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REVIEW ARTICLE

The prevalence of restless legs syndrome (RLS) in patients with multiple sclerosis (MS): a systematic review and meta-analysis—an update

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Abstract

Introduction The prevalence of restless legs syndrome (RLS) is reported to vary in patients with multiple sclerosis (MS) in studies which are conducted in different populations. The goal of this systematic review and meta-analysis is to update the prevalence of RLS in MS cases.

Methods We searched PubMed, Scopus, EMBASE, CINAHL, Web of Science, Google Scholar, and gray literature including references from identified studies and conference abstracts which were published up to June 2021. Data on the total number of participants, first author, country, disease duration, number of controls, mean patient age, male and female numbers, mean EDSS, and number of cases and/or controls with RLS were extracted from the included studies.

Results The literature search revealed 855 articles; after deleting duplicates, 530 remained. For the meta-analysis, 75 studies were included (Fig. 1). In six articles, the authors did not differentiate between CIS and MS cases when reporting RLS cases. In total, 15,411 MS/CIS patients were evaluated and 4309 had RLS. The pooled prevalence of RLS was 28% (95% CI: 24–33%). The pooled prevalence of RLS in men was 22% (95% CI: 17–26%), and the pooled prevalence of RLS in women was 30% (95% CI: 25–35%). The pooled prevalence of RLS in controls was 8% (95% CI: 6–10%).

Conclusion The results of this systematic review and meta-analysis show that the pooled prevalence of RLS is 28% in MS cases and 8%. The pooled prevalence is higher in women than men (30% vs 22%).

Keywords Multiple sclerosis · Restless legs syndrome · Prevalence

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Introduction

Multiple sclerosis (MS) is an autoimmune disease, affecting women more than men with a wide range of complications [1]. Physical and mental complications lead to impaired quality of life and interferes with daily activities [2]. Restless legs syndrome (RLS), extrapyramidal hyperkinesia, is considered as a sleep-related movement disorder according to the German Society for Sleep Research and Sleep Medicine (DGSM) [3]. The International Restless Legs Syndrome Study Group (IRLSSG) revised the diagnostic criteria and declared the characteristics of RLS as strong urge to move limbs along with unpleasant sensations which worsens at rest and in the evening [4].

For the first time, in 2005, RLS in MS cases was introduced, and up to now, various studies reported a wide range of prevalence of RLS in MS cases, ranging from 14 to 65% [5–8].

The last systematic review and meta-analysis which was conducted in 2018 estimated the pooled prevalence of RLS as 20% which is higher in women [7].

The goal of this systematic review and meta-analysis is to update the prevalence of RLS in MS cases.

Methods

Literature search

We searched PubMed, Scopus, EMBASE, CINAHL, Web of Science, Google Scholar, and gray literature including references from identified studies and conference abstracts which were published up to June 2021.

Inclusion criteria were cross-sectional/case–control studies evaluating prevalence of RLS in patients with MS.

Exclusion criteria were letter to editors, cohort, or randomized clinical trials.

Data search and extraction

The search strategy included the MeSH and text words as ((Sclerosis AND multiple) OR (sclerosis AND disseminated) OR "disseminated sclerosis" OR "multiple sclerosis" OR "acute fulminating") AND("Restless Leg*" OR "Willis Ekbom Disease" OR (Disease AND "Willis Ekbom") OR "Wittmaack-Ekbom Syndrome" OR (Syndrome AND "Wittmaack-Ekbom") OR "Willis-Ekbom Disease" OR (Disease AND "Willis-Ekbom") OR "Willis-Ekbom Syndrome" OR (Syndrome AND "Willis-Ekbom") OR "Wittmaack Ekbom Syndrome" OR (Syndrome AND "Wittmaack Ekbom") OR "Restless Leg Syndrome" OR (Syndrome AND "Restless Leg") OR "Willis Ekbom Syndrome" OR (Syndrome AND "Willis Ekbom")).

Two independent researchers independently assessed the articles. Data on the total number of participants, first author, country, disease duration, number of controls, mean patient age, male and female numbers, mean EDSS, and number of cases and/or controls with RLS were extracted from the included studies.

Risk of bias assessment

We evaluated the risk of potential bias by the Newcastle–Ottawa Quality Assessment Scale (adapted for cross-sectional/case–control studies) [9, 10].

