of bias/7
Boulos MI, 2017 [27]	Canada High Developed	No	67.4 51.1	RLS after stroke and transient ischemic attack/Healthy Control	Stroke-Specific Quality of Life	Disease Specific	IRLSSG 2003	92 (23, 71)	Low risk of bias/6
Giannaki CD, 2018 [56]	Greece High Developed	No	41.5 -	MS patients/Same disease RLS free	SF36	Generic	IRLSSG 2014	50 (10, 40)	High risk of bias/4

(*continued on next page*)

Table 1 (*continued*)

Author Year Reference #	Country Income Development	Population based study	Mean age Female %	Target population with RLS/ Comparison group	QoL scale	Type of QoL measure	RLS scale	N (RLS, control)	NOS category/ total NOS score
Akbaş P, 2018 [57]	Turkey Upper middle Developed	No	28.1 100	Pregnant women/ Same condition RLS free	SF36	Generic	IRLSSG 2001	250 (116, 134)	Low risk of bias/6
Yatsu S, 2019 [58]	Japan High Developed	No	66.2 27.8	Heart Failure/Same disease RLS free	SF-8	Generic	IRLSSG 2014	133 (18, 115)	Low risk of bias/6
Cederberg KLJ, 2020 [59]	USA High Developed	No	59.7 81.1	MS patients/Same disease RLS free	MSIS-29	Disease Specific	Cambridge-Hopkins Restless Legs Syndrome Questionnaire	275 (74, 201)	Low risk of bias/6
Seferoğlu M, 2020 [60]	Turkey Upper middle Developed	No	40.5 -	MS patients/ Same disease RLS free	MSQoL-54	Disease Specific	IRLSSG 2014	46 (19, 27)	High risk of bias/4
Tuna Oran N, 2021 [61]	Turkey High Developed	No	28.3 100	Pregnant women/ Same condition RLS free	SF-12	Generic	IRLSSG 2014	693 (154, 539)	Low risk of bias/6
Minar M, 2022 [62]	Slovakia Upper middle Developed	No	66.9 39.1	Parkinson's disease/ Same disease RLS free	European Quality of Life–5 Dimensions (EQ-5D)	Generic	IRLSSG 2003	101 (23, 78)	Low risk of bias/6

compared RLS to healthy controls, and in 16 studies all patients had another specified condition (i.e., MS patients (3 studies)/Parkinson's disease (2 studies)/Pregnant women (2 studies)/other conditions, each in one paper including: Cancer patients undergoing chemotherapy/ Acromegalic patients/Haemodialysis patients/Fibromyalgia syndrome/ Ankylosing spondylitis/Somatoform pain disorder/Inflammatory bowel disease/Heart Failure/Palliative care patients) but the controls did not also have RLS. Table 1 provides a summary of characteristics of all included studies.

3.3. Risk of bias in studies

Almost all studies (n = 24) were categorized as having low risk of bias based on acquiring scores higher than 5 in the NOS. No study was excluded based on methodological quality, instead, subgroup analysis based on risk of bias status was conducted to assess the impact of methodological quality on pooled estimate of effect measures. The most common problems were (*I*) non-respondents were not reported, statistically described, and not compared with respondents (100 %); (*II*) sample size was not estimated or justified (90 %). The results of the quality assessments are provided in Table 1 and Appendix 2.

3.4. Outcome measures

3.4.1. Pooled mean score of total QoL among patients with RLS

The pooled estimated mean score for total QoL was 54.59 in a range of 0–100 [27 studies; 95 % CI: 50.21 to 58.97, I^2: 98.1 %, $\tau^2 = 128.64$]. Appendix 3 provides the forest plot showing the pooled mean score. The probability of publication bias was ruled out based on a symmetric funnel plot (Appendix 4) but based on Begg's test (p = 0.06) it seemed probable, so the fill and trim method was used. Using this method, an additional eight studies were imputed and the corrected pooled mean

Table 2
Results of subgroup analysis regarding different effect sizes.

