Review Article

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Effects of robotic rehabilitation on fatigue experience, disability, and quality of life in patients with multiple sclerosis (MS): A systematic review and meta-analysis

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Abstract

Background: Rehabilitation plays an important role in improving symptoms in patients with multiple sclerosis (MS). There are studies evaluating the effects of robotic rehabilitation in patients with MS, but the results varied between the studies. So, we designed this systematic review and meta-analysis to estimate pooled effects of robotic rehabilitation on fatigue, disability, and quality of life in subjects with MS.

Methods: We systematically searched PubMed, Scopus, EMBASE, Web of Science, Google Scholar, and also gray literature including references of the included studies, and also conference abstracts on October 1th 2022**.** Data regarding the total number of participants, first author, publication year, country of origin, mean age, EDSS, and results of fatigue and quality of life were recorded.

Results: The first literature search revealed 6878 results, after deleting duplicates, 5019 studies remained. Two researchers, evaluated the titles and abstracts, and finally 77 full texts were assessed. For meta-analysis, we included 11 studies. The pooled Standardized Mean Difference (SMD) of Kurtzke Expanded Disability Status Scale (EDSS) (after-before) estimated as -0.56 (95%CI: -0.89,-0.23). The pooled SMD of Fatigue Severity Scale (FSS) estimated as -0.54(95%CI: -1.06, -0.01) (I^2=66.7%, P=0.01). The pooled SMD of physical health subscale of multiple sclerosis quality of life (MSQOL-54) estimated as 0.36(95%CI:-0.23, 0.96) (I^2=51.4%, P=0.1). The pooled SMD of mental health subscale of MSQOL54 estimated as 0.48 (95%CI: 0.07, 0.88) (I^2=0%, P=0.6).

Conclusions: The results of this systematic review and meta-analysis show that robotic rehabilitation has positive effects on fatigue, and disability in patients with MS.

Keywords: Multiple sclerosis, Robotic, Rehabilitation.

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Multiple sclerosis, an inflammatory disease of the central nervous system (CNS), is one of the main causes of the disabilities in youth all over the world (1, 2). Women are more affected, and the exact cause is not clear, while genetics as well as environmental factors play an important role in disease development (3-5). Affected cases suffer from a wide range of psychological problems such as depression, anxiety, fatigue, sexual dysfunction, and sleep disturbances (6-9). Lack of physical and psychological energy along with heat sensation and worsening during the day are characteristics of fatigue in patients with MS (10). Between 50% and 90% of patients with MS report fatigue, while between 15% and 60% reported fatigue as one of the disabling symptoms that affect their quality of life (11-13). The exact cause of fatigue is not clear, but pharmacological and non-pharmacological treatments are used to treat fatigue in these patients.

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Rehabilitation plays an important role in improving symptoms in patients with MS, and is part of therapy. New technologies: robotics, neuro-modulation and more recently tele-rehabilitation provide better rehabilitation options for patients with MS (14). Robotics for rehabilitation treatment is an apparent field which could replace traditional physical training with reasonable cost and better results (15).

Neuro-rehabilitation through robots is considered more after COVID-19 pandemic as they provide remote presence robots for virtual consultations, and also clinical practice in a variety of specialties such as exoskeletons assisting mobility (16). Robotic rehabilitation helps patients with MS to improve their muscle strength, mobility, and cognition (17), so its application should be considered in clinical settings. There are studies evaluating the effects of robotic rehabilitation in patients with MS, but the results varied between the studies. So, we designed this systematic review and meta-analysis to estimate pooled effects of robotic rehabilitation on fatigue, disability, and quality of life in subjects with MS.

Methods

We systematically searched PubMed, Scopus, EMBASE, Web of Science, google scholar, and also gray literature including references of the included studies, and also conference abstracts on October 1th 2022. We followed The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (18).

The MeSH terms were: (((((((((((((((((((((((((((((((((((((((Artificial intelligence[MeSH Terms]) OR (Machine learning[MeSH Terms])) OR (Deep learning[MeSH Terms])) OR (Robotics[MeSH Terms])) OR (Exoskeleton Device[MeSH Terms])) OR (Artificial intelligence[Text Word])) OR (Intelligence, Artificial[Text Word])) OR (Computational Intelligence[Text Word])) OR (Intelligence, Computational[Text Word])) OR (Machine Intelligence[Text Word])) OR (Intelligence, Machine[Text Word])) OR (Computer Reasoning[Text Word])) OR (Reasoning, Computer[Text Word])) OR (Computer Vision System*[Text Word])) OR (System*, Computer Vision[Text Word])) OR (Vision System*, Computer[Text Word])) OR (Knowledge Acquisition[Text Word])) OR (Acquisition, Knowledge[Text Word])) OR (Knowledge Representation*[Text Word])) OR (Representation, Knowledge[Text Word])) OR (Machine learning[Text Word])) OR (Learning, machine[Text Word])) OR (Learning, transfer[Text Word])) OR (Transfer learning[Text Word])) OR (Deep learning[Text Word])) OR (Hierarchical Learning[Text Word])) OR (Learning, deep[Text Word])) OR (Learning, Hierarchical[Text Word])) OR (Robotic*[Text Word])) OR (Operation*, Remote[Text Word])) OR (Remote Operation*[Text Word])) OR (Telerobotic*[Text Word])) OR (Soft Robotic*[Text Word])) OR (Robotic*, Soft[Text Word])) OR (Exoskeleton Device*[Text Word])) OR (Device*, Exoskeleton[Text Word])) OR (Robotic Exoskeleton*[Text Word])) OR (Exoskeleton*, Robotic[Text Word])) OR (Exosuit*[Text Word])) AND ((((((Multiple sclerosis[MeSH Terms]) OR (Multiple sclerosis[Text Word])) OR (Disseminated sclerosis[Text Word])) OR (Sclerosis, disseminated[Text Word])) OR (Sclerosis, Multiple[Text Word])) OR (Multiple Sclerosis, Acute Fulminating[Text Word])).