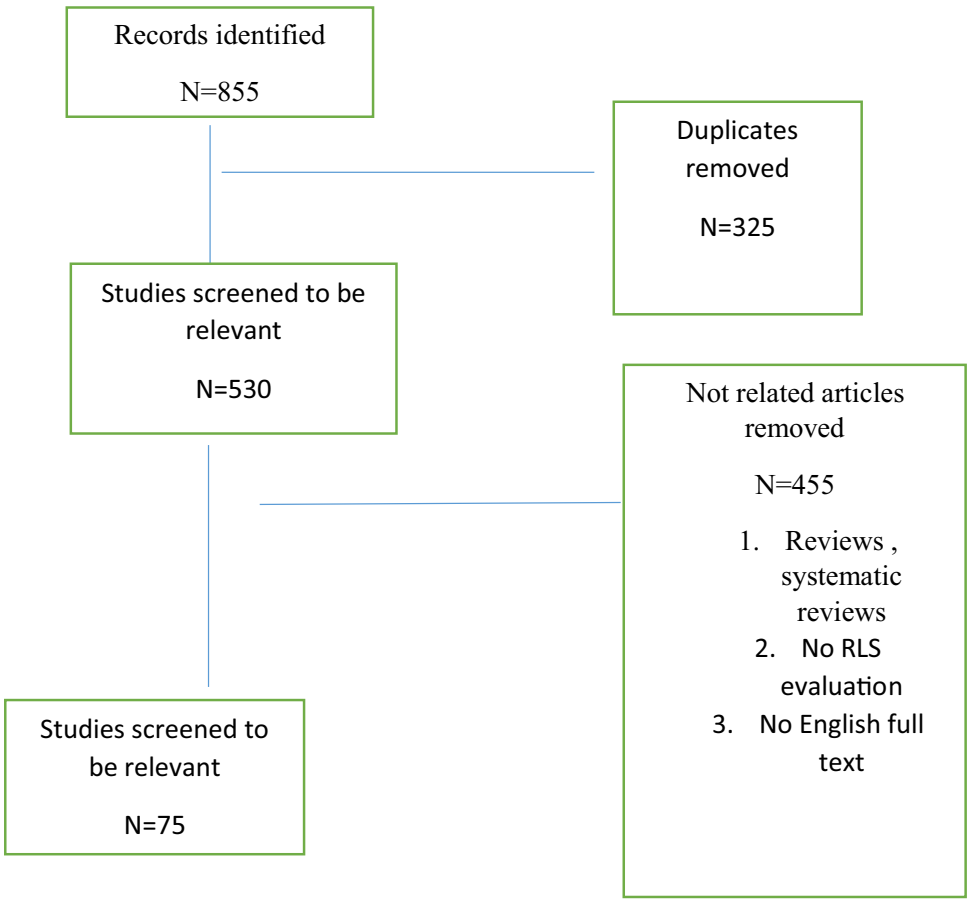

Fig. 1 Flow diagram of including studies

Table 1 Data extracted from the studies

Author	Year	Country	Study scale	N_control Total Female Male	N_Ms Total Female Male	MS-Type	Age_MS	Disease duration	EDSS	Total RLS. MS	F.RLS.MS	M.RLS. MS	Total RLS cont	QA score
Gianna C. Riccitelli[11]	2021	Switzerland	Validated self-administered International RLS Rating Scale		76 55 21	CIS/RRMS 70 PMS 6	49.0 (41.75–54.25)		2.5 (2.0–3.0)	22				7 out of 9
Tobias Monschein[12]	2021	Austria	(IRLSSG)	119 87 32	117 79 38	RR 105 SP 4 PP 8	36.3 (9.6)	7.3 (2.7–12.9)	1.5 (0–7.0)	28 RR 22 SP 2 PP 4	20	8	4	6 out of 10
Serhan Sevim[13]	2020	Turkey	(IRLSSG)		1068 797 271	RR 883 CIS 71 SP 73 PP41	Mean age of 37.6 Standard deviation (SD) of 10.3 years [minimum (min),18; maximum (max), 76]			173 CIS 9 RRMS 150 SPMS 3 PPMS 11	133	40		7 out of 10
H.A. Hensen[14]	2020	Australia	NR		111 85 26				Range 2–6	29				
Bouhlal, M[15]	2020	Netherlands	(IRLSSG)		80 53 27					27				
Cederberg Katie L.J[16]	2020	Brazil	(IRLSSG)		275 223 52	91 progressive MS Unknown 3 RR 181	59.7 (10.1)	20.4 (9.7)		74 RR 48 SP 17 PP 9	60	14		7 out of 10
Meral Seferoğlu[17]	2020	Turkey	(IRLSSG)		46	RR 46	45.32 (10.61) ($n=19$) 38.07 (7.74) ($n=27$)		1.87 (1.03) ($n=19$) 1.22 (0.58) ($n=27$)	19				5 out of 10
Gülin SÜNTER[18]	2020	Turkey	(IRLSSG)		93 67 26	RR 93	34.6 (8.61)	4.7(3.7)		30	21	9		6 out of 10
Vahid Shayganejad[19]	2020	Iran	(IRLSSG)		359	RR 309 SP 50	34.90 (8.36) ($N=309$) 43.52 (9.95) ($N=50$)		0.99 (1.34) ($N=309$) 4.89 (2.47) ($N=50$)	110 RR 100 SP 10				7 out of 9

Table 1 (continued)

Author	Year	Country	Study scale	N_control Total Female Male	N_Ms Total Female Male	MS-Type	Age_MS	Disease duration	EDSS	Total RLS. MS	F.RLS.MS	M.RLS. MS	Total RLS cont	QA score
Edgar Carnero Contentti[20]	2019	Argentina	(IRLSSG)	238 174 64	189 134 55	RR 171 SP 7 PP 11	39.80 (14.62)			55 50 RRMS 3 PPMS 2SPMS	42	13	31	6 out of 9
Katie L.J. Cederberg[21]	2019	USA	Cambridge-Hopkins Question-naire (CH-RLSq)		253 204 49	RR 170 SP 51 PP 29 Benign 3	59.4 (10.0)	20.3 (9.7)		66 RRMS 43 SPMS 14 PPMS 9 Benign 0				6 out of 10
S. Canbaz Kabay [22]	2019	Turkey	NR		43 29 14				2.58 (2.11)	23				6 out of 10
Taşkın Güneş [23]	2021	Turkey	(IRLSSG)		102 69 33	RR 74 CIS 7 PR 3 SP 14 PP 4	36.0 (11.2)	6.9 (5.8)		31 PP 1 SP 9 RR 17 PR 2 CIS 2	24	7		
Nazanin Razazian[24]	2019	Iran	(IRLSSG)	84 75 9	84 75 9					38			19	
Katie L. Cederberg[25]	2019	USA	Cambridge-Hopkins Question-naire (CH-RLSq)		275					74				8 out of 10
R. Türkoğlu[26]	2018	Turkey	NR		30					4				7 out of 9
A.T. Ozdogar1[27]	2018	Turkey	(IRLSSG)		299					88				
Hensen, H A[28]	2018	Australia	NR		88					23				
Vanessa Schellaert[29]	2018	France	(IRLSSG)		57 36 21	RR 21 SP 20 PP 16	47.5 (12.8) ($n=26$) 46.2 (11.3) ($n=31$)	13.5 (10.7) ($n=26$) 11.5 (9.5) ($n=31$)	5.3 (1.9) ($n=26$) 4.3 (2.4) ($n=31$)	9				
L. Lebrato Hernández[30]	2019	Spain	(IRLSSG)		120 79 41	RR 105 SP 12 PP 3	40.26 (10.37)	46.17 (44.47)	2.46 (1.92)	28	21	7		5 out of 10
Giannaki[31]	2018	Cyprus	(IRLSSG)		50 24 26					10				6 out of 10

Table 1 (continued)

Author	Year	Country	Study scale	N_control Total Female Male	N_Ms Total Female Male	MS-Type	Age_MS	Disease duration	EDSS	Total RLS. MS	F.RLS.MS	M.RLS. MS	Total RLS cont	QA score
Sylvia Kotterba[32]	2018	Germany	(IRLSSG)		128 91 37	RR 114 CIS 14	41.5 (11.3)	43.0 (71.6) *N* = 113 (month)	2.0 (0–5)	6				5 out of 10
Ayşenur Önalan[33]	2018	Turkey	(IRLSSG)	100 54 46	97 73 24	RR 85 SP 12	35.0 (4.1) Range [17–62]	101.6 (91.1) (1–564) months		22 20 RRMS 2 SPMS	14	8	10	5 out of 10
Sajid I. Al-Hussainy[34]	2018	Iraq	(IRLSSG)		110 74 36	RR 88 SP 16 PP 6	28 [22–39]			19 RR 16 SP 2 PP 1	15	4		6 out of 10
M. Minár[35]	2017	Slovakia	(IRLSSG)		200 53 147		39.75 (9.72)	7.89 (5.26)		31	14	17		5 out of 10
Marzieh Khatooni[36]	2017	Iran	(IRLSSG)		118 80 38		26.28 (6.75) (*n* = 67) 24.80 (4.68) (*n* = 51)			67 44 23				5 out of 10
Hesham Abboud [37]	2017	USA	NR		60 34 26		38.3 (12.7)			28				
Shengli Ma[38]	2017	China	(IRLSSG)	265 159 106	231 135 96		40.22 (7.8)	58.47 (7.2) months		50			14	6 out of 10
I. Gómez-Estévez [39]	2017	Spain	(IRLSSG)		59					21				
Özdoğar, A T[40]	2017	Turkey	(IRLSSG)		46 34 12					11				
Merisanda Časar Rovazdi[41]	2017	Croatia	(IRLSSG)		60 37 23	RR 30 SP 30	Mean 49.5 (range, 29–71)	Mean 12.2 years (range, 6 months to 32 years)	Mean EDSS 4.9 (range of 1.5–9)	24	19	5		5 out of 10
Aurélie Basille-Fantinato[42]	2016	France	NR		81					20				
V. Agostini [43]	2016	Puerto Rico	(IRLSSG)		50					19	15	4		
Nahid Ashjazadeh [44]	2016	Iran	(IRLSSG)		120 91 29		33.1 (7.4)	6.39 (5.16)		78	62	16		
B. Petek Balci[45]	2016	Turkey	(IRLSSG)		100 70 30	RR 90 SP 10	35.1 (8.8)	7.3 (4.7)	2.6 (1.2)	35				6 out of 10

Table 1 (continued)