		Overall QoL mean score			Overall QoL score difference among patients with RLS vs. control groups		
Variables		**No. studies**	**Pooled Mean QoL score (95 % CI)**	**I^2 (%)**	**No. studies**	**Pooled prevalence (95 % CI)**	**I^2 (%)**
Methodological Quality	High risk of bias	3	51.92 (36.87; 66.96)	90.8	3	−1.32 (−2.78; 0.14)	88.1
	Low risk of bias	24	54.91 (50.28; 59.54)	98.3	21	−0.77 (−0.99; −0.54)	92.2
Community based survey	No	25	54.42 (49.86; 58.98)	98.2	22	−0.81 (−1.05; −0.57)	92.1
	Yes	2	56.66 (35.45; 77.88)	98.2	2	−0.50 (−0.69; −0.31)	0
Development status of country	Developing	1	49.41 (47.26; 51.55)	–	1	−2.34 (−2.73; −1.95)	–
	Developed	26	54.82 (50.17; 59.46)	98.2	23	−0.70 (−0.89; −0.509)	88.4
Income status of country	Lower middle	1	49.41 (47.26; 51.56)	–	1	−2.34 (−2.73; −1.95)	–
	Upper middle	6	51.61 (35.16; 68.06)	99.1	6	−0.76 (−1.35; −0.18)	94.3
	High	20	55.67 (51.23; 60.11)	97.4	17	−0.67 (−0.86; −0.48)	83.9
Gender	Female only	3	51.27 (24.84; 77.69)	99.6	3	−0.35 (−0.51; −0.19)	22.8
	Both gender	24	54.88 (51.06; 58.71)	97.0	21	−0.85 (−1.10; −0.60)	92.0
Target population with RLS	RLS only	9	53.50 (48.13; 58.86)	97.5	6	−0.70 (−1.02; −0.38)	93.2
	RLS as comorbidity	18	55.26 (48.33; 62.19)	98.4	18	−0.83 (−1.15; −0.52)	91.3
RLS scale	IRLSSG_2001	1	51.98 (47.24; 56.72)	–	1	−0.36 (−0.61;-0.11)	–
	IRLSSG_2003	17	55.71 (50.61; 60.80)	97.8	15	−0.78 (−1.04; −0.52)	88.5
	IRLSSG_2014	6	54.58 (42.51; 66.66)	98.1	6	−1.01 (−1.80; −0.22)	96.1
	Other scales	3	48.88 (39.38; 58.39)	96.8	2	−0.38 (−0.52; −0.24)	–
QoL measure type	Generic	19	54.38 (49.61; 59.15)	98.1	16	−0.70 (−0.93; −0.46)	91.4
	Disease specific	8	55.19 (43.60; 66.78)	98.1	8	−1.06 (−1.64; −0.48)	92.3
Control group	Same disease RLS free				16	−0.88 (−1.24; −0.52)	92.4
	Healthy control				8	−0.67 (−0.93; −0.40)	90.8
Overall Estimated Prevalence		27	54.59 (50.21; 58.97)	98.1	24	−0.78 (−1.00; −0.56)	91.4

Note: CI: Confidence Interval, I^2: Heterogeneity Index.

total score of QoL was estimated to be 47.92 [CI 95 %: 43.11 to 52.72; τ2 = 203.21]. The corrected funnel plot is presented in Appendix 5. Also, sensitivity analysis showed that the pooled effect size was not affected by a single study effect (Appendix 6).

Subgroup analysis (Table 2) and univariable meta-regression (Table 3) showed that total QoL was marginally affected of publication year. Total QoL was associated with an increase of 0.89 per year, the more recently the study was published. This indicated a slight, but not statistically significant (p = 0.12) improvement of QoL explaining 5.84 % of the variance regarding mean score of QoL. None of the examined variables were identified as sources of heterogeneity.

3.4.2. Pooled mean score of the mental health component among patients with RLS

The pooled estimated mean score for the mental health component was 49.29 in a range of 0–100 [17 studies; 95 % CI: 44.88 to 53.71, I^2: 98.3, τ^2 = 80.77]. Appendix 7 provides the forest plot showing the pooled mean score. Publication bias was probable based on the funnel plot (Appendix 8), but not on Begg's test (p = 0.71). In the fill and trim method, three studies were imputed with a corrected pooled mean score estimated to be 47.32 [95 % CI: 43.12 to 51.51; τ2 = 84.42]. Sensitivity analysis showed that the pooled effect size was not affected by a single study effect. Univariable meta-regression (Table 3) showed that risk of bias categories (p = 0.23), RLS measure type (p = 0.29) and female % of participants (p = 0.22) seem to be probable mediators of the mental health component. In multivariable meta-regression (Table 4), RLS measure type remained as the significant mediator (p = 0.05) which explained 30 % of the variance. The scores were decreased by −1.20 score when recent versions of IRLSSG were used compared to the earlier ones (IRRLSSG versions: 2001, 2003 and 2014). None of the examined variables were identified as sources of heterogeneity.

3.4.3. Pooled mean score of the physical health component among patients with RLS

The pooled estimated mean score for the physical health component was 45.27 in a range of 0–100 [17 studies; 95 % CI: 39.56 to 50.98, I^2: 98.7 %, τ^2 = 137.85]. Appendix 9 provides the forest plot showing the pooled mean score. Publication bias was probable based on funnel plot (Appendix 10), but not based on Begg's test (p = 0.48). In the fill and trim method, five studies were imputed with corrected pooled mean score estimated to be 39.08 [95 % CI: 33.05 to 45.10; τ2 = 198.95]. Sensitivity analysis showed that pooled effect size was not affected by a single study effect. None of the examined variables were identified as sources of heterogeneity (Table 3).

3.4.4. Total QoL score difference among RLS patients vs. control groups

The pooled estimated total QoL score was significantly lower in patients with RLS compared to the control groups that were used with SMD of −0.78 [24 studies; 95 % CI: −1.00 to −0.56, I^2: 91.4 %, Tau^2 = 0.24]. Fig. 2 provides the forest plot showing the pooled SMD score. Publication bias seemed probable based on Begg's test (p = 0.007) and an asymmetric funnel plot (Appendix 11), but as no study was imputed when the fill and trim method was conducted to correct probable publication bias, publication bias was ruled out. Also, sensitivity analysis showed that pooled effect size was not affected by a single study effect.