Inclusion criteria were: Trials with before-after design which reported scores of the fatigue, disability, and quality of life scores.

Exclusion criteria were: Letters to the Editor, case-control, case reports, and cross-sectional studies.

Data regarding the total number of participants, first author, publication year, country of origin, mean age, EDSS, and results of fatigue and quality of life were recorded.

Risk of bias assessment: The Cochrane Collaboration's tool was used for assessing the risk of bias of clinical trials and ROBINSON RISK OF BIAS for non-randomized studies (19, 20). Two independent researchers did this section, and in the case of disagreement, they asked a third party.

Statistical analysis: All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). Inconsistency (I^2) was calculated to determine heterogeneity. We used fixed-effects model for meta-analysis as the heterogeneity between study results (I^2) was less than 50%. Standardized mean difference (SMD) was calculated as the effect size.

Results

The first literature search revealed 6878 results, after deleting duplicates, 5019 studies remained. Two researchers, evaluated the titles and abstracts, and finally 77 full texts were assessed. For meta-analysis, we included 11 studies (figure 1).

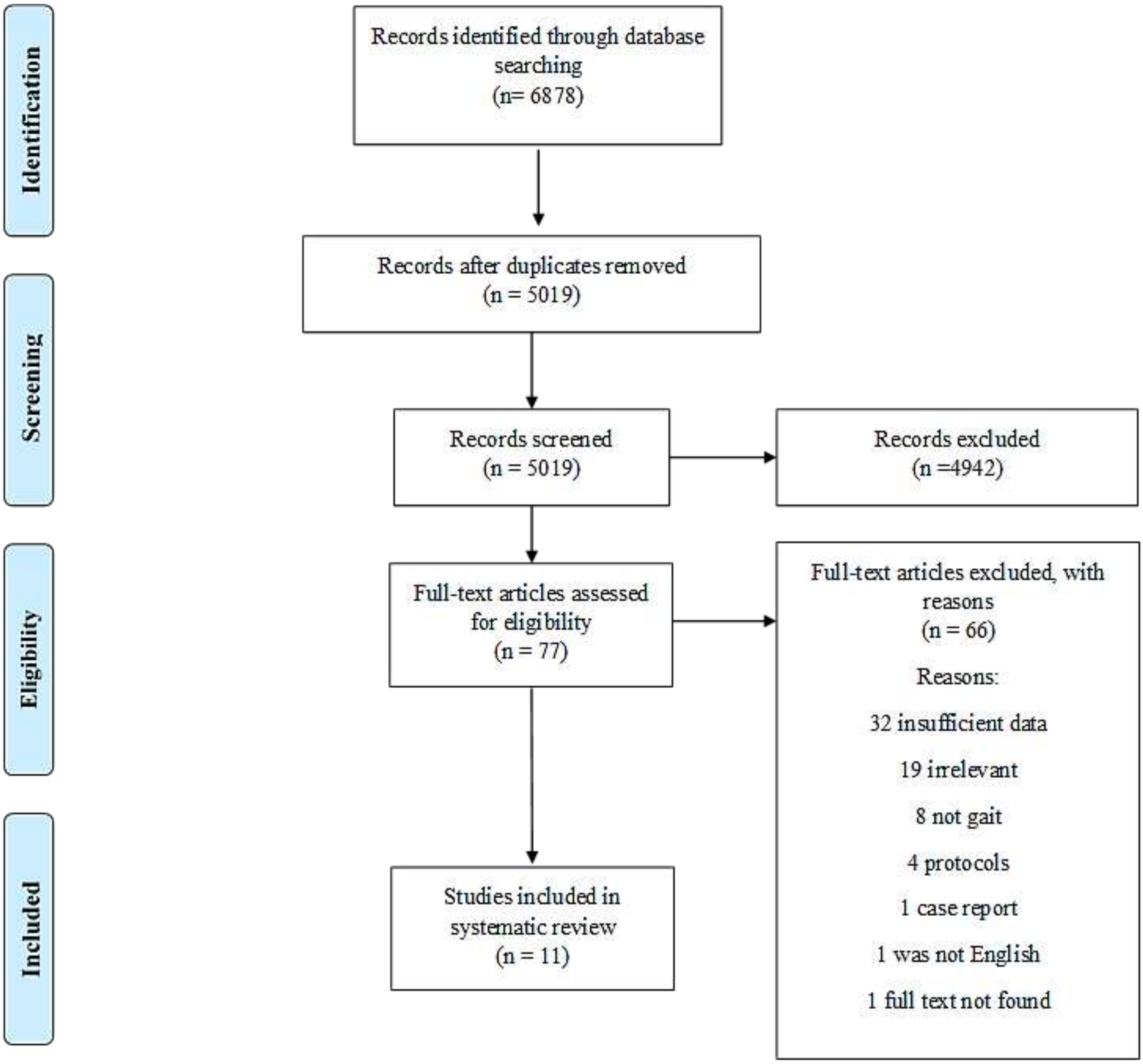

Figure 1. The flow chart of studies inclusion

The most country of origin was Italy, and the mean age ranged between 43 and 51 years. The mean EDSS in included studies ranged between 3.9 and 6.7, and duration of treatment was between 4 and 10 weeks (table 1). The SMD for EDSS ranged between -0.91, and -0.2 (figure 2). The pooled SMD od EDSS (after-before) estimated as -0.56 (95%CI: -0.89,-0.23) (I^2=0, P=0.8) (figure 2).

The SMD of FSS ranged between -1.68, and 0.14 (figure 3). The pooled SMD of FSS estimated as -0.54 (95%CI: -1.06, -0.01) (I^2=66.7%, P=0.01) (figure 3). The SMD of physical health subscale of MSQOL-54 ranged between -0.42, 1.13 (figure 4). The pooled SMD of physical health subscale of MSQOL54 estimated as 0.36 (95%CI:-0.23, 0.96) (I^2=51.4%, P=0.1) (figure 4).

The SMD of mental health subscale of MSQOL54 ranges between 0.13-0.8 (figure 5). The pooled SMD of mental health subscale of MSQOL54 estimated as 0.48 (95%CI: 0.07, 0.88) (I^2=0%, P=0.6) (figure 5). The quality assessment of randomized and non-randomized studies are summarized in table 2 and 3.

Table 1. Data extracted from the studies

MSQoL-54(MH)	Post			
	Pre			
MSQoL-54(PH)	Post			
	Pre			
FSS	Post	Treatment: 3.96±1.19 / Control: 5.12±1.46	Experiment: 3.6±0.5/ Control: 6.2±0.6	72.8±16.8
	Pre	Treatment: 5.31±1.02 / Control: 5.40±1.54	Experiment: 4.2±0.2/ Control: 6.1±0.3	70.2±19.3
EDSS	Post	Treatment: 6.48±0.37 / Control: 6.50±0.49	Experiment: 6.2±0.5/ control: 6.4±0.4	
	Pre	Treatment: 6.62±0.42 / Control: 6.50±0.49	Experiment: 6.3±0.5/ control: 6.1±0.4	
Duration of study		4 weeks	6 weeks	6 weeks
Type of robotic intervention		Robot-assisted gait training	Exoskeleton-Assisted Rehabilitation	Keeogo exoskeleton
Disease duration		Experiment: 17.05 ± 9.12/ control: 14.09 ±5.71	N/A	N/A
EDSS		Experiment: 6.62±0.42/ control: 6.50±0.49	Experiment: 6.3±0.5/ control: 6.1±0.4	5.3±1.3
Gender		Experiment: 10 F, 11 M/ control: 12 F, 10 M	Experiment: 2 F, 3 M/ control: 2 F, 2 M	F 17, M 12
Age		Experiment: 47.00 ± 11.17/ control: 49.86 ± 8.21	Experiment: 49.0±7.3/ control: 50.3±7.3	49.2±10.6
Participants		43(21 experiment / 22 control)	9(5 experiment, 4 control)	29
Study design		A pilot randomized control trial	Randomized control trial	open-label randomized cross-over trial
Year		2016	2021	2021
Country		Italy	Italy	Canada
Author		Pompa et al(21).	Sulpizio et al.	McGibbon et al.
		7	10	12