Author	Year	Country	Study scale	N_control Total Female Male	N_Ms Total Female Male	MS-Type	Age_MS	Disease duration	EDSS	Total RLS. MS	F.RLS.MS	M.RLS. MS	Total RLS cont	QA score
A. Koskderelio-glu[46]	2015	Turkey	(IRLSSG)		183	RR 154 SP 21 PP 8	40.95 (1.09)	9.43 (6.22)	2.1 (1.74)	43				7 out of 9
V. Mery[47]	2015	Canada	IRLDQ		71 48 23	RR 56 SP 13 PP 2	46.6 (10.6)	Median 8.2 years (range 0.9–27.2, SD 6.36)	Median EDSS 3 (range 1–6.5, SD 1.6)	22 MS form (RR/SP/ PP/PR) 18/4/0/0	19	3		
Pedro Viana[48]	2015	Portugal	Translated version of the Johns Hopkins Telephone Diagnostic Interview		206 144 62	RR 183 SP 6 PP 17	42.1 (10.7)	Median (IQR) 7.00 [10]	EDSS, median (IQR) 1.50 (2.0)	52				5 out of 9
Christian Veauthier[49]	2015	Germany	Clinical interview		66 45 21	RR 46 SP 16 PP 4	43.6(10.0)		2.7 (1.8)	12				
Gangqiong Liu[50]	2015	china	(IRLSSG)	603 416 187	695 482 213	RR 548 SP 117 PP 30	37.9(8.8)	13.8 (9.4) ($n=171$) 10.5 (12.1) ($n=524$)	2.5 (2.1) ($n=171$) 2.4 (1.9) ($n=524$)	171 RRMS 137 SPMS 32 PPMS 2	125	46	48	5 out of 10
Mine Hayriye SORGUN [51]	2015	Turkey	(IRLSSG)	44 27 17	91 67 24	RR 56 SP 8 PP 9	37.6	8.0 [1–32]	3 (0–9)	16 RRMS 15 PPMS 1	14	2	1	6 out of 10
Zuzana Čarnická[52]	2015	Slovakia	(IRLSSG)		50 35 15	RR 38 SP 11 PP 1	40.3 (10.71)	Median 5 (IQR 9, range 0.5–23.0 y)		14				5 out of 10
El-Nabil, L M[53]	2015	Egypt	NR	30	50					10			2	5 out of 10
Minar, M[54]	2015	Slovakia	(IRLSSG)		200					52	40	12		
Timm, P C[55]	2015	USA	NR		131 88 43		62.4 [25–92]			61				
Christian Veauthier [56]	2015	Germany	Clinical interview		66 45 21		Aged 20–66 years			24				5 out of 10
M Terzi[57]	2014	Turkey	(IRLSSG)	163	177					59			21	
E. Bruno[58]	2014	Italy	(IRLSSG)	431 292 139	152 97 55		46.0 (10.8)	14.3 (9.3)	2.8 (2.4)	22 RRMS 18 SPMS 4 PPMS 0	15	7	26	6 out of 9

Table 1 (continued)

Author	Year	Country	Study scale	N_control Total Female Male	N_Ms Total Female Male	MS-Type	Age_MS	Disease duration	EDSS	Total RLS. MS	F.RLS.MS	M.RLS. MS	Total RLS cont	QA score
Steven D. Brass[59]	2014	USA	(IRLSSG)		2367 1917 450		54.7 (12.4)			866				8 out of 10
Jian-Hua Chen[60]	2014	China	(IRLSSG) Walter 1995	11 8 3	21 15 6		Mean 29.0 (8.5) years (range, 18–51 years)	Mean 39.7 (27.1) months (range, 9–119 months)	Mean 4.0 (2.0) (range, 1–6)	1			0	5 out of 10
Olga Krökki [61]	2013	Finland	Clinical interview		491 340 151	RR 376 PP 33 Benign 82				2				7 out of 9
Isik, N[62]	2013	Turkey	(IRLSSG)	45 27 18	187 130 57		40.64 (9.44)			41			1	
Vahid Shaygannejad[5]	2013	Iran	(IRLSSG)	126 96 30	126 96 30	RR 74 CIS 7 PR 3 SP 14 PP 4	32.37 (8.7)	43.2(33.4) months	1.8 (1.74) (range 0–7)	82	60	22	16	6 out of 10
Y. Li[63]	2012	USA	(IRLSSG)	65,280	264		50.3 (4.6)			41			4182	8 out of 10
D. Rotstein[64]	2012	Canada	Restless legs was defined as often or always having a self-reported feeling of discomfort in the legs at night that improved with move-ment		49 32 17		42.7 (10.7)		Median EDSS was 2.0 (range 0–7.5)					6 out of 10
J. Vávrová[65]	2012	Germany	(IRLSSG)		765 553 212		36.5 (9.5)	9.1 (7.36)	2.0 (quartiles 1.5 and 3.5)	245				7 out of 9
Shahnaz Miri[66]	2012	Iran	(IRLSSG)		205 164 41	RR 179	32.8 (8.9)	6.0 (4.8)		57 RRMS 52 Progressive MS 5	49	8		6 out of 9

Table 1 (continued)

Author	Year	Country	Study scale	N_control Total Female Male	N_Ms Total Female Male	MS-Type	Age_MS	Disease duration	EDSS	Total RLS. MS	F.RLS.MS	M.RLS. MS	Total RLS cont	QA score
C Veauthier[67]	2011	Germany	Clinical interview		66 45 21					8				7 out of 9
Yára Dadalti Fragoso[68]	2011	Brazil	(IRLSSG)	180 120 60	80 60 20	RR 75 SP 5		7.5 (4.7)		46			33	6 out of 9
Gülay Aydar[69]	2011	Turkey	(IRLSSG)	129 81 48	98 72 26	RR 79 SP 16 PP 3	36.85 (8.70)	7.91 (6.59)	3.34 (2.04)	27			13	5 out of 10
J. Makhoul[70]	2010	Lebanon	(IRLSSG)		300					28				
A. Mendes[71]	2010	Portugal	(IRLSSG)	39	56 32 24	RR 43 SP 2 PP 11	41.1 (1.95)	7.1 (0.88)	2.67 (0.29)	11			2	6 out of 10
I. Aydin Canturk[72]	2010	Turkey	(IRLSSG)	39 23 16	142 98 42		40.64 (9.44)			26			1	
Sieminski M[73]	2009	Poland	Clinical interview		53 40 13		Mean age 40.8			18				6 out of 9
Marcello Deriu[74]	2009	Italy	(IRLSSG)	212	202 135 67	RR 181 SP 16 PP 5	40.7 (10.3)	9 (6.3)	2.5 (1.7)	29 RR 25 SP 4	22	7	6	
Sorgun, M H[75]	2009	Turkey	Clinical interview		100 73 27					20				
Bamer A[76]	2009	USA	Clinical interview		473					240				
Mauro Manconi [77]	2008	Italy	(IRLSSG)	649 431 218	861 596 265		41.2 (10.66)	Median 10.4 years (range 1–46 years)		164			27	
N.C.V. Moreira[78]	2008	Brazil	(IRLSSG)		44 32 12	RR 35 SP 4 PP 5	43 (14)			12 RRMS 11 PPMS 1	8	4		7 out of 9
M Manconia[79]	2008	Italy	(IRLSSG)		82 48 34		41.9 (12.5)	9 [1–36]	Median EDSS 4.2 (range 0.0–7.5)	30	21	9		5 out of 10
Zambrano [80]	2008	USA	(IRLSSG)	NA	251					84				6 out of 10
M. Manconia [81]	2007	Italy	Clinical interview		156 100 56	RR 119 SP 22 PP 15	40.7 (10.4)	Median 9 years (range 1–36 years)	3.2 (range 0.0–7.5, SD 1.7)	51 RRMS 35 SPMS 7 PPMS 9	36	15		6 out of 10

Table 1 (continued)

Author	Year	Country	Study scale	N_control Total Female Male	N_Ms Total Female Male	MS-Type	Age_MS	Disease duration	EDSS	Total RLS. MS	F.RLS.MS	M.RLS. MS	Total RLS cont	QA score
MJ Go´mez-Choco[6]	2007	Spain	IRLSSG	118 69 49	135 82 53	RR 100 SP 23 PP 12	43.1 (12.3)	11.3 (8.6)	2.9 [2]	18 RRMS 13 SPMS 3 PPMS 2	12	6	11	7 out of 10
Chantale Auger[82]	2005	Canada	(IRLSSG)	100 54 46	200 151 49		46 (11.3)			75			16	4 out of 10
Alex D Rae-Grant[83]	1999	USA	Clinical interview	93 76 15	224 161 63		43 [9]			119			13	6 out of 10

Statistical analysis

All statistical analyses were performed using STATA (version 13.0; Stata Corp LP, College Station, TX, USA).

Inconsistency (I^2) was calculated to determine heterogeneity.

Subgroup analysis was done based on sex.

Results

The literature search revealed 855 articles; after deleting duplicates, 530 remained. For the meta-analysis, 75 studies were included (Fig. 1). In six articles, the authors did not differentiate between CIS and MS cases when reporting RLS cases.

Studies were published between 1999 and 2021. Most studies were conducted in Turkey and the USA. Twenty-two studies reported data regarding the control group. Mean age and mean EDSS ranged between 28 and 59 years, 0.9 and 5.3, respectively.

