Contents lists available at ScienceDirect

# Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

# Efficacy of robot-assisted gait training in multiple sclerosis: A systematic review and meta-analysis

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# ARTICLE INFO

Keywords: Robot-assisted gait training Multiple sclerosis Walking performance Fatigue Quality of life

# ABSTRACT

*Background:* Multiple sclerosis is a progressive disease responsible for gait disabilities and cognitive impairment, which affect functional performance. Robot-assisted gait training is an emerging training method to facilitate body-weight-supported treadmill training in many neurologic diseases. Through this study, we aimed to determine the efficacy of robot-assisted gait training in patients with multiple sclerosis.

*Methods*: We performed a systematic review and meta-analysis of randomized controlled trials evaluating the effect of robot-assisted gait training for multiple sclerosis. We searched PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov registry for articles published before May 2019. The primary outcome was walking performance (gait parameters, balance, and ambulation capability). The secondary outcomes were changes in perceived fatigue, severity of spasticity, global mobility, physical and mental quality of life, severity of pain, activities of daily living, and treatment acceptance.

*Results:* We identified 10 studies (9 different trials) that included patients with multiple sclerosis undergoing robot-assisted gait training or conventional walk training. The meta-analysis showed comparable effectiveness between robot-assisted gait training and conventional walking therapy in walking performance, quality of life, pain, or activities of daily living. The robot-assisted gait training was even statistically superior to conventional walking therapy in improving perceived fatigue (pooled SMD: 0.34, 95% CI: 0.02–0.67), spasticity (pooled SMD: 0.70, 95% CI: 0.08–1.33,  $I^2 = 53\%$ ), and global mobility (borderline) after the intervention.

*Conclusion:* Our results provide the most up-to-date evidence regarding the robot-assisted gait training on multiple sclerosis. In addition to the safety and good tolerance, its efficacy on multiple sclerosis is comparable to that of conventional walking training and is even superior in improving fatigue and spasticity.

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<sup>2</sup> Chien-Hsiung Hong and Yi-Chun Kuan contributed equally to this study.

https://doi.org/10.1016/j.msard.2020.102034

Received 26 June 2019; Received in revised form 12 January 2020; Accepted 29 February 2020 2211-0348/ @ 2020 Elsevier B.V. All rights reserved.







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#### 1. Introduction

Multiple sclerosis (MS) is a progressive disease that affects the entire central nervous system (Thompson et al., 2018). The immune system plays an important role in its pathogenesis, causing inflammatory demyelination and neurodegeneration. The estimated prevalence of MS is 50-300 per 100 000 individuals, with approximately 2.3 million affected individuals worldwide (Thompson et al., 2018). MS predominantly occurs in early adult life, with increased awareness of presentation in childhood, and it strongly impacts mobility, function, and quality of life (OOL) (Confavreux and Vukusic, 2006; Thompson et al., 2018). MS is responsible for several symptoms, such as fatigue, gait disabilities, and psychological and cognitive impairment (Confavreux and Vukusic, 2006; Thompson et al., 2018). As diseasemodifying agents show limited efficacy in preventing the deterioration of disabilities caused by MS (Confavreux and Vukusic, 2006; Feinstein et al., 2015), symptomatic therapies and a comprehensive and tailored rehabilitation program are strongly recommended to enhance the QOL or function of patients with MS (Thompson et al., 2018).

Conventional walking training (CWT) or traditional over-ground walking training is effective in improving mobility in patients with MS (Wiles et al., 2001). However, the treatment was associated with a high risk of falls in patients with severe gait disturbance (Cattaneoet al., 2002). Subsequent treadmill training was found to have a longer lasting effect on walking distance and velocity; however, treadmill training is difficult in individuals with fatigue or severe gait disabilities (Benedetti et al., 2009; Gervasoni et al., 2014; Newman et al., 2007; van den Berg et al., 2006). A bodyweight support (BWS) system characterized by patients suspended in a harness by an overhead support system over a treadmill, known as body-weight-supported treadmill training (BWSTT), is an alternative. It provides an environment for balance control and assists trunk and leg movement during gait cycle (Gardner et al., 1998; Giesser et al., 2007; Hesse et al., 1999). Previous studies have demonstrated that BWSTT had a positive effect on patients with stroke, incomplete spinal cord injuries (SCI), and MS; however, BWSTT had to be manually administered by physical therapists (Gardner et al., 1998; Giesser et al., 2007; Hesse et al., 1999; Pilutti et al., 2011).

Therefore, robot-assisted gait training (RAGT), which is more stable, physiological, and less demanding for practitioners, was developed to facilitate BWSTT (Colombo et al., 2001). RAGT has two common

approaches, namely the exoskeleton approach using Lokomat<sup>®</sup> (Hocoma, Zurich, Switzerland) to control the kinematics of the pelvis and knees and the end-effector approach using Gait Trainer GTII<sup>®</sup> (Reha-Stim, Berlin, Germany) to control the distal part of the leg with motor-driven footplates.

Considering the benefits mentioned above, it is of great importance to evaluate the efficacy of RAGT among patients with MS. Although clinical trials have indicated that RAGT potentially improves mobility and the symptoms of MS (Beer et al., 2008; Gandolfi et al., 2014; Lo and Triche, 2008; Schwartz et al., 2012; Straudi et al., 2013, 2016; Vaney et al., 2012), controversies still exist. A previous meta-analysis focusing on the impact of RAGT on gait function concluded that RAGT can significantly improve gait endurance when compared with CWT and is as effective as CWT in improving balance, gait speed, ambulation capability, and stride length among patients with MS (Xie et al., 2017). As more randomized controlled trials (RCTs) were recently published, we decided to conduct a more updated and comprehensive systematic review and meta-analysis to contribute to an evidence-based decisionmaking and policy-making regarding the use of RAGT. We investigated not only gait-related outcomes but also several aspects of MS, such as fatigue, QOL, and activities of daily living (ADL). The adverse effects of RAGT were also reviewed.

# 2. Materials and methods

#### 2.1. Selection criteria

We reviewed the RCTs evaluating the efficacy of RAGT for MS. We included trials that (1) compared the results of RAGT with CWT in patients with MS, (2) described the inclusion and exclusion criteria for patient selection, and (3) reported the speed, amount of bodyweight support, training duration, and detailed training procedure. We excluded trials that (1) combined RAGT with other treatments (i.e., virtue reality) as intervention and (2) used animal models.

# 2.2. Search strategy and study selection

We searched PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov registry for studies on MS. The following MeSH terms and Boolean operator were used: (multiple sclerosis OR disseminated sclerosis) AND (robot-assisted gait rehabilitation OR robot-assisted gait



Fig. 1. Flowchart of study selection process.

Table 1 Characteristics of selected	RCTs.				
Study	Inclusion criteria	No. of patients	Age (years)	Intervention	Outcomes
Straudi et al. (2019), Italy	Age 18–65 y, primary or secondary progressive MS and severe gait impairments (EDSS: 6–7)	1: 36 (33% °) C: 36 (31%)	l: 56 ± 11 C: 55 ± 11	I: RAGT (Lokomat <sup>d</sup> ), training parameters (speed, BWS, guidance force, and torque of the knee and hip drives) were individually set. First session: guidance and 50% of BWS; as training progressed, adjustments (10% of each) were made, 1 h/session (30 min for walking) + exercise <sup>e</sup> 1 h/session × 12 session/4 wits C: Assisted over-ground walking with habitual walking device, speed based on tolerance, 1 h/session (30 min for walking) + exercise <sup>e</sup> 1 h/session × 12 session/4 wits	TZ5FW, 6WMT, BBS, TUG, FSS, PHQ, SF-36, MSIS-29, MSWS-12
Pompa (2016), Italy	Age 25–65 y, diagnosis of MS according to the McDonald criteria, high disability (EDS: 6–7.5) and MMSE score $\geq 24$	1: 21 (52.4%) C:22 (45.5%)	I: 47.00 ± 11.17 C: 49.86 ± 8.21	I: RAGT (Gait Trainer GTII <sup>40</sup> ), speed: 1.3–1.8 km/h depending on patient comfort. First session: 40%–50% of BWS; subsequent sessions, BWS was reduced. 40 min/session (20 min of walking, 20 min preparing for device), 3 sessions/wk × 4 wks C. CWT, 40 min/session (20 min of walking exercises on the ground whose difficulty was gradually increased, 20 min received exercises designed to prepare for walking'). 3 session/wk × 4 wks	2MWT, FAC, RMI, EDSS, FSS, VAS (lower limb spasticity)
Pompa (2015), Italy	Age ≥ 18 y, diagnosis of MS (PP, SP) according to McDonald criteria, severe gait impairments (EDSS: 6.0–7.0).	1: 27 (37.0%) C:25 (32.0%)	I: 52.26 ± 11.11 C:54.12 ± 11.44	I: RAGT (Lokomat), speed: 0.1–3.0 km/h. First session: 50% of BWS; as training progressed, adjustments (10% of each) were made. 1 h/session (30 min for walking), 2 sessions/wk × 6 wks C: CWT, 1 h/session (first 10–15 min: lower limb and core- stretching exercises, followed by lower limb muscle stretching exercises, followed by lower limb muscle balance exercises (30 min) tailored to the patient's baseline 2 sessions/wk × 6 wks	10MWT, 6MWT, BBS, TUG, FSS, PHQ-9, SF-36, VAS (treatment acceptance)
Gandolff (2014), Italy	Age 30–60 y, diagnosis of MS (RR, SP), MMSE $\geq$ 24, able to maintain standing position without aids (at least 1 min), walk independently (at least 15 min), no concomitant neurological or or thopedic conditions that may interfere with ambulation. (EDSS: 1.5–6.5)	I: 12 (41.7%) C: 10 (10.0%)	I: 50.83 ± 8.42 C: 50.1 ± 6.29°	<ol> <li>RAGT (Gait Trainer GTII<sup>9</sup>). First session: 20% of BWS, speed: 1.3 km/h; second session: 10% of BWS, speed: 6 km/h. 40 min/session (net RAGT: 30 min, two 15-min sessions, separated by a 5-min rest, if required by the patient.)</li> <li>followed by 10 passive lower limb joint mobilizations and stretching exercises. Total: 50 min/session, 2 sessions/wk × 6 wks</li> <li>C. SIBT, each session comprised exercises with three different levels of difficulty. Repeated 2-5 times under three different sensory conditions. Total 10 exercises (3 from level I, 3 from level II, 4 from level II) within a 5-min period. Total: 50 min/session, 2</li> </ol>	GAITRite system (including gait speed, cadence, step length, single support time, double support time), BBS, ABC, SOT, SA, FSS, MSQOL-54
Straudi (2013), Italy	Age ≥ 18 y, diagnosis of MS (PP, SP, RR), without relapses in recent 6 months. (EDSS: 4.5–6.5)	I: 8 (50.0%) C: 8 (12.5%)	I: 49.6 ± 12.0 C: 61.0 ± 8.8	I: RAGT (Lokomat), speed: $0-3.0 \text{ km/h}$ ; as training progressed, training parameters were adjusted according to subject performance. I h/session (30 min for walking), 2 sessions/wk × 6 wks C: Conventional therapy, 1 h/session (First 10–15 min: lower limb and core stretching exercises, followed by lower limb muscle strengthening tailored according to the patient's baseline. Coordination, gait, and balance performed according to the	Gait analysis by VICON 460 (including gait speed, cadence, step length, double support time, step time, minimum pelvic rotation, hip flexion at heel strike; maximum hip extension and flexion. Hip total sagittal plane excursion), 6MWT, TUG, FSS, VAS (treatment acceptance)