MSQoL-54(MH)	Post	Experiment: 58.78 ± 60.78 / Control: 60.78 ± 23.19	70.63 ± 7.66	
	Pre	Experiment: 59 ± 21 / Control: 56.75 ± 19.38	66.9 ± 8.87	
MSQoL-54(PH)	Post	Experiment: 60.8 ± 9 / Control: 43.18 ± 18.75	49.81 ± 12.95	
	Pre	Experiment: 64.1 ± 6.5/ Control: 43.85 ± 17.17	44.76 ± 14.12	
FSS	Post			
	Pre			
EDSS	Post			Experiment: 5.9 ± 0.6/ Control: 5.7 ± 0.7
	Pre			Experiment: 6.2 ± 0.5/ Control: 6.0 ± 0.6
Duration of study		5 weeks	6 weeks	4 weeks
Type of robotic intervention		robot-assisted hand training Amadeo	robot-assisted gait training	robot-assisted gait training
Disease duration		Experiment: 13.48±7.82 / control: 14.19±9.78	13.9±9.23	Experiment: 11.3 ± 6.7/Control: 14.9 ± 8.1
EDSS		Experiment: median 6(IQR 5-6)/ control: 6(4-7.25)	5±1.01	Experiment: 6.2 ± 0.5 /Control: 6 ± 0.6
Gender		Experiment: female 13, male 10 / control: N/A	5 F, 4 M	Experiment: 8 f, 7 m /Control: 10 f, 7 m
Age		Experiment: 51.96±10.87 / control: 50.67±10.80	51.7±10.24	Experiment: 46.8 ± 11.5 /Control: 50.5 ± 11.5
Participants		44(experiment: 23, conventional therapy: 21)	9	28 (experiment: 12/ control: 16)
Study design		Randomized controlled single-blinded trial	A pilot, single-blind, randomized controlled trial	Randomized control trial
Year		2018	2020	2011
Country		Italy	Italy	Israel
Author		Gandolfi et al.	Munari et al.	Schwartz et al.
		13	14	28

MSQoL-54(MH)	Post		Experiment: 61.11 ± 19.58 / Control: 65.24 ± 15.34	
	Pre		Experiment: 59.01 ± 21.69 / Control: 59.51 ± 20.7	
MSQoL-54(PH)	Post		Experiment: 60.84 ± 9.01 / Control: 61.34 ± 8.16	
	Pre		Experiment: 64.17 ± 6.53 / Control: 59.59 ± 10.67	
FSS	Post		Experiment: 4.03±2.25 / Control: 3.02±1.50	Experiment: 46.1 ± 10.6 / Control: 41.1 ± 13.1
	Pre		Experiment: 4.40±1.38 / Control: 3.96±1.17	Experiment: 48.1 ± 9.3/ Control: 42.9 ± 14.2
EDSS	Post	Experiment: 5.2 ± 1.0 Control: 5.4 ± 1.0		
	Pre	Experiment: 5.6 ± 1.0 Control: 5.5 ± 1.1		
Duration of study		10 weeks	6 weeks	
Type of robotic intervention		Lokomat	electromechanical Gait Trainer GT1	Upper limb training with PABLO-Tyromotion.
Disease duration		N/A	Experiment: 13.5±7.60 / Control: 14.9±8.68	Experiment: 17.3 ± 7.06 / Control: 22.4 ± 9.50
EDSS		N/A	Experiment: 3.96±0.75 / Control: 4.35±0.67	Experiment: 6.7 ± 1.8 / Control: 7.1 ± 1
Gender		16 f, 3 m	Experiment: 7F, 5M / Control: 9F, 1M	Experiment: 8F, 6M / Control: 10F, 6M
Age		N/A	Experiment: 50.83±8.42 / Control: 50.1±6.29	Experiment: 46.7 ± 10.4 / Control: 52.3 ± 5.4
Participants		17	22(12 Experiment/ 10 Control)	30(14 Experiment, 16 control)
Study design		randomized controlled crossover trial	A randomized controlled trial	A randomized controlled trial
Year		2021	2014	2020
Country		Italy	Italy	Italy
Author		Sconza et al.	Gandolfi et al.	Tramontano et al.
		30	32	41

