

Robotic Rehabilitation for Gait Imbalance in Patients with Multiple Sclerosis (MS): a Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To estimate the pooled effect of robotic rehabilitation on gait in subjects with multiple sclerosis (MS).

Methods: We conducted a systematic search in PubMed, Scopus, EMBASE, IEEE and Web of Science databases on October 1st 2022, without any time or language limitation. Also, we investigated the grey literature, including conference abstract and references of references, to identify potentially relevant articles. The primary outcomes were the six-minute walking test (6MWT) and Timed Up and Go (TUG). The risk of bias in the included studies was evaluated using the Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) and the Cochrane risk-of-bias tool for randomized trials (RoB2). Meta-analyses were performed using a fixed-effects model as the heterogeneity between study results (I^2) was less than 50%. The standardized mean difference (SMD) was calculated as the effect size for study outcomes.

Results: Our systematic search retrieved 6878 studies and, after deleting duplicate results, 5019 articles remained. Two researchers screened the titles and abstracts, with 4942 studies remaining for further screening. After full-text assessment, 12 studies were included for meta-analysis, most of which were conducted in the USA and Italy and were published between 2007 and 2022. The mean age of participants in the selected studies ranged between 46-55 years and the mean expanded disability status scale (EDSS) between 5 and 6.5. The SMD of 6MWT (AFTER-BEFORE) was 0.22 (95% CI -0.01-0.45) ($I^2=0\%$, $P=0.90$). The SMD of TUG (AFTER-BEFORE) was -0.29 (95% CI -0.56, -0.02) ($I^2=0\%$, $P=0.70$).

Conclusion: This systematic review and meta-analysis concluded that robotic rehabilitation was effective for gait rehabilitation in patients with MS.

Keywords: multiple sclerosis, rehabilitation, systematic review.

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INTRODUCTION

Multiple sclerosis (MS) is a neurological disease of the central nervous system (CNS) characterized by demyelination and axonal injury, which affects youth all over the world (1).

Gait problems are common in subjects with MS and it has been estimated that nearly 80% of patients will have mobility and ambulation problems during their lives, affecting their daily activities and quality of life (2). Reduced muscle strength, fatigue, pain, spasticity and disease progression are potential contributors to gait imbalance in individuals with MS (3, 4). Studies showed that around 15 years after the diagnosis of MS, 50% of cases needed walking assistance and 10% would need a wheelchair (5, 6). Patients with CNS disorders and gait imbalance often exhibit decreased step length, reduced walking speed, increased step width and diminished ankle dorsiflexion angle (7, 8).

Different approaches have been used to improve gait in MS such as pharmacotherapies, exercise interventions, conventional physiotherapy (CT) and body weight supported treadmill treatment (BWSTT) (9-11). Conventional walking training (CWT), subsequent treadmill training and traditional over-ground walking training are effective in improving gait balance in cases with MS, but the risk of falling is high if someone is suffering from fatigue (12, 13), while BWSTT has to be manually administered by physical therapists (14).

Recently, advancements in robotics administration in healthcare make rehabilitation robots a promising rehabilitation method for people with physical and cognitive disabilities (15). Robots can enhance communication and interaction between patients and caregivers by offering greater consistency and reduced fatigue (16).

Robotic rehabilitation is a new rehabilitation method for subjects with MS, helping them improve their motor function by applying repetitive movements, which result in the development or restoring motor pathways (17).

Robotic rehabilitation will lead to neuro-muscular adaptations and improvements by increasing muscle strength, not muscle size. Studies on robotic rehabilitation in MS showed positive effects on gait, balance and finally, on the quality

of life (1, 18). Compared to conventional therapies, robotic rehabilitation is more steady and less burdensome for practitioners (13).

Up to now, there have been lots of studies regarding the effects of robotic rehabilitation on subjects with MS but no pooled results. So, we designed this systematic review and meta-analysis to estimate the pooled effect of robotic rehabilitation on gait in subjects with MS. ■

METHODS

The present study was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Eligibility criteria

All randomized controlled clinical trials and non-randomized studies which reported the effect of robotic rehabilitation on gait imbalance in patients with MS were included by us, while letters to the editor, case reports, case-control studies and cross-sectional studies as well as all studies that had no clear data regarding the scores of the walking tests were excluded.

