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## Research Article

# The Effectiveness of Physiotherapy Interventions for Mobility in Severe Multiple Sclerosis: A Systematic Review and Meta-Analysis

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**Background.** People with Multiple Sclerosis (pwMS) prioritise gait as the most valuable function to be affected by MS. Physiotherapy plays a key role in managing gait impairment in MS. There is little evidence on the effectiveness of physiotherapy for severe MS. **Objective.** To undertake a systematic review and meta-analysis of the literature to identify evidence for the effectiveness of physiotherapy for gait impairment in severe MS. **Methods.** The available literature was systematically searched, using a predetermined protocol, to identify research studies investigating a physiotherapy intervention for mobility in people with severe MS (EDSS  $\geq 6.0$ ). Data on mobility related endpoints was extracted. Meta-analysis was performed where a given mobility end point was reported in at least 3 studies. **Results.** 37 relevant papers were identified, which included 788 pwMS. Seven mobility-related endpoints were meta-analysed. Robot-Assisted Gait Training (RAGT) was found to improve performance on the 6-minute walk test, 10-metre walk test, fatigue severity scale, and Berg Balance Scale. Neither body weight supported training nor conventional walking training significantly improved any mobility-related outcomes. **Conclusion.** Physiotherapy interventions are feasible for mobility in severe MS. There is some evidence for the effectiveness of RAGT.

## 1. Introduction

Multiple Sclerosis (MS) is an inflammatory immune-mediated disease characterised by demyelination of axons within the CNS that is frequent in young adults and commonly causes a lifelong disability [1]. 85% of people with MS (pwMS) are concerned about their gait problems [2], and 80% have gait problems 10-15 years after onset of MS [3, 4]. The problems in gait in pwMS are due to muscle weakness, spasticity, fatigue, ataxia, and loss of proprioception [5]. Impairment of mobility reduces physical activity. pwMS are less physically active compared to the general population. Approximately 78% of pwMS are not involved in regular physical activity [6]. pwMS with more advanced disease (Expanded Disability Status Scale (EDSS) of 6 or higher) have less muscular strength, aerobic fitness, and reduced balance compared to those with less severe disease [7]. The disease burden of MS is exacerbated by secondary

effects of low levels of physical activity, such as obesity, and increased cardiovascular morbidity.

Exercise intervention in the form of regular aerobic, balance, and strengthening exercise has been shown to be particularly effective to improve mobility for pwMS [8, 9]. They improve MS symptoms, overall fitness, mobility, fatigue, and quality of life (QoL). However, most of the interventions targeted mild to moderate MS patients, and the impact of exercise therapies on those with more severe disabilities is yet limited [7]. This reflects the fact that the PT (physiotherapy) programs commonly used to improve mobility are not feasible for this population. In particular, gait training for severely impaired patients is technically challenging because of their motor weakness and balance abnormalities [10].

While there are many studies on PT interventions for pwMS, there are only a limited number of studies on the effect of PT in people with severe MS. In this review, we

TABLE 1: PICO describing inclusion criteria/exclusion criteria.

| Study component | Inclusion criteria   | Exclusion criteria   |
|-----------------|--|--|
| Population      | (1) Diagnosed with Multiple Sclerosis according to McDonald criteria<br>(2) Adults (>18 years old)<br>(3) Severe mobility disability (reported EDSS score > 6.0 or narrative description of mobility disability E.G. use of walking aid) | (1) Not MS patients<br>(2) Paediatric participant (<18 years old)<br>(3) Mild-moderate mobility disability (EDSS < 6.0)  |
| Intervention    | (1) Physical therapy intervention  | (1) Study group includes physiotherapy intervention and concomitant drug or other intervention<br>(2) Study group includes more than one type of physiotherapy |
| Comparism       | No intervention or sham  |  |
| Outcomes        | Paper reports mobility-related endpoints or outcome  | Study reports only nonmobility-related outcomes  |

sought to answer the question: what are the most beneficial PT interventions to improve walking in people with severe MS (EDSS  $\geq 6$ )?

## 2. Methods

The available literature was systematically searched using a predetermined protocol ([https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?RecordID=204284](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=204284)). The PICO framework was used to structure the design of the systematic review and determine the inclusion and exclusion criteria (Table 1). Studies of interest (including randomised controlled trials (RCT), prospective studies, case-control studies, and cohort studies) investigated the effect of a physiotherapy intervention on mobility endpoints for adults (>18 years old), who are diagnosed with MS with severe mobility disability (reported EDSS score  $\geq 6.0$  or narrative description of mobility disability, e.g., use of walking aid). Articles were excluded when written in a language other than English, when more than one intervention (including trials of medication) was used or mobility endpoints were not reported.

**2.1. Search Strategy.** The search strategy and search terms were agreed by 2 researchers (TB and AM) to reflect and address the research question. Titles and abstracts were searched in 3 databases (Scopus, Pedro, and Web of Science) from 2000 till April 2022. The keyword combinations utilised as search terms as follows: “multiple sclerosis” AND “Physical therapy” OR Exercise OR Physiotherapy OR Training OR Rehabilitation OR Neurorehabilitation OR “Virtual reality” OR “Balance training” OR “Robot\* assisted” OR Exoskeleton OR Aerobic OR “Strength training” OR Resistance OR “Treadmill training” OR “Exercise bike” OR Cycling OR Exergaming OR “Tai Chi” OR “Core stability” OR Yoga OR Pilates OR “Assistive device.” Papers were downloaded into EndNote and duplicates removed. Searches were performed in July 2021; repeated in April 2022. Citation lists of included articles were hand searched and identified studies assessed according to the search strategy.

**2.2. Study Screening Process.** Article screening was guided by the preestablished inclusion/exclusion criteria (Table 1).

Two independent reviewers (TB and AM) screened the titles, and 10% of the titles were checked by both reviewers for agreement. Initially, 19 692 papers were identified and 11 884 were removed as duplicates. Title and abstract screening was applied to 7172. The screening process is summarised in Figure 1 (PRISMA chart). Articles, which passed screening, went on to full text evaluation, decisions on inclusion being undertaken in discussion by 2 researchers (TB and AM).

**2.3. Data Extraction.** Table 2 summarizes the participant demographics, intervention characteristics, and pre- and postintervention mobility endpoint data. Studies were grouped according to exercise modalities. All data were collated in Microsoft Excel.

Where studies included a mixed cohort of MS patients with mild, moderate, and severe disease (according to EDSS score) authors were contacted to provide individual data for severe MS participants (Table 3).

**2.4. Data Synthesis and Meta-Analysis.** Cohort demographic descriptive statistics (mean, standard deviation, and range) were calculated using PASW statistics for Windows (IBM). Meta-analysis was completed using the Comprehensive Meta-Analysis software (Biostat, New Jersey). For mobility end-points where results were available for at least 3 studies, meta-analysis was undertaken. Standardised Mean Difference (SMD), 95% confidence intervals and  $Z$ -score for overall effect were calculated using a random effects model. Heterogeneity was assessed with  $I^2$  statistic. Forest plots were generated to visualise the effect of a given PT intervention on mobility end-points. We assessed the robustness of our results in sensitivity analyses by using fixed-effects models, an alternative statistical metric of mean difference (MD), and by repeating meta-analysis with exclusion of the lowest quality study (largest standard error).

For PT interventions where meta-analysis could not be performed, the intervention was included in a vote counting exercise. The PT intervention was counted as successful if it significantly improved at least one mobility related outcome.

Statistical considerations from the Cochrane Handbook for Systematic Reviews of Interventions were followed to handle missing data. In case of missing standard deviation or standard error, we used the formula  $SD = SE \times \sqrt{N}$ . To