MSQoL-54(MH)	Post	Experiment: Median 43.90 (IQR 40.34-48.14) / Control: 40.24 (35.90-56.02)	Experiment: median 72.5 (IQR 68.8–95.8) / Control: 43.7 (41.5–60.5)
	Pre	Experiment: Median 36.36 (IQR 32.71-45.30) / Control: 38.73 (29.36-51.20)	Experiment: median 56.2 (IQR 42.9–64.4) / Control: 42.1 (41.6–57.1)
MSQoL-54(PH)	Post	Experiment: Median 34.22 (IQR 24.90-38.08) / Control: 33.79 (24.60-47.96)	Experiment: median 91.6 (IQR 71.6–132.0) / Control: 66.1 (48.0–84.5)
	Pre	Experiment: Median 28.57 (IQR 17.43-36.99) / Control: 29.90 (22.70-45.60)	Experiment: median 53.4 (IQR 38.0–61.0) / Control: 60.0 (36.0–83.0)
FSS	Post	Experiment: median 4.44 (IQR 3.50–5.80) / Control: 5.88 (4.44–6.66)	
	Pre	Experiment: median 5.55 (IQR 4.22–6.77) / Control: 6.00 (4.77–6.77)	
EDSS	Post	Experiment: median 6 (IQR 5.87–6.50) / Control: 6 (5.5–6.5)	
	Pre	Experiment: median 6.5 (IQR 5.87–6.62)/ Control: 6 (5.5–6.5)	
Duration of study		4 weeks	8 weeks
Type of robotic intervention		RoboGait, an automated locomotor therapy system	Ekso-GT
Disease duration		Experiment: 14.11 ± 5.94/ Control: 13.47 ± 6.21	Experiment: 8.4 ± 3.5 / Control: 8.4 ± 3.5
EDSS		Experiment: median 6.5 (IQR 5.87–6.62)/ Control: 6 (5.5–6.5)	Experiment: 4.9/ Control: 4.9
Gender		Experiment: 11f, 7m/ Control: 13f, 6m	Experiment: 4f, 6m / Control: 4f, 6m
Age		Experiment: 45.05 ± 9.22/ Control: 44.73 ± 8.43	Experiment: 43.7 ± 10.3 / Control: 43.7 ± 5.6
Participants		37 (18 Experiment, 19 Control)	20 (10 Experiment, 10 Control)
Study design		A Single-Blinded Randomized Controlled Study	A retrospective study
Year		2022	2021
Country		Turkey	Italy
Author		Ozsoy-Unubol et al.	Russo et al.
		44	45

EDSS: Expanded Disability Status Scale / FSS: Fatigue Severity Scale / MSQoL-54 (PH): Multiple Sclerosis Quality of Life (physical health) / MSQoL-54 (MH): Multiple Sclerosis Quality of Life (mental health).