(continued on next page)

Table 1 (continued)					
Study	Inclusion criteria	No. of patients	Age (years)	Intervention	Outcomes
Schwartz (2012), İsrael	Diagnosis of MS according to McDonald criteria (Pp, SP, RR), stable phase of disease, chronic progressive pattern or RR with no relapse in last 3 months, severe walking disabilities (EDSS: 5–7)	l: 12 (46.7%) C: 16 (41.2%)	I: 46.8 ± 11.5 C: 50.5 ± 11.5	I: RAGT (Lokomat), speed: 0–3.0 km/h Beginning: 40% of BWS, after 2 weeks: 30% of BWS and in another 2 weeks: 20% of BWS. 45 min/ time (net RAGT: 30 min), 2–3 times/wk × 4 wks C. Gati and dynamic balance exercises, standing from sitting training and walking ± walking aids. 30 min/session. 2–3 sessions/wk × 4 wks	10MWT, 6MWT, TUG, BBS, EDSS, FIM, RAND-36 scales
Vaney (2012), Switzerland	Age $\geq$ 18 y, diagnosis of MS by McDonald criteria, men and nonpregnant women (EDSS: 3–6.5), able to walk 14 $m \pm$ assistive devices	I: 26 (not provided) C: 23 (not provided)	I: 54.22 ± 11.28 C: 58.23 ± 9.42	<ul> <li>I: RAGT (Lokomat), speed depending on observation of gait and changed</li> <li>randomly to simulate normal gait. First session: 50% of BWS, adapted on observation of the gait. 30 min/session,</li> <li>× 9 sessions</li> <li>C: Over-ground walking training. Walk for 30 min in the gym room or sometimes outside on uneven ground</li> <li>± walking aids</li> <li>20 min/session</li> </ul>	Well-being VAS, EQ-5D VAS, Activity before rehab (min > 3 MET), activity before rehab (total accelerometer counts/day), 10MWT, 3-min walking speed, BBS, WEIMuS (including cognitive and physical fatigue), Pain- VAS, RMI, spasticity (Ashworth)
Lauren [2011], U.S.	Age $\geq$ 18 y, diagnosis of MS by McDonald criteria (PP, SP, RR) with east difficulties but ability to walk 25 ft.	I: 6 (50.0%) C: 7 (57.1%)	I: 50.2 ± 11.4 C: 49.6 ± 11.8	I: RAGT (Lokomat). 40 min/time, 2 sessions/wk $\times$ 3 wks C: BWSTT. 40 min/session, 2 sessions/wk $\times$ 3wks	MSQLI (including SF-36), FSS, LS
Lo [2008], U.S.	Diagnosis of MS by McDonald criteria (PP, SP, RR) Self-reported gait difficulty confirmed by clinician observation, and the shifty to walk 75.6 without escience	I: 6 (50.0%) C: 7 (57.1%)	I: 50.2 ± 11.4 C: 49.6 ± 11.8	I: RAGT (Lokomat). 40 min/session, 2 sessions/wk × 3 wks C: BWSTT. 40 min/session, 2 sessions/wk × 3 wks	T25FW, 6MWT, DST, SLR
Beer (2008), Switzerland	The function of the stable phase of disease (chronic progressive or RR with no relapse during in last 3 months), severe walking disabilities (EDSS 6.0–7.5)	I: 19 (58.3%) C: 16 (45.5%)	I: 49.7 ± 11.0 C: 51.0 ± 15.5	I: RAGT (Lokomat). Started with an individually adapted BWS (40–80%), speed :1–1.5 km/h; as training Progressed, BWS was reduced and speed increased (maximal speed: 2.8 km/h). 60 min/time (net RAGT: 30 min), 5 sessions/ wk $\times$ 3 wks C: CWT, walking over ground $\pm$ walking aids with assistance of physical therapists. 30 min/session, 5 sessions/wk $\times$ 3 weeks	Walking velocity (20-m timed walking), 6MWT, stride length, knee-extensor strength, EBI, subjective walking safety (VAS), overall satisfaction with RAGT (VAS)
<ul> <li>PP: Primary progressive; Functional Ambulatory C Status Scale; FSS: Fatigue Short Form 36 SF-36; AB balance training; FIM: fun Form Health Survey (SF- satisfaction; BWSTT: bod- metabolic equivalents; T2 scale-29; MSWS-12: MS v a (): % male.</li> <li><sup>b</sup> Patients stood with t trajectories' control (end <sup>c</sup> Static exercises on th <sup>d</sup> Every patient wore a <sup>e</sup> Exercise: lower limb</li> </ul>	SP: secondary progressive; RR: relapse-remitting: ategory; RMI: Rivermead Mobility Index; mBI: mo Severity Scale; VAS: visual analog scale; 10MWT: C: Activities-Specific Balance Confidence Scale; SO C: Activities-Specific Balance Confidence Scale; SO Sof from the Medical Outcomes Study (MOS), ar y-weight-supported treadmill training (Individuals 55FW: timed 25-foot walk; DST: double support tin walking scale-12. Age is presented as mean $\pm$ SD the feet on the motor-driven footplates and were effector). effector). the parallel bars for lower limb movement and con tharness attached to a system that provided body and core stretching exercise.	BWS: body wei liffed Barthel In- fen-Meter Walk Fr. Sensory Orgai T: Sensory Orgai d nine sympton of a nine sympton of a tradie or mean (range or mean (range or mean (range trol; exercises f weight support	ght support; EDS: exp dex; MS: multiple scle Test; 6MWT: 6-min wi nization Balance Test; fthe Medical Outcomn i-based scales that rej nill while a portion oi gth ratio; EBI: Extende gth ratio; EBI: Extende of arress and practiced arress and pelvis co art runk and pelvis co	anded disability status scale; MMSE: Mini-Mental State I rosis; RAGT: robot-assisted gait training; CWT: convention alk test; TUG: Timed up and go test; BBS: Berg Balance Sca SS: study Short-Form 36; MSQL.54: Multiple Sclero es Study Short-Form 36; MSQL. comprising a well-establis present areas of specific concern to individuals with MS; f their body weight is supported by a parachute-style harm ed Barthel Index; WEIMUS: Würzburger Erschöpfungsinven gait-like movements. The electromechanical device appli ntrol; exercises for balance and coordination. admill with the help of Lokomat. Legs were guided base	xamination; 2MWT: 2-min walking test; FAC. al walking training: EDSS: Expanded Disability e; PHQ-9: Patient Health Questionnaire; SF-36: its Quality of Life-54; SIBT: sensory integration factor and a consure, the 36-ften Short MS Quality of Life Inventory, LS: general life as linked to an overhead pulley system.); MET tar bei Multipler Sklerose; MSIS-29: MS impact ar bei Multipler Sklerose; MSIS-29: MS impact ar bei miverse control approach with end point es an inverse control approach with end point on a physiological gait pattern.

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#### Table 2

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Methodological quality assessment of selected RCTs.

Study	Bias arising from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of reported result	Overall risk of bias
Straudi (2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pompa (2016)	Low risk	Low risk	Some concerns <sup>c</sup>	Low risk	Low risk	Some concerns
Straudi (2015)	Low risk	Some concerns <sup>b</sup>	Low risk	Low risk	Low risk	Some concerns
Gandolfi (2014)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Straudi (2013)	Some concerns <sup>a</sup>	Some concerns <sup>b</sup>	Low risk	Some concerns <sup>e</sup>	Low risk	High risk
Schwartz (2012)	Low risk	Some concerns <sup>b</sup>	Some concerns <sup>d</sup>	Low risk	Low risk	Some concerns
Vaney (2012)	Low risk	Low risk	Low risk	Some concerns <sup>e</sup>	Low risk	Some concerns
Lauren (2011)	Some concerns <sup>a</sup>	Low risk	Low risk	Some concerns <sup>e</sup>	Some concerns <sup>f</sup>	High risk
Lo (2008)	Some concerns <sup>a</sup>	Low risk	Low risk	Some concerns <sup>e</sup>	Low risk	Some
Beer (2008)	Low risk	Low risk	Low risk	Low risk	Some concerns <sup>g</sup>	concerns Some concerns

Methodological quality assessment was based on the Cochrane risk-of-bias tool (RoB 2.0).

<sup>a</sup> No information of allocation concealment.

<sup>b</sup> Patients and personnel were not blinded and with unclear information of co-intervention.

<sup>c</sup> 14% (7 patients) of loss to follow-up rate, but 2 of these patients withdrew informed consent at first RAGT session without a clear reason. Moreover, data analysis was performed using per-protocol analysis.

<sup>d</sup> 12.5% (4 patients) discontinued intervention during the intervention period, with 3 of them being uncooperative with treatment; 14.3% dropped out (4 patients) at the 3-month follow-up, with 3 of them reporting no clear reason; 35.7% (6 patients) dropped out at the 6-month follow-up, with 4 of them reporting no clear reason. Data analysis at 3-month and 6-month follow-up was performed using per-protocol analysis.

<sup>e</sup> Lack of information on outcome assessor blinding.

<sup>f</sup> Outcome data reported as only mean without standard deviation.

<sup>g</sup> Outcome data reported as median and interquartile range.