Subgroup analysis (Table 2) and univariable meta-regression (Table 3) showed that country development status (p = 0.04), country income level (p = 0.19), and female % of participants (p = 0.29) were potential mediators affecting pooled SMD in difference of RLS patients vs. control groups. The pooled SMD was −0.88 in individuals suffering a chronic disease compared with patients having the same condition without RLS [16 studies; 95 % CI: −1.24 to −0.52, I2: 92.4 %] and −0.67 in patients suffering RLS in comparison with healthy control [8 studies; 95 % CI: −0.93 to −0.40, I2: 90.8 %]. Based on multivariable meta- regression (Table 4), only female % of participants remained as a significant moderator of pooled SMD and explained 36.21 % of variance in SMD of QoL mean scores. None of the examined variables were identified as sources of heterogeneity.

3.4.5. Mental health component score difference among RLS patients vs. control groups

The pooled estimated SMD of the mental health component was significantly lower (−0.50 [14 studies; 95 % CI: −0.80 to −0.19, I^2: 93.4 %, Tau^2 = 0.29]) in patients with RLS compared to control groups. Fig. 3 provides the forest plot showing the pooled SMD score. Based on Begg's test (p = 0.04) and an asymmetric funnel plot, publication bias seemed probable. But no study was imputed in the fill and trim method. A small study effect was ruled out based on the jack-knife method.

Based on univariable meta-regression (Table 3) RLS measure (p = 0.27), Female % of participants (p = 0.27), country income level (p = 0.26) and when the study was conducted (p = 0.14) seemed to be probable moderators. But in the multivariable meta-regression, none of them remained significant. None of the examined variables were identified as sources of heterogeneity.

3.4.6. Physical health component score difference among RLS patients vs. control groups

The pooled estimated SMD of the physical health component was −0.57 [14 studies; 95 % CI: −0.83 to −0.30, I^2: 90.8 %, Tau^2 = 0.20] in patients with RLS compared to control groups. Fig. 4 provides the forest plot showing the pooled SMD score. Based on Begg's test (p = 0.83) and a symmetric funnel plot, publication bias was ruled out. Also, small study effect was ruled out based on the jack-knife method.

Based on univariable meta-regression (Table 3), physical health component score difference among RLS patients vs. control groups were marginally affected of when the study was conducted. Each year of increase in when the study was performed was associated with 0.06 increase in SMD of QoL of the physical health component. This indicated a slight, but not statistically significant (p = 0.20), improvement explaining 17.82 % of variance regarding mean score. None of the examined variables were identified as sources of heterogeneity.

4. Discussion

The result in the present meta-analysis showed that the corrected pooled estimated mean score for total QoL was low, which also applied to the mental and physical health components. The low QoL can also be verified by comparisons to norm data for general populations on generic instruments that were used by several of the included studies. Unfortunately, doing more accurate comparisons of our pooled estimates of mean QoL score to norm data is complicated, since norm data are depicted according to both gender and age groups [63,64]. However, when we compared patients with RLS to controls, the pooled estimated QoL scores were statistically significantly lower for the RLS group regarding total QoL, mental and physical health components. No statistically significant moderator was identified for total QoL or the physical health component, while the mental health component was influenced by RLS measurement type (i.e., which version of RLS criteria that had been used). Moreover, no variables were identified as sources of heterogeneity.

Three important aspects for the practical and clinical interpretation of our findings are: (I) the way RLS was identified (i.e., the version of diagnostic RLS criteria), (II) the instrumentation used to measure QoL, and (III) the occurrence of comorbidities. To begin with, looking at the identification of RLS, most studies (n = 17) used the 2003 criteria [65], followed (n = 6) by the updated 2014 criteria [5]. Sensitivity, specificity, and positive and negative predictive values are important for self-assessment instruments both in research, but also to identify complex clinical conditions, such as RLS, which often occur together with other conditions. More specifically, the identification of patients with RLS symptoms with less sensitive and specific instruments may have been different in studies that used the 2001 or 2003 criteria [65] compared to

Table 3
Results of uni-variable meta-regression.