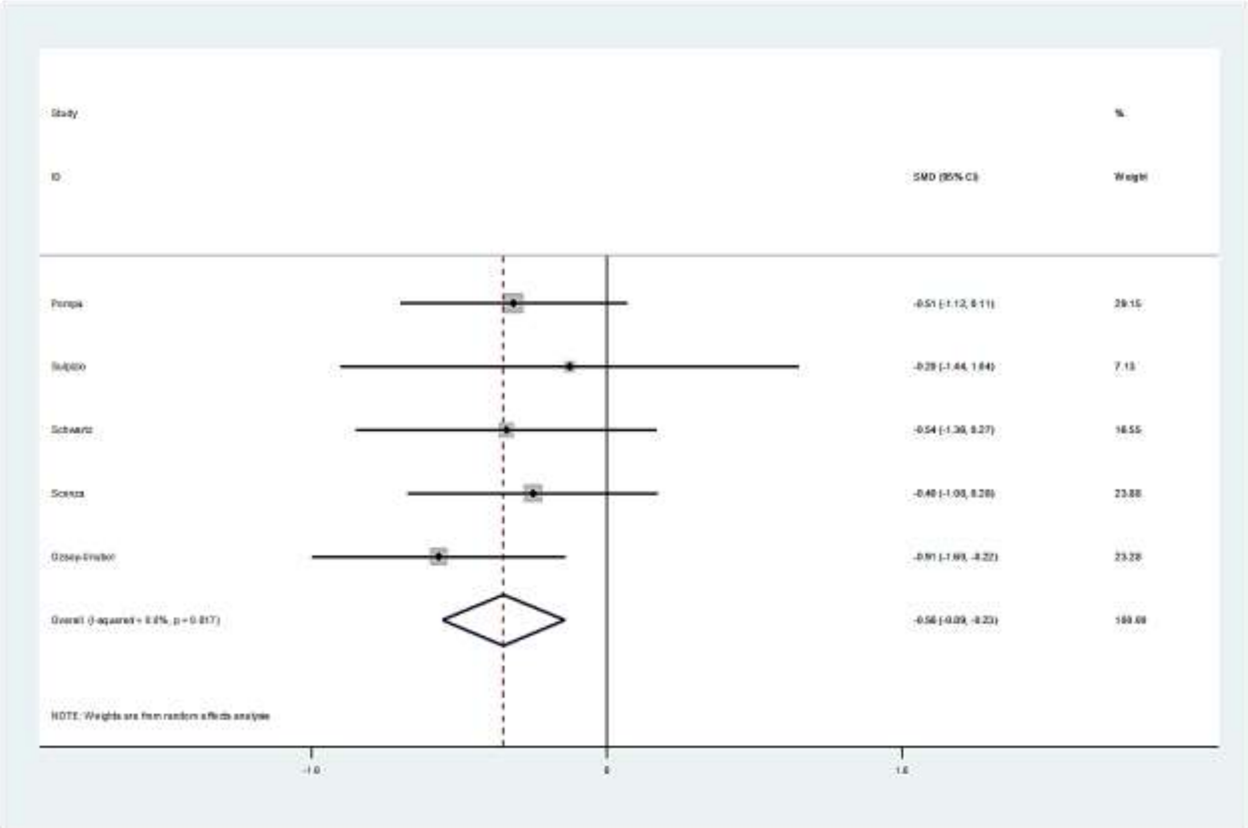

Figure 2. The pooled SMD od EDSS

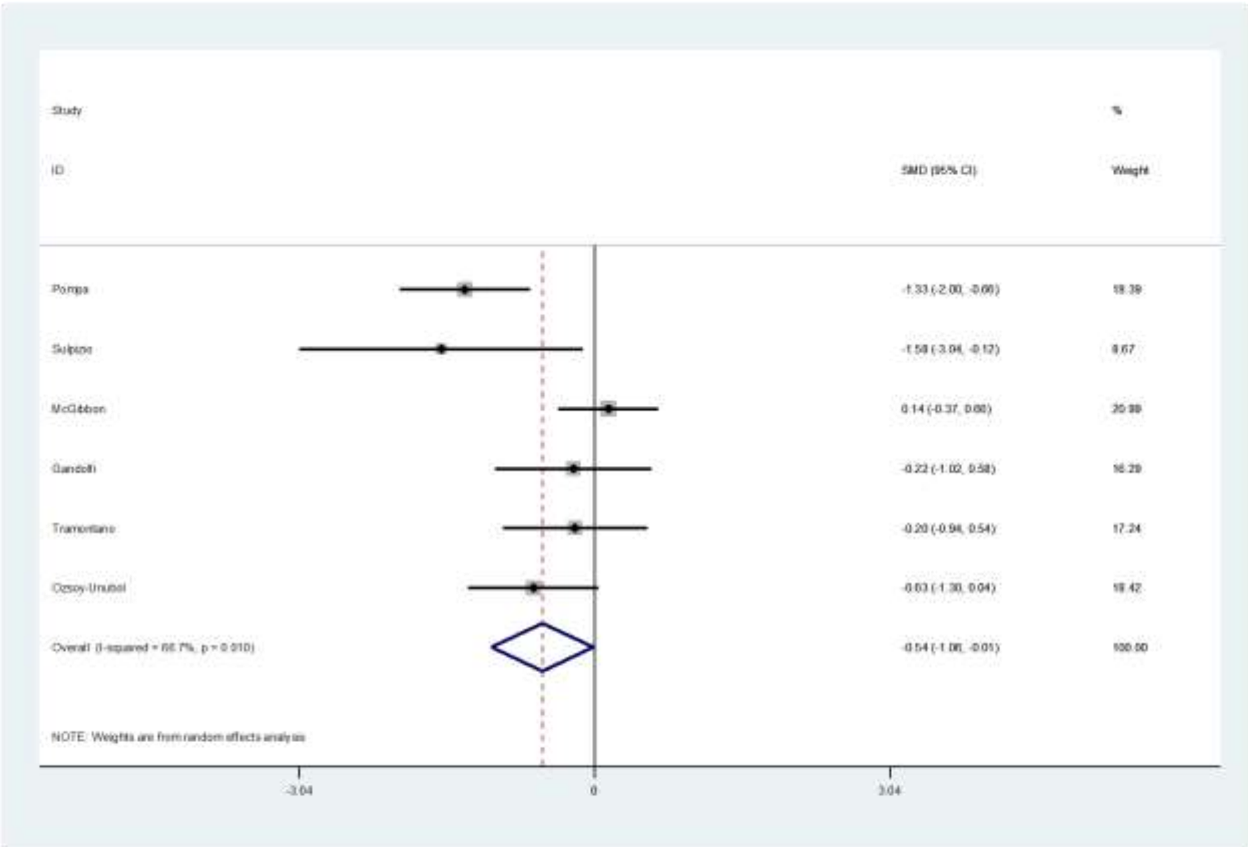

Figure 3. The pooled SMD of FSS

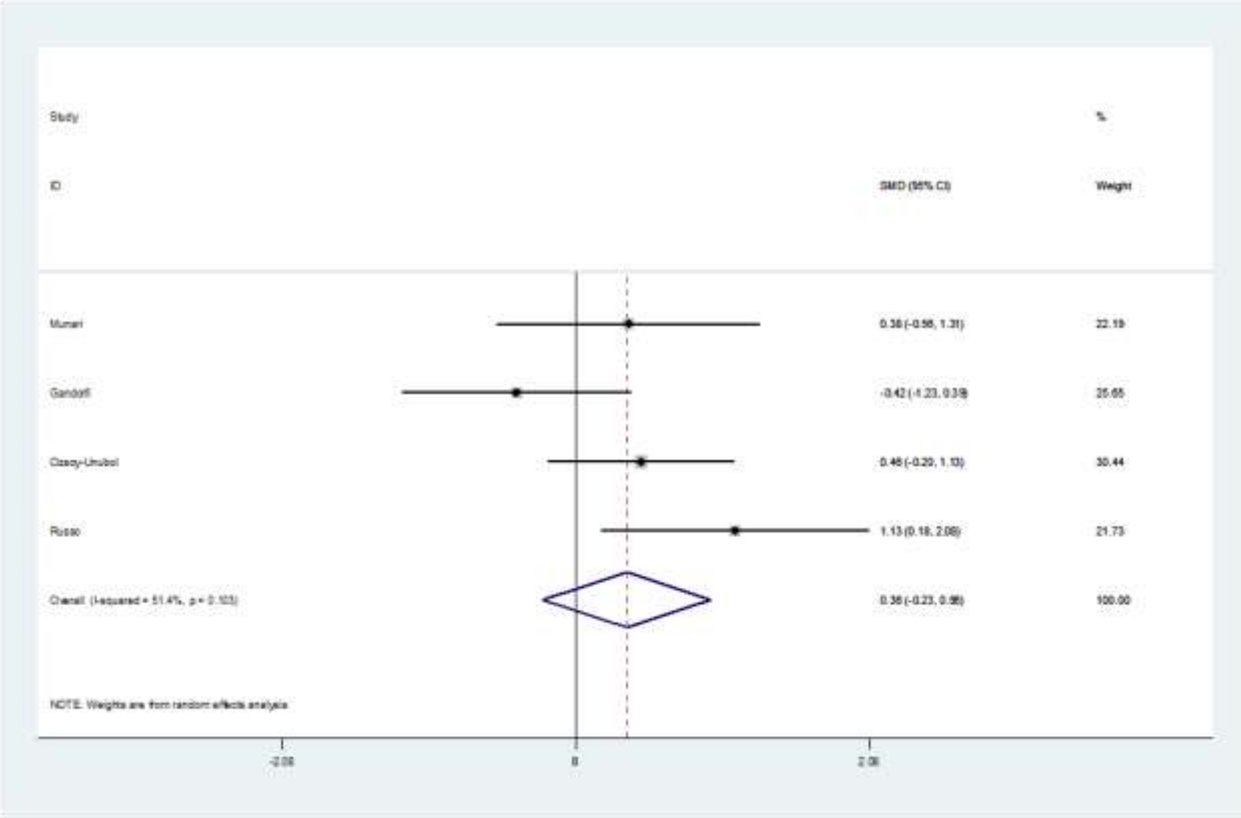

Figure 4. The pooled SMD of physical health subscale of MSQOL54

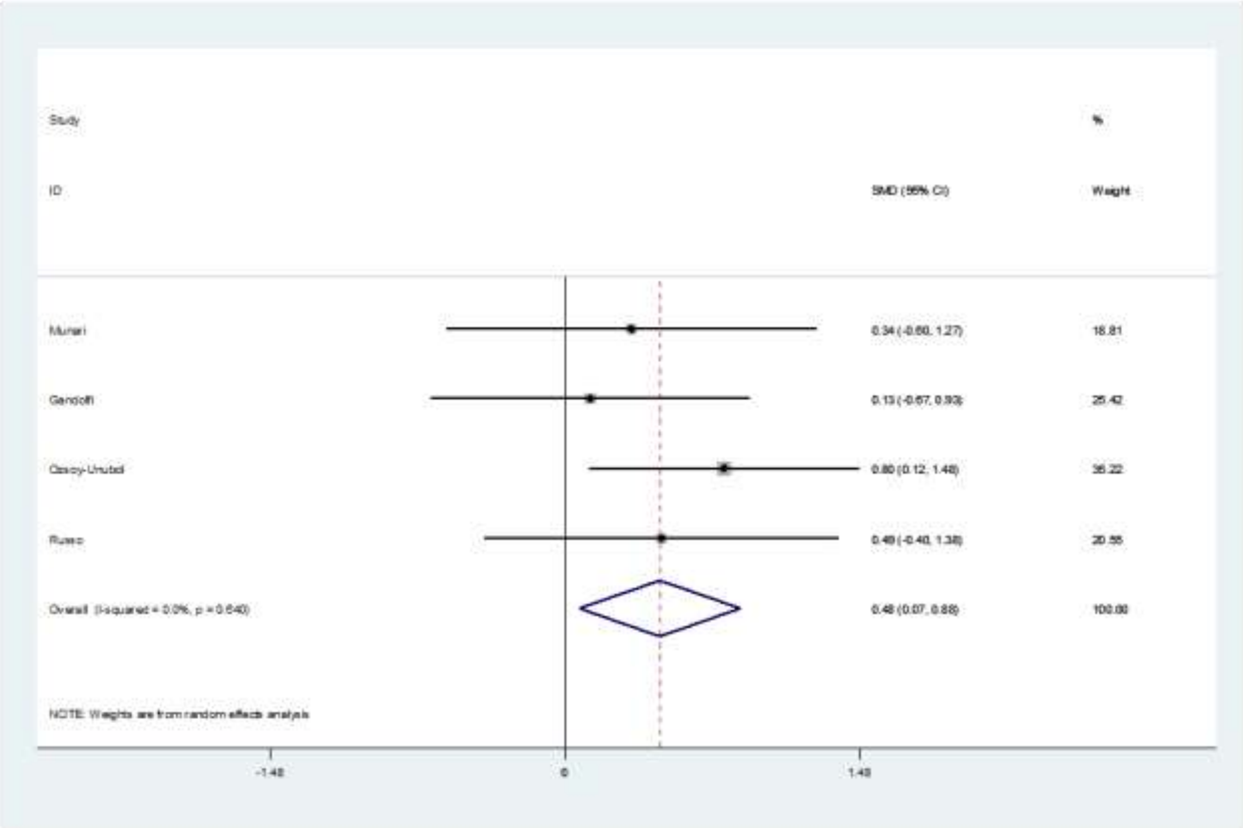

Figure 5. The pooled SMD of mental health subscale of MSQOL54

Table 2. Quality assessment of nan-randomized studies (ROBINS-I)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Bias
Russo et al.	Low	Moderate	Low	Low	Low	Low	Low	Moderate

Table 3. Quality assessment of randomized trials (ROB2)

Study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Pompa et al.	Low	Low	Low	Low	Low	Low
Sulpizio et al.	Some concerns	Low	Low	Low	Low	Some concerns
McGibbon et al.	Some concerns	Low	Low	Low	Low	Some concerns
Gandolfi et al.	Low	Low	Low	Low	Low	Low
Munari et al.	Low	Low	Low	Low	Low	Low
Schwartz et al.	Low	Low	Low	Low	Low	Low
Sconza et al.	Low	Low	Low	Low	Low	Low
Gandolfi et al.	Low	Low	Low	Low	Low	Low
Tramontano et al.	Low	Low	Low	Low	Low	Low
Ozsoy-Unubol et al.	Low	Some concerns	Low	Low	Low	Some concerns

Discussion