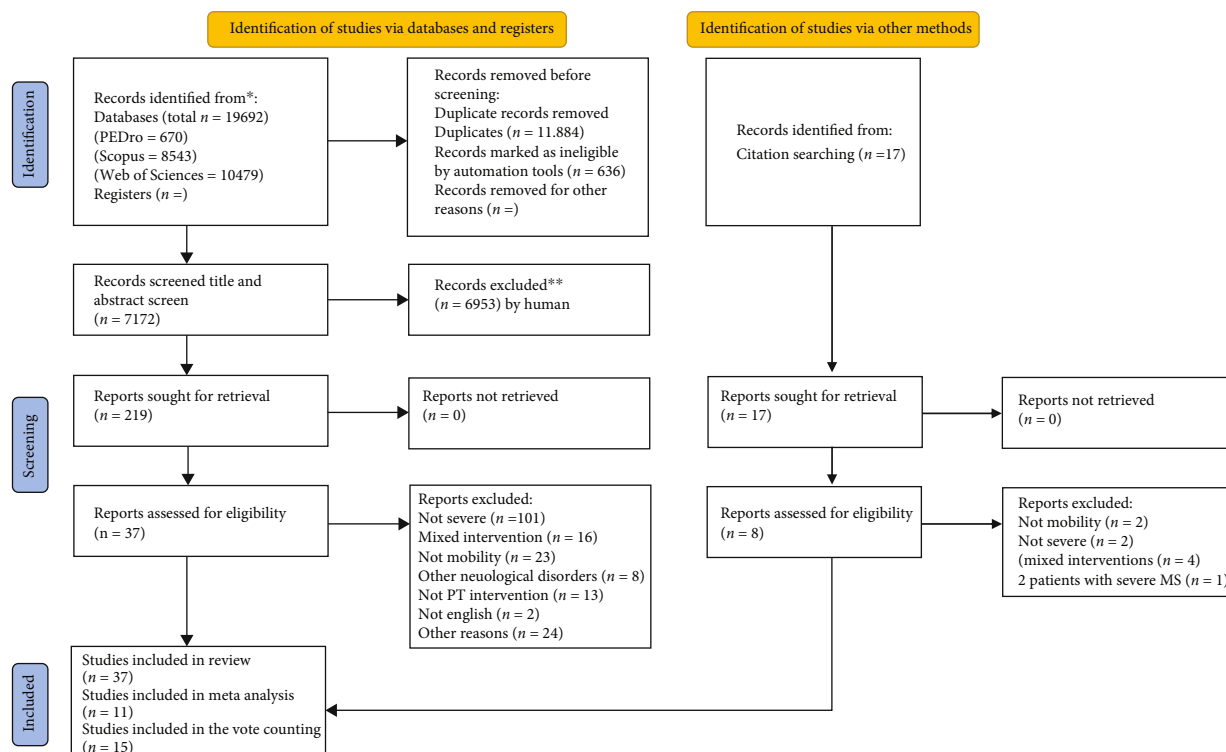


FIGURE 1: PRISMA flow chart (2020). \*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). \*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

obtain the standard deviations in cases where 95% confidence intervals were presented for the small sample size, we followed this formula  $SD = \sqrt{N} \times (\text{upper limit} - \text{lower limit}) / 4.128$ . Where only the median and interquartile ranges are presented. A multiple of 0.75 times the interquartile range or 0.25 times the range was used as a proxy for the standard deviation values, while the median was used as a proxy for the mean.

**2.5. Quality Assessment.** Included studies underwent quality assessment using the Pedro scale (Physiotherapy Evidence database) to assess the methodological quality of the clinical trials (Table 4) [11]. Two reviewers (TB and AM) undertook the quality assessment and resolved differences through discussion.

### 3. Results

**3.1. Study Selection.** A total of 19,692 studies were identified via searches of 3 databases and reference lists (Figure 1). Thirty-seven articles were selected for data extraction (Table 2) [12–48]. In 20 articles, authors were contacted and asked to provide data for severe MS patients from their cohort and only 4 authors responded (Table 3).

**3.2. Critical Appraisal.** Table 2 presents a summary of the 37 included studies. In total, these include 788 MS patients,

with 59.6% female and a mean age of 51.88 (standard deviation 3.54). These studies assessed 11 different PT interventions, including robot-assisted-gait training (RAGT) (17 studies), body-weight-supported treadmill training (BWSTT) (5 studies), home-based-exercise (resistance and task specific training) (2 studies), electrical stimulation (2 studies), conventional exercise training (resistance and aerobic exercise) (3 studies), community-based exercise (1 study), total body recumbent stepper training (1study), blood flow restriction (2 study), exergaming (1study), assistive device training (1 study), community exercise (2 study), and ankle robotic training (1 study). In 7 studies, conventional walking training (CWT) was used in a control arm of severe MS patients.

These studies reported more than 15 distinct mobility endpoints, including 6-minute walk test (6MWT) (16 studies), 25-Foot Walk Test (T25FW) (7 studies), Timed Up and Go (TUG) (11 studies), 10-Meter Walk Test (10WMT) (7 studies), 2-minute walk test (2MWT) (5 studies), step length (4 studies), stance phase (%) (4 studies), swing phase (%) (4 studies), total double support phase (2 studies), stride length (2 studies), 20-meter walk test (1 study), five times sit to stand (1study), fast walking speed (1 study), self-selected walking speed (1 study), step length ratio (SLR) (2 studies), step time (1 study), 3- minute walking speed (1 study). Other mobility-related clinical rating scales reported included the Berg Balance Scale (BBS) (4 studies), the Fatigue Severity

TABLE 2: Main characteristics of studies included in the review (including both cohorts with only severe MS and mixed cohorts).

| Study characteristics                            |    |   | Participant characteristics |                           |                                   |                   | Exercise training characteristics |   |                          |  | Outcomes   |
|--|----|---|-----------------------------|---------------------------|-----------------------------------|-------------------|-----------------------------------|---|--------------------------|--|--|
| Ref. (quality)                                   | n  | Exercise modality                                   | Gender (% F)                | EDSS                      | Disease duration(y) mean $\pm$ SD | Age mean $\pm$ SD | Duration (weeks)                  | Frequency (x/week)  | Time (min/ session)      | Intensity  | Outcomes postintervention  |
| Robot-Assisted Gait Training (RAGT) (17 studies) |    |   |                             |                           |                                   |                   |                                   |   |                          |  |  |
| Andrewis, G. et al. [45]                         | 6  | RAGT  | 50%                         | Ambulation index $\geq 2$ | NR                                | 46.5 $\pm$ 5.2    | 4 weeks                           | 2/week  | 45 min                   | Gradually $\downarrow$ BWS   | $\uparrow$ cognitive function, $\uparrow$ thalamocortical resting-state functional connectivity, $\downarrow$ TUG  |
| Berriozabalgoitia et al. [46]                    | 18 | RAGT+gait training Ex.                              | 50%                         | 4.5-7.0                   | 12.94_8.11                        | 49.8 $\pm$ 7.26   | 3 months                          | 2/week  | 40 min                   | Gradually $\uparrow$ time and $\downarrow$ BWS                           | $\downarrow$ 10WMT, $\uparrow$ balance, $\downarrow$ fatigue, $\downarrow$ TUG   |
| Druzbecki, M et al. [47]                         | 14 | RAGT  | 57%                         | 5-6                       | NR                                | 48.08 $\pm$ 7.6   | 3 weeks                           | 5/week  | 45-60 min                | Gradually $\downarrow$ BWS   | $\leftrightarrow$ balance, $\downarrow$ fatigue, $\downarrow$ T25-FW*  |
| Sconza, C.,et al. [48]                           | 10 | RAGT+general Ex. (cross-over design)                | 84.2%                       | 3.5-7                     | NR                                | (36-74)           | 5 weeks                           | 5/week  | 90 min                   | 40% BWS treadmill speed of 1.5 km ( $\downarrow$ gradually)              | $\uparrow$ 6MWT*, $\downarrow$ EDSS, $\downarrow$ T25FW*, SLR, $\downarrow$ spasticity   |
| Afzal et al. [36]                                | 10 | RAGT  | 80%                         | 6.0-7.5                   | 15 $\pm$ 7.1                      | 54.3 $\pm$ 12.4   | 3 weeks                           | 5/week  | 90 min                   | Gradually $\uparrow$ intensity   | $\leftrightarrow$ 6MWT, $\uparrow$ T25FW-self-selected*, $\leftrightarrow$ T25FW-fast speed, $\downarrow$ NVO2 peak*, $\leftrightarrow$ TUG  |
| Berchicci et al. [37]                            | 5  | RAGT  | 40%                         | 5.0-7.0                   | NR                                | 49.0 $\pm$ 7.3    | 6 weeks                           | 2x/5/week   | 45 min                   | NR   | $\uparrow$ T25FW*, $\uparrow$ 2MWT*, $\uparrow$ Tinetti test*, $\uparrow$ BBS*, $\downarrow$ fatigue*, $\uparrow$ FSS*, $\uparrow$ EBI*, $\downarrow$ EDSS*  |
| Daniele Munaria et al. [42]                      | 8  | RAGT-VR   | 62.50%                      | 3.0-6.0                   | 17.7 $\pm$ 9.62                   | 57 $\pm$ 5.83     | 6 weeks                           | 2/week  | 40 min                   | Gradually $\downarrow$ BWS   | $\uparrow$ 2MWT*, $\downarrow$ 10WMT*, $\uparrow$ mental function*, $\uparrow$ BBS*, $\downarrow$ sway area*   |
| Manfredini et al. [41]                           | 23 | RAGT  | 67%                         | 6.0-7.0                   | 13.30 $\pm$ 6.55                  | 56 $\pm$ 10       | 6 weeks                           | 2/week  | 40 min                   | Gradually $\uparrow$ (distance, speed), $\downarrow$ guidance force      | $\uparrow$ 6MWT*, improve mitochondrial function biomarker, $\uparrow$ rmVO2   |
| Straudi et al. [43]                              | 36 | RAGT  | 67%                         | 6.0-7.0                   | 12 (6-9)                          | 56 $\pm$ 11       | 4 weeks                           | 3/week  | 120 min                  | Gradually $\uparrow$ (distance, speed), $\downarrow$ guidance force      | $\downarrow$ T25FW*, $\uparrow$ 6MWT*, $\downarrow$ TUG, $\uparrow$ PHQ-9, $\downarrow$ FSS, $\uparrow$ balance*, $\uparrow$ QoL, $\uparrow$ mental health*  |
| McGibbon et al. [34]                             | 35 | Home lower exoskeleton (Keeogo) (cross-over design) | 58.60%                      | 4-6.5                     | NR                                | 49.2 $\pm$ 10.6   | 6 weeks                           | 4 weeks at home (2 weeks with Keeogo, 2 weeks without Keeogo) | All the day              | NR   | 6 MWT + Keeogo < without Keeogo, TUG + Keeogo > TUG without Keeogo*, TST + Keeogo > TST without Keeogo; post 2 weeks with Keeogo at home $\rightarrow$ $\uparrow$ unassisted 6MWT distance*, $\uparrow$ unassisted stair climbing performance* |
| Pompa et al. [31]                                | 25 | RAGT  | 47.60%                      | 6.0-7.5                   | 17.05 $\pm$ 9.12                  | 47.00 $\pm$ 11.17 | 4 weeks                           | 3/week  | 40                       | 40-50% BWS ( $\downarrow$ gradually)                                     | $\uparrow$ 2MWT*, $\uparrow$ FAC*, $\downarrow$ EDSS*, $\downarrow$ FSS**, $\uparrow$ RMI**, $\uparrow$ mBI**, $\downarrow$ VAS*   |
| Straudi et al. [29]                              | 30 | RAGT  | 62.90%                      | 6.0-7.0                   | 13.30 $\pm$ 6.55                  | 52.26 $\pm$ 11.11 | 6 weeks                           | 2/week  | 60 min (30: walking)     | 100% guidance +50% BWS ( $\downarrow$ gradually)                         | $\uparrow$ 6MWT*, $\downarrow$ 10WMT, $\uparrow$ BBS*, $\downarrow$ PHQ-9*, $\uparrow$ QoL*, $\downarrow$ FSS  |
| Straudi et al. [24]                              | 9  | RAGT  | 50%                         | 4.5-6.5                   | 17.1 $\pm$ 12.0                   | 49.6 $\pm$ 12.0   | 6 weeks                           | 2/week  | 60 min (30 min/ walking) | Gradually ( $\uparrow$ distance, speed), ( $\downarrow$ guidance force)  | Improvements in spatiotemporal parameters ( $\uparrow$ gait speed*, $\uparrow$ cadence*, $\downarrow$ double support*, $\downarrow$ step length* and step time*), $\uparrow$ 6MWT*   |
| Claude Vaney et al. [23]                         | 26 | RAGT  | NR                          | 3.0-6.5                   | NR                                | 58.23 (9.42)      | 3 weeks                           | 3/week  | (30 min/ walking)        | 50% BWS ( $\downarrow$ gradually), $\uparrow$ speed to normal gait speed | $\uparrow$ QoL*, $\uparrow$ 3-minute walking speed*, $\downarrow$ fatigue*, $\uparrow$ balance*, $\downarrow$ spasticity*, $\downarrow$ activity level, $\leftrightarrow$ 10WMT, $\leftrightarrow$ RMI, $\leftrightarrow$ pain level           |
| Schwartz et al. [22]                             | 15 | RAGT  | 57%                         | 5.5-7                     | 11.3 $\pm$ 6.7                    | 46.8 $\pm$ 12.0   | 4 weeks                           | 2-3/week  | 45 min (30 min/ walking) | 40% BWS ( $\downarrow$ gradually)  | $\uparrow$ 6MWT, $\downarrow$ 10WMT, $\downarrow$ TUG*, $\uparrow$ BBS*, $\downarrow$ EDSS*, $\uparrow$ FIM**  |
| Beer et al. [14]                                 | 19 | RAGT  | 63.20%                      | 6.0-7.5                   | 15.0 $\pm$ 8.0                    | 49.7 $\pm$ 11.0   | 3 weeks                           | 5/week  | 30 min                   | 40-80% BWS, gradually $\uparrow$ (distance, speed), $\downarrow$ BWS     | $\uparrow$ 20 m walking velocity*, $\uparrow$ 6MWT*, $\uparrow$ knee extensor strength*, $\uparrow$ EBI*   |
| Lo et al. [15]                                   | 13 | RAGT+BWST (cross-over design)                       | 48% F                       | 3.0 -7.0                  | NR                                | 49.8 $\pm$ 11.1   | 6 weeks (3 weeks/ phase)          | 2/week  | 40 min                   | 30%-40% BWS ( $\downarrow$ gradually), $\uparrow$ speed                  | $\downarrow$ T25FW**, $\uparrow$ 6MWT*, $\downarrow$ DST**, $\downarrow$ EDSS**, SLR   |