Totally, 15,411 MS/CIS patients were evaluated and 4309 had RLS. As controls, 66,053 were enrolled and 4496 cases with RLS were reported.

Risk of bias which was assessed by NOS was more than 5 which indicates that the quality of included studies was satisfactory.

The data extracted from studies are summarized in Table 1.

The pooled prevalence of RLS was 28% (95% CI: 24–33%) ($I^2 = 98.3\%$, $P < 0.001$) (Fig. 2).

The pooled prevalence of RLS in women was 30% (95% CI: 25–35%) ($I^2 = 90.6\%$, $P < 0.001$) (Fig. 3).

The pooled prevalence of RLS in men was 22% (95% CI: 17–26%) ($I^2 = 78\%$, $P < 0.001$) (Fig. 4).

The pooled prevalence of RLS in controls was 8% (95% CI: 6–10%) ($I^2 = 99.5\%$, $P < 0.001$) (Fig. 5).

The pooled odds of RLS in patients with MS was 4.03 (95% CI: 1.83–3.57) ($I^2 = 64.8$, $P = 0.001$) (Fig. 6).

Discussion

This systematic review and meta-analysis is the update of previous studies, including 75 studies.

We found that the pooled prevalence of RLS in subjects with MS was estimated as 28%, while the pooled prevalence in controls was estimated as 8%.

The pooled prevalence of RLS was higher in women than men (30% vs 22%).

The previous systematic review and meta-analysis was conducted by Ning et al. They included 25 articles and reported the pooled prevalence of RLS in patients with MS

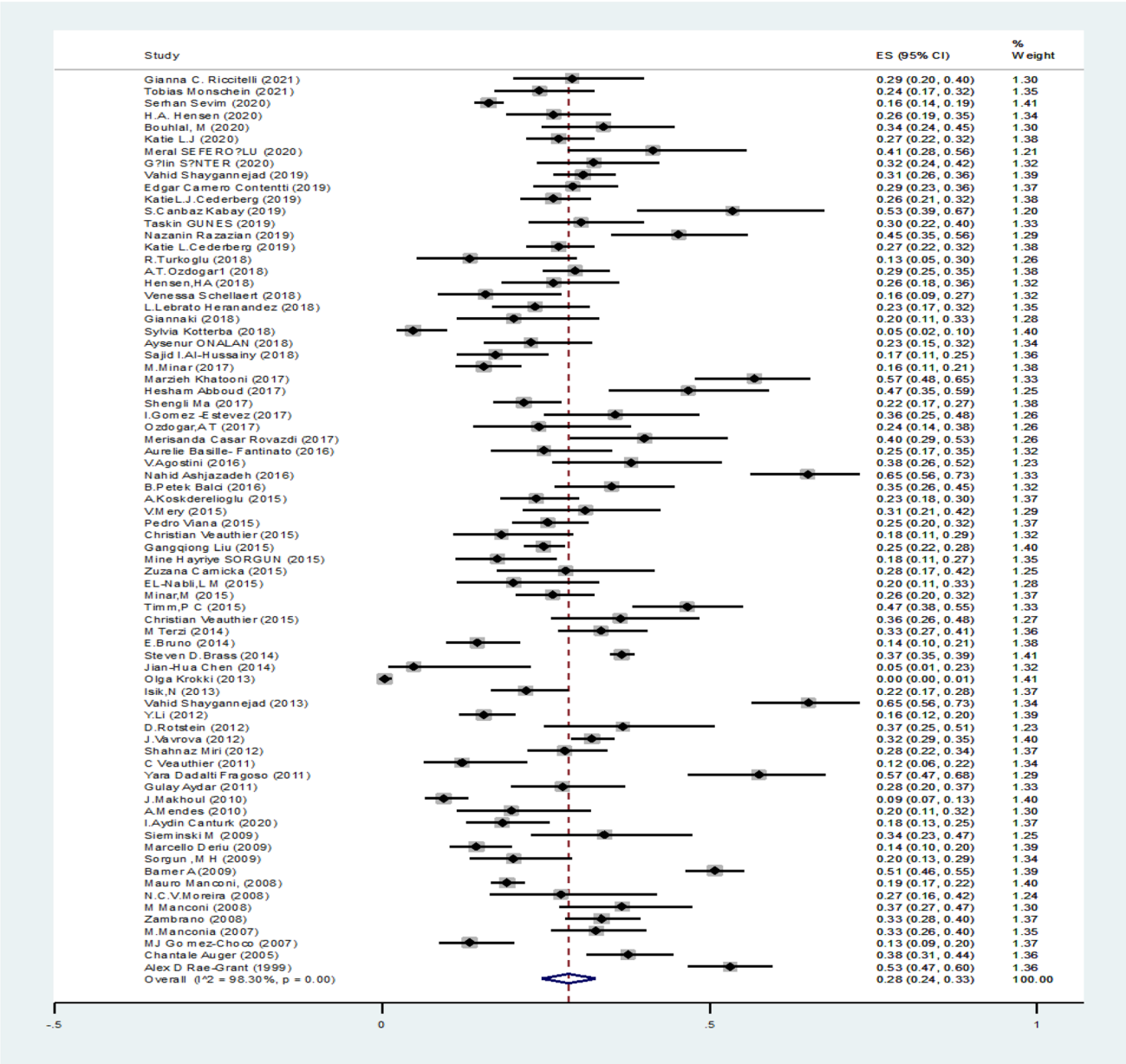

Fig. 2 The pooled prevalence of RLS in MS/CIS cases

as 27%. In their study, like our study, the pooled prevalence was higher in females than males (26 vs 17%). They also found that the odds of RLS was near fourfold among MS cases than controls [7] which is in agreement with our findings (OR = 4.03).

In another systematic review which was conducted in 2013 by Schürks, they investigated that the prevalence of RLS in subjects with MS ranged between 12.1 and 57% and also the prevalence ranged between 2.5 and 18.3% in controls. They reported the pooled OR of 4.1 (95% CI: 3.1–5.6) for RLS in MS [84]. They did not report the pooled prevalence.

Bruno et al. enrolled 152 patients with MS and 431 healthy controls and reported RLS as 14.5% in MS group vs 6% in controls. They found that the presence of cervical cord lesions was associated with RLS development (OR = 3.7, 95% CI: 1.1–13.5) [85].

Liu et al. evaluated 695 individuals with MS and 603 controls and found the prevalence of RLS as 24.6% in MS group vs 8% in controls. They noticed that RLS in MS group was more severe than controls and sleep quality in MS patients with RLS was more impaired [50].

In a recent study which is conducted by Monschein et al., the prevalence of RLS estimated as 23.9% in MS