Study or Subgroup         Mean         SD         Total         Weight         IV, Random, 95% CI         Year         IV, Random, 95% CI           1.1.1 Changes from baseline to posttreatment         Beer 2008         0.14         0.21         14         0.07         0.11         15         12.4%         0.41 [-0.33, 1.16]         2007           Lo 2008         1.4         2.6         6         4.1         3         7         6.6%         -0.089 [-2.05, 0.28]         2008           Vaney 2012         0.03         0.09         2.6         0.09         0.17         23         16.2%         -0.44 [-1.01, 0.13]         2011           Schwartz 2012         -0.01         0.1         12         0.1         0.2         16         11.8%         -0.65 [-1.42, 0.12]         2011           Straudi 2013         0.07         0.11         8         -0.01         0.13         8         8.2%         0.63 [-0.38, 1.64]         2013           Gandolfi 2014         7.07         17.21         12         3.8         10.5%         0.21 [-0.63, 0.45]         2014         Image: statuli 2015         0.01         0.1         23         16.0%         0.46 [-0.12, 1.03]         2015         Image: statuli 2019         Image: statuli 2015 <t< th=""><th></th><th></th><th>RAGT</th><th></th><th></th><th>CWT</th><th></th><th></th><th>Std. Mean Difference</th><th></th><th>Std. Mean Difference</th></t<>			RAGT			CWT			Std. Mean Difference		Std. Mean Difference
1.1.1 Changes from baseline to posttreatment         Beer 2008       0.14       0.21       14       0.07       0.11       15       12.4%       0.41 [-0.33, 1.15]       2007         Lo 2008       1.4       2.6       6       4.1       3       7       6.6%       -0.89 [-2.05, 0.28]       2008         Vaney 2012       0.03       0.09       26       0.09       0.17       23       16.2%       -0.44 [-1.01, 0.13]       2011         Schwartz 2012       -0.01       0.1       12       0.1       0.2       16       11.8%       -0.65 [-1.42, 0.12]       2011         Straudi 2013       0.07       0.11       8       -0.01       0.13       8       8.2%       0.63 [-0.38, 1.64]       2013         Gandolfi 2014       7.07       17.21       12       3.8       12.06       10       10.5%       0.21 [-0.63, 1.05]       2014         Straudi 2015       0.07       0.15       25       0.01       0.1       23       16.0%       0.46 [-0.12, 1.03]       2015         Straudi 2019       0.05       0.25       34       0.06       0.28       30       18.3%       -0.04 [-0.53, 0.45]       2019         Subtotal (95% CI)       137       <	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Beer 2008 $0.14$ $0.21$ $14$ $0.07$ $0.11$ $15$ $12.4\%$ $0.41$ $[-0.33, 1.15]$ $2007$ Lo 2008 $1.4$ $2.6$ $6$ $4.1$ $3$ $7$ $6.6\%$ $-0.89$ $[-2.05, 0.28]$ $2008$ Vaney 2012 $0.03$ $0.09$ $26$ $0.09$ $0.17$ $23$ $16.2\%$ $-0.44$ $[-1.01, 0.13]$ $2011$ Schwartz 2012 $-0.01$ $0.1$ $12$ $0.1$ $0.2$ $16$ $11.8\%$ $-0.65$ $[-1.42, 0.12]$ $2011$ Straudi 2013 $0.07$ $0.11$ $8$ $-0.01$ $0.13$ $8$ $8.2\%$ $0.63$ $[-0.38, 1.64]$ $2013$ Gandolfi 2014 $7.07$ $7.21$ $12$ $3.8$ $12.06$ $10$ $10.5\%$ $0.21$ $[-0.63, 1.05]$ $2014$ Straudi 2015 $0.07$ $0.15$ $25$ $0.01$ $0.12$ $30$ $18.3\%$ $-0.04$ $[-0.3]$ $2015$ Subtotal (95% CI) $137$ $132$ $100.0\%$ $-0.02$ $[-0.$	1.1.1 Changes from b	aseline	to post	treatm	ent						
Lo 2008 1.4 2.6 6 4.1 3 7 6.6% $-0.89$ [-2.05, 0.28] 2008 Vaney 2012 0.03 0.09 26 0.09 0.17 23 16.2% $-0.44$ [-1.01, 0.13] 2011 Schwartz 2012 -0.01 0.1 12 0.1 0.2 16 11.8% $-0.65$ [-1.42, 0.12] 2011 Straudi 2013 0.07 0.11 8 -0.01 0.13 8 8.2% $0.63$ [-0.88, 1.64] 2013 Gandolfi 2014 7.07 17.21 12 3.8 12.06 10 10.5% $0.21$ [-0.63, 1.05] 2014 Straudi 2015 0.07 0.15 25 0.01 0.1 23 16.0% $0.46$ [-0.12, 1.03] 2015 Straudi 2019 0.05 0.25 34 0.06 0.28 30 18.3% $-0.04$ [-0.53, 0.45] 2019 Subtotal (95% CI) 137 132 100.0% $-0.02$ [-0.36, 0.33] Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 12.64, df = 7 (P = 0.08); I <sup>2</sup> = 45% Test for overall effect: Z = 0.09 (P = 0.93) <b>1.1.2 posttreatment 3 months</b>	Beer 2008	0.14	0.21	14	0.07	0.11	15	12.4%	0.41 [-0.33, 1.15]	2007	
Vaney 2012 $0.03$ $0.09$ $26$ $0.09$ $0.17$ $23$ $16.2\%$ $-0.44$ [-1.01, 0.13] $2011$ Schwartz 2012 $-0.01$ $0.1$ $12$ $0.1$ $0.2$ $16$ $11.8\%$ $-0.66$ [-1.42, 0.12] $2011$ Straudi 2013 $0.07$ $0.11$ $8$ $-0.01$ $0.13$ $8$ $8.2\%$ $0.63$ [-0.38, 1.64] $2013$ Gandolfi 2014 $7.07$ $17.21$ $12$ $3.8$ $12.06$ $10.5\%$ $0.21$ [-0.63, 1.05] $2014$ Straudi 2015 $0.07$ $0.15$ $25$ $0.01$ $0.1$ $23$ $16.0\%$ $0.46$ [- $0.12, 1.03$ ] $2015$ Straudi 2019 $0.05$ $0.25$ $34$ $0.06$ $0.28$ $30$ $18.3\%$ $-0.04$ [- $0.53, 0.45$ ] $2019$ Subtotal (95% CI) $137$ $132$ $100.0\%$ $-0.02$ [- $0.36, 0.33$ ] $-0.02$ [- $0.36, 0.33$ ]         Heterogeneity: Tau <sup>2</sup> = $0.10$ ; Chi <sup>2</sup> = $12.64$ , df = 7 (P = $0.08$ ); I <sup>2</sup> = $45\%$ $-12.64$ , df = $7$ (P = $0.93$ ) $-12.64$ , df = $7$ (P = $0.93$ ) $-12.64$ , df = $7$ (P = $0.93$ ) $-12.64$ , df = $7$ (P = $0.93$ )   <	Lo 2008	1.4	2.6	6	4.1	3	7	6.6%	-0.89 [-2.05, 0.28]	2008	
Schwartz 2012 $-0.01$ $0.1$ $12$ $0.1$ $0.2$ $16$ $11.8\%$ $-0.65$ $[-1.42, 0.12]$ $2011$ Straudi 2013 $0.07$ $0.11$ $8$ $-0.01$ $0.13$ $8$ $8.2\%$ $0.63$ $[-0.38, 1.64]$ $2013$ Gandolfi 2014 $7.07$ $17.21$ $12$ $3.8$ $12.06$ $10$ $10.5\%$ $0.21$ $[-0.63, 1.05]$ $2014$ Straudi 2015 $0.07$ $0.15$ $25$ $0.01$ $0.1$ $23$ $16.0\%$ $0.46$ $[-0.12, 1.03]$ $2015$ Straudi 2019 $0.05$ $0.25$ $34$ $0.06$ $0.28$ $30$ $18.3\%$ $-0.04$ $[-0.53, 0.45]$ $2019$ Subtotal (95% CI)       137       132 $100.0\%$ $-0.02$ $[-0.36, 0.33]$ $-0.02$ $-0.36$ $0.33$ Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 12.64, df = 7 (P = $0.08$ ); I <sup>2</sup> = 45%       Test for overall effect: Z = $0.09$ (P = $0.93$ ) $-1.22$ $-1.22$ $-1.22$ $-1.22$ $-1.22$ $-1.22$ $-1.22$ $-1.22$ $-1.22$ $-1.22$ $-1.22$ $-$	Vaney 2012	0.03	0.09	26	0.09	0.17	23	16.2%	-0.44 [-1.01, 0.13]	2011	
Straudi 2013 $0.07$ $0.11$ $8$ $-0.01$ $0.13$ $8$ $8.2\%$ $0.63$ [ $-0.38$ , $1.64$ ] $2013$ Gandolfi 2014 $7.07$ $17.21$ $12$ $3.8$ $12.06$ $10$ $10.5\%$ $0.21$ [ $-0.63$ , $1.05$ ] $2014$ Straudi 2015 $0.07$ $0.15$ $25$ $0.01$ $0.1$ $23$ $16.0\%$ $0.46$ [ $-0.12$ , $1.03$ ] $2015$ Straudi 2019 $0.05$ $0.25$ $34$ $0.06$ $0.28$ $30$ $18.3\%$ $-0.04$ [ $-0.53$ , $0.45$ ] $2019$ Subtotal (95% CI) $137$ $132$ $100.0\%$ $-0.02$ [ $-0.36$ , $0.33$ ]       Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 12.64, df = 7 (P = $0.08$ ); I <sup>2</sup> = 45\%         Test for overall effect: Z = $0.09$ (P = $0.93$ )       Image: Distribute of the image: Distret of the image: Distribute of the image: Di	Schwartz 2012	-0.01	0.1	12	0.1	0.2	16	11.8%	-0.65 [-1.42, 0.12]	2011	
Gandolfi 2014       7.07       17.21       12       3.8       12.06       10       10.5%       0.21 [-0.63, 1.05]       2014         Straudi 2015       0.07       0.15       25       0.01       0.1       23       16.0%       0.46 [-0.12, 1.03]       2015         Straudi 2019       0.05       0.25       34       0.06       0.28       30       18.3%       -0.04 [-0.53, 0.45]       2019         Subtotal (95% Cl)       137       132       100.0%       -0.02 [-0.36, 0.33]       -0.02 [-0.36, 0.33]         Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 12.64, df = 7 (P = 0.08); I <sup>2</sup> = 45%       -0.09 (P = 0.93)       -0.09 (P = 0.93) <b>1.1.2 posttreatment 3 months</b> -0.09 (P = 0.93)       -0.09 (P = 0.93)       -0.09 (P = 0.93)	Straudi 2013	0.07	0.11	8	-0.01	0.13	8	8.2%	0.63 [-0.38, 1.64]	2013	
Straudi 2015 $0.07$ $0.15$ $25$ $0.01$ $0.1$ $23$ $16.0\%$ $0.46$ $[-0.12, 1.03]$ $2015$ Straudi 2019 $0.05$ $0.25$ $34$ $0.06$ $0.28$ $30$ $18.3\%$ $-0.04$ $[-0.53, 0.45]$ $2019$ Subtotal (95% CI)       137       132 $100.0\%$ $-0.02$ $[-0.36, 0.33]$ Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 12.64, df = 7 (P = 0.08); P = 45\%       Test for overall effect: $Z = 0.09$ (P = 0.93) $-1.12$ posttreatment 3 months	Gandolfi 2014	7.07	17.21	12	3.8	12.06	10	10.5%	0.21 [-0.63, 1.05]	2014	
Straudi 2019       0.05       0.25       34       0.06       0.28       30       18.3%       -0.04 [-0.53, 0.45]       2019         Subtotal (95% CI)       137       132       100.0%       -0.02 [-0.36, 0.33]         Heterogeneity: Tau² = 0.10; Chi² = 12.64, df = 7 (P = 0.08); I² = 45%         Test for overall effect: Z = 0.09 (P = 0.93)         1.1.2 posttreatment 3 months	Straudi 2015	0.07	0.15	25	0.01	0.1	23	16.0%	0.46 [-0.12, 1.03]	2015	
Subtotal (95% CI)         137         132         100.0%         -0.02 [-0.36, 0.33]           Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 12.64, df = 7 (P = 0.08); I <sup>2</sup> = 45%         -0.02 [-0.36, 0.33]         -0.02 [-0.36, 0.33]           Test for overall effect: Z = 0.09 (P = 0.93)         -0.02 [-0.36, 0.33]         -0.02 [-0.36, 0.33]         -0.02 [-0.36, 0.33]           1.1.2 posttreatment 3 months         -0.09 (P = 0.93)         -0.09 (P = 0.93)         -0.09 (P = 0.93)         -0.09 (P = 0.93)	Straudi 2019	0.05	0.25	34	0.06	0.28	30	18.3%	-0.04 [-0.53, 0.45]	2019	
Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 12.64, df = 7 (P = 0.08); I <sup>2</sup> = 45% Test for overall effect: Z = 0.09 (P = 0.93) 1.1.2 posttreatment 3 months	Subtotal (95% CI)			137			132	100.0%	-0.02 [-0.36, 0.33]		-
Test for overall effect: Z = 0.09 (P = 0.93) 1.1.2 posttreatment 3 months	Heterogeneity: Tau <sup>2</sup> =	0.10; CI	hi <b>²</b> = 12.	64, df=	:7 (P=	0.08); l <sup>a</sup>	= 45%				
1.1.2 posttreatment 3 months	Test for overall effect: J	Z = 0.09	(P = 0.9)	33)	-						
1.1.2 posttreatment 3 months											
	1.1.2 posttreatment 3	month	S								
Schwartz 2012 0.05 0.1 9 0.06 0.2 15 15.1% -0.06 [-0.88, 0.77] 2011	Schwartz 2012	0.05	0.1	9	0.06	0.2	15	15.1%	-0.06 [-0.88, 0.77]	2011	
Straudi 2013 0.03 0.12 8 0.02 0.08 8 10.7% 0.09 0.89 1.07 2013	Straudi 2013	0.03	0.12	8	0.02	0.08	8	10.7%	0.09 [-0.89, 1.07]	2013	
Straudi 2015 0.03 0.15 25 -0.02 0.11 23 31.5% 0.37 F0.20 0.94 2015	Straudi 2015	0.03	0.15	25	-0.02	0.11	23	31.5%	0.37 [-0.20, 0.94]	2015	
Straudi 2019 0.02 0.25 34 0.03 0.28 30 42.7% -0.04 0.53 0.45 2019	Straudi 2019	0.02	0.25	34	0.03	0.28	30	42.7%	-0.04 [-0.53, 0.45]	2019	
Subtotal (95% CI) 76 76 100.0% 0.10 [-0.22, 0.42]	Subtotal (95% CI)			76			76	100.0%	0.10 [-0.22, 0.42]		+
Heterogeneity: Tau <sup>2</sup> = 0.00: Chi <sup>2</sup> = 1.31, df = 3 (P = 0.73); l <sup>2</sup> = 0%	Heterogeneity: Tau <sup>2</sup> =	0.00° CI	hi <sup>z</sup> = 1.3	1.df=	3 (P = 0	73): I <sup>2</sup> =	= 0%				
Test for overall effect $Z = 0.63$ ( $P = 0.53$ )	Test for overall effect:	7 = 0.63	IP = 0.5	53)							
				,							
1.1.3 Changes from basline to posttreatment (severe diasability)	1.1.3 Changes from b	asline t	o posttr	reatme	nt (sev	ere dias	ability				
Beer 2008 0.14 0.21 14 0.07 0.11 15 21.2% 0.41 F0.33 1.151 2007	Beer 2008	0.14	0.21	14	0.07	0.11	15	21.2%	0 41 60 33 1 151	2007	
Schwartz 2012 -0.01 0.1 12 0.1 0.2 16 20.2% -0.65 [-1.42, 0.12] 2011	Schwartz 2012	-0.01	0.1	12	0.01	0.2	16	20.2%	-0.65[-1.42_0.12]	2011	
	Straudi 2015	0.07	0.15	25	0.01	0.1	23	27.4%	0.46[-0.12, 1.03]	2015	
	Straudi 2010 Straudi 2019	0.05	0.75	34	0.06	0.28	30	31.7%	-0.04 [-0.53 0.45]	2010	<b>_</b>
Subtotal (95% CI) 85 81 84 100.0% 0.07 [-0.38 0.52]	Subtotal (95% CI)	0.00	0.20	85	0.00	0.20	84	100.0%	0.07 [-0.38, 0.52]	2010	-
Heterogeneity: Tou? - 0.10: Chi? - 6.08. df - 3.(P - 0.11): i? - 51%	Heterogeneity: Tau <sup>2</sup> -	0 1 0· CI	hi≅−60	9 df-	3 (P - 0	11):12-	- 51%				
The fore variable for $T = 0.31$ ( $P = 0.76$ )	Test for overall effect:	7 – 0 31	P = 0.0	0, ui – 76)	5(1 - 0		- 51 /0				
	reactor overall ellect.	2 - 0.51	(i = 0.1	0)							
1.1.4 Changes from basline to posttreatment (mild-moderate diasability)	1.1.4 Changes from b	asline t	o posttr	reatme	nt (mild	l-mode	rate dia	sability)			
	L o 2008	14	2.6	6	4.1	3	7	17 2%	-0.891-2.05_0.281	2008	
	Vaney 2012	0.03	0.00	26	n ng	017	23	26.2%	-0.44 [-1.01.0.13]	2000	
	Stroudi 2012	0.03	0.03	20	-0.03	0.17	20	20.3%	0.63 [.0.38 1.64]	2011	
Candel 2014 7.07 0.11 0 2.0 0.13 0 25.78 0.03 (0.05 (0.04) 2013	Condolfi 2014	7.07	17.21	12	20.01	12.06	10	26.7%	0.00[-0.00, 1.04]	2013	<b>_</b>
Subtotal (95% Cl) 52 48 100.0% -0.13 [-0.71, 0.45]	Subtotal (95% CI)	1.07	17.21	52	3.0	12.00	48	100.0%	-0.13 [-0.71, 0.45]	2014	
Heterogeneity: Tau <sup>2</sup> = 0.16; Chi <sup>2</sup> = 5.51, df = 3 (P = 0.14); i <sup>2</sup> = 46%	Heterogeneity: Tau <sup>2</sup> =	0.16; CI	hi² = 5.5	1, df =	3 (P = 0	.14); I² =	= 46%				
Test for overall effect: Z = 0.44 (P = 0.66)	Test for overall effect: 2	Z = 0.44	(P = 0.6	66)							
Eavours ICWTL Eavours IRAGT											Favours ICWTI Favours IRAGTI