TABLE 2: Continued.

| Study characteristics  |    | Participant characteristics                |        |                             | Exercise training characteristics |             |            |  |   | Outcomes   |  |
|--|----|--|--------|-----------------------------|-----------------------------------|-------------|------------|--|---|--|--|
| Body weight-supported treadmill training (BWSTT) (5 studies) |    |  |        |                             |                                   |             |            |  |   |  |  |
| Devasahayam et al. [39]                                      | 10 | BWSTT+ cooling room (16°C)                 | 90%    | 6.0-7.0 (sensitive to heat) | 17.6 ± 10.17                      | 53.2 ± 15.6 | 10 weeks   | 3/week   | 40 min  | Gradually increased to vigorous intensity (40–65% HRR)         | ↑fast walking speed*, ↑self – selected walking speed, ↓stance phase (%), ↓swing phase (%), ↓total double support phase, ↓T25FW*, ↓mFIS*, ↓FSS, ↑QoL, ↑aerobic fitness, ↓fatigue* |
| Willingham et al. [35]                                       | 6  | BWSTT+ antigavity treadmill training       | 50%    | 6.0-6.5                     | NR                                | 50 ± 4.9    | 8 weeks    | 2/week   | 20 min  | 35%-70% BWS, speed (0.2 – 2.5 mph) < RPE of 8.0                | ↑muscle oxidative capacity*, ↑muscle endurance*, ↑2 MWT  |
| Jonsdottir et al. [32]                                       | 26 | BWSTT if needed +dual task training        | 44.70% | 3.5–7                       | 16.3 ± 7.1                        | 51.4 ± 10.7 | 4 weeks    | 5/week   | 30 min  | ↑treadmill speed + slope = 14 –16 RPE                          | ↑2MWT**, ↓10WMT, ↓TUG*, ↑DGI*  |
| Pilutti et al. [20]  | 6  | BWSTT                                      | 66%    | 5.5–8.0                     | 11.5 ± 6.60                       | 48.2 ± 9.30 | 12 weeks   | 3/week   | 30 min  | Gradually ↑ speed, ↓ BWS                                       | ↓ T25-FW, ↓ fatigue, ↑ QoL, ↓ EDSS   |
| Giesser et al. [13]  | 4  | BWSTT                                      | 75%    | 7.0-8.0                     | 20 ± 5                            | 47 ± 5.3    | 20 weeks   | 2/week   | 60 min  | 100% BWS (↓ gradually), ↑ speed to normal gait speed           | ↓ 10WMT, ↑ 6MWT, ↑ balance, ↑ QoL, ↓ spasticity, ↑ muscle strength (not all patients were able to complete the 10WMT, 6MWT)  |
| Total-body recumbent stepper training (TBRST) (1 study)      |    |  |        |                             |                                   |             |            |  |   |  |  |
| Pilutti et al. [28]  | 5  | TBRST                                      | 40%    | 6.0-8.0                     | 15.2 ± 8.9                        | 58.8 (3.0)  | 12 weeks   | 3/week   | 30 min  | Gradually ↑ according to participant ability                   | ↓ fatigue, ↑ QoL, ↔ T25FW  |
| Home-based exercise (2 studies)                              |    |  |        |                             |                                   |             |            |  |   |  |  |
| de Bolt et al. [12]  | 19 | Home based resistance Ex.                  | 78.95% | 1.0 – 6.5.                  | 15 ± 12.23                        | 51.6 ± 7.26 | 8 weeks    | 3/week   | 50 min  | Resistance by 0.5% of body weight, ↑ (.05%–1.5%) every 2 weeks | ↓ TUG, ↑ leg extensor power*, ↑balance,  |
| Miller et al. [19]   | 15 | Home Ex. of task-specific programme        | 73.30% | 6.5–8                       | 13 ± 9.1                          | 56.3 ± 9.0  | 8 weeks    | 2/week   | 60 min  | NR   | ↑ MSIS-29, ↓ 10WMT, ↑ muscle strength, ↓ timed sit-stand, ↓ EDSS, ↓ FIM  |
| Electrical stimulation (2 studies)                           |    |  |        |                             |                                   |             |            |  |   |  |  |
| JE Esnouf et al. [17]  | 32 | FES (ODFS)                                 | 61.50% | 4.0-6.5                     | 12.5                              | 53          | 18 weeks   | Daily mobility   | All the day   | NR   | ↓ effort for walking, ↓ tripping, ↑ confidence while walking, ↑ walking distance   |
| CL Barrett et al. [16]                                       | 25 | FES (ODFS)                                 | 75%    | 4.0-6.5                     | 13.6 ± 8.3                        | 52.1 ± 6.7  | 18 weeks   | Daily mobility   | All the day   | Gradually to be worn all the day                               | ↑ walking speed, ↑ walking distance, ↔ physiological cost index  |
| Blood flow-restriction (2 study)                             |    |  |        |                             |                                   |             |            |  |   |  |  |
| Chotiyarnwong, C et al. [38]                                 | 39 | Remote ischaemic preconditioning (RIPC)    | 44.7%  | 1.0-7.0                     | 10 ± 10.6                         | 47.6 ± 11.3 | 1 session  | Blood pressure cuff inflated to (30 mm Hg) above resting systolic pressure | Inflation for 5 min followed by deflation for 5 min/3 | NR   | ↑6MWT*, ↑walking speed*, ↓Borg RPE test  |
| Lamberti et al. [40]   | 12 | Blood flow restricted slow walking (BFR-W) | 46%    | 6.1 ± 0.2                   | 14 ± 9                            | 54 ± 11     | 6 weeks    | 2/week   | 60 min  | ↑ speed by 3 steps/min, BFR stable                             | ↑walking speed*, ↓perceived exertion*, ↑6MWT*, ↓MSIS – 29 (psychological)*, ↓MSIS – 29 (motor), ↓MFIS*, ↓5STS time*  |
| Conventional exercise training (3 studies)                   |    |  |        |                             |                                   |             |            |  |   |  |  |
| Resistance training  |    |  |        |                             |                                   |             |            |  |   |  |  |
|  | 12 | Arm Ergometry                              | 50%    | 4.0-6.0                     | 17.1 ± 7.2                        | 49.1 ± 8.5  | 8-10 weeks | 2-3/week   | 15-45 min   |  | ↑6MWT*, ↓fatigue*, ↓depression*  |
| S Briken et al. [25]   | 12 | Rowing                                     | 36.60% | 4.0-6.0                     | 14.1 ± 6.1                        | 50.9 ± 9.2  | 8-10 weeks | 2-3/week   | 15-45 min   | Gradually increase   | ↔ 6MWT   |
|  | 12 | Bicycle ergometry                          | 54.50% | 4.0-6.0                     | 13.3 ± 5.4                        | 48.8 ± 6.8  | 8-10 weeks | 2-3/week   | 15-45 min   |  | ↑6MWT*, ↑VO2 peak*, ↓depression*   |