The results of this systematic review and meta-analysis showed that robotic rehabilitation is effective in improving disability status, fatigue experience, and also mental health subscale of quality of life score in patients with MS. Ozsoy-Unubol et al. evaluated the effects of robotic rehabilitation in patients with MS and found that it has positive effects on fatigue, which confirms the results of Pompa et al. Pompa et al. evaluated robotic rehabilitation and conventional rehabilitation and found that robotic intervention was more effective in decreasing fatigue severity in patients with MS (21). During robotic rehabilitation, body weight support is done, so positive effects on fatigue is expected. The pooled SMD of FSS was estimated as -0.54, showing that robotic rehabilitation helps patients with MS to overcome fatigue. We also found that the pooled SMD of EDSS estimated significantly negative, showing positive effects of robotic rehabilitation on disability status. Previous studies demonstrated that there is a positive correlation between disability level and fatigue experience in MS, higher disability was associated with higher fatigue experience (22, 23). Patients with higher levels of disability need more attempts to walk or complete their daily activities, so they feel more fatigue. On the other hand, demyelination, inflammation, and axonal injury in MS may lead to both higher level of disability, and fatigue.

One suggestion for fatigue is reduced glucose metabolism in prefrontal cortex and basal ganglia in subjects with MS using fluorodeoxyglucose positron emission tomography (FDG-PET) (24). We found that the pooled SMD of physical health is not significantly improved, while mental health subscale in significantly improved after robotic rehabilitation. MSQOL-54 is a structured, self-report questionnaire containing 14 subscales, and two main subscales physical health, and mental health. Higher the score is related with better quality of life. It has been shown that robotic rehabilitation improves gait, and balance in patients with MS (25).

So, we expected to find significant positive effects on physical health. Gandolfi et al. randomly assigned 22 patients into two groups: 12 in robot-assisted gait training, and 10 in sensory integration balance training. The mean physical health scores before, and after treatment in robotic group were 64, and 60, while mean scores of mental health were 59, and 61, respectively (26). Nowadays, there are different rehabilitation approaches for improving physical, and mental health in patients with MS. Robotics is defined as the application of devices with electronic or computerized systems, which are designed to do human functions (27).

A therapeutic robot can adjust the user's parameters after detecting the parameters, and providing visual, and sensory feedback to the clients (28). Robotic rehabilitation has some advantages: reproducible, easy to control, quantified progression, decreased energy cost, and independency for both the client and the provider (29). So, nowadays, robotic rehabilitation continues to undertake promising development and growth (30). This systematic review has some strengths. First, we analyzed fatigue, quality of life, and disability. Second, the number of included studies was high. It also has some limitations. First, the duration of follow-up was not the same for all included studies. Second, all studies did not provide data regarding all desired outcomes. The results of this systematic review and meta-analysis show that robotic rehabilitation has positive effects on fatigue, and disability in patients with MS.

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None.

Ethics Approval: As this is a systematic review, it does not need any ethics approval.

Funding: None.

Conflict of Interests: Not.

Authors' contribution: ANM: study consneption, data gathering, article writing. MR: data gathering, article writing. MM: data gathering, article writing. AM: data gathering, article writing. MM: data analysis, article writing and editing.

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