Fig. 2. Forest plot of changes in gait speed after RAGT.



Fig. 3. Forest plot of changes in gait endurance after RAGT.

training OR robotic locomotor training OR robot assisted locomotor training OR driven-gait orthosis OR footplate OR exoskeleton OR end effector OR motor-driven devices OR mechanical devices). The "Related Articles" option in PubMed was used to broaden the search. No language restrictions were applied. The final search was performed in May 2019. We selected studies on the basis of the titles and abstracts meeting the selection criteria. The systematic review described here was accepted by PROSPERO, the online international prospective register of systematic reviews of the National Institute for Health Research (CRD42019128766).

# 2.3. Data extraction

Two authors (SWY and CHH) independently selected the RCTs and extracted the relevant details, such as number, age, and sex of participants; inclusion and exclusion criteria; RAGT strategies; and outcome parameters. The individually recorded information of both reviewers was compared, and a third reviewer (YCK) resolved any discrepancies.

#### 2.4. Methodological quality appraisal

The three aforementioned reviewers independently evaluated the methodological quality of the RCTs according to the Cochrane risk-forbias method 2.0, with several domains being evaluated (Sterne et al., 2019).

#### 2.5. Outcome assessment

The meta-analysis comprised two sections of comparison according to outcome changes from baseline to two specific timepoints: end of treatment and 3 months after treatment (long-term follow-up).

In each section, we evaluated the walking performance as the primary outcome, namely improvement in gait parameters (speed, endurance, stride length, double support time [DST], cadence), balance, and ambulation capability and several secondary outcomes, namely improvement in perceived fatigue, spasticity, global mobility, physical QOL, mental QOL, pain, ADL, Expanded Disability Status Scale (EDSS) (Kurtzke, 1983), and treatment acceptance. Improvement in gait speed was assessed using the 10-meter walking test (10MWT) (Kieseier and Pozzilli, 2012), timed 25-foot walk (T25FW) (Kieseier and Pozzilli, 2012), 20-meter timed walking, GAITRite system (Gold version 3.2b; CIR System Inc, Havertown, PA, USA) (Menz et al., 2004), or a 6camera motion capture system called VICON 460 (Oxford Metrics, Oxford, UK) surrounding a walkway. Improvement in gait endurance was assessed using the 6-min walking test (6MWT) (Kieseier and Pozzilli, 2012) or 2-min walking test (2MWT) (Kieseier and Pozzilli, 2012). Improvements in stride length, DST, and cadence were assessed using the GAITRite system or VICON 460. The Berg Balance Scale was used to assess improvement in balance (Berg et al., 1992). Improvement in ambulation mobility was assessed using functional ambulatory category (Holden et al., 1986) or timed up and go test (Podsiadlo and Richardson, 1991).

Improvement in perceived fatigue was assessed using Fatigue Severity Scale (Braley and Chervin, 2010) or by combining the

Chudu an Cubannun		RAGT	Tetel		CWT	Tetal	Mainhé	Mean Difference		Mean Difference
1.3.1 Changes from	baseline	to post	treatm	ent	50	Total	vvelqnt	IV, Random, 95% CI	rear	IV, Random, 95% CI
Schwartz 2012	3.4	4.1	12	5.8	5.3	16	18.8%	-2.40 [-5.88, 1.08]	2011	
Vaney 2012	1.69	3.93	26	2.91	3.29	23	33.4%	-1.22 [-3.24, 0.80]	2011	
Gandolfi 2014	6.08	4.55	12	4.2	4.89	10	15.6%	1.88 [-2.10, 5.86]	2014	
Straudi 2015	3.24	4.99	27	0.87	6.45	25	21.3%	2.37 [-0.78, 5.52]	2015	
Straudi 2019 Subtotal (95% CI)	3	10.63	34 111	2	9.93	30 104	10.9% <mark>100.0%</mark>	1.00 [-4.04, 6.04] <mark>0.05 [-1.81, 1.91]</mark>	2019	•
Heterogeneity: Tau <sup>2</sup> =	= 1.62; Cł	hi² = 6.33	3, df = -	4 (P = 0	.18); I <sup>z</sup> :	= 37%				
Test for overall effect	: Z = 0.05	(P = 0.9	96)							
1.3.2 posttreatment	3 month	s								
Schwartz 2012	0.7	7.6	9	3.1	8.9	15	15.5%	-2.40 [-9.10, 4.30]	2011	
Straudi 2015	1.72	6.05	25	-0.17	6.04	23	59.3%	1.89 [-1.53, 5.31]	2015	
Straudi 2019	0	11.1	34	0	10.34	30	25.2%	0.00 [-5.25, 5.25]	2019	
Subtotal (95% CI)			68			68	100.0%	0.75 [-1.89, 3.39]		
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Cł	hi <sup>2</sup> = 1.3	5, df = 3	2 (P = 0	.51); I²∍	= 0%				
Test for overall effect	: Z = 0.56	(P = 0.5	98)							
1.3.3 Changes from	basline t	o posttr	eatme	nt (sev	ere disa	ability)				
Schwartz 2012	3.4	4.1	12	5.8	5.3	16	36.3%	-2.40 [-5.88, 1.08]	2011	<b>_</b>
Straudi 2015	3.24	4.99	27	0.87	6.45	25	39.5%	2.37 [-0.78, 5.52]	2015	
Straudi 2019	3	10.63	34	2	9.93	30	24.2%	1.00 [-4.04, 6.04]	2019	
Subtotal (95% CI)			73			71	100.0%	0.31 [-2.81, 3.42]		
Heterogeneity: Tau <sup>2</sup> =	= 3.80; Cl	hi <sup>2</sup> = 4.04	4,df=∶ √_>	2 (P = 0	.13); P*	= 50%				
l est for overall effect	:Z=0.19	(P = 0.8	(5)							
1.3.4 Changes from	basline t	o posttr	eatme	nt (mild	-mode	rate dia	sability)			_
Vaney 2012	3.4	4.1	12	5.8	5.3	16	52.6%	-2.40 [-5.88, 1.08]	2011	
Gandolfi 2014	6.08	4.55	12	4.2	4.89	10	47.4%	1.88 [-2.10, 5.86]	2014	
Subtotal (95% CI)			24			26	100.0%	-0.37 [-4.56, 3.82]		
Heterogeneity: Tau <sup>2</sup> =	= 5.52; Cl	hif= 2.5:	2, df = 1	1 (P = 0	.11); <b>I</b> ≧⊧	= 60%				
Test for overall effect	: Z = 0.17	(P = 0.8	56)							
									-	
										-10 -5 0 5 10
										Favours [CWT] Favours [RAGT]

Fig. 4. Forest plot of changes in balance after RAGT.