TABLE 2: Continued.

| Study characteristics   |    | Participant characteristics             |        |                                       |             | Exercise training characteristics |          |        |           | Outcomes  |   |
|---|----|---|--------|---------------------------------------|-------------|-----------------------------------|----------|--------|-----------|---|---|
| Hayes et al. [18]   | 11 | Lower limb resistance ex                | 55.50% | 3.5-6.5                               | 11.9 ± 7.3  | 48.0 (11.9)                       | 12 weeks | 3/week | 45-60 min | Gradually increase                                  | ↑ lower limb strength, ↔ TUG, ↔ 10WMT, ↔ 6MWT, ↑ balance, ↔ fatigue   |
| Aerobic exercise  |    |   |        |                                       |             |                                   |          |        |           |   |   |
| Jackson et al. [21]   | 15 | Kick boxing                             | 81.80% | 1.0-6.0                               | 12.09 ± 5.5 | 52.27 ± 8.8                       | 5 weeks  | 3/week |           | Gradually increased ≤75% HRR or ≤5 RPE              | ↑gait speed*, ↓TUG*, ↑balance, ↑Mini – BESTest*   |
| Exergaming (1 study)  |    |   |        |                                       |             |                                   |          |        |           |   |   |
| Robinson et al. [27]  | 20 | (Exergaming) Nintendo Wii Fit           | 70%    | 6.00                                  | NR          | 52.6 ± 6.1                        | 4 weeks  | 2/week | 40-60 min | ↑ difficulty  | ↓ postural sway, ↑ balance, ↑ step length, ↑ stride length, ↓ MSWS-12   |
|   | 18 | Balance training                        | 63%    | 6.00                                  | NR          | 53.9 ± 6.5                        | 4 weeks  | 2/week | 40-60 min | ↑ difficulty  | ↓ postural sway, ↑ balance, ↑ step length, ↑ stride length, ↓ MSWS-12   |
| Assistive device selection, training and education program (ADSTEP) (1 study) |    |   |        |                                       |             |                                   |          |        |           |   |   |
| Martini et al. [33]   | 20 | ADSTEP                                  | 14%    | 6.0 ± 0 (history of fall)             | NR          | 56.0 ± 9                          | 6 weeks  | 1/week | 40 min    | Aid selection, fitting, task-oriented gait training | ↓falling*, ↓time spent setting*, ↔ TUG, ↔ T25FW, ↔ 2MWT, ↔ FSS, ↓MSWS – 12, ↓MSIS – 29, ↑walking aid satisfaction |
| Community exercise (2 study)  |    |   |        |                                       |             |                                   |          |        |           |   |   |
| KL Williams et al. [44]   | 26 | Community group exercise                | 65.4%  | 0-5 disease step rating scale         | 12.4(10.2)  | 52.7(11.9)                        | 8 weeks  | 2/week | 60 min    | ↑intensity  | ↑ 6MWT, ↑ 10WMT, ↑ balance  |
|   | 66 | Group physiotherapy                     | 62.50% |                                       | 18(9)       | 57 (10)                           | 10 weeks | 1/week | 60 min    | Increase the set of (12 repetitions)                | ↑6MWT, ↑balance**, ↑QOL*, ↓MSIS – 29v2 physical component*, ↓MFIS*  |
| Hogan et al. [26]   | 45 | 1:1 physio-therapy                      | 57%    | 3–4 on the mobility section of (GNDS) | 13(8)       | 52 (11)                           | 10 weeks | 1/week | 60 min    | Increase the set of 12 repetitions                  | ↑balance**, ↑QOL*, ↓MSIS – 29v2 physical component*, ↓MSIS – 29v2 psychological component*, ↓MFIS*, ↑6MWT*        |
|   | 16 | Yoga                                    | 61.50% |                                       | 15(8)       | 58 (8)                            | 10 weeks | 1/week | 60 min    | NR  | ↑balance**, ↑QOL, ↓MSIS – 29v2 physical component, ↓MSIS – 29v2 psychological component, ↓MFIS, ↑6 MWT            |
| Ankle robotic training (1 study)  |    |   |        |                                       |             |                                   |          |        |           |   |   |
| Lee Y et al. [30]   | 7  | Ankle robotic training for impaired leg | 83.30% | 5.2 ± 2.5                             | 16.0 ± 6.5  | 55.3 ± 11.2                       | 6 weeks  | 3/week | 45 min    | NR  | ↑ROM*, ↑balance*, ↑walking performance, ↑6MWT*, ↓10WMT*   |

2MWT: 2 minutes walking test; 5TST: 5-time sit to stand; 6MWT: 6 min walk test; 10WMT: Ten-Meter Walking Test; ADSTEP: Assistive Device Selection Training and Education Program; BBS: Berg Balance Scale; BFR-W: Blood flow-restricted slow walking; BWS: body weight support; BWST: body weight supported training; DGI: dynamic gait index; DST: double support time; EBI: Extended Barthel Index; EDSS: Expanded Disability Status Scale; FAC: Functional Ambulation Category; FSS: Fatigue Severity score; FES: functional electrical stimulation; FSST: Four Square Step Test; FIM: Functional Independence Measure; GNDS: The Guy's Neurological Disability Scale; MAS: Modified Ashworth Scale; mBI: modified Barthel Index; mFIS: modified Fatigue Impact Scale; Mini-BESTest: mini Balance Evaluation System Test; MSIS-29: multiple sclerosis impact scale; MSWS: Multiple Sclerosis Walking Scale questionnaire; ODFS: Odstock dropped foot stimulator; PHQ: patient health questionnaire; QoL: quality of life; RAGT: Robot-Assisted Gait Training; RAGT-VR: Robot-Assisted Gait Training combined with Virtual Reality; rmVO2: resting muscle oxygen consumption; RMI: Rivermead Mobility Index; ROM: range of motion; RPE: rating of perceived exertion; SLR: step length ratio; TBRST: Total-Body Recumbent Stepper Training; T25FW: timed 25-foot walk test; TST: timed stair test; TUG: Timed Up and Go; VAS: Visual Analogue Scale; VO2peak: peak oxygen consumption; NR: not reported. Disease duration in years presented in mean ± SD, otherwise Mean (range). Abbreviations are presented in an alphabetical order. \*Statistically significant at  $p \leq 0.05$  or \*\* $p \leq 0.001$ .