Information sources

Without any limitation, we conducted a comprehensive search on PubMed, Scopus, EMBASE, IEEE and Web of Science databases on October 1st 2022. Also, we investigated the grey literature, including conference abstract and references of references, to identify potentially relevant articles.

Search strategy

A search strategy was designed using MeSH terms and related keywords to conduct a comprehensive search of databases. The keywords were examined by searching relevant articles and consulting experts as follows: ((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])).

Selection process

The search results were transferred to the EndNote reference manager (v 20.0) and one researcher removed duplicate entries. Then, two independent reviewers screened the title/abstract of remaining entries based on pre-defined criteria. Finally, the full text of potentially eligible articles was examined by two independent reviewers to include relevant studies. In case of disagreement on the inclusion of a study, a third reviewer was consulted.

Data collection process

Data collection was performed by two independent researchers using a pre-defined data collection table. The data items were selected based on reviewing previous articles and expert consultation, which included the total number of participants, first author, publication year, country of origin, mean age, gender, disease duration, EDSS, type of robotic intervention, duration of study and results of walking tests.

Risk of bias assessment

Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) and Cochrane risk of bias tool for randomized trials (RoB2) were used to assess the risk of bias in the included studies (19, 20). The assessment was performed by two independent researchers and in case of discrepancy, a third assessor was consulted.

Statistical analysis

All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). Inconsistency (I²) was calculated to determine heterogeneity. We used a fixed-effects model for meta-analysis as the heterogeneity between study results (I²) was less than 50%. Standardized mean difference was calculated as the effect size. To assess publication bias, we applied Begg's and Eger's tests. $\square$

RESULTS

Our systematic search retrieved 6878 studies and, after deleting duplicate results, 5019 articles remained. Two researchers screened the title and abstracts, with 4942 studies remaining for full texts screening. After careful assessment, 12 studies were included for meta-analysis (Figure 1).