		RAGT			CWT			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
1.4.1 Changes from I	baseline	to post	ttreatm	ent						
Schwartz 2012	6.5	9.1	12	3.2	8	16	18.5%	0.38 [-0.38, 1.13]	2011	
Straudi 2013	5.9	10	8	-0.6	2.4	8	13.8%	0.85 [-0.19, 1.88]	2013	
Straudi 2015	-2.66	13.79	27	3.96	10.5	25	22.6%	-0.53 [-1.08, 0.02]	2015	
Pompa 2016	0.66	1.08	21	0	0.85	22	21.3%	0.67 [0.05, 1.28]	2016	
Straudi 2019	-1.3	24.59	34	6.3	31.81	30	23.9%	-0.27 [-0.76, 0.23]	2019	
Subtotal (95% CI)			102			101	100.0%	0.15 [-0.37, 0.67]		
Heterogeneity: Tau <sup>2</sup> =	0.23; C	hi² = 12	.61, df=	= 4 (P =	0.01); P	²= 68%				
Test for overall effect:	Z = 0.55	5 (P = 0.	58)							
1.4.2 posttreatment	3 month	S								
Schwartz 2012	12.5	14.9	9	6	14.7	15	20.5%	0.42 [-0.41, 1.26]	2011	
Straudi 2013	5.5	11.9	8	0.7	2.3	8	16.3%	0.53 [-0.47, 1.53]	2013	
Straudi 2015	-4.6	15.3	25	3.63	10.61	23	29.7%	-0.61 [-1.19, -0.03]	2015	
Straudi 2019	-7.1	31.65	34	0	31.54	30	33.6%	-0.22 [-0.71, 0.27]	2019	
Subtotal (95% CI)			76			76	100.0%	-0.08 [-0.57, 0.41]		
Heterogeneity: Tau² =	: 0.12; C	hi² = 6.0	16, df =	3 (P = 0	.11); I² =	= 51%				
Test for overall effect:	Z = 0.33	3 (P = 0.	74)							
1.4.3 Changes from I	basline t	to postt	reatme	ent (seve	ere disa	ability)				
Schwartz 2012	6.5	9.1	12	3.2	8	16	21.3%	0.38 [-0.38, 1.13]	2011	
Straudi 2015	-2.66	13.79	27	3.96	10.5	25	26.2%	-0.53 [-1.08, 0.02]	2015	
Pompa 2016	0.66	1.08	21	0	0.85	22	24.7%	0.67 [0.05, 1.28]	2016	
Straudi 2019	-1.3	24.59	34	6.3	31.81	30	27.8%	-0.27 [-0.76, 0.23]	2019	
Subtotal (95% CI)			94			93	100.0%	0.03 [-0.51, 0.58]		
Heterogeneity: Tau² =	: 0.21; C	hi <sup>2</sup> = 10	.05, df=	= 3 (P =	0.02); P	²= 70%				
Test for overall effect:	Z = 0.12	? (P = 0.	91)							
										-2 -1 0 1 2
										Favours [CWT] Favours [RAGT]

Fig. 5. Forest plot of changes in ambulation capability after RAGT.



		RAGT			CWT			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.6.1 Changes from I	baseline	to posttre	eatmen	t (also	only severe	disab	ility)			
Vaney 2012	0.17	0.21	26	0.09	0.18	23	52.8%	0.40 [-0.17, 0.97]	2011	
Pompa 2016	1.65	0.89685	21	0.08	1.874935	22	47.2%	1.04 [0.40, 1.68]	2016	
Subtotal (95% CI)			47			45	100.0%	0.70 [0.08, 1.33]		
Heterogeneity: Tau <sup>2</sup> =	0.11; C	hi² = 2.15,	df = 1 (	P = 0.14	4); I <sup>2</sup> = 53%					
Test for overall effect:	Z = 2.20	) (P = 0.03	)							
									-	-2 -1 0 1 2
										Favours (CWT) Favours (RAGT)

Fig. 7. Forest plot of changes in spasticity after RAGT.

cognitive and physical fatigue score in Würzburger Erschöpfungsinventar bei Multipler Sklerose scale, developed by Flachenecker (Flachenecker et al., 2008). Spasticity was assessed using the Ashworth Scale (Nuyens et al., 1994) or 100-mm visual analog scale (VAS, from "no problem" to "very bad"), whereas global mobility was assessed using the Rivermead Mobility Index (Forlander and Bohannon, 1999). Improvement in physical/mental QOL was evaluated by extracting the physical component summary/mental component summary from the 36-Item Short Form Survey (SF-36) (Ware and Sherbourne, 1992) or the Hebrew version of the Medical Outcomes Study Short-Form 36 (RAND-36) (Lewin-Epstein et al., 1998) or by extracting the summary scores of physical health/mental health from the Multiple Sclerosis Quality of Life-54 (MSQOL-54) questionnaire (Solari et al., 1999). Improvement in pain was evaluated using VAS (0–10) (P. Jensen and Karoly, 1992) or by extracting the subitem "bodily pain" from SF-36. Improvement in ADL was evaluated using the modified Barthel Index (Shah et al., 1989) or functional independence measure (Keith et al., 1987). Finally, treatment acceptance was assessed using VAS (0–10).

#### 2.6. Subgroup analysis

Owing to the variation in the severity of MS in the included trials, we further performed a subgroup analysis after treatment. The RCTs were divided into two subgroups: trials enrolling patients with severe disability (EDSS: 5–7.5) (Beer et al., 2008; Pompa et al., 2017; Schwartz et al., 2012; Straudi et al., 2016; Straudi et al., 2019) and trials enrolling patients with mild-to-moderate disability (EDSS: 1.5–6.5 or being able to walk 25 ft without assistance) (Gandolfi et al., 2014; Lo and Triche, 2008; Straudi et al., 2013; Vaney et al., 2012).

	F	RAGT			CWT			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
1.7.1 Changes from b	aseline	to pos	sttreat	ment						
Schwartz 2012	1.98	8.6	12	9.5	15.5	16	16.2%	-0.56 [-1.33, 0.20]	2011	
Gandolfi 2014	-3.33	6.44	12	1.75	7.65	10	12.5%	-0.70 [-1.57, 0.17]	2014	
Straudi 2015	1.67	7.74	27	1.84	6.77	25	32.0%	-0.02 [-0.57, 0.52]	2015	
Straudi 2019 Subtotal (05% CI)	1	6.66	34	2	8.9	30	39.2%	-0.13 [-0.62, 0.36]	2019	
Subtotal (95% CI)			CO	a (6	0.470.	10	100.0%	-0.24 [-0.34, 0.07]		-
Heterogeneity: Tau* =	0.00; C	nr= 2.	.55, at =	= 3 (P =	0.47);	1~= 0%				
Test for overall effect.	Z = 1.50	I (P = U	).13)							
1.7.2 posttreatment 3	month	S								
Schwartz 2012	-3.9	15.3	9	-0.34	16	15	18.5%	-0.22 [-1.05, 0.61]	2011	
Straudi 2015	5.11	16.6	25	1.04	6.24	23	35.9%	0.31 [-0.26, 0.88]	2015	
Straudi 2019	-1	7.33	34	1	8.9	30	45.6%	-0.24 [-0.74, 0.25]	2019	
Subtotal (95% CI)			68			68	100.0%	-0.04 [-0.41, 0.33]		-
Heterogeneity: Tau <sup>2</sup> =	0.02; C	hi² = 2.	.32, df=	= 2 (P =	0.31);	$ ^2 = 149$	Хо			
Test for overall effect:	Z = 0.20	) (P = 0	).84)							
1.7.3 Changes from b	asline t	o post	treatm	ent (se	vere d	isabilit	y)			
Schwartz 2012	1.98	8.6	12	9.5	15.5	16	18.5%	-0.56 [-1.33, 0.20]	2011	
Straudi 2015	1.67	7.74	27	1.84	6.77	25	36.6%	-0.02 [-0.57, 0.52]	2015	
Straudi 2019	1	6.66	34	2	8.9	30	44.9%	-0.13 [-0.62, 0.36]	2019	
Subtotal (95% CI)			73			71	100.0%	-0.17 [-0.50, 0.16]		
Heterogeneity: Tau <sup>2</sup> =	0.00; C	hi <b>²</b> = 1.	.31, df=	= 2 (P =	0.52);	I <sup>2</sup> = 0%				
Test for overall effect:	Z = 1.01	(P = 0	).31)							
										-2 -1 0 1 2
										Favours [CWT] Favours [RAGT]

Fig. 8. Forest plot of changes in physical QOL after RAGT.

		RAGT			CWT			Std. Mean Difference		Std. Mean Difference
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random. 95% CI	Year	IV. Random, 95% Cl
1.8.1 Changes from I	baseline	to post	treatm	ent						
Schwartz 2012	-0.38	13.3	12	12.1	17	16	23.1%	-0.78 [-1.56, 0.00]	2011	
Gandolfi 2014	2.1	16.1	12	5.73	14.81	10	22.0%	-0.22 [-1.07, 0.62]	2014	
Straudi 2015	5.37	9.58	27	1.6	9.47	25	27.2%	0.39 [-0.16, 0.94]	2015	+
Straudi 2019	9	8.88	34	1	9.93	30	27.8%	0.84 [0.33, 1.36]	2019	
Subtotal (95% CI)			85			81	100.0%	0.11 [-0.57, 0.79]		
Heterogeneity: Tau² =	0.37; C	hi <b>²</b> = 13.	22, df=	= 3 (P =	0.004);	<sup>2</sup> = 779	Ж			
Test for overall effect:	Z = 0.32	? (P = 0.7	75)							
4.0.2 poottrootmont	month									
1.8.2 postireaunent .	5 monu	5			40.0		40.000		0044	
Schwartz 2012	4	30.2	9	6.3	16.2	15	16.2%	-0.10 [-0.93, 0.73]	2011	
Straudi 2015	-2.52	14.11	25	1.08	8.74	23	34.2%	-0.30 [-0.87, 0.27]	2015	
Straudi 2019	-1	10.33	30	-1	9.33	40	49.6%	0.00 [-0.47, 0.47]	2019	
Subiotal (95% CI)			04			18	100.0%	-0.12 [-0.45, 0.21]		
Heterogeneity: Tau* =	0.00; C	hr= 0.6	3, df =	2 (P = 0	.73); I*=	= 0%				
Test for overall effect:	Z = 0.70	) (P = 0.4	19)							
1.8.3 Changes from I	basline t	to posttr	eatme	ent (sev	ere disa	ability)				
Schwartz 2012	-0.38	13.3	12	12.1	17	16	30.1%	-0.78 [-1.56, 0.00]	2011	
Straudi 2015	5.37	9.58	27	1.6	9.47	25	34.6%	0.39 [-0.16, 0.94]	2015	
Straudi 2019	9	8.88	34	1	9.93	30	35.3%	0.84 [0.33, 1.36]	2019	
Subtotal (95% CI)			73			71	100.0%	0.20 [-0.64, 1.04]		
Heterogeneity: Tau <sup>2</sup> =	0.45; C	hi² = 11.	59, df=	= 2 (P =	0.003);	I <sup>2</sup> = 839	%			
Test for overall effect:	Z = 0.48	6 (P = 0.6	64)							
										-2 -1 U I Z
										Favours [CWF1] Favours [RAG1]

Fig. 9. Forest plot of changes in mental QOL after RAGT.