	Variables	No. of studies	Coeff.	S.E.	*p*	I^2 res. (%)	Adj. R^2 (%)	*Tau*^{2}
Total QoL mean score	Publication year	27	0.89	0.56	0.12	97.52	5.84	155.3
	Country development status	27	5.45	13.37	0.69	98.19	−3.60	170.8
	Country income level	27	3.79	4.76	0.43	98.17	−1.68	167.7
	Community based survey	27	2.17	9.75	0.83	98.18	−3.95	171.4
	Mean age of participants	26	0.007	0.23	0.98	98.09	−4.35	178.8
	Female % of participants	23	0.09	0.15	0.57	98.31	−3.31	196.1
	RLS as comorbidity	27	1.65	5.41	0.76	98.16	−3.91	171.3
	QoL measure type	27	−0.63	5.64	0.91	98.11	−4.11	171.7
	RLS measure type	27	−0.08	0.58	0.89	97.80	−4.57	175.6
	Risk of bias categories	27	2.98	8.43	0.73	98.14	−3.20	170.2
Mental health component	Publication year	17	−0.40	0.44	0.38	96.66	0.27	71.65
	Country development status	All included studies were from developed countries						
	Country income level	17	0.93	5.82	0.88	95.86	−6.66	76.62
	Community based survey	17	−1.47	9.20	0.88	98.40	−7.30	77.09
	Mean age of participants	17	−0.09	0.19	0.64	97.99	−6.48	76.49
	Female % of participants	14	−0.15	0.12	0.22	95.83	6.23	73.19
	RLS as comorbidity	17	−2.93	4.51	0.53	98.15	−3.56	74.4
	QoL measure type	17	−0.12	5.22	0.98	98.11	−7.14	76.97
	RLS measure type	17	−0.48	0.43	0.29	94.48	6.90	55.87
	Risk of bias categories	17	−7.43	5.91	0.23	98.38	2.19	70.27
Physical health component	Publication year	17	0.17	0.65	0.80	98.70	−6.83	162.9
	Country development status	All included studies were from developed countries						
	Country income level	17	−2.67	8.37	0.76	98.69	−6.34	162.2
	Community based survey	17	−1.62	13.42	0.91	98.75	−6.92	163.1
	Mean age of participants	17	−0.18	0.27	0.51	98.75	−4.46	159.3
	Female % of participants	14	−0.10	0.17	0.57	98.85	−5.39	165.3
	RLS as comorbidity	17	−0.74	6.58	0.91	98.71	−6.85	163
	QoL measure type	17	−1.34	7.51	0.86	98.75	−6.73	162.8
	RLS measure type	17	0.005	0.75	0.99	98.82	−8.33	191
	Risk of bias categories	17	−0.44	8.66	0.96	98.33	−6.57	162.5
Total QoL score difference among patients with RLS vs. control groups	Publication year	24	0.02	0.04	0.59	91.80	−5.98	0.51
	Country development status	24	1.62	0.73	0.04	88.40	27.07	0.35
	Country income level	24	0.39	0.29	0.19	91.45	9.12	0.44
	Community based survey	24	0.34	0.59	0.57	91.77	−4.59	0.51
	Mean age of participants	23	0.009	0.01	0.54	90.52	−3.34	0.49
	Female % of participants	20	0.01	0.01	0.29	90.31	3.46	0.53
	RLS as comorbidity	24	−0.15	0.38	0.71	91.80	−6.30	0.52
	QoL measure type	24	0.34	0.36	0.36	91.73	−3.96	0.50
	RLS measure type	22	−0.02	0.04	0.58	92.11	−3.01	0.54
	Risk of bias categories	24	0.31	0.58	0.60	91.80	−7.22	0.52
	Comparison group	24	−0.21	0.35	0.55	91.80	−5.14	0.51
Mental health component score difference among patients with RLS vs. control groups	Publication year	14	0.06	0.04	0.14	93.67	9.54	0.50
	Country development status	All included studies were from developed countries						
	Country income level	14	−0.59	0.50	0.26	93.80	1.43	0.55
	Community based survey	14	0.24	0.84	0.78	93.91	−9.49	0.61
	Mean age of participants	14	−0.003	0.02	0.87	93.84	−9.98	0.61
	Female % of participants	11	0.01	0.01	0.27	93.94	5.47	0.62
	RLS as comorbidity	14	−0.45	0.51	0.39	93.63	−2.95	0.57
	QoL measure type	14	0.52	0.48	0.31	93.62	−0.58	0.56
	RLS measure type	14	0.05	0 0.04	0.27	94.03	1.88	0.57
	Risk of bias categories	14	0 0.28	0.57	0.64	93.89	−7.89	0.60
	Comparison group	14	−0.43	0.46	0.37	93.73	−2.55	0.57
Physical health component score difference among patients with RLS	Publication year	14	0.06	0 0.05	0.20	89.52	17.82	0.33
	Country development status	All included studies were from developed countries						
	Country income level	14	−0.51	0 0.61	0.42	91.00	−4.52	0.42
	Community based survey	14	0.01	1.01	0.99	91.47	−19.56	0 48
	Mean age of participants	14	−0.002	0.02	0.94	91.48	−20.24	0 48
	Female % of participants	11	0 0.008	0.02	0.61	92.13	−13.39	0.70
	RLS as comorbidity	14	−0.02	0.63	0.97	91.11	−20.26	0.48
	QoL measure type	14	0.46	0.62	0.47	91.48	−24.85	0.50
	RLS measure type	14	0.05	0.05	0.43	89.09	−7.90	0.45
	Risk of bias categories	14	0.44	0.75	0.53	91.47	−31.43	0.53
	Comparison group	14	−0.08	0.58	0.89	91.18	−21.04	0.49

Note 1: Coeff: coefficient; I^2res: I^2 residual; Adj R^2: Adjusted R square; NOS: The Newcastle Ottawa Scale, S.E.: Standard Error, *Tau*^{2}: between-study variance.
Note 2: When interpreting the results please consider these points: *a)* Study time is publishing year; *b)* country development status is comparison of developed vs. developing countries; *c)* Country income level is comparison of high, upper- middle and low- income level respectively; *d)* RLS as comorbidity is comparison of RLS being a comorbidity vs. RLS as only diagnosed disease; *e)* QoL measure is comparison of disease specific vs. generic measures; *f)* RLS measure is comparison of IRLSSG

2014, 2003 vs. 2001; *g)* Risk of bias categories referred to comparison of low vs. high risk of bias; *h)* Comparison group categories is either comparison of groups with a disease/condition with RLS vs. the same disease/condition without RLS, or one disease/condition with RLS vs. healthy controls.