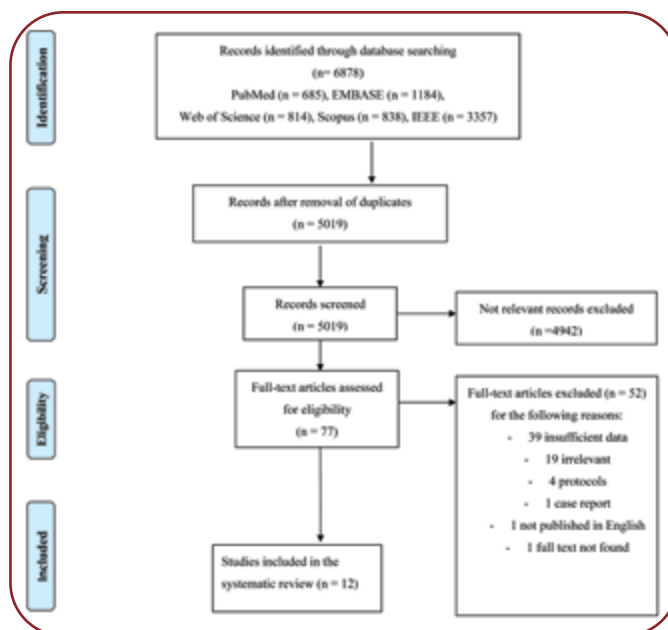


FIGURE 1. Flow chart of study inclusion

TABLE 1.
Data
extracted
from
different
studies

Authors	Country	Year	Participants	Age	Gender	EDSS	Disease duration	Type of robotic intervention	Duration of study	6MWT (m)	TUG (s)	Post	Pre	Post
Straudi <i>et al</i> (9)	Italy	2013	16 (8 Exp, 8 Ctr)	Exp: 49.6±12.0 Ctr: 61.0±8.8	Exp: 4 f, 4 m Ctr: 7 f, 1 m	Exp: 5.8±0.8 Ctr: 5.7±0.7	Exp: 17.1±12.0 Ctr: 18.6±10.8	Robot-assisted gait training	Six weeks	Exp: 210.2±98.6 Ctr: 197.6±93.7	Exp: 25.1±18.9 Ctr: 21.6±11.2	Exp: 19.1±10.1 Ctr: 22.3±10.0	Exp: 25.1±18.9 Ctr: 21.6±11.2	Exp: 19.1±10.1 Ctr: 22.3±10.0
McGibbon <i>et al</i> (10)	Canada	2018	15	48.4±11.4	7 m, 8 f	5.5±1.1	N/A	Exoskeleton Keego	Six weeks	Mean 252.37 (95% CI 216.08-311.75)	Mean 273.81 (95% CI 13.79-1.36)	Mean 14.98 (95% CI 12.56-17.39)	Mean 17.55 (95% CI 13.79-1.36)	Mean 14.98 (95% CI 12.56-17.39)
Afzal <i>et al</i> (21)	USA	2019	10	54.3±12.4	8 f, 2 m	6.55±0.44	15.00±7.10	Exoskeleton Ekso L1	Three weeks	121.2±64.7	128.0±63.4	28.6±13.7	33.4±12.2	28.6±13.7
Lo <i>et al</i> (22)	USA	2008	6	50.2±11.4	3 f, 3 m	5.0±1.6	N/A	BWSTT used in conjunction with a robot-driven gait orthotic	Three weeks	166±57.6	217.3±65.9			
Andrewis <i>et al</i> (23)	USA	2021	10 (6 Exp, 4 Ctr)	Exp: 46.5±5.2 Ctr: 55.0±9.6	Exp: 3 f, 3 m Ctr: 3 f, 1 m	N/A	N/A	Supervised and progressive walking training over-ground in the ground in the RE (Ekso-GT)	Four weeks	Exp: 291.0±103.7 Ctr: 147.5±26.7	Exp: 322.7±129.4 Ctr: 145.7±27.7	Exp: 14.3±7.1 Ctr: 22.8±3.2	Exp: 19.3±10.9 Ctr: 22.4±4.9	Exp: 14.3±7.1 Ctr: 22.8±3.2
Schwartz <i>et al</i> (24)	Israel	2011	28 (12 Exp, 16 Ctr)	Exp: 46.8±11.5 Ctr: 50.5±11.5	Exp: 8 f, 7 m Ctr: 10 f, 7 m	Exp: 6.2±0.5 Ctr: 6±0.6	Exp: 11.3±6.7 Ctr: 14.9±8.1	Robot-assisted gait training	Four weeks	Exp: 125.8±74.7 Ctr: 151.5±92.0	Exp: 133.4±85.1 Ctr: 175.7±119.0	Exp: 28.7±14.2 Ctr: 30.9±28.3	Exp: 34.5±19.9 Ctr: 33.1±28.2	Exp: 28.7±14.2 Ctr: 30.9±28.3
Beer <i>et al</i> (25)	Switzerland	2007	35 (19 Exp, 16 Ctr)	Exp: 49.7±11.0 Ctr: 51.0±15.5	Exp: 12 f, 7 m Ctr: 11 f, 5 m	Exp: median 6.5 (range 6-7.5) Ctr: 6.5 (6-7.5)	Exp: 15±8 Ctr: 15±9	Lokomat with a robot-driven orthosis and Locomobility for body weight support in combination with a Woodway treadmill system	Three weeks	Exp: median 74 (IQR 34-97) Ctr: 87 (62-101)	Exp: median 81 (IQR 44-137) Ctr: 83 (64-145)			
Sconza <i>et al</i> (26)	Italy	2021	17	N/A	16 f, 3 m	N/A	N/A	Lokomat	10 weeks	Exp: 137±84 Ctr: 146±95	Exp: 158±89 Ctr: 159±98			
Straudi <i>et al</i> (27)	Italy	2019	72 (36 Exp, 36 Ctr)	Exp: 56±11 Ctr: 55±11	Exp: 24 f, 12 m Ctr: 25 f, 11 m	Exp: median 6.5 (IQR 6-6.5) Ctr: 6.5 (6-6.5)	Exp: median 12 (IQR 6-19) Ctr: 18 (9-25)	Lokomat	Four weeks	Exp: mean 153 (95% CI 121-185) Ctr: 144 (105-183)	Exp: mean 172 (95% CI 135-209) Ctr: 158 (117-200)	Exp: mean 34.1 (95% CI 22.6-45.8) Ctr: 34.3 (24.6-44.1)	Exp: mean 32.8 (95% CI 22.5-43.2) Ctr: 40.6 (26.1-55.0)	Exp: mean 34.1 (95% CI 22.6-45.8) Ctr: 34.3 (24.6-44.1)
Lee <i>et al</i> (28)	USA	2016	6	55.3±11.2	5 f, 1 m	5.2±2.5	16.0±6.5	Ankle sensorimotor training	Six weeks	235.19±195.01	257.39±215.92	22.88±12.63	25.57±11.42	22.88±12.63
Calabrò <i>et al</i> (29)	Italy	2017	20	Median 44 (range 40-48)	13 f, 7 m	Median 4.4 (range 4-4.9)	Median 11.5 (range 8-16)	Lokomat pro (RAGT+VR)	Eight weeks			Median 7.9 (range 2-15)	Median 10b (range 0-14)	Median 7.9 (range 2-15)
Ozsoy-Unbol <i>et al</i> (30)	Turkey	2022	60 (18 Exp, 19 Ctr)	Exp: 45.05±9.22 Ctr: 44.73±8.43	Exp: 11 f, 7 m Ctr: 13 f, 6 m	Exp: median 6.5 (IQR 5.87-6.62) Ctr: 6 (5.5-6.5)	Exp: 14.1±5.94 Ctr: 13.47±6.21	RoboGait, an automated locomotor therapy system	Four weeks	Exp: median 50 (IQR 30-105) Ctr: 60 (20-120)	Exp: median 70 (IQR 38-122.50) Ctr: 70 (25-132)			