# 2.7. Sensitivity analysis

As two types of RAGT (Lokomat and Gait Trainer GTII) were applied in the RCTs and we included only two trials using Gait Trainer GTII, there were inadequate data to perform subgroup analysis to evaluate the respective effect of these two devices. Therefore, we performed a sensitivity analysis only including the trials using Lokomat.

# 2.8. Statistical analysis

We used Review Manager (version 5.3; Cochrane Collaboration, Oxford, UK) to perform a meta-analysis of the RCTs according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Liberati et al., 2009). The mean difference (MD) or standardized mean difference (SMD) was calculated as the effect size for continuous outcomes. The accuracy of the result was reported as a 95% confidence interval (CI). P < 0.05 was considered statistically



Fig. A.1. Forest plot of changes in stride strength after RAGT.



Fig. A.2. Forest plot of changes in double support time after RAGT.



Fig. A.3. Forest plot of changes in cadence after RAGT.

		RAGT			CWT			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.12.1 Changes from	baselin	e to posttre	eatmen	t (also	only severe	disab	lity)			
Vaney 2012	0.77	0.82	26	0.35	0.93	23	52.8%	0.47 [-0.10, 1.04]	2011	
Pompa 2016	2	1.883481	21	1.27	2.257251	22	47.2%	0.34 [-0.26, 0.95]	2016	
Subtotal (95% CI)			47			45	100.0%	0.41 [-0.00, 0.83]		-
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	hi² = 0.09, d	f=1 (P	= 0.76)	; I² = 0%					
Test for overall effect:	Z = 1.95	i (P = 0.05)								
										Favours (CWT) Favours (RAGT)

Fig. A.4. Forest plot of changes in global mobility after RAGT.

significant. When necessary, the means and standard deviations of pretreatment–post-treatment changes were estimated according to the reported pre- and post-treatment data (Hozo et al., 2005; Wan et al., 2014). DerSimonian and Laird random-effects model was used for calculating a pooled estimate of the MD (DerSimonian and Laird, 2015). To assess the heterogeneity among these trials, the  $I^2$  test was performed.

# 3. Results

# 3.1. Study selection and characteristics of included studies

Fig. 1 illustrates a flowchart of the study selection process. We initially identified 339 potential trials but excluded 119 duplicates and 151 ineligible articles after screening their titles and abstracts. Subsequently, 59 additional reports were excluded owing to the following reasons: 21 were on different topics, 6 used different comparisons, 11 were review articles, 3 were systematic reviews, 2 were meta-analyses, 1 was a protocol, 5 were conference abstracts, 1 was an ongoing RCT, 2 were RCTs with unknown status, and 7 were case studies. Finally, 10 RCTs were further analyzed.

The characteristics of the 10 eligible studies (Beer et al., 2008; Gandolfi et al., 2014; Lo and Triche, 2008; Pompa et al., 2017; Schwartz et al., 2012; Straudi et al., 2013, 2016; Straudi et al., 2019; Vaney et al., 2012; Wier et al., 2011) are summarized in Table 1. Given that the studies by Lo and Wier consisted of the same group participants (Lo and Triche, 2008; Wier et al., 2011), 9 different trials were included. These trials were published between 2008 and 2019, with





Fig. A.6. Forest plot of changes in ADL after RAGT.



Fig. A.7. Forest plot of changes in EDSS after RAGT.

Study or Subgroup	F	RAGT	Total	Moan	CWT	Total	Woight	Std. Mean Difference	Voar	Std. Mean Difference
Study of Subgroup	Mean	30	Total	Mean	30	Total	weight	IV, Nanuoni, 55% CI	Tear	IV, Randolli, 55% Cl
Straudi 2013	9	1.7	8	7.7	2.5	8	22.8%	0.57 [-0.43, 1.58]	2013	
Straudi 2015	8.62	1.63	27	8.09	1.72	25	77.2%	0.31 [-0.24, 0.86]	2015	
Total (95% CI)			35			33	100.0%	0.37 [-0.11, 0.85]		-
Heterogeneity: Tau <sup>2</sup> =	0.00; CI	hi² = 0. ∕⊡ = 0	.20, df=	= 1 (P =	0.65);	I <sup>2</sup> = 0%				-2 -1 0 1 2
restion overall effect.	2 = 1.52	(F=0	1.13)							Favours [CWT] Favours [RAGT]

Fig. A.8. Forest plot of treatment acceptance after RAGT.

sample sizes of 13–64 patients aged 46–61 years. The gender distribution in the intervention and control groups was comparable in most RCTs, with two trials including more female patients in control groups (Gandolfi et al., 2014; Straudi et al., 2013). One study provided no information about gender distribution (Vaney et al., 2012). All patients had been diagnosed with MS, using McDonald's criteria (Polman et al., 2011), with a wide range of disability (EDSS: 1.5–7.5) and different clinical status, including primary progressive (PP), secondary progressive (SP), or relapsing-remitting (RR); however, patients with recent relapse were excluded. Studies by Lo and Lauren reported no



Fig. A.9. Forest plot of changes in gait speed after Lokomat-based RAGT.

baseline EDSS of participants, but claimed that only patients with gait difficulties but being able to walk 25 feet were included.

Regarding RAGT devices and parameters, eight studies used Lokomat (Beer et al., 2008; Lo and Triche, 2008; Schwartz et al., 2012; Straudi et al., 2013, 2016; Straudi et al., 2019; Vaney et al., 2012; Wier et al., 2011) while two RCTs applied Gait Trainer GTII (Gandolfi et al., 2014; Pompa et al., 2017). The overall walking speed ranged from 0.1 to 3 km/h, with one trial adjusting the speed to 6 km/h in the second session of training (Gandolfi et al., 2014). One RCT regulated the speed on observation of gait (Vaney et al., 2012), and two studies offered no information about walking speed (Lo and Triche, 2008; Wier et al., 2011). Most RCTs initiated the training with 0%–100% (mostly 40%–50%) of BWS and regulated the support in later sessions according to subject performance; however, two studies did not provide any information on BWS (Lo and Triche, 2008; Wier et al., 2011). The training ranged from 6 to 15 sessions over 3–6 weeks, and the net walking duration in each session ranged 20–40 min.

With regard to CWT, the details of the procedure in each study are summarized in Table 1. The components of CWT mostly comprised walking exercises over the ground, stretching, and muscle-strengthening exercises, with two studies using BWSTT (Lo and Triche, 2008; Wier et al., 2011) and one study (Gandolfi et al., 2014) applying sensory integration balance training (SIBT), a specific training program featuring three levels of exercise difficulty under three different sensory conditions (Nichols, 1997; Smania et al., 2010).

#### 3.2. Study quality

As shown in Table 2, the methodological quality of the 10 studies was summarized. Two RCTs had a low overall risk of bias (Gandolfi et al., 2014; Straudi et al., 2019), another six studies showed some concerns (Beer et al., 2008; Lo and Triche, 2008; Pompa et al., 2017; Schwartz et al., 2012; Straudi et al., 2016; Vaney et al., 2012), and the other two trials had high overall risk of bias (Straudi et al., 2013; Wier et al., 2011). Thus, all RCTs reported acceptable methods of randomization, but seven studies described possible or unclear allocation concealment methods (Beer et al., 2008; Gandolfi et al., 2014; Lo and Triche, 2008; Schwartz et al., 2012; Straudi et al., 2013, 2016; Wier et al., 2011). Six RCTs reported outcome assessor blinding (Beer et al., 2008; Gandolfi et al., 2014; Pompa et al., 2017; Schwartz et al., 2012; Straudi et al., 2016; Straudi et al., 2019), whereas the remaining RCTs did not provide any relevant information. With regard to data analysis, four RCTs used a modified intention-to-treat analysis (Gandolfi et al., 2014; Schwartz et al., 2012; Straudi et al., 2016; Vaney et al., 2012), two studies used an intention-to-treat analysis (Lo and Triche, 2008; Wier et al., 2011), and the other four trials used a per-protocol analysis (Beer et al., 2008; Pompa et al., 2017; Straudi et al., 2013; Straudi et al., 2019). One RCT used a per-protocol analysis for long-term follow-up (Schwartz et al., 2012). The follow-up time-points were as follows: end of the treatment (3-6 weeks from initiation) in all studies, 1 month after treatment in one trial (Gandolfi et al., 2014), 3 months after treatment in four RCTs