Table 4
Results of multivariable meta-regression.

	Variables	No. of studies	Coeff.	S.E.	*p*	I^2 res. (%)	Adj. R^2 (%)	Tau^2
Mental health component	Risk of bias categories	11	0.74	7.65	0.93	94.41	30.11	48.14
	RLS measure type		−1.20	0.50	0.05			
	Female % of participants		−0.10	0.10	0.35			
QoL SMD among patients with RLS vs. control groups	Country development status	20	0.83	1.08	0.45	85.47	36.21	0.35
	Country income level		0.40	0.42	0.35			
	Female % of participants		0.01	0.01	0.20			
Mental health component SMD among patients with RLS vs. control groups	RLS measure type	9	−0.02	0.10	0.84	95.53	−21.99	0.81
	Female % of participants		0.002	0.03	0.96			
	Country income level		0.27	1.82	0.89			
	Publication year		0.16	0.15	0.34			

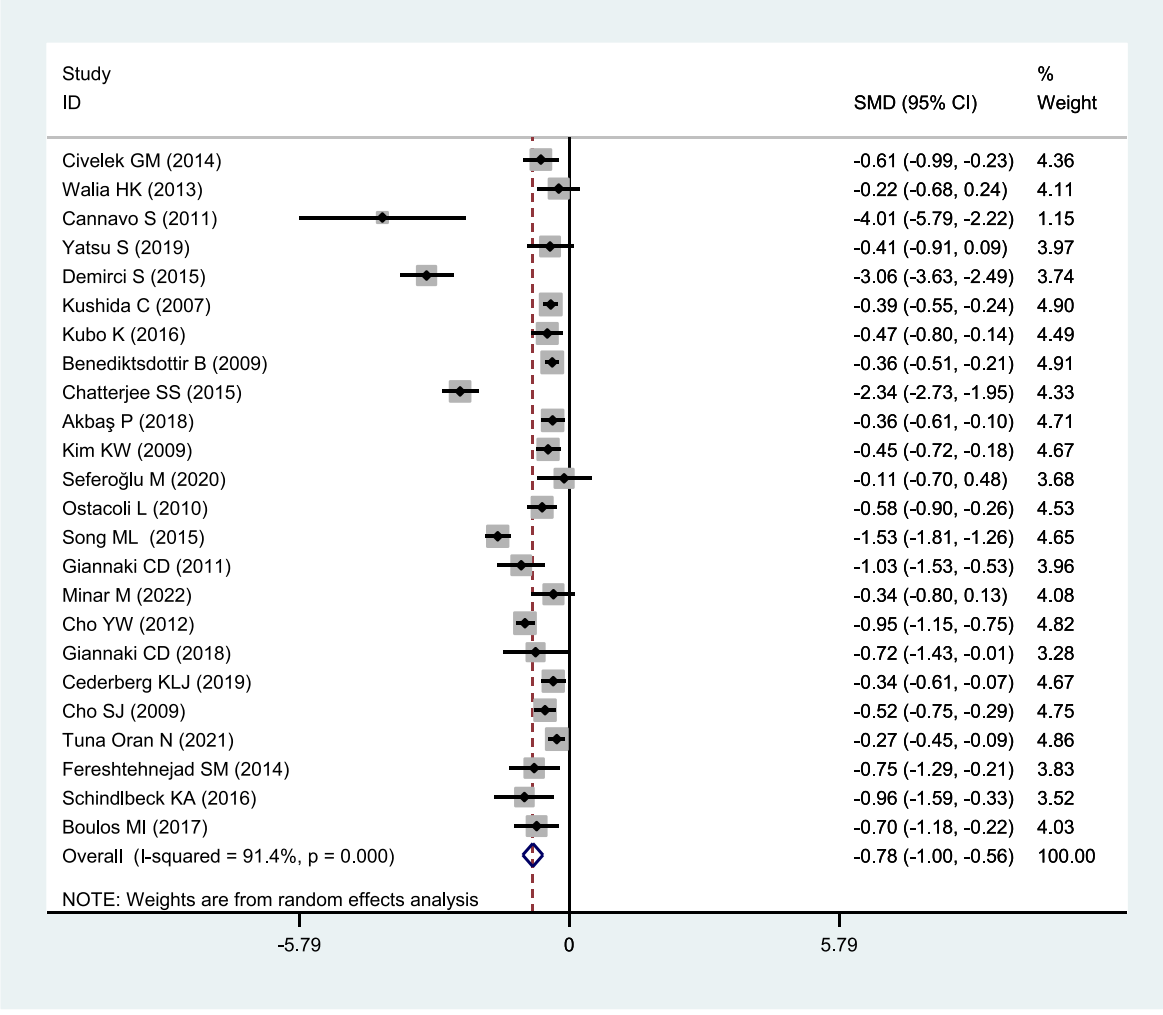

Fig. 2. Forest plot showing the pooled SMD of QoL score among patients with RLS vs. control group.