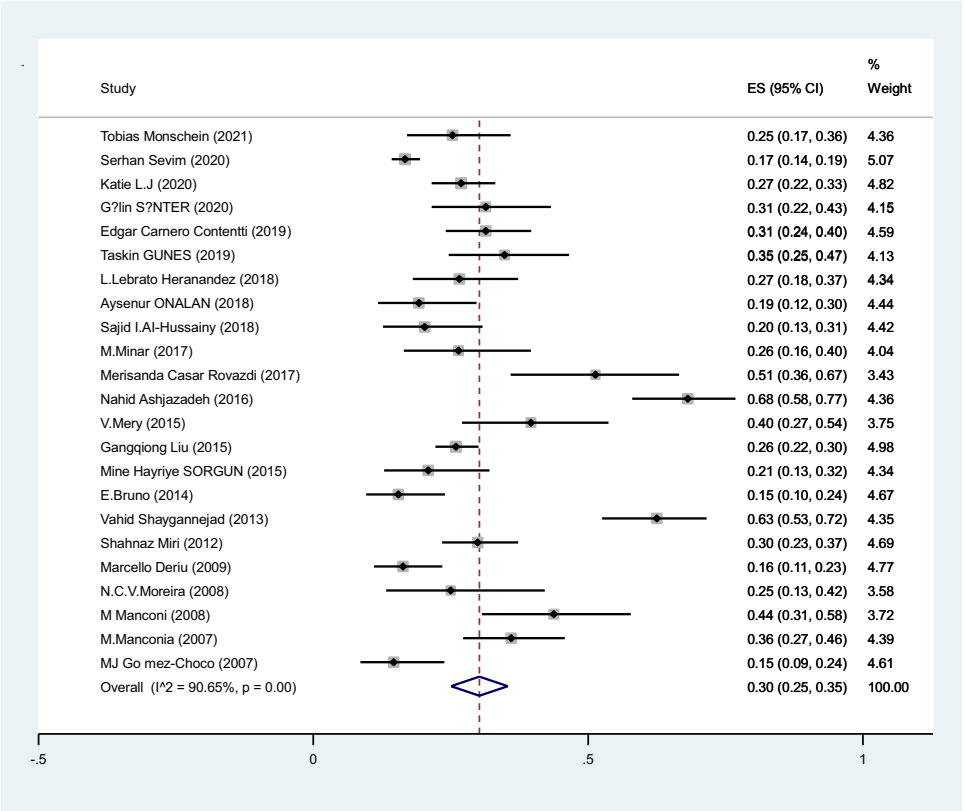

Fig. 3 The pooled prevalence of RLS in female patients

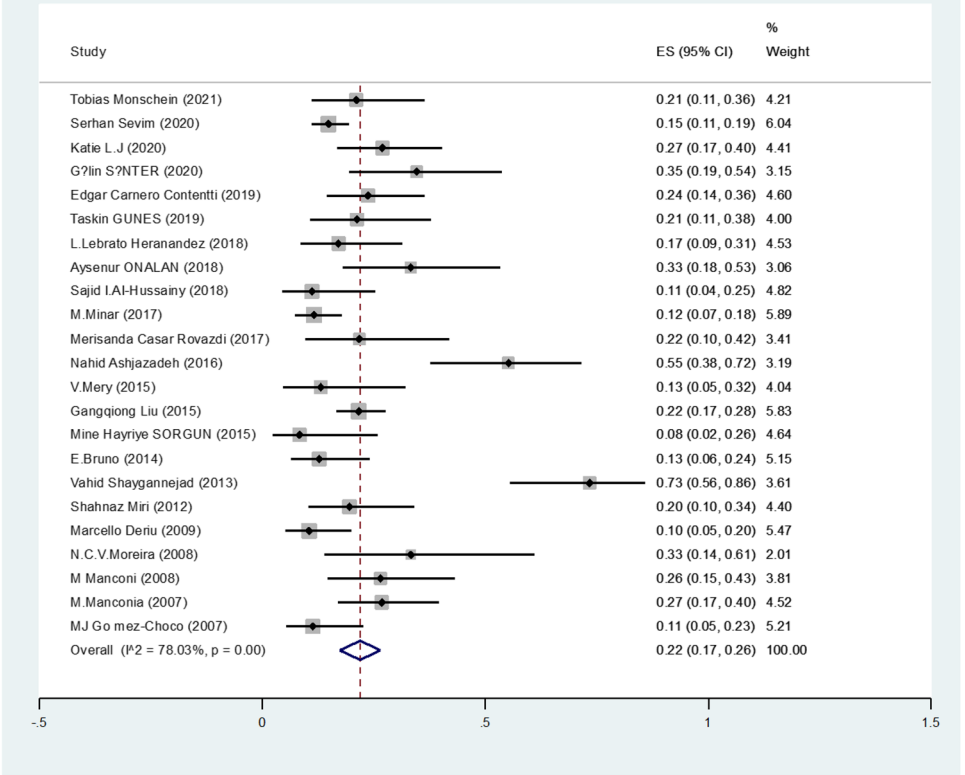

Fig. 4 The pooled prevalence of RLS in male patients

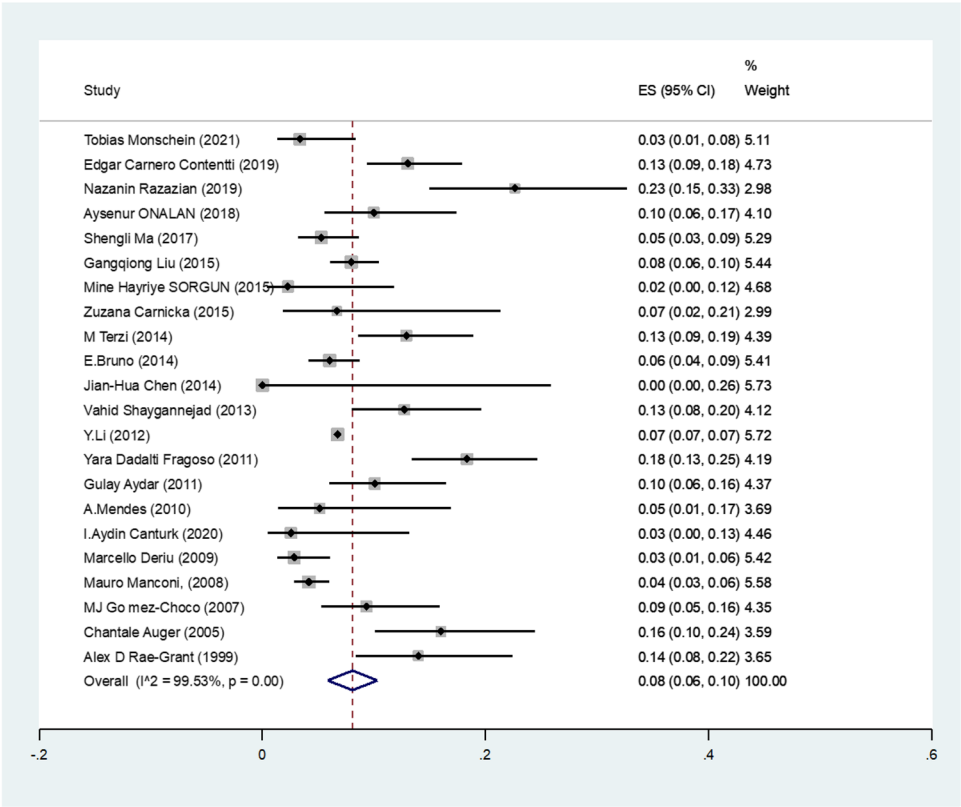

Fig. 5 The pooled prevalence in controls

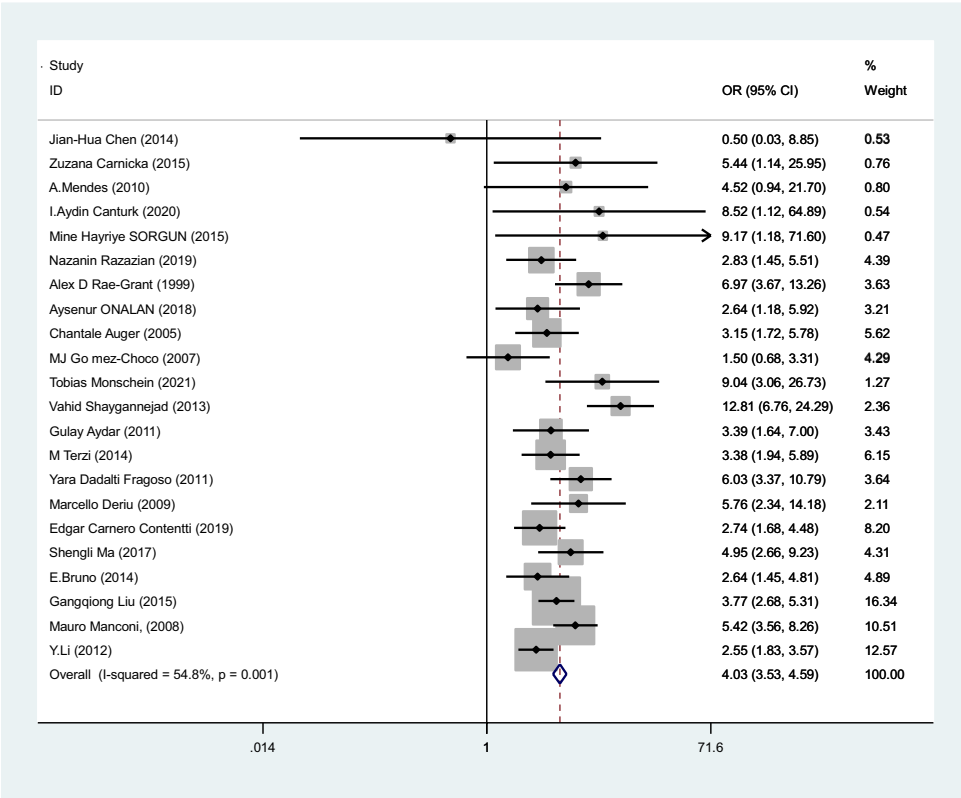

Fig. 6 The pooled OR of developing RLS in the MS group compared with controls

group and 3.4% in healthy group and MS cases with RLS had higher proportion of sleep impairment and excessive daytime sleepiness. They also found that disability level and spinal lesions in MRI are independent predictors of RLS development in MS [12]. Maybe spinal lesions disturb hypothalamo-spinal dopaminergic system [86], leading to RLS in MS.