Study or Subgroup         Mean         SD         Total         Weight         IV, Random, 95% CI         Year         IV, Random, 95% CI           2.2.1 Changes from baseline to posttreatment         Beer 2008         20.54         29.65         14         12.73         46.62         15         17.2%         0.19 [-0.54, 0.92]         2007           Lo 2008         51.3         69.7         6         72.1         54.8         7         10.4%         -0.31 [-1.41, 0.79]         2008           Schwartz 2012         17.6         31.5         12         30.2         37.6         16         16.66%         -0.35 [-1.10, 0.41]         2011           Straudi 2013         33.2         25.1         8         -0.7         31.4         8         10.7%         1.13 [0.05, 2.21]         2013           Straudi 2015         23.22         32.2         5         -0.75         26.4         23         21.0%         0.80 [0.21, 1.39]         2015           Subtotal (95% CI)         99         100.0%         0.25 [-0.18, 0.67]         0.25 [-0.18, 0.67]         0.25 [-0.18, 0.67]         0.25 [-0.18, 0.67]           Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); P <sup>2</sup> = 49%         -0.28 [-1.11, 0.55]         2011         -0.28 [-1.11, 0.55]         2011			RAGT			CWT			Std. Mean Difference		Std. Mean Difference
2.2.1 Changes from baseline to posttreatment         Beer 2008       20.54       29.65       14       12.73       46.62       15       17.2%       0.19 [-0.54, 0.92]       2007         Lo 2008       51.3       69.7       6       72.1       54.8       7       10.4%       -0.31 [-1.41, 0.79]       2008         Schwartz 2012       17.6       31.5       12       30.2       37.6       16       16.6%       -0.35 [-1.10, 0.41]       2011         Straudi 2013       33.2       25.1       8       -0.7       31.4       8       10.7%       1.13 [0.05, 2.21]       2013         Straudi 2015       23.22       32.2       32.5       -0.75       26.4       23       21.0%       0.80 [0.21, 1.39]       2015         Subtotal (95% CI)       99       99       100.0%       0.25 [-0.18, 0.67]       0.25 [-0.18, 0.67]         Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); P = 49%       7       12.8 %       -0.28 [-1.11, 0.55]       2011         Schwartz 2012       12       35.1       9       22.2       35       15       18.8%       -0.28 [-1.11, 0.55]       2011         Straudi 2013       32.1       26.2       8       -3.8       32.9       8	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
Beer 2008 $20.54$ $29.65$ $14$ $12.73$ $46.62$ $15$ $17.2\%$ $0.19 [-0.54, 0.92]$ $2007$ Lo 2008 $51.3$ $69.7$ $6$ $72.1$ $54.8$ $7$ $10.4\%$ $-0.31 [-1.41, 0.79]$ $2008$ Schwartz 2012 $17.6$ $31.5$ $12$ $30.2$ $37.6$ $16$ $16.6\%$ $-0.35 [-1.10, 0.41]$ $2011$ Straudi 2013 $33.2$ $25.1$ $8$ $-0.7$ $31.4$ $8$ $10.7\%$ $1.13 [0.05, 2.21]$ $2013$ Straudi 2015 $23.22$ $32.2$ $32.2$ $-0.75$ $26.4$ $23$ $21.0\%$ $0.80 [0.21, 1.39]$ $2015$ Subtotal (95% CI)       99       99 $100.0\%$ $0.25 [-0.18, 0.67]$ $0.25 [-0.18, 0.67]$ Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); P = 49\% $99$ $100.0\%$ $0.28 [-1.11, 0.55]$ $2011$ Schwartz 2012       12 $35.1$ $9$ $22.2$ $35$ $15$ $18.8\%$ $-0.28 [-1.11, 0.55]$ $2011$ Straudi 2013 $32.1$ $26.2$ $8$ $3$	2.2.1 Changes from	baseline	to posttrea	tment							
Lo 2008 51.3 69.7 6 72.1 54.8 7 10.4% -0.31 [-1.41, 0.79] 2008 Schwartz 2012 17.6 31.5 12 30.2 37.6 16 16.6% -0.35 [-1.10, 0.41] 2011 Straudi 2013 33.2 25.1 8 -0.7 31.4 8 10.7% 1.13 [0.05, 2.21] 2013 Straudi 2015 23.22 32.23 25 -0.75 26.4 23 21.0% 0.80 [0.21, 1.39] 2015 Straudi 2019 19 77.2 34 14 84.15 30 24.0% 0.06 [-0.43, 0.55] 2019 Subtotal (95% CI) 99 99 100.0% 0.25 [-0.18, 0.67] Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); P = 49% Test for overall effect: $Z = 1.14$ (P = 0.26) 2.2.2 posttreatment 3 months Schwartz 2012 12 35.1 9 22.2 35 15 18.8% -0.28 [-1.11, 0.55] 2011 Straudi 2013 32.1 26.2 8 -3.8 32.9 8 12.3% 1.14 [0.06, 2.22] 2013 Straudi 2015 10.64 35.07 25 4.51 33.59 23 31.7% 0.18 [-0.39, 0.74] 2015	Beer 2008	20.54	29.65	14	12.73	46.62	15	17.2%	0.19 [-0.54, 0.92]	2007	
Schwartz 2012       17.6       31.5       12       30.2       37.6       16       16.6%       -0.35 [-1.10, 0.41]       2011         Straudi 2013       33.2       25.1       8       -0.7       31.4       8       10.7%       1.13 [0.05, 2.21]       2013         Straudi 2015       23.22       32.23       25       -0.75       26.4       23       21.0%       0.80 [0.21, 1.39]       2015         Straudi 2019       19       77.72       34       14       84.15       30       24.0%       0.06 [-0.43, 0.55]       2019         Subtotal (95% CI)       99       99       100.0%       0.25 [-0.18, 0.67]       0.25 [-0.18, 0.67]         Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); P = 49%       Test for overall effect: Z = 1.14 (P = 0.26)	Lo 2008	51.3	69.7	6	72.1	54.8	7	10.4%	-0.31 [-1.41, 0.79]	2008	
Straudi 2013 $33.2$ $25.1$ $8$ $-0.7$ $31.4$ $8$ $10.7\%$ $1.13$ $[0.05, 2.21]$ $2013$ Straudi 2015 $23.22$ $32.23$ $25$ $-0.75$ $26.4$ $23$ $21.0\%$ $0.80$ $[0.21, 1.39]$ $2015$ Straudi 2019       19 $77.72$ $34$ $14$ $84.15$ $30$ $24.0\%$ $0.06$ $[-0.43, 0.55]$ $2019$ Subtotal (95% Cl)       99       99 $100.0\%$ $0.25$ $[-0.18, 0.67]$ Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); I <sup>2</sup> = 49%       Test for overall effect: $Z = 1.14$ (P = 0.26) $Z$ $25.1$ $9$ $22.2$ $35.1$ $9$ $22.2$ $35.1$ $15.8\%$ $-0.28$ [-1.11, 0.55] $2011$ Straudi 2013 $32.1$ $26.2$ $8$ $12.3\%$ $1.14$ [ $0.06, 2.22$ ] $2013$ Straudi 2015 $10.64$ $36.07$ $25.4.51$ $33.59$ $23.31.7\%$ $0.18$ [-0.39, 0.74] $2015$	Schwartz 2012	17.6	31.5	12	30.2	37.6	16	16.6%	-0.35 [-1.10, 0.41]	2011	
Straudi 2015       23.22 $32.23$ $25$ $-0.75$ $26.4$ $23$ $21.0\%$ $0.80$ $[0.21, 1.39]$ $2015$ Straudi 2019       19 $77.72$ $34$ $14$ $84.15$ $30$ $24.0\%$ $0.06$ $[-0.43, 0.55]$ $2019$ Subtotal (95% CI)       99       99       100.0% $0.25$ $[-0.18, 0.67]$ Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); I <sup>2</sup> = 49%       Test for overall effect: $Z = 1.14$ (P = 0.26) $Z$ $2.2.2$ posttreatment 3 months         Schwartz 2012       12 $35.1$ 9 $22.2$ $35$ $15$ $18.8\%$ $-0.28$ [-1.11, 0.55] $2011$ Straudi 2013 $32.1$ $26.2$ $8$ $32.9$ $8$ $12.3\%$ $1.14$ [0.06, 2.22] $2013$ Straudi 2015 $10.64$ $35.07$ $25$ $4.51$ $33.59$ $23$ $31.7\%$ $0.18$ [-0.39, 0.74] $2015$	Straudi 2013	33.2	25.1	8	-0.7	31.4	8	10.7%	1.13 [0.05, 2.21]	2013	
Straudi 2019       19       77.72       34       14       84.15       30       24.0%       0.06 [-0.43, 0.55]       2019         Subtotal (95% Cl)       99       99       100.0%       0.25 [-0.18, 0.67]       0.25 [-0.18, 0.67]         Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); I <sup>2</sup> = 49%       7       7       7       7         Test for overall effect: Z = 1.14 (P = 0.26)       2.2.2 posttreatment 3 months       -0.28 [-1.11, 0.55]       2011         Schwartz 2012       12       35.1       9       22.2       35       15       18.8%       -0.28 [-1.11, 0.55]       2011         Straudi 2013       32.1       26.2       8       -3.8       32.9       8       12.3%       1.14 [0.06, 2.22]       2013         Straudi 2015       10.64       35.07       25       4.51       33.59       23       31.7%       0.18 [-0.39, 0.74]       2015	Straudi 2015	23.22	32.23	25	-0.75	26.4	23	21.0%	0.80 [0.21, 1.39]	2015	<b>-</b> _
Subtotal (95% Cl)       99       99       100.0%       0.25 [-0.18, 0.67]         Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); I <sup>2</sup> = 49%       -       -       -         Test for overall effect: Z = 1.14 (P = 0.26)       -       -       -       -         2.2.2 posttreatment 3 months       -       -       -       -       -         Schwartz 2012       12       35.1       9       22.2       35       15       18.8%       -0.28 [-1.11, 0.55]       2011         Straudi 2013       32.1       26.2       8       -3.8       32.9       8       12.3%       1.14 [0.06, 2.22]       2013         Straudi 2015       10.64       35.07       25       4.51       33.59       23       31.7%       0.18 [-0.39, 0.74]       2015	Straudi 2019	19	77.72	34	14	84.15	30	24.0%	0.06 [-0.43, 0.55]	2019	
Heterogeneity: Tau <sup>2</sup> = 0.13; Chi <sup>2</sup> = 9.85, df = 5 (P = 0.08); I <sup>2</sup> = 49% Test for overall effect: Z = 1.14 (P = 0.26) 2.2.2 posttreatment 3 months Schwartz 2012 12 35.1 9 22.2 35 15 18.8% -0.28 [-1.11, 0.55] 2011 Straudi 2013 32.1 26.2 8 -3.8 32.9 8 12.3% 1.14 [0.06, 2.22] 2013 Straudi 2015 10.64 35.07 25 4.51 33.59 23 31.7% 0.18 [-0.39, 0.74] 2015	Subtotal (95% CI)			99			99	100.0%	0.25 [-0.18, 0.67]		-
Test for overall effect: Z = 1.14 (P = 0.26)         2.2.2 posttreatment 3 months         Schwartz 2012       12       35.1       9       22.2       35       15       18.8%       -0.28 [-1.11, 0.55]       2011         Straudi 2013       32.1       26.2       8       -3.8       32.9       8       12.3%       1.14 [0.06, 2.22]       2013         Straudi 2015       10.64       36.07       25       4.51       33.59       23       31.7%       0.18 [-0.39, 0.74]       2015	Heterogeneity: Tau <sup>2</sup> =	0.13; Ch	ni² = 9.85, df	f= 5 (P	= 0.08)	; I² = 49%					
2.2.2 posttreatment 3 months           Schwartz 2012         12         35.1         9         22.2         35         15         18.8%         -0.28 [-1.11, 0.55]         2011           Straudi 2013         32.1         26.2         8         -3.8         32.9         8         12.3%         1.14 [0.06, 2.22]         2013           Straudi 2015         10.64         35.07         25         4.51         33.59         23         31.7%         0.18 [-0.39, 0.74]         2015	Test for overall effect:	Z=1.14	(P = 0.26)								
2.2.2 posttreatment 3 months           Schwartz 2012         12         35.1         9         22.2         35         15         18.8%         -0.28 [-1.11, 0.55]         2011         Image: colspan="5">Image: colspan="5">Image: colspan="5"           Straudi 2013         32.1         26.2         8         -3.8         32.9         8         12.3%         1.14 [0.06, 2.22]         2013         Image: colspan="5">Image: colspan="5"           Straudi 2015         10.64         35.07         25         4.51         33.59         23         31.7%         0.18 [-0.39, 0.74]         2015         Image: colspan="5">Image: colspan="5"											
Schwartz 2012         12         35.1         9         22.2         35         15         18.8%         -0.28 [-1.11, 0.55]         2011           Straudi 2013         32.1         26.2         8         -3.8         32.9         8         12.3%         1.14 [0.06, 2.22]         2013           Straudi 2015         10.64         35.07         25         4.51         33.59         23         31.7%         0.18 [-0.39, 0.74]         2015	2.2.2 posttreatment	3 months	6								
Straudi 2013         32.1         26.2         8         -3.8         32.9         8         12.3%         1.14 [0.06, 2.22]         2013           Straudi 2015         10.64         35.07         25         4.51         33.59         23         31.7%         0.18 [-0.39, 0.74]         2015         Image: Contrast of the strand stran	Schwartz 2012	12	35.1	9	22.2	35	15	18.8%	-0.28 [-1.11, 0.55]	2011	
Straudi 2015 10.64 35.07 25 4.51 33.59 23 31.7% 0.18 [-0.39, 0.74] 2015	Straudi 2013	32.1	26.2	8	-3.8	32.9	8	12.3%	1.14 [0.06, 2.22]	2013	
	Straudi 2015	10.64	35.07	25	4.51	33.59	23	31.7%	0.18 [-0.39, 0.74]	2015	
Straudi 2019 5 74.79107 34 0 81.42993 30 37.3% 0.06 (-0.43, 0.55) 2019	Straudi 2019	5	74.79107	34	0	81.42993	30	37.3%	0.06 [-0.43, 0.55]	2019	
Subtotal (95% CI) 76 76 100.0% 0.17 [-0.25, 0.58]	Subtotal (95% CI)			76			76	100.0%	0.17 [-0.25, 0.58]		-
Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup> = 4.39, df = 3 (P = 0.22); l <sup>2</sup> = 32%	Heterogeneity: Tau <sup>2</sup> =	: 0.06; Ch	ni² = 4.39, df	f= 3 (P	= 0.22)	; I² = 32%					
Test for overall effect: Z = 0.79 (P = 0.43)	Test for overall effect:	Z = 0.79	(P = 0.43)								
2.2.3 Changes from basline to posttreatment (severe disability)	2.2.3 Changes from	basline to	o posttreati	ment (	severe	disability)					
Beer 2008 20.54 29.65 14 12.73 46.62 15 21.5% 0.19 [-0.54, 0.92] 2007	Beer 2008	20.54	29.65	14	12.73	46.62	15	21.5%	0.19 [-0.54, 0.92]	2007	
Schwartz 2012 17.6 31.5 12 30.2 37.6 16 20.8% -0.35 [-1.10, 0.41] 2011	Schwartz 2012	17.6	31.5	12	30.2	37.6	16	20.8%	-0.35 [-1.10, 0.41]	2011	
Straudi 2015 23.22 32.23 25 -0.75 26.4 23 26.7% 0.80 [0.21, 1.39] 2015	Straudi 2015	23.22	32.23	25	-0.75	26.4	23	26.7%	0.80 [0.21, 1.39]	2015	
Straudi 2019 19 77.72 34 14 84.15 30 31.0% 0.06 (-0.43, 0.55) 2019	Straudi 2019	19	77.72	34	14	84.15	30	31.0%	0.06 [-0.43, 0.55]	2019	
Subtotal (95% Cl) 85 84 100.0% 0.20 [-0.25, 0.66]	Subtotal (95% CI)			85			84	100.0%	0.20 [-0.25, 0.66]		
Heterogeneity: Tau <sup>2</sup> = 0.11; Chi <sup>2</sup> = 6.25, df = 3 (P = 0.10); l <sup>2</sup> = 52%	Heterogeneity: Tau <sup>2</sup> =	: 0.11; Ch	ni² = 6.25, df	f= 3 (P	= 0.10)	; I² = 52%					
Test for overall effect: Z = 0.87 (P = 0.39)	Test for overall effect:	Z = 0.87	(P = 0.39)								
2.2.4 Changes from basline to posttreatment (mild-moderate diasability)	2.2.4 Changes from	basline to	o posttreati	ment (I	mild-mo	oderate dia	sability	)			
Lo 2008 51.3 69.7 6 72.1 54.8 7 49.7% -0.31 [-1.41, 0.79] 2008	Lo 2008	51.3	69.7	6	72.1	54.8	7	49.7%	-0.31 [-1.41, 0.79]	2008	
Straudi 2013 33.2 25.1 8 -0.7 31.4 8 50.3% 1.13 [0.05, 2.21] 2013	Straudi 2013	33.2	25.1	8	-0.7	31.4	8	50.3%	1.13 [0.05, 2.21]	2013	
Subtotal (95% Cl) 14 15 100.0% 0.41 [-1.00, 1.82]	Subtotal (95% CI)			14			15	100.0%	0.41 [-1.00, 1.82]		
Heterogeneity: Tau <sup>2</sup> = 0.73; Chi <sup>2</sup> = 3.36, df = 1 (P = 0.07); l <sup>2</sup> = 70%	Heterogeneity: Tau <sup>2</sup> =	: 0.73; Ch	ni² = 3.36, df	f=1 (P	= 0.07)	; I² = 70%					
Test for overall effect: Z = 0.57 (P = 0.57)	Test for overall effect:	Z=0.57	(P = 0.57)								
										-	-2 -1 0 1 2
Favours ICWTI Favours IRAGTI											Favours [CWT] Favours [RAGT]