TABLE 3: List of authors who we contacted for data and who responded.

| No. | Authors                        | Responded |
|-----|--------------------------------|-----------|
| 1.  | Androwis, G. J., et al. [45]   | No        |
| 2.  | Berriozabalgoitia, et al. [46] | No        |
| 3.  | Druzicki, M., et al. [47]      | No        |
| 4.  | Sconza, C., et al. [48]        | No        |
| 5.  | Chotiarnwong, C., et al. [38]  | Yes       |
| 6.  | Berchicci et al. [37]          | No        |
| 7.  | CL Barrett et al. [16]         | No        |
| 8.  | Claude et al. [23]             | No        |
| 9.  | Daniele et al. [42]            | Yes       |
| 10. | De Bolt et al. [12]            | No        |
| 11. | Hayes et al. [18]              | No        |
| 12. | Jackson et al. [21]            | Yes       |
| 13. | JE Esnouf et al. [17]          | No        |
| 14. | Jonsdottir et al. [32]         | Yes       |
| 15. | Lee et al. [30]                | No        |
| 16. | Lo et al. [15]                 | No        |
| 17. | McGibbon et al. [34]           | No        |
| 18. | S Briken et al. [25]           | No        |
| 19. | Straudi et al. [24]            | No        |
| 20. | Berchicci et al. [37]          | No        |

Scale (FSS) (10 studies), and Multiple Sclerosis Impact Scale (MSIS-29) (6 studies).

From 17 distinct mobility-related endpoints that were reported, only the 6MWT, T25FWT, TUG, 10WMT, BBS, and FSS were described in at least 3 studies of the same PT intervention to enable meta-analysis to be undertaken. We meta-analysed mobility-related endpoints that are related to patients' ambulation, to investigate which PT intervention could alleviate issues that affect mobility in pwMS.

**3.3. Quality Assessment.** Using the Pedro scale, 1 study was rated "excellent" (score 9-10), 12 studies were rated "good" (score 8-6), 15 studies were rated "fair" (score 6-4), and 9 studies were rated "poor" (score <4). The quality assessment is summarised in Table 4.

### 3.4. Meta-Analysis Results

**3.4.1. Robot-Assisted Gait Training (RAGT).** Five studies [14, 22, 29, 36, 43] reported the effect of RAGT on the 6MWT ( $n = 96$  patients), with a significant improvement post-intervention (SMD 0.444, 95% CI [0.199-0.689],  $p \leq 0.001$ ,  $I^2 = 19.49\%$ ) (Figure 2(a)). The mean increase in 6MWT of all included studies achieved the MCID with a 7% increase in the distance walked except for one study by Afzal et al. [36]. After sensitivity analysis by excluding the lowest quality studies [22, 36], the result remained statistically significant (SMD 0.498, 95% CI [0.124-0.873],  $p = 0.009$ ,  $I^2 = 58.43\%$ ). An alternative analysis using the fixed model and the mean difference showed similar results (MD 9.030, 95% CI [4.944-13.117],  $p \leq 0.001$ ,  $I^2 = 38.92\%$ ).

Three studies [22, 29, 42] reported the effect of RAGT on the 10WMT ( $n = 34$  patients), with a significant effect post-intervention (SMD 0.424, 95% CI [0.072-0.777],  $p = 0.018$ ,  $s\%$ ) (Figure 2(b)). Four studies [22, 29, 36, 43] described a nonsignificant effect of RAGT on TUG ( $n = 76$  patients) (SMD 0.2, 95% CI [-0.056-0.52],  $p = 0.155$ ,  $I^2 = 24.9\%$ ) (Figure 3(a)).

Three studies [29, 31, 43] reported a significant effect of RAGT on the FSS postintervention ( $n = 82$  patients) (SMD 0.54, 95% CI [0.027-1.06],  $p = 0.039$ ,  $I^2 = 77.7\%$ ) (Figure 3(b)). Sensitivity analysis by using the fixed model and the mean difference showed also similar results (MD 0.596, 95% CI [0.350-0.843],  $p \leq 0.001$ ,  $I^2 = 85.39\%$ ).

Three studies [29, 42, 43] reported a significant effect of RAGT on the BBS post-intervention ( $n = 64$  patients) (SMD 0.46, 95% CI [0.06-0.863],  $p = 0.024$ ,  $I^2 = 43\%$ ) (Figure 3(c)). Sensitivity analysis by using the fixed model and the mean difference showed also similar results (MD 2.646, 95% CI [1.330-3.962],  $p \leq 0.001$ ,  $I^2 = 0\%$ ).

**3.4.2. Body Weight-Supported Treadmill Training (BWSTT).** Three studies [20, 28, 39] described the effect of BWSTT on the T25FW for ( $n = 21$  patients), showing no significant effect of intervention (SMD 0.242, 95% CI [-0.192-0.677],  $p = 0.275$ ,  $I^2 = 0\%$ ) (Figure 4(a)).

**3.4.3. Conventional Walking Training (CWT).** Five studies [14, 22, 29, 40, 43] examined the effect of CWT on the 6mwt for ( $n = 91$  patients), showing no significant effect (SMD 0.162, 95% CI [-0.046-0.369],  $p = 0.127$ ,  $I^2 = 0\%$ ) (Figure 4(b)).

**3.5. Vote Counting Results.** 16 interventions from 15 studies (Table 5) were included in the vote counting (RAGT [41], RAGT+VR [42], CWT [31, 41], BWSTT+antigravity treadmill training [35], BWSTT [13], BWSTT+dual tasks [32], blood flow restriction [38, 40], total body recumbent stepper training [28], home exercise [19], exergaming [27], balance training [27], ADSTEP [33], group physiotherapy [26, 44], 1:1 physiotherapy [26], yoga [26], and kickboxing [21]).

Seven interventions from 6 studies were defined as beneficial in improving mobility in severely disabled MS patients (RAGT, CWT, BWSTT+ dual task training, BFR, group physiotherapy, 1:1 physiotherapy and Yoga) [26, 31, 32, 40, 41, 44].

The significant findings from the vote counting results can be summarised as follows: A study by Manfredini et al. [41] showed that RAGT and CWT significantly increased the distance in 6MWT. The Rivermead Mobility Index was significantly improved post CWT in severely disabled MS patients [31]. A study by Jonsdottir et al. [32] reported that a treadmill with dual task training significantly improved 2MWT. Blood flow restricted walking study demonstrated a significant improvement in the 6MWT, walking speed, 5 time sit to stand, and FSS [40]. In addition, a study by Williams et al. [44] found that group physiotherapy significantly improved the 10WMT. Hogan et al.'s study [26] with three intervention groups showed that individual physiotherapy significantly improved 6MWT, balance, and fatigue and

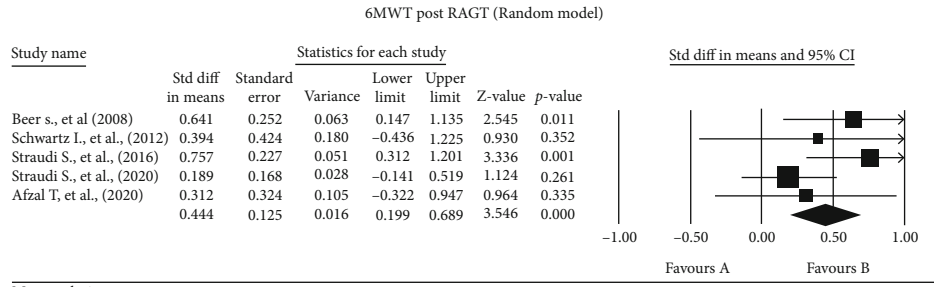


TABLE 4: Pedro scores for included studies (total score out of 10).