Exp=experiment; Ctr=control; f=female; m=male; 6MWT=six-minute walking test; TUG=Timed Up and Go

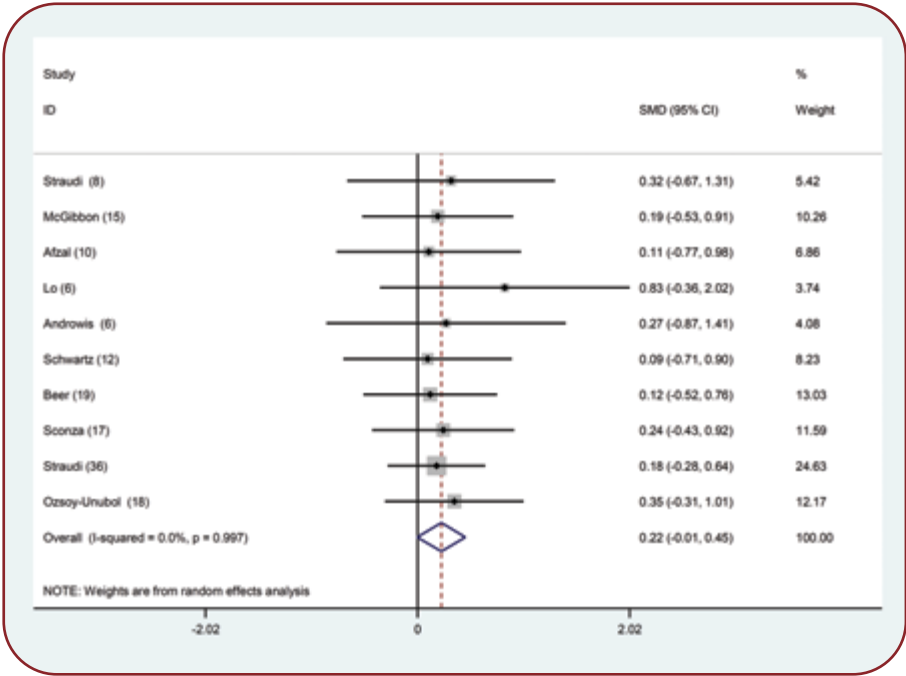


FIGURE 2. The standardized mean difference (SMD) of six-minute walk test (6MWT) (AFTER-BEFORE)