Minar et al. enrolled 200 MS cases and reported RLS in 26% while RLS development was assumed to be associated with spinal cord lesions (OR = 3.846, 95% CI: 1.304–11.346) [87].

RLS is a sensory motor disorder which characterized by an impulse to move the legs that may be accompanied by dysesthesias and unpleasant sensation [88]. Untreated RLS is associated with sleep disturbances, daytime sleepiness, depression, and impaired quality of life [88]. The average sleep time in cases with RLS estimated as 5 h a day [88].

The diversity between studies regarding the prevalence of RLS in patients with MS could be due to variety of diagnostic method. In some studies, International RLS Rating Scale (IRLSS)/ Cambridge-Hopkins Questionnaire (CH-RLSq) and others administered clinical interview. We did not do meta-analysis based on diagnostic method as some studies which are included in our study did not report the diagnostic report.

In general population, iron deficiency is related with presence of RLS, while iron deficiency and vitamin D and B deficiencies were not associated with RLS in MS patients [87].

As reported previously, disability level and location of MS-related lesions were associated with RLS development. It is shown that infra-tentorial lesion increase the risk of RLS by sevenfold [89].

Administration of disease-modifying therapies have various effects on RLS development [89]. Some researchers found that interferons negatively affect sleep quality and daytime sleepiness leading to RLS worsening in subjects with MS [16, 90, 91]. On the other hand, natalizumab use is related with sleep quality improvement [92]. The controversies are based on cross-sectional nature of studies.

This systematic review has some strengths. First, we calculated the pooled prevalence in patients and controls. Second, we included 75 articles. Third, the pooled prevalence is calculated in both sexes separately.

Conclusion

The results of this systematic review and meta-analysis show that the pooled prevalence of RLS is 28% in MS cases and 8%. The pooled prevalence is higher in women than men (30% vs 22%).

Declarations

Ethical approval None.

Conflict of interest None.

References

1. Azimi A, Doosti R, Samani SMV, Roostaei B, Gashti SH, Navardi S et al (2021) Psychometric properties of the Persian version of the PARADISE-24 questionnaire. Int J Prev Med 12(1):50
2. Sarraf P, Azizi S, Moghaddasi AN, Sahraian MA, Tafakhori A, Ghajarzadeh M (2014) Relationship between sleep quality and quality of life in patients with multiple sclerosis. Int J Prev Med 5(12):1582
3. Roy M, Zwaan M, Tuin I, et al (2018) Association between restless legs syndrome and adult ADHD in a German Community-Based Sample.J Atten Disord 22(3):300–308
4. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW et al (2014) Restless legs syndrome/ Willis–Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med 15(8):860–873
5. Shaygannejad V, Ardestani PE, Ghasemi M, Meamar R (2013) Restless legs syndrome in Iranian multiple sclerosis patients: a case-control study. Int J Prev Med 4(Suppl 2):S189
6. Gomez-Choco M, Iranzo A, Blanco Y, Graus F, Santamaria J, Saiz A (2007) Prevalence of restless legs syndrome and REM sleep behavior disorder in multiple sclerosis. Mult Scler J 13(6):805–808
7. Ning P, Hu F, Yang B, Shen Q, Zhao Q, Huang H et al (2018) Systematic review and meta-analysis of observational studies to understand the prevalence of restless legs syndrome in multiple sclerosis: an update. Sleep Med 50:97–104
8. Schürks M, Bussfeld P (2013) Multiple sclerosis and restless legs syndrome: a systematic review and meta-analysis. Eur J Neurol 20(4):605–615
9. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S et al (2016) Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. PLoS One 11(1):e0147601
10. Peterson J, Welch V, Losos M, Tugwell P (2011) The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute, Ottawa, pp 1–12
11. Riccitelli GC, Disanto G, Sacco R, Sparasci D, Sacco L, Castelnovo A et al (2021) Contribution of sleep disturbances to fatigue in ms: a prospective study using clinical and polysomnographic parameters. Eur J Neurol 28(9):3139–3146
12. Monschein T, Schestak C, Schillerwein-Kral C, Leutmezer F, Berger T, Bsteh G et al (2021) Restless legs syndrome in multiple sclerosis: risk factors and effect on sleep quality–a case-control study. Mult Scler Relat Disord 51:102916
13. Sevim S, Demirkıran M, Terzi M, Yüceyar N, Taşdelen B, Idiman E et al (2020) Is RLS a harbinger and consequence of MS?: striking results of the 'RELOMS-T'study. Mult Scler Relat Disord 42:102055
14. Hensen H, Toson B, van Schooten K, Menant J, Hoang P, Lord S et al (eds.) (2020) Sleep disorders and poor sleep are common and associated with fatigue and depression in people with mild