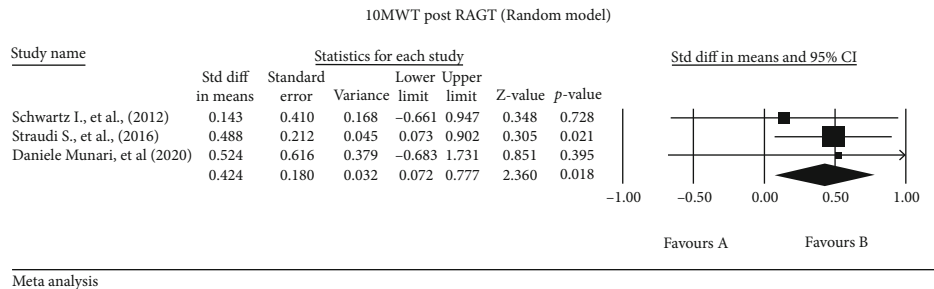
| No. | Study                         | Score (out of 10) | Eligibility criteria (external validity) | Random allocation | Concealed allocation | Group similar in baseline | Participant blinding | Therapist blinding | Assessor blinding | <15% dropout | Intention-to-treat | Between-group difference | Point estimate and variability |
|-----|-------------------------------|-------------------|--|-------------------|----------------------|---------------------------|----------------------|--------------------|-------------------|--------------|--------------------|--------------------------|--------------------------------|
|     | Afzal, et al. [36]            | 2                 | Y  | N                 | N                    | N                         | N                    | N                  | N                 | Y            | N                  | N                        | Y                              |
|     | Androwis, G. J., et al. [45]  | 5                 | Y  | Y                 | N                    | N                         | N                    | N                  | Y                 | Y            | N                  | Y                        | Y                              |
|     | Beer et al. [14]              | 5                 | Y  | Y                 | N                    | Y                         | N                    | N                  | N                 | N            | N                  | Y                        | Y                              |
|     | Berchicci et al. [37]         | 4                 | Y  | Y                 | N                    | Y                         | N                    | N                  | N                 | N            | N                  | Y                        | Y                              |
|     | Berriozabalgoitia et al. [46] | 5                 | Y  | Y                 | Y                    | N                         | N                    | N                  | N                 | Y            | N                  | Y                        | Y                              |
|     | Chotiyarnwong, C et al. [38]  | 8                 | Y  | Y                 | N                    | N                         | Y                    | Y                  | Y                 | Y            | Y                  | Y                        | Y                              |
|     | CL Barrett et al. [16]        | 5                 | Y  | Y                 | Y                    | N                         | N                    | N                  | N                 | Y            | N                  | Y                        | Y                              |
|     | Claude et al. [23]            | 4                 | Y  | Y                 | Y                    | N                         | N                    | N                  | N                 | N            | N                  | Y                        | Y                              |
|     | Daniele et al. [42]           | 7                 | Y  | Y                 | Y                    | Y                         | N                    | N                  | Y                 | Y            | N                  | Y                        | Y                              |
|     | De Bolt et al. [12]           | 5                 | Y  | Y                 | N                    | Y                         | N                    | N                  | N                 | Y            | N                  | Y                        | Y                              |
|     | Devasahayam et al. [39]       | 1                 | Y  | N                 | N                    | N                         | N                    | N                  | N                 | N            | N                  | N                        | Y                              |
|     | Druzbecki, M., et al. [47]    | 1                 | Y  | N                 | N                    | N                         | N                    | N                  | N                 | N            | N                  | N                        | Y                              |
|     | Giesser et al. [13]           | 2                 | Y  | N                 | N                    | N                         | N                    | N                  | N                 | Y            | N                  | N                        | Y                              |
|     | Hayes et al. [18]             | 5                 | Y  | Y                 | N                    | Y                         | N                    | N                  | N                 | Y            | N                  | Y                        | y                              |
|     | Hogan et al. [26]             | 4                 | Y  | Y                 | N                    | N                         | N                    | N                  | Y                 | N            | N                  | Y                        | Y                              |
|     | Jackson et al. [21]           | 2                 | Y  | N                 | N                    | N                         | N                    | N                  | N                 | Y            | N                  | N                        | Y                              |
|     | JE Esnouf et al. [17]         | 5                 | Y  | Y                 | N                    | Y                         | N                    | N                  | N                 | Y            | N                  | Y                        | Y                              |
|     | Jonsdottir et al. [32]        | 8                 | Y  | Y                 | Y                    | Y                         | N                    | N                  | Y                 | Y            | Y                  | Y                        | Y                              |
|     | KL Williams, et al. [44]      | 7                 | Y  | Y                 | Y                    | N                         | N                    | N                  | Y                 | Y            | Y                  | Y                        | Y                              |
|     | Lamberti et al. [40]          | 8                 | Y  | Y                 | Y                    | Y                         | N                    | N                  | Y                 | Y            | Y                  | Y                        | Y                              |
|     | Lee et al. [30]               | 2                 | Y  | N                 | N                    | N                         | N                    | N                  | N                 | Y            | N                  | N                        | Y                              |
|     | Lo et al. [15]                | 5                 | Y  | Y                 | N                    | N                         | N                    | N                  | N                 | Y            | Y                  | Y                        | Y                              |
|     | Manfredini et al. [41]        | 4                 | Y  | Y                 | N                    | N                         | N                    | N                  | Y                 | N            | N                  | Y                        | Y                              |
|     | Martini et al. [33]           | 7                 | Y  | Y                 | N                    | Y                         | N                    | N                  | Y                 | Y            | Y                  | Y                        | Y                              |

TABLE 4: Continued.

| No. | Study                      | Score<br>(out of<br>10) | Eligibility criteria<br>(external validity) | Random<br>allocation | Concealed<br>allocation | Group<br>similar in<br>baseline | Participant<br>blinding | Therapist<br>blinding | Assessor<br>blinding | <15%<br>dropout | Intention-<br>to-treat | Between-<br>group<br>difference | Point estimate<br>and variability |
|-----|----------------------------|-------------------------|---|----------------------|-------------------------|---------------------------------|-------------------------|-----------------------|----------------------|-----------------|------------------------|---------------------------------|-----------------------------------|
|     | McGibbon et al.<br>[34]    | 6                       | Y   | Y                    | N                       | Y                               | N                       | N                     | N                    | Y               | Y                      | Y                               | Y                                 |
|     | Miller et al. [19]         | 6                       | y   | Y                    | N                       | Y                               | N                       | N                     | Y                    | Y               | N                      | Y                               | Y                                 |
|     | Pilutt et al. [20]         | 2                       | Y   | N                    | N                       | N                               | N                       | N                     | N                    | Y               | N                      | N                               | Y                                 |
|     | Pilutti et al. [28]        | 4                       | Y   | Y                    | N                       | N                               | N                       | N                     | N                    | Y               | N                      | Y                               | Y                                 |
|     | Pompa et al. [31]          | 8                       | Y   | Y                    | Y                       | Y                               | N                       | N                     | Y                    | Y               | Y                      | Y                               | Y                                 |
|     | Robinson et al.<br>[27]    | 5                       | Y   | Y                    | N                       | Y                               | N                       | N                     | N                    | N               | Y                      | Y                               | Y                                 |
|     | S Briken et al.<br>[25]    | 6                       | Y   | Y                    | Y                       | N                               | N                       | N                     | N                    | y               | Y                      | Y                               | Y                                 |
|     | Schwartz et al.<br>[22]    | 5                       | Y   | Y                    | N                       | Y                               | N                       | N                     | Y                    | N               | N                      | Y                               | Y                                 |
|     | Sconza, C., et al.<br>[48] | 9                       | Y   | Y                    | Y                       | Y                               | N                       | Y                     | Y                    | Y               | Y                      | Y                               | Y                                 |
|     | Straudi et al. [29]        | 7                       | Y   | Y                    | Y                       | Y                               | N                       | N                     | Y                    | N               | Y                      | Y                               | Y                                 |
|     | Straudi et al. [43]        | 8                       | Y   | Y                    | Y                       | Y                               | Y                       | N                     | N                    | Y               | Y                      | Y                               | Y                                 |
|     | Straudi et al. [24]        | 3                       | Y   | Y                    | N                       | N                               | N                       | N                     | N                    | Y               | N                      | Y                               | Y                                 |
|     | Willingham et al.<br>[35]  | 1                       | Y   | N                    | N                       | N                               | N                       | N                     | N                    | N               | N                      | N                               | Y                                 |

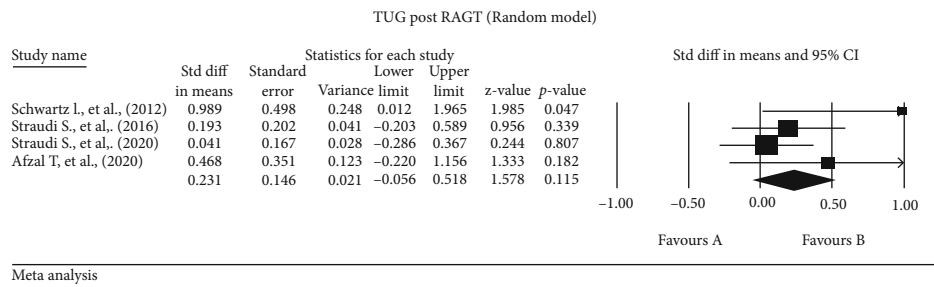


(a)

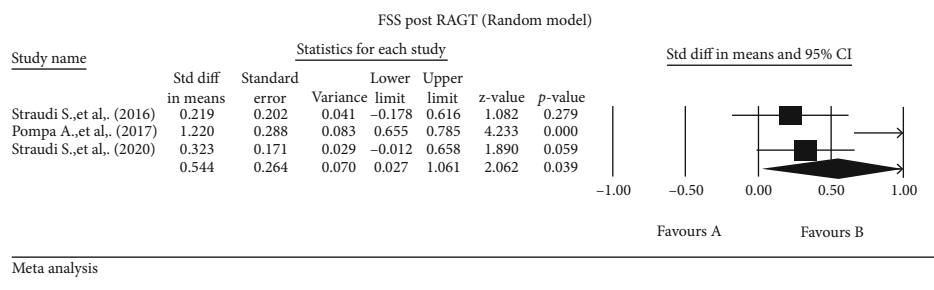


(b)

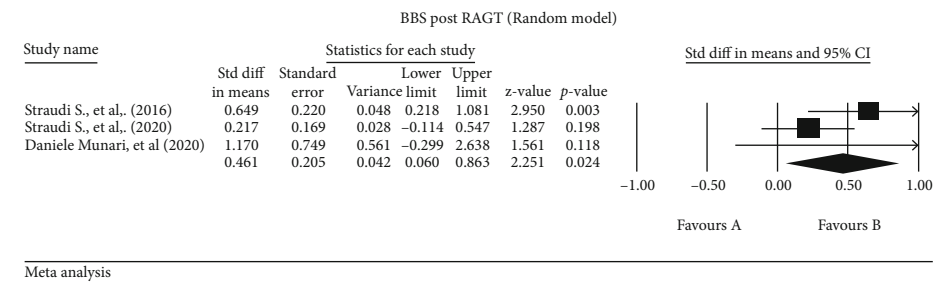
FIGURE 2: Standardised mean differences in (a) 6MWT and (b) 10MWT post-RAGT.