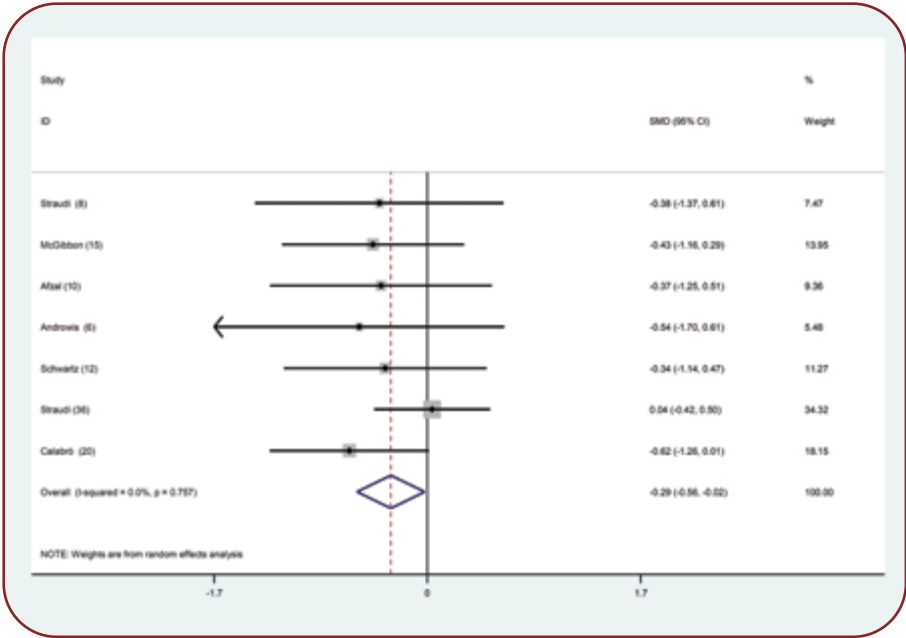


FIGURE 3. The standardized mean difference (SMD) of Time Up and Go (TUG) test (AFTER-BEFORE)

Most studies were conducted in the USA and Italy and were published between 2007 and 2022. Participants' mean age ranged between 46-55 years and the mean EDSS between 5 and 6.5. The duration of intervention ranged between three and ten weeks and the duration of disease between 11.3-18.6 years (Table 1).

The results of Begg's test (Kendall's tau = 0.3333, p = 1.0000) (Kendall's tau = 0.74, p = 0.45) and Eager's tests (t = 0.3912, df = 7,

p = 0.8196) (t = 0.67, df = 5, p = 0.5) showed no publication bias.

The SMD of 6MWT from the included studies ranged between 0.09 and 0.83, while the pooled SMD was estimated as (AFTER-BEFORE) 0.22 (95% CI -0.01–0.45) (I2=0%, P=0.90) (Figure 2).

The SMD of TUG from the included studies ranged between -0.62 and 0.04, while the pooled SMD was estimated as (AFTER-BEFORE) -0.29 (95% CI -0.56, -0.02) (I2=0%, P=0.70) (Figure 3).

TABLE 2.
Quality assessment of non-randomized studies (ROBINS-I)

Study	Bias due to confounding	Bias in selection of participants in 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
Afzal <i>et al</i>	Low	Low	Low	Low	Low	Low	Low	Low
Lee <i>et al</i>	Moderate	Serious	Low	Low	Moderate	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
Straudi <i>et al</i>	Low	Low	Some concerns	Low	Low	Some concerns
McGibbon <i>et al</i>	Low	Low	Low	Low	Low	Low
Lo <i>et al</i>	Low	Low	Low	Low	Low	Low
Andrewis <i>et al</i>	Some concerns	Low	Low	Low	Low	Some concerns
Schwartz <i>et al</i>	Low	Low	Low	Low	Low	Low
Beer <i>et al</i>	Low	Some concerns	Low	Low	Low	Some concerns
Sconza <i>et al</i>	Low	Low	Low	Low	Low	Low
Straudi <i>et al</i>	Some concerns	Low	Low	Low	Low	Some concerns
Calabrò <i>et al</i>	Low	Low	Low	Some concerns	Low	Some concerns
Ozsoy-Unubol <i>et al</i>	Low	Some concerns	Some concerns	Low	Low	Some concerns