those that used the updated 2014 criteria [4]. The measurement of QoL have previously been reviewed [24] and only one instrument, The Restless Legs Syndrome Quality of Life Questionnaire-Abetz [66,67], met the set validity criteria. Most QoL instruments used in the analysed studies were generic (n = 19), with SF-36 the most frequent (n = 11). Notably, the rather long SF-36 could be difficult to use and may not capture RLS specific aspects of QoL. Only six studies used disease-specific instruments [27,28,40,46,49,50]. However, none of these were RLS-related, as all focused QoL aspects of the specific comorbidity. Still, the presence of RLS seems to lower the score also in these measures.

As anticipated, the comorbidities varied greatly and may, via an increased emotional stress, increase RLS-related symptoms, which in

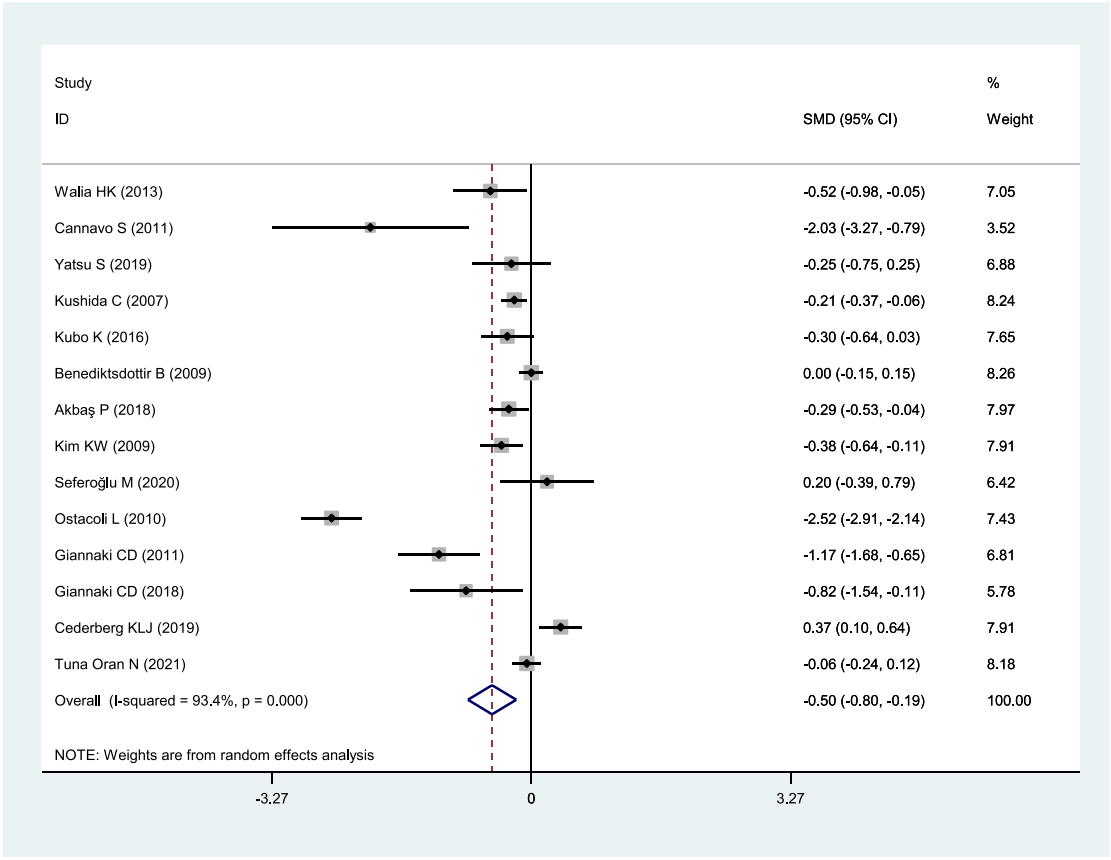

Fig. 3. Forest plot showing the pooled SMD of the mental health component score among patients with RLS among patients with RLS vs. control group.

turn may affect QoL negatively. Admittedly, as causes, symptoms, and effects of RLS can vary between patients, so can comorbidities, but noteworthy is that different comorbidities may cause different impact on QoL. For example, having the combination of RLS and a major life-threatening disorder (e.g., cancer [46]) may affect QoL differently compared to having RLS together with a long-lasting and burdensome condition [49,50]. Heterogeneity of the included populations may therefore be a complicating aspect of the findings in the present meta-analysis. However, when we examined heterogeneity with the I2 index [35] we did not identify any sources of heterogeneity neither for total QoL, nor the mental- and physical health components of QoL. Even so, results stemming from the studies using a comparative design of RLS patients with comorbidities measuring QoL with a disease specific instrument related to the target population may be taken with caution, and not be seen as applicable to QoL scores for RLS patients in general without the actual condition.