(a)



(b)



(c)

FIGURE 3: Standardised mean differences in (a) TUG, (b) FSS, and (c) BBS post-RAGT.

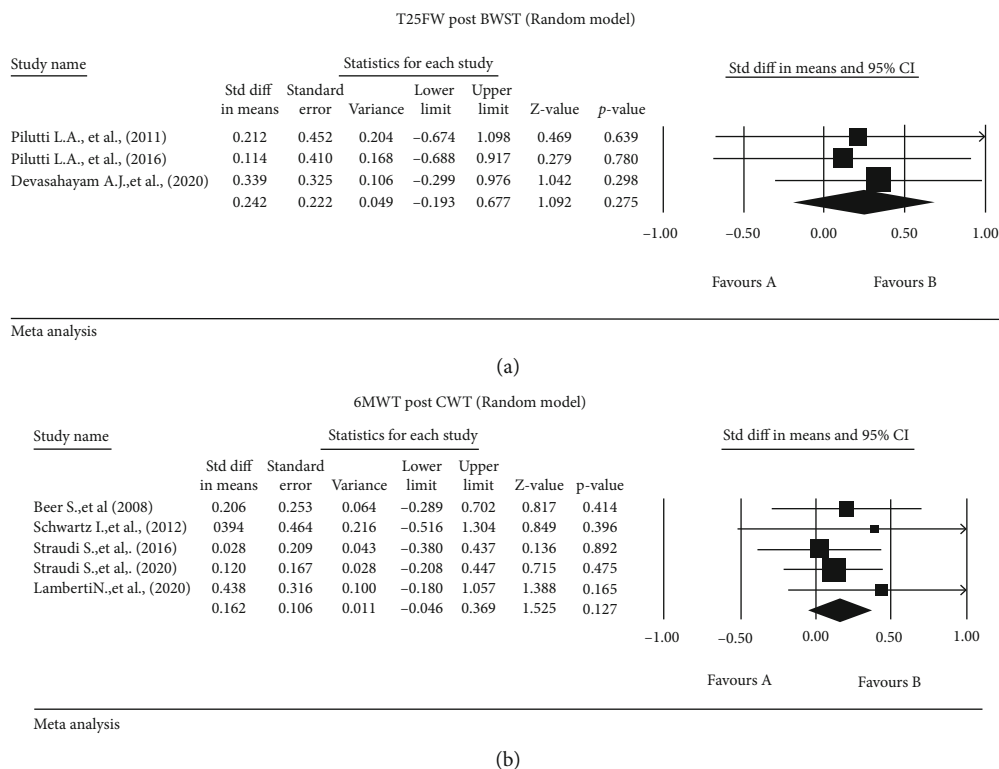


FIGURE 4: Standardised mean differences: (a) 25-foot walk test after body weight-supported training and (b) 6MWT postconventional walking training.

group physiotherapy significantly improved balance and fatigue, while yoga only improved balance significantly after the intervention.

#### 4. Discussion

We report a systematic review and meta-analysis of the evidence for PT interventions to improve walking performance in severely disabled pwMS (defined as EDSS  $\geq$  6.0). We include 37 studies that investigated a range of PT interventions in 788 pwMS. Forty three percent of studies included only severely affected pwMS (EDSS  $\geq$  6.0), and 57% had mixed cohorts with mild, moderate, and severely affected pwMS. Overall study quality was variable; with only 1/37, study rated “excellent,” 12/37 included papers rated “good” on the Pedro scale and 9/30 rated poor. Weaknesses of study design included lack of blinding (for participant, therapist and/or assessor), nonconcealment of allocation, missing data, and lack of intention-to-treat analysis.

A major concern limiting the use of PT interventions for mobility in severely disabled pwMS is increasing the barrier to exercise [49], in particular, health and cognitive barriers. As disease progresses, the health and cognitive status of patients are significantly impaired. Moreover, severely disabled PwMS suffer from fatigue, mobility disability, depression, safety concerns, and hesitation to engage in tasks they cannot perform as simply or effectively as they did previously and an inaccessibility to appropriate places. Moreover, they are uncertain of their capacity to engage in physical activity [49]. Therefore, they need more social and physical

support to overcome these obstacles compared to other less affected pwMS [49]. However, our systematic review indicates that severely disabled pwMS can utilise a variety of PT interventions. Of note, 27/37 (73%) studies had a drop-out rate of less than 15%, suggesting that the majority of people with severe MS can complete PT protocols for mobility.

There was significant heterogeneity in the mobility outcome measures and statistical analyses reported. There were more than 15 mobility-related outcome measures reported in 37 studies, but there was little overlap in the outcome measures used between studies. Because of this, we could only meta-analyse 6 outcomes (Figures 2–4) from 11 studies.

Based on our meta-analysis, RAGT is the PT intervention for which there is most evidence of effectiveness to improve mobility in severe MS. RAGT significantly improved scores on the 6MWT [14, 22, 29, 36, 43], 10WMT [22, 29, 42], FSS [29, 31, 43], and BBS [29, 42, 43]. In addition, one paper from the vote counting exercise demonstrated a significant effect of RAGT on the 6MWT [31]. Improvements in 6MWT scores likely reflect improved aerobic capacity and endurance. Improvements in the 10WMT scores reflect increases in walking speed after RAGT [50].

Fatigue in MS is multifactorial, reflecting both physical and psychological factors [13]. It is likely that improved aerobic capacity and endurance could lead to reduce perceived fatigue (as measured by the FSS) [31]. Improvements in the BBS are likely associated with general improvements in mobility after RAGT. In contrast, there was no significant effect of RAGT on the TUG. This is likely because TUG is

TABLE 5: Vote counting of studies for severe MS patients, not included in the meta-analysis.

| Studies                     | Study characteristics |                                     | Intervention                   |                     | Outcomes              |   | Vote counting<br>Significant mobility-related<br>outcomes |
|-----------------------------|-----------------------|-------------------------------------|--------------------------------|---------------------|-----------------------|---|---|
|                             | N                     | PT intervention                     | Disability scale               | Duration<br>(weeks) | Frequency<br>(X/week) | Outcomes post intervention  |   |
| Williams et al. [44]        | 26                    | Community group exercise            | 3-5 disease step rating scale  | 8 weeks             | 2/week                | ↑6MWT, ↑10WMT*, ↑balance  | ↑10WMT*   |
| Chotiyarnwong et al. [38]   | 10                    | BFR                                 | 6.0-7.0                        | 1 session           | 1 day                 | ↑ 6MWT, ↑ waking speed, ↓ perceived exertion  | None  |
| Daniele Munaria et al. [42] | 5                     | RAGT+VR                             | EDSS ≥ 6                       | 6 weeks             | 2/week                | ↑ 2MWT, ↓ 10 MW, ↑ BBS, ↑ cognitive function, ↓ double support time, ↓ sway area  | None  |
| Manfredini et al. [41]      | 23                    | RAGT                                | 6.0-7.0                        | 6 weeks             | 2/week                | ↑ 6MWT*, improve mitochondrial function biomarker, ↑ rmVO2*   | ↑6MWT*  |
|                             | 23                    | CWT                                 | 6.0-7.0                        |                     | 2/week                | ↑6MWT*, improve mitochondrial function biomarker, ↑rmVO2  | ↑6MWT*  |
| Lamberti et al. [40]        | 12                    | BFR-W                               | 6.1 ± 0.2                      | 6 weeks             | 2/week                | ↑6MWT*, ↓5STS time*, ↓mFIS*, ↓MSIS – 29 (psychological)*, ↓MSIS – 29 (motor), ↑walking speed*, ↓perceived exertion*         | ↑walking speed*, ↑6MWT*, ↓5STS time*, ↓mFIS*              |
| Willingham et al. [35]      | 6                     | BWST+antigravity treadmill training | 6.0-6.5                        | 8 weeks             | 2/week                | ↑2MWT, ↑muscle oxidative capacity*, ↑muscle endurance*  | None  |
| Jonsdottir et al. [32]      | 8                     | BWST if needed dual task training   | EDSS ≥ 6                       | 4 weeks             | 5/week                | ↑ 2MWT*, ↓ 10WMT, ↑ balance, ↑ DGI, ↓ TUG   | ↑2MWT*  |
|                             | 2                     | Resistance ex.                      |                                | 4 weeks             | 5/week                | ↑ 2MWT, ↓ 10WMT, ↑ balance, ↑ DGI, ↓ TUG  | None  |
| Martini et al. [33]         | 20                    | ADSTEP                              | 6.0 ± 0 (history of fall)      | 6 weeks             | 1/week                | ↔ 2 MW, ↓falling*, ↔ FSST, ↓MSIS – 29, ↓MSWS – 12, ↔ T25W, ↓time spent setting*, ↔ TUG, ↑walking aid satisfaction           | None  |
| Pompa et al. [31]           | 25                    | CWT                                 | 6.0–7.5                        | 4 weeks             | 3/week                | ↑2MWT, ↓EDSS, ↑FAC, ↓FSS, ↑mBI**, ↓↑RMI**, ↓VAS   | RMI **  |
| Pilutti et al. [28]         | 5                     | TBRST                               | 6.0-8.0                        | 12 weeks            | 3/week                | ↓ fatigue, ↑ QoL, ↔ T25FW   | None  |
| Robinson et al. [27]        | 20                    | (Exergaming) Nintendo Wii fit       | 6.00                           | 4 weeks             | 2/week                | ↑ balance, ↓ MSWS-12, ↓ postural sway, ↑ step length, ↑ stride length   | None  |
|                             | 18                    | Balance training                    |                                | 4 weeks             | 2/week                | ↑ balance, ↓ MSWS-12, ↓ postural sway, ↑ step length, ↑ stride length   | None  |
|                             | 66                    | Group physio-therapy                |                                | 10 weeks            | 1/week                | ↑6MWT, ↑balance**, ↑QOL*, ↓MSIS – 29v2 physical component*, ↓mFIS*  | ↑balance**, ↓mFIS*  |
| Hogan et al. [26]           | 45                    | 1 : 1 physiotherapy                 | 3–4 mobility section of (GNDS) | 10 weeks            | 1/week                | ↑balance**, ↑QOL*, ↓MSIS – 29v2 physical component*, ↓MSIS – 29v2 psychological component*, ↓mFIS*, ↑6MWT*                  | ↑balance **, ↓mFIS*, ↑6MWT*                               |
|                             | 16                    | Yoga                                |                                | 10 weeks            | 1/week                | ↑balance**, ↑QOL, ↓MSIS – 29v2 physical component, ↓MSIS – 29v2 psychological component, ↓mFIS, ↑6MWT                       | ↑balance **   |
| Jackson et al. [21]         | 4                     | Kickboxing                          | 6.0-6.5                        | 5 weeks             | 3/week                | ↑ balance, gait speed, ↑ Mini-BESTest, ↓ TUG  | None  |
| Miller et al. [19]          | 15                    | Home ex                             | 6.5–8                          | 8 weeks             | 2/week                | ↓ 10WMT, ↓ FIM, ↓ EDSS, ↑ MSIS 29, ↑ muscle strength, ↓ timed sit-stand   | None  |
| Giesser et al. [13]         | 4                     | BWST                                | 7.0-8.0                        | 20 week             | 2/week                | ↓ 10WMT, ↑ 6MWT, ↑ balance, ↑ muscle strength, ↑ QoL, ↓ spasticity (not all patients were able to complete the 10WMT, 6MWT) | None  |