TABLE 4. Summary of findings based on GRADE approach

Outcome	Standardized mean difference (95% CI)	No of participants (studies)	Certainty	Conclusion
6MWT	0.22 (95% CI -0.01, 0.45)	269 (eight RCTs, two non-randomized studies)	⊕⊕○○ ¹	The confidence in the effect of robotic rehabilitation on 6MWT is limited. The true effect may be different from the estimated effect.
TUG test	-0.29 (95% CI -0.56, -0.02)	171 (six RCTs, one non-randomized study)	⊕⊕○○ ¹	The confidence in the effect of robotic rehabilitation on TUG is limited. The true effect may be different from the estimated effect.

6MWT=six-minute walk test; RCTs=randomized controlled trials; TUG=Time Up and Go.

¹As the SMD was calculated using data from both RCTs and non-randomized studies, the initial uncertainty was considered low.

The overall risk of bias in the included non-randomized and randomized studies was low (Tables 2 and 3). Table 4 shows the summary of findings based on GRADE approach. □

DISCUSSION

This systematic review and meta-analysis focused on the effects of robotic rehabilitation

on gait impairment in subjects with MS. The results show that robotic rehabilitation significantly improved the 6MWT score and also significantly decreased the TUG score. These findings are indicative of positive effects of robotic rehabilitation on gait imbalance in subjects with MS.

The 6MWT score shows the distance covered over a time of six minutes, which is indicative of performance capacity. An increase in the dis-

tance walked shows basic mobility improvement. The results of the included studies demonstrated that the SMD increased in all, ranging between 0.09 and 0.83. A change of 7-33 meters in walking endurance is considered clinically significant in patients with MS.

We also found that the pooled SMD of TUG test was negative, which indicated that the time patients could use for walking three meters decreased after robotic rehabilitation. In all included studies, except one (Straudi *et al*), the SMD for TUG was negative. In our study, we compared the findings of each group (after and before study findings).

In a study conducted by Straudi *et al*, 16 patients with MS were randomly assigned to either a robotic rehabilitation group or a control group. The results showed that the mean 6MWT improved by 33 meters in the intervention group, while the mean TUG time decreased by six seconds. Their results demonstrated that walking endurance and spatio-temporal gait parameters significantly improved after robotic rehabilitation (9).

In another study by Straudi *et al*, the authors found that 12 sessions of robotic rehabilitation resulted in a 19-meter improvement in walking endurance, reaching the minimal clinically important difference (MCID) (27). Beer *et al* randomly assigned 29 cases with MS into robotic rehabilitation and conventional walking training. They found that robot-assisted gait training was effective in improving walking abilities in subjects with MS suffering from mobility difficulties (25).

Gait and balance impairments are common in MS patients who are prone to falling. Specific

interventions focusing on improving balance in subjects with MS are essential. In recent years, robotic devices are replaced traditional rehabilitation methods using novel rehabilitation programs to improve walking, gait and balance in patients with MS (31). Individually adjusted body weight support and assisted walking have been shown to reduce the experience of central fatigue in individuals with MS. As a result, patients were better able to tolerate longer treatment sessions and experienced reduced anxiety and task-related demands (25). Robotics provides high-intensity, certain motor training, and effective support of walking movements (9).

It should be noted that some patients would not tolerate the intervention for mechanical reasons or skin problems during the program.

This review has two main strengths: it is the first systematic analysis to compare pre- and post-intervention outcomes in receivers of robotic rehabilitation and it incorporates data on both the 6MWT and TUG test.

However, there are also some limitations. First, not all included studies reported outcomes for both the 6MWT and TUG test. Secondly, a direct comparison between robotic intervention and control groups was not performed.

Future systematic reviews and meta-analyses that address these limitations are warranted. □

CONCLUSION

The present systematic review and meta-analysis shows that robotic rehabilitation is effective for gait improvement in patients with MS. □

Conflicts of interest: none declared.

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