Notably, despite RLS being a long-term condition with often difficult-to-treat and disabling symptoms, where QoL should be an appropriate clinical outcome, large-scale studies evaluating QoL were few in the present data set. Only two studies had a sample size of 200 participants with RLS or more [44,48] while fourteen studies [27–30,40,46,49,50,54–56,58,60,62] had 50 or less participants. Even if the probability of a small study effect and publication bias was investigated (Appendix 4 and 5), and sensitivity analysis showed that the pooled effect size was not affected by a single study effect (Appendix 6), this should be considered when evaluating the current result. An ultra-short RLS specific QoL instrument may be beneficial to include patients in research, but also to evaluate e.g., treatment effects in clinical practice, but the risk of such an instrument to systematically produce a larger effect due to its brevity must be considered. In research, using generic instruments may be justified to simplify comparisons of RLS samples with other clinical or general populations. However, a combination of disease specific and generic QoL instruments could be preferable. The Restless Legs Syndrome Quality of Life Questionnaire-Abetz, containing 18 items, is still the recommended alternative for clinical trials [66,67].

As seen in several of the analysed studies, RLS is present in addition to several other conditions, and the benefits of RLS specific pharmacological treatment on QoL may then be reduced because of impairments not only by RLS symptoms, but also by the other condition and psychosocial stressors [68]. Unfortunately, there is no standardized treatment for RLS. A multiple treatment strategy often needs to be considered [69], and the treatment can be seen as complex and difficult to adjust [1,2,15–17]. Treatment interventions that provide improved QoL and relief for the often very distressing symptoms are individual [10] and needs attention, especially regarding medication [70]. A holistic patient-centred approach may therefore be important to improve QoL. Various non-pharmacological therapies have been used, but more studies are needed [9,71]. Cognitive behavioural therapy (CBT) has in one face-to-face intervention been shown to improve insomnia in patients with RLS [72], while internet delivered CBT interventions (I-CBT) improved functioning in patients with other chronic conditions, such as chronic pain [73]. I-CBT has recently also been developed for serious somatic conditions such as asthma [74] and atrial fibrillation [75], where it also improved QoL [76]. This implies that RLS specific CBT interventions delivered through the internet could be developed and if evaluated favourably be used as a complement to traditional pharmacological RLS treatment to improve functioning and QoL.

4.1. *Strength and limitations*

There are some strengths and limitations of the current systematic review and meta-analysis that are relevant to mention. In terms of strengths, a multiprofessional research team, used to conduct systematic