to moderately-severe MS. Mult Scler J. Sage Publications LTD 1 Olivers Yard 55 City road, London EC1Y 1SP, England
15. Bouhlal M, Chtaou N, Bouchal S, Elmidaoui A, Souirti Z, Belahsen M (2020) Restless leg syndrome in patients with multiple sclerosis. Mult Scler J 26(3_SUPPL MA - P0490):352
16. Cederberg KL, Jeng B, Sasaki JE, Motl RW (2020) Restless legs syndrome, sleep quality, and perceived cognitive impairment in adults with multiple sclerosis. Mult Scler Relat Disord 43:102176
17. Seferoğlu M, Sivaci AÖ, Tunç A (2020) Restless legs syndrome/Willis-Ekbom disease in multiple sclerosis: a contributing factor for anxiety, disability, sleep disorder, and quality of life. Arq Neuropsiquiatr 78:708–712
18. Sünter G, Kilinç Ö, Ahmet B, Akçabey S, Saldüz E, Öztürkçü H et al (2020) Restless legs syndrome/Willis-Ekbom disease in multiple sclerosis patients with spinal cord lesions. Arch Neuropsychiatry 57(4):299
19. Shaygannejad V, Bahmani DS, Soleimani P, Mirmosayyeb O, Barzegar M, Amra B et al (2020) Comparison of prevalence rates of restless legs syndrome, self-assessed risks of obstructive sleep apnea, and daytime sleepiness among patients with multiple sclerosis (MS), clinically isolated syndrome (CIS) and Neuromyelitis Optica Spectrum Disorder (NMOSD). Sleep Med 70:97–105
20. Carnero Contentti E, López PA, Nadur D, Balbuena ME, Finkelstein AM, Tkachuk V (2019) Impact, frequency, and severity of restless legs syndrome in patients with multiple sclerosis in Argentina. Int JMS Care 21(4):157–165
21. Cederberg KL, Jeng B, Sasaki JE, Braley TJ, Walters AS, Motl RW (2019) Physical activity, sedentary behavior, and restless legs syndrome in persons with multiple sclerosis. J Neurol Sci 407:116531
22. Kabay SC, Yurekdeler N (2019) Restless legs syndrome and lesion location association in Multiple sclerosis
23. Taşkın Güneş UE, Erdal Y, Yalin OÖ (2021) Restless Legs Syndrome in Multiple Sclerosis. Archives of Neuropsychiatry 58(2):94
24. Razazian N, Mohammadi M, Hosseini F, Moradian N, Mohammadi H (2019) The frequency of restless legs syndrome in patients with multiple sclerosis and its related factors. J Kermanshah Univ Med Sci 23(4)
25. Cederberg KL, Jeng B, Sasaki JE, Braley TJ, Walters AS, Motl RW (2019) 0662 Restless legs syndrome and health-related quality of life in adults with multiple sclerosis. Sleep 42:A264
26. Turkoglu R, Tuzun E, Benbir G, Ozyurt S, Iskender M, Karadeniz D (eds) (2018) Benign multiple sclerosis patients display increased prevalence of sleep disorders. Mult Scler J. Sage Publications LTD 1 Olivers Yard, 55 City road, London EC1Y 1SP, England
27. Ozdogar A, Abasiyanik Z, Kahraman T, Ertekin O, Ozakbas S (eds) (2018) Factors related to restless leg syndrome in multiple sclerosis. Mult Scler J. Sage Publications LTD 1 Olivers Yard, 55 City road, London EC1Y 1SP, England
28. Hensen H, Lord S, Gandevia S, Krishnan A, Eckert D (eds) (2018) Poor sleep and sleep disorders are very common in people with multiple sclerosis. J Sleep Res. Wiley 111 river St., Hoboken 07030–5774, NJ, USA
29. Schellaert V, Labauge P, Lebrun C, Maudarbocus KH, Bernard J, Blache J-B et al (2018) Psychological processes associated with insomnia in patients with multiple sclerosis. Sleep 41(3):zsy002
30. Hernández LL, León MP, Fuentes NC, Sánchez AU, Chocán JC, Sánchez MD (2021) Restless legs syndrome in patients with multiple sclerosis: evaluation of risk factors and clinical impact. Neurología (English Edition)
31. Giannaki CD, Aristotelous P, Stefanakis M, Hadjigeorgiou GM, Manconi M, Leonidou E et al (2018) Restless legs syndrome in Multiple Sclerosis patients: a contributing factor for fatigue, impaired functional capacity, and diminished health-related quality of life. Neurol Res 40(7):588–594
32. Kotterba S, Neusser T, Norenberg C, Bussfeld P, Glaser T, Dörner M et al (2018) Sleep quality, daytime sleepiness, fatigue, and quality of life in patients with multiple sclerosis treated with interferon beta-1b: results from a prospective observational cohort study. BMC Neurol 18(1):1–10
33. Önalan A, Matur Z, Pehlıvan M, Akman G (2020) Restless legs syndrome in patients with Behçet's Disease and multiple sclerosis: prevalence, associated conditions and clinical features. Arch Neuropsychiatry 57(1):3
34. Al-Hussainy SI, Hatem AK (2018) The Prevalence of Restless Leg Syndrome in Iraqi Multiple Sclerosis Patients. Ind J Public Health Res Dev 9(6):155
35. Minár M, Petrleničová D, Valkovič P (2017) Higher prevalence of restless legs syndrome/Willis-Ekbom disease in multiple sclerosis patients is related to spinal cord lesions. Mult Scler Relat Disord 12:54–58
36. Khatooni M, Samiee-Siboni F, Alimoradi Z, Atashi V, Momeni M (2017) Is sleep quality associated with restless legs syndrome in patients suffering from multiple sclerosis? Shiraz E-Med J 18(10):e14521
37. Abboud H, Yu XX, Fernandez H, Cohen J (2017) Prospective evaluation of movement disorders in early multiple sclerosis and other CNS demyelinating diseases (P3. 362). AAN Enterprises
38. Ma S, Rui X, Qi P, Liu G, Yang J (2017) Sleep disorders in patients with multiple sclerosis in China. Sleep and Breathing 21(1):149–154
39. Gomez-Estevez I, El Berdei Montero Y, Fiz Santelesforo M, Gomez-Sanchez J (eds) (2017) Sleep disorders in patients with multiple sclerosis and their link with fatigue. Mult Scler J. Sage Publications LTD 1 Olivers Yard, 55 City road, London EC1Y 1SP, England
40. Ozdogar AT, Kahraman T, Yigit P, Hosgel I, Ertekin O, Ozakbas S (2017) Restless legs syndrome and related factors in persons with multiple sclerosis. Multiple Sclerosis J 23(6):907
41. Rovazdi MČ, Vidović V, Kraml O, Kes VB (2017) Restless Legs Syndrome in Multiple Sclerosis Patients-Patient Experience at Lipik Special Hospital for Medical Rehabilitation. Acta Clin Croat 56(1):80–83
42. Basille-Fantinato A, Al Khedr A, Rose D, Godefroy O (2012) Prevalence and Etiology of Sleep Disorders and Alertness in Multiple Sclerosis with Assessing the Impact on Quality of Life (P07. 077). AAN Enterprises
43. Agostini V, Chavez M, Condor Y, Guzman A, Harris T, Silva K, et al (eds) (2016) Prevalence of Restless Legs Syndrome in Puerto Rican patients with Multiple Sclerosis. Mult Scler J. Sage Publications LTD 1 Olivers Yard, 55 City road, London EC1Y 1SP, England
44. Ashjazadeh N, Shamszadeh Z (2016) Restless Leg Syndrome in Patients with Multiple Sclerosis and its Effect on Frequency of Daytime Sleepiness and Fatigue of the Patients. Galen Med J 5(1):7–12
45. Balci FB, Mutlu A, Cokar AO (2017) The incidence and severity of restless legs syndrome in patients with multiple sclerosis, and its clinical impact. Mult Scler J 23 MA - P1919:1022–3
46. Koskderelioglu A, Gedizlioglu M, Onder O (eds.) (2015) Evaluation of the relationship between restless legs syndrome, sleep disturbance and quality of life measures in patients with multiple sclerosis. Eur J Neurol. Wiley 111 river St., Hoboken 07030–5774, NJ, USA
47. Mery V, Kimoff R, Suarez I, Benedetti A, Kaminska M, Robinson A et al (2015) High false-positive rate of questionnaire-based restless legs syndrome diagnosis in multiple sclerosis. Sleep Med 16(7):877–882