2MWT: 2 minutes walking test; 5TST: 5-time sit to stand; 6 MWT: 6 min walk test; 10WMT: Ten-Meter Walking Test; ADSTEP: Assistive Device Selection Training and Education Program; BBS: Berg Balance Scale; BFR-W: Blood Flow-Restricted Slow Walking; BWST: Body weight supported training; DGI: dynamic gait index; DST: double support time; EBI: Extended Barthel Index; EDSS: Expanded Disability Status Scale; FAC: Functional Ambulation Category; FSS: Fatigue Severity score; FES: functional electrical stimulation; FSST: Four Square Step Test; FIM: Functional Independence Measure; GNDS: The Guy's Neurological Disability Scale; MAS: Modified Ashworth Scale; mBI: modified Barthel Index; mFIS: modified Fatigue Impact Scale; Mini-BESTest: mini Balance Evaluation System Test; MSIS-29: multiple sclerosis impact scale; MSWS: Multiple Sclerosis Walking Scale questionnaire; ODFS: Odstock dropped foot stimulator; PHQ: patient health questionnaire; QoL: quality of life; RAGT: Robot-Assisted Gait Training; RAGT-VR: Robot-Assisted Gait Training combined with Virtual Reality; rmVO2: resting muscle oxygen consumption; RMI: Rivermead Mobility Index; ROM: Range of motion; SLR: Step Length ratio; TBRST: Total-Body Recumbent Stepper Training; T25FW: timed 25-foot walk test; TST: timed stair test; TUG: Timed Up and Go; VAS: Visual Analogue Scale.; VO2peak: peak oxygen consumption; NR: not reported. Abbreviations are presented in an alphabetical order. \*Statistically significant at  $p \leq 0.05$  or \*\* $p \leq 0.001$ .



a demanding function particularly for severely disabled patients that requires the patient to stand upright from sitting position, then walk (acceleration-deceleration), and turn to return to the starting point [51]. Moreover, RAGT is designed to improve dynamic walking as an independent function; it is not targeting tasks like sit-to-stand or turning [52]. This suggests that RAGT may need to be complemented with additional PT interventions to target activities like getting up from sitting or transfers.

Seven studies with ( $n = 150$  patients) reported the use of CWT in severely disabled pwMS. However, meta-analyses of 6MWT did not show any improvement post-CWT. CWT as a stand-alone intervention might not improve the distance walked in 6 minutes in pwMS. CWT bearing has other advantages like reducing osteoporosis, improving balance, improving self-esteem, and better control of spasticity [29, 53]. It also does not require specialist equipment and could be delivered widely in community [29]. We did not look into these aspects. Further research is required to understand the role of CWT in people with advanced MS.

Five studies investigated the role of BWSTT, though no clear evidence of benefit on mobility related outcomes emerged from our meta-analysis. A number of other PT interventions were identified as being utilised for severely disabled pwMS, including kickboxing [21], exergaming [27], and electrical stimulation [16, 17]. Although there are various rehabilitation programs that work empirically for MS patients, there was relatively few studies on the effect of PT in people with severe mobility impairment [54, 55]. Therefore, further studies are needed particularly for this population.

It may however be noted that the RAGT included studies have been administered to patients with EDSS score ranges (3-7.5), and no study has examined the feasibility of RAGT for patient of EDSS higher than 7.5. On the other hand, 4 studies have been applied to patients with  $EDSS \leq 8$ . Two studies used BWSTT [13, 20] and another study used home Exercise of task-specific programme [19], while Pilutti et al.'s study [28] used total body recumbent stepper training for this population. Although not all severely disabled participants were able to complete the intervention protocol or the outcome measures, the overall effect was positive by increasing the mobility related outcomes and decreasing their disability. We cannot discount that there may be significant numbers of unpublished clinical studies that failed to recruit sufficient numbers of severely disabled pwMS (or in which the intervention could not be completed). Such publication bias may lead to an overestimation of the feasibility of certain PT for severely disabled pwMS. Nonetheless, a range of PT interventions are likely to be feasible for severely disabled pwMS.

There are several factors, which might explain the apparent superiority of RAGT compared to other PT interventions for severely disabled pwMS. Appropriate PT intervention programs must be tailored to the patient's abilities with sufficient stimulus to push present competence to produce effect [49]. Therefore, it possible that RAGT is less demanding for severely disabled pwMS, who might not be able to complete other forms of PT effectively. Moreover,

progression in RAGT is easily adjusted by increasing the intensity (frequency and duration) of the training session to challenge patients' abilities [5, 41]. There is evidence that personalised RAGT program might more effectively activate motor areas of the brain and have the potential to induce neuroplastic compensatory mechanisms that might benefit gait and mobility [42]. Moreover, RAGT might also target underlying factors in MS pathogenesis. RAGT has been demonstrated to improve blood mitochondrial function biomarkers, blood oxidative stress markers, and resting muscle oxygen consumption in severely disabled pwMS [41].

There are several limitations to our systematic review. We did not systematically search the grey literature to identify unpublished studies of PT interventions for severely disabled pwMS. We attempted to obtain patient level data on severely disabled pwMS from studies that reported cohorts of mixed MS severity. However, only 4 authors provided the requested data. So, data that could not be obtained was excluded from further analysis. The overall quality of our systematic review and meta-analysis is also influenced by the quality of the included studies. A significant number of included studies were rated "poor" on the Pedro scale. Besides, significant heterogeneity in the mobility-related outcomes was reported. These limited our ability to undertake a meta-analysis.

Our systematic review and meta-analysis provides evidence to guide design of future clinical trials for PT interventions in severely disabled pwMS. The strongest evidence of efficacy is for RAGT. Future clinical trials could focus upon further investigating the effectiveness of RAGT in larger cohorts and defining the most effective and feasible treatment protocols: for example, optimal exercise intensity, duration, and frequency of training episodes. Agreement on a consensus package of mobility-related outcome measures across studies would also be beneficial. There is evidence that longer duration walking tests (e.g., 2MWT) and the Multiple Sclerosis Walking Scale (MSWS-12) are the most sensitive to changes in mobility after PT [56]. A recent systematic review also identified that the 6MWT can discriminate between mild, moderate, and severe MS and in theory measure response to PT [50]. Clinical trials of PT interventions for severely disabled pwMS should be considered a priority given that mobility impairment is considered the most disabling feature of MS by pwMS.

## Data Availability

Search results can be obtained by reasonable request of the corresponding author.

## Conflicts of Interest

There are no financial or other conflicts of interest.

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