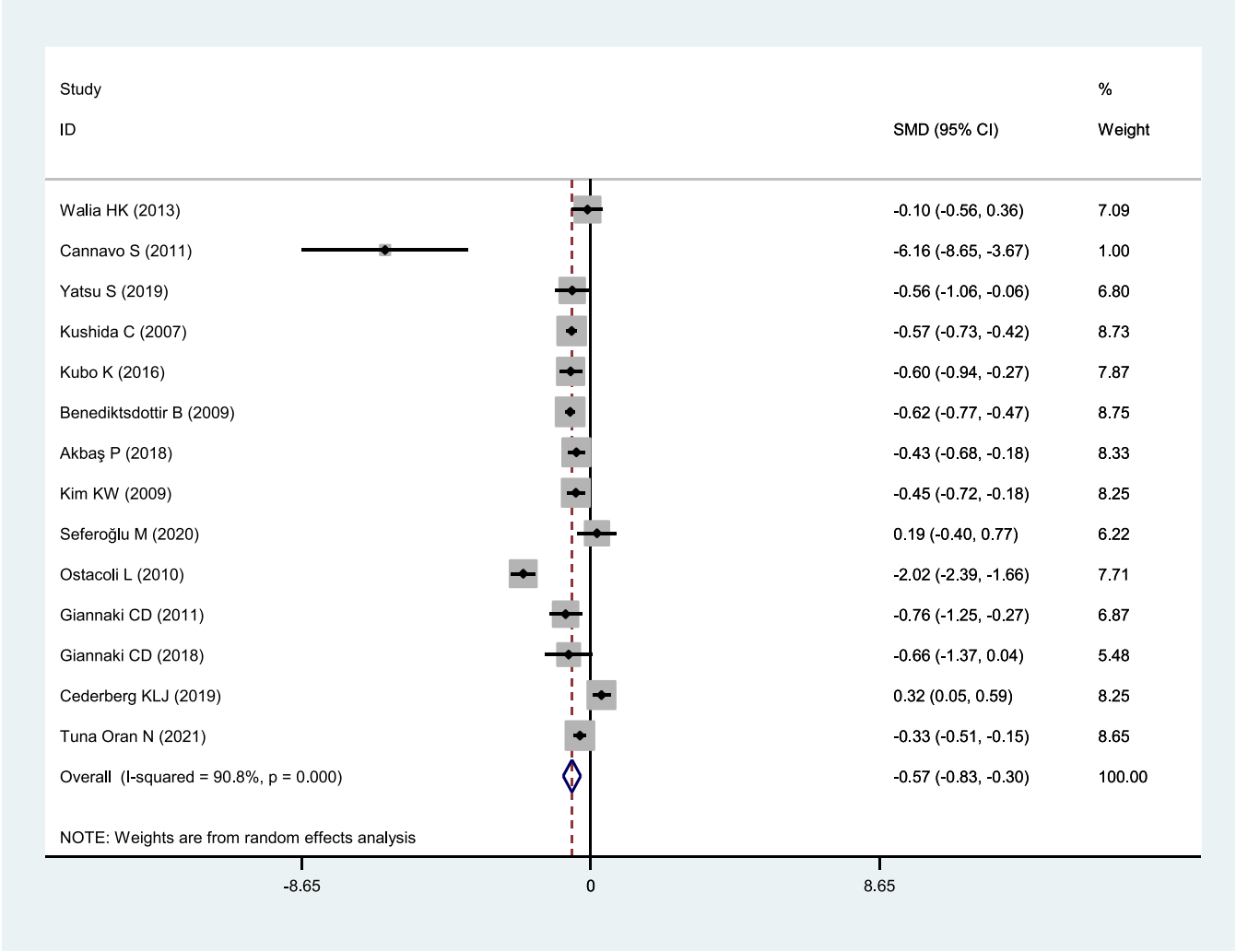

Fig. 4. Forest plot showing the pooled SMD of the physical health component score among patients with RLS vs. control groups.

reviews with meta-analysis, was responsible for data collection strategies, data extraction, quality assessment, meta-regression and sensitivity testing which ensured that all methodological aspects used in this study were carried out rigorously. More specifically, in the first step, a thorough and comprehensive literature search based on distinct and relevant keywords based on MeSH, primary studies and published reviews were used to identify relevant studies. The search was conducted in four large and relevant academic databases (i.e., PubMed, Scopus, Web of Science, and ProQuest). The following steps, data extraction, assessment of methodological quality and risk of bias were conducted independently by two researchers using the international standard in the updated PRISMA guidelines [25]. The well-established NOS [31] was used to determine the quality of each study. The quantitative synthesis used an advanced approach, including assessment of heterogeneity, moderator and subgroup analysis, meta-regression, and risk for bias assessment. Relevant outcome measures were used in line with the aims.

In terms of limitations, both RLS symptoms and QoL were assessed using various self-reports. Therefore, commonly encountered biases (e.g., recall bias and social desirability bias) cannot be overlooked, although there are no obvious reasons for why such biases should systematically differ for patients with RLS compared to those without, especially since no RLS-specific QoL measures were included. Moreover, the identification of patients RLS symptoms may be different in studies that used the IRLSSG 2001 and 2003 [65] compared to those that used the updated IRLSSG 2014 [4]. This can also be assumed to have influenced the link between RLS and QoL. Also, estimates of QoL were derived from several instruments, where generic ones were more often used (n = 19) than disease-specific ones (n = 6). To begin with, instruments differ in terms of psychometric properties, but it should also be noted that generic and disease-specific instruments capture heterogeneous aspects of QoL. However, an advantage with generic instruments is the possibility to make comparisons with control groups. In addition, it is important to remember that a cross-sectional design was used among all included studies, and thus the causal relationship between RLS and QoL should be evaluated with caution. Finally, RLS is a condition where the often pronounced and fluctuating symptoms require an individualized treatment [2], not always optimized according to guidelines [8,16], which might have affected QoL.

4.2. Research implications

There are several implications for future research. Firstly, studies with large samples should by using e.g., structural equation modelling explore associations between patient reported RLS symptoms and perceptions of general health and QoL, including total, mental and physical health components. Secondly, studies should, using adequate instruments adapted to the included conditions, explore how RLS that is coexisting with other conditions (i.e., comorbidities) are associated to QoL, but also how the combination affect QoL over time in clinical treatment situations (i.e., aiming to identify specific moderating

variables). Thirdly, a new brief RLS specific outcome measure for QoL should be developed and validated using modern test theory. Finally, RLS specific CBT interventions, used as a complement to traditional pharmacological RLS treatment and delivered through the internet, should be developed, and evaluated in randomised controlled trials regarding RLS symptoms and QoL.

5. Conclusion

RLS has previously been shown to be a highly prevalent condition with world-wide distribution, and the present systematic review and meta-analysis indicate a potential effect on total QoL, as well as on physical and mental health components of QoL. With the hindsight that a relatively low number of studies have studied QoL, as well as the small sample sizes in several studies, further evidence needs to be accumulated, to help future meta-analyses to further clarify whether different phases and severity levels of RLS symptoms affect various aspects of QoL differently and how pharmacological and psychological interventions affect QoL in this patient group.

Author Contributions

AB devised the research question together with AP. ZA and AP performed the searches and completed the analyses together with AB. MU contributed to the analysis and conducted cross-checks. AB and AP wrote the initial draft of the manuscript in consultation with EO, VK, SJ, JL, and MU. All authors provided critical feedback and assisted in shaping the manuscript. All authors approved the final version of the manuscript before submission.

CRediT authorship contribution statement

Anders Broström: Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zainab Alimoradi:** Formal analysis, Data curation. **Elzana Odzakovic:** Writing – review & editing. **Viktor Kaldo:** Writing – review & editing. **Susanna Jernelöv:** Writing – review & editing. **Jonas Lind:** Writing – review & editing. **Martin Ulander:** Writing – review & editing, Validation, Methodology, Conceptualization. **Amir Pakpour:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2024.02.027.

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