48. Viana P, Rodrigues E, Fernandes C, Matas A, Barreto R, Mendonça M et al (2015) InMS: chronic insomnia disorder in multiple sclerosis–a Portuguese multicentre study on prevalence, subtypes, associated factors and impact on quality of life. Mult Scler Relat Disord 4(5):477–483
49. Veauthier C, Gaede G, Radbruch H, Sieb J-P, Wernecke K-D, Paul F (2015) Periodic limb movements during REM sleep in multiple sclerosis: a previously undescribed entity. Neuropsychiatr Dis Treat 11:2323
50. Liu G, Feng X, Lan C, Zhu Z, Ma S, Guo Y et al (2015) Restless leg syndrome and multiple sclerosis: a case-control study in China. Sleep Breath 19(4):1355–1360
51. Sorgun MH, Aksun Z, Atalay YB, Yücesan C (2015) Restless legs syndrome in multiple sclerosis. Turk J Med Sci 45(6):1268–1273
52. Čarnická Z, Kollár B, Šiarnik P, Krížová L, Klobučníková K, Turčáni P (2015) Sleep disorders in patients with multiple sclerosis. J Clin Sleep Med 11(5):553–557
53. El-Nabil LM, Lotfy N, Elkhayat N, Abdulghani KO, Ahmed Abdulghani M, Ossama M (2015) Restless leg syndrome in a sample of egyptian patients with multiple sclerosiss Egyptian. J Neurol Psychiatr Neurosurg 52:1
54. Minár M, Petrleničová D, Valkovič P (2015) Restless legs syndrome leads to reduced quality of life in patients with multiple sclerosis. Mov Disord 1248(30)
55. Timm PC, Tabatabai GM, Commers NA, Sandness DJ, Duwell EJ, Jinnus P et al (2015) Sleep disturbances are underrecognized and erode quality of life in progressive multiple sclerosis. Sleep. 38:A276-A
56. Veauthier C, Gaede G, Radbruch H, Wernecke K-D, Paul F (2015) Sleep disorders reduce health-related quality of life in multiple sclerosis (Nottingham health profile data in patients with multiple sclerosis). Int J Mol Sci 16(7):16514–16528
57. Terzi M, Yazici D, Onar M (2014) Restless leg syndrome and multiple sclerosis. Mult Scler 20(1):467–468
58. Bruno E, Nicoletti A, Messina S, Lo Fermo S, Raciti L, Quattrocchi G et al (2015) Restless legs syndrome and multiple sclerosis: a population based case-control study in Catania, Sicily. Eur J Neurol 22(6):1018–1021
59. Brass SD, Li CS, Auerbach S (2014) The Underdiagnosis of Sleep Disorders in Patients with Multiple Sclerosis. J Clin Sleep Med 10(9):1025–1031
60. Chen J-H, Liu X-Q, Sun H-Y, Huang Y (2014) Sleep disorders in multiple sclerosis in China: clinical, polysomnography study, and review of the literature. J Clin Neurophysiol 31(4):375–381
61. Krökki O, Bloigu R, Ansakorpi H, Reunanen M, Remes AM (2014) Neurological comorbidity and survival in multiple sclerosis. Mult Scler Relat Disord 3(1):72–77
62. Isik N, Canturk IA, Turkes M, Candan F, Cakir A (2013) Restless legs syndrome and multiple sclerosis. Mult Scler J 19(11):114–115
63. Li Y, Munger K, Batool-Anwar S, De Vito K, Ascherio A, Gao X (2012) Association of multiple sclerosis with restless legs syndrome and other sleep disorders in women. Neurology 78(19):1500–1506
64. Rotstein D, O'Connor P, Lee L, Murray B (2012) Multiple sclerosis fatigue is associated with reduced psychomotor vigilance. Can J Neurol Sci 39(2):180–184
65. Vavrova J, Kemlink D, Šonka K, Havrdová E, Horáková D, Pardini B et al (2012) Restless legs syndrome in Czech patients with multiple sclerosis: an epidemiological and genetic study. Sleep Med 13(7):848–851
66. Miri S, Rohani M, Sahraian MA, Zamani B, Shahidi GA, Sabet A et al (2013) Restless legs syndrome in Iranian patients with multiple sclerosis. Neurol Sci 34(7):1105–1108
67. Veauthier C, Radbruch H, Gaede G, Pfueller C, Dörr J, Bellmann-Strobl J et al (2011) Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study. Mult Scler J 17(5):613–622
68. Fragoso YD, Finkelsztejn A, Gomes S, Maciel DRK, Oliveira CLS, Lopes J et al (2011) Restless legs syndrome and multiple sclerosis: a Brazilian multicenter study and meta-analysis of the literature. Arq Neuropsiquiatr 69(2a):180–183
69. Aydar G, Kurt S, Unaldi HK, Erkorkmaz U (2011) Restless legs syndrome in multiple sclerosis. Eur Neurol 65(5):302–306
70. Makhoul J, Ghaoui N, Sleilaty G, Koussa S, Abbas S, Azar C et al (2020) Restless legs syndrome among multiple sclerosis patients in Lebanon. Mult Scler Relat Disord 41:101997
71. Mendes A, Abreu P, Mendonca T, Guimaraes J, Reis J, Rio E et al (2010) Restless legs syndrome and multiple sclerosis: a cohort study. Mult Scler 16(10):S65-S
72. Canturk I, Turkes M, Isik N, Aydin T, Arici Duz O, Candan F (2010) Restless legs syndrome in multiple sclerosis. Mult Scler 16:S220
73. Siemiński M, Wojcik-Draczkowska H, Nyka W (2009) P3 185 Restless legs syndrome, sleep quality and interferon therapy in multiple sclerosis patients. Parkinsonism and Related Disorders 15:S195
74. Deriu M, Cossu G, Molari A, Murgia D, Mereu A, Ferrigno P et al (2009) Restless legs syndrome in multiple sclerosis: a case-control study. Mov Disord 24(5):697–701
75. Sorgun MH, Yucesan C, Mutluer N (2009) Restless leg syndrome in multiple sclerosis. Mult Scler 15(9):S48-S
76. Bamer A, Amtmann D, Johnson K, Kraft G (2009) Prevalence of restless legs and association with MS disease duration and course. Mult Scler 15(9):S48-S
77. Manconi M, Ferini-Strambi L, Filippi M, Bonanni E, Iudice A, Murri L et al (2008) Multicenter case-control study on restless legs syndrome in multiple sclerosis: the REMS study. Sleep 31(7):944–52
78. Moreira NCV, Damasceno RS, Medeiros CAM, de Bruin PFC, Teixeira CAC, Horta WG et al (2008) Restless leg syndrome, sleep quality and fatigue in multiple sclerosis patients. Braz J Med Biol Res 41(10):932
79. Manconi M, Rocca M, Ferini-Strambi L, Tortorella P, Agosta F, Comi G et al (2008) Restless legs syndrome is a common finding in multiple sclerosis and correlates with cervical cord damage. Mult Scler J 14(1):86–93
80. Zambrano GAS, Pena JA, Hutton G, Avila M, Rivera V (2008) Frequency and severity of restless legs syndrome in multiple sclerosis: a population study from southeast Texas. Neurology 70(11):A334-A
81. Manconi M, Fabbrini M, Bonanni E, Filippi M, Rocca M, Murri L et al (2007) High prevalence of restless legs syndrome in multiple sclerosis. Eur J Neurol 14(5):534–539
82. Auger C, Montplaisir J, Duquette P (2005) Increased frequency of restless legs syndrome in a French-Canadian population with multiple sclerosis. Neurology 65(10):1652–1653
83. Rae-Grant AD, Eckert NJ, Bartz S, Reed JF (1999) Sensory symptoms of multiple sclerosis: a hidden reservoir of morbidity. Mult Scler J 5(3):179–183
84. Schürks M, Bussfeld P (2013) Multiple sclerosis and restless legs syndrome: a systematic review and meta-analysis. Eur J Neurol 20(4):605–615
85. Bruno E, Nicoletti A, Messina S, Lo Fermo S, Raciti L, Quattrocchi G et al (2015) Restless legs syndrome and multiple sclerosis: a population based case− control study in Catania, Sicily. Eur J Neurol 22(6):1018–1021
86. Koblinger K, Füzesi T, Ejdrygiewicz J, Krajacic A, Bains JS, Whelan PJ (2014) Characterization of A11 neurons projecting to the spinal cord of mice. PLoS One 9(10):e109636
87. Minár M, Petrleničová D, Valkovič P (2017) Higher prevalence of restless legs syndrome/Willis-Ekbom disease in multiple sclerosis

patients is related to spinal cord lesions. Mult Scler Relat Disord 12:54–58
88. Nagandla K, De S (2013) Restless legs syndrome: pathophysiology and modern management. Postgrad Med J 89(1053):402–410
89. Monschein T, Schestak C, Schillerwein-Kral C, Leutmezer F, Berger T, Seidel S (2020) Prevalence of restless legs syndrome in multiple sclerosis patients in a tertiary centre-a case-control study. Eur J Neurol 27:908
90. Kotterba S, Schwenkreis P, Schölzel W, Haltenhof C (2016) Fatigue and sleep problems in patients with relapsing-remitting multiple sclerosis (RRMS) under treatment with interferon beta-1b. Klin Neurophysiol 47(3):136–141
91. Kotterba S, Neusser T, Norenberg C, Bussfeld P, Glaser T, Dörner M et al (2018) Sleep quality, daytime sleepiness, fatigue, and quality of life in patients with multiple sclerosis treated with interferon beta-1b: results from a prospective observational cohort study. BMC Neurol 18(1):123
92. Penner I-K, Sivertsdotter EC, Celius EG, Fuchs S, Schreiber K, Berkö S, et al (2015) Improvement in fatigue during natalizumab treatment is linked to improvement in depression and day-time sleepiness. Front Neurol 6