Fig. A.10. Forest plot of changes in gait endurance after Lokomat-based RAGT.

(Schwartz et al., 2012; Straudi et al., 2013, 2016; Straudi et al., 2019), and 6 months after treatment in two studies (Beer et al., 2008; Schwartz et al., 2012). Participants of both intervention and control groups in three RCTs underwent standardized rehabilitation programs (Beer et al., 2008; Pompa et al., 2017; Vaney et al., 2012), and those in one RCT performed lower limb and core-stretching exercises during the study period (Straudi et al., 2019). Patients in two studies continued their normal physical activities (Lo and Triche, 2008; Wier et al., 2011), and in another two RCTs, physiotherapies other than RAGT or CWT were not allowed; however, no other restrictions of activity were imposed (Gandolfi et al., 2014; Straudi et al., 2019). Three studies did not provide any information in this regard (Schwartz et al., 2012; Straudi et al., 2013, 2016).

# 3.3. Changes from baseline to end of treatment

# 3.3.1. Primary outcomes

The meta-analysis showed comparable improvement in gait speed (pooled SMD: -0.02, 95% CI: -0.36-0.33,  $I^2 = 45\%$ ; Fig. 2), gait endurance (pooled SMD: 0.26, 95% CI: -0.08-0.61,  $I^2 = 40\%$ ; Fig. 3), stride length (Fig. A.1), DST (Fig. A.2), cadence (Fig. A.3), balance (pooled MD: 0.05, 95% CI: -1.81-1.91,  $I^2 = 37\%$ ; Fig. 4), and ambulation capability (pooled SMD: 0.15, 95% CI: -0.37-0.67,  $I^2 = 68\%$ ; Fig. 5) between RAGT and CWT.

# 3.3.2. Secondary outcomes

After the intervention, individuals receiving RAGT felt less fatigue and spasticity than those undergoing CWT (pooled SMD: 0.34, 95% CI: 0.02–0.67,  $I^2 = 34\%$ ; pooled MD: 0.70, 95% CI: 0.08–1.33,  $I^2 = 53\%$ ,

respectively; Figs. 6 and 7). The result also demonstrated a trend of more beneficial in global mobility after RAGT compared with that after CWT (pooled SMD: 0.41, 95% CI: -0.00-0.83, I<sup>2</sup> = 0%; Fig. A.4). Besides, RAGT was as effective as CWT in improving the other secondary outcomes including physical/mental QOL, pain, ADL, and EDSS (Fig. 8 and 9, Fig. A.5–7). Treatment acceptance of RAGT was comparable with that of CWT (Fig. A.8).

3.4. Changes from baseline to 3 months after treatment (long-term followup)

#### 3.4.1. Primary outcomes

Three months after treatment, the results showed comparable improvement in gait speed (Fig. 2), gait endurance (Fig. 3), balance (Fig. 4), and ambulation capability (Fig. 5) between RAGT group and CWT group.

#### 3.4.2. Secondary outcomes

Our analysis revealed that RAGT lost its superiority over CWT in reducing perceived fatigue 3 months after treatment (Fig. 6), but comparable improvement in other secondary outcomes between RAGT and CWT were still observed (Figs. 8 and 9, Fig. A.5).

#### 3.5. Subgroup analysis

In the "severe disability" subgroup, we found comparable effectiveness between RAGT and CWT in any of the outcomes being assessed (Figs. 2–6, 8 and 9, Figs. A.5–7). RAGT showed even more benefits in improving spasticity and global mobility (borderline) than CWT did

	RAGT CWT							Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl		
2.3.1 Changes from	baseline	to post	treatm	ent								
Schwartz 2012	3.4	4.1	12	5.8	5.3	16	22.6%	-2.40 [-5.88, 1.08]	2011			
Vaney 2012	1.69	3.93	26	2.91	3.29	23	38.6%	-1.22 [-3.24, 0.80]	2011			
Straudi 2015	3.24	4.99	27	0.87	6.45	25	25.4%	2.37 [-0.78, 5.52]	2015			
Straudi 2019 Subtotal (95% CI)	3	10.63	34 99	2	9.93	30 94	13.4% 100.0%	1.00 [-4.04, 6.04] -0.28 [-2.36, 1.81]	2019	-		
Heterogeneity: Tau <sup>2</sup> = 1.87; Chi <sup>2</sup> = 5.15, df = 3 (P = 0.16); l <sup>2</sup> = 42%												
Test for overall effect	Z = 0.28	6 (P = 0.8	30)									
2.3.2 posttreatment	3 month	S										
Schwartz 2012	0.7	7.6	9	3.1	8.9	15	15.5%	-2.40 [-9.10, 4.30]	2011			
Straudi 2015	1.72	6.05	25	-0.17	6.04	23	59.3%	1.89 [-1.53, 5.31]	2015			
Straudi 2019	0	11.1	34	0	10.34	30	25.2%	0.00 [-5.25, 5.25]	2019			
Subtotal (95% CI)			68			68	100.0%	0.75 [-1.89, 3.39]				
Heterogeneity: Tau² =	= 0.00; C	hi <b>²</b> = 1.3	5, df =	2 (P = 0	.51); I²∍	= 0%						
Test for overall effect	: Z = 0.56	6 (P = 0.9	58)									
2.3.3 Changes from	basline t	to postti	reatme	nt (sev	ere disa	ability)						
Schwartz 2012	3.4	4.1	12	5.8	5.3	16	36.3%	-2.40 [-5.88, 1.08]	2011			
Straudi 2015	3.24	4.99	27	0.87	6.45	25	39.5%	2.37 [-0.78, 5.52]	2015			
Straudi 2019	3	10.63	34	2	9.93	30	24.2%	1.00 [-4.04, 6.04]	2019			
Subtotal (95% CI)			73			71	100.0%	0.31 [-2.81, 3.42]				
Heterogeneity: Tau² =	= 3.80; C	hi² = 4.0	4, df =	2 (P = 0	.13); I²∍	= 50%						
Test for overall effect	:Z=0.19	9 (P = 0.8	35)									
2.3.4 Changes from	basline t	to postti	reatme	nt (mild	-mode	rate dia	asability)			_		
Vaney 2012	3.4	4.1	12	5.8	5.3	16	100.0%	-2.40 [-5.88, 1.08]	2011			
Subtotal (95% CI)			12			16	100.0%	-2.40 [-5.88, 1.08]				
Heterogeneity: Not ap	oplicable	•										
Test for overall effect	Z = 1.35	5 (P = 0.1	18)									
										-4 -2 0 2 4		
										Favours [CWT] Favours [RAGT]		

Fig. A.11. Forest plot of changes in balance after Lokomat-based RAGT.

	RAGT CWT							Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
2.4.1 Changes from b	baseline	to post	treatm	ent						
Schwartz 2012	6.5	9.1	12	3.2	8	16	22.9%	0.38 [-0.38, 1.13]	2011	
Straudi 2013	5.9	10	8	-0.6	2.4	8	16.2%	0.85 [-0.19, 1.88]	2013	
Straudi 2015	-2.66	13.79	27	3.96	10.5	25	29.4%	-0.53 [-1.08, 0.02]	2015	
Straudi 2019	-1.3	24.59	34	6.3	31.81	30	31.5%	-0.27 [-0.76, 0.23]	2019	
Subtotal (95% CI)			81			79	100.0%	-0.02 [-0.54, 0.51]		
Heterogeneity: Tau² =	0.17; C	hi² = 7.4	2, df =	3 (P = 0	.06); I <sup>z</sup> =	= 60%				
Test for overall effect:	Z = 0.08	6 (P = 0.9	95)							
2.4.2 posttreatment :	3 month	S								
Schwartz 2012	12.5	14.9	9	6	14.7	15	20.5%	0.42 [-0.41, 1.26]	2011	
Straudi 2013	5.5	11.9	8	0.7	2.3	8	16.3%	0.53 [-0.47, 1.53]	2013	
Straudi 2015	-4.6	15.3	25	3.63	10.61	23	29.7%	-0.61 [-1.19, -0.03]	2015	
Straudi 2019	-7.1	31.65	34	0	31.54	30	33.6%	-0.22 [-0.71, 0.27]	2019	
Subtotal (95% CI)			76			76	100.0%	-0.08 [-0.57, 0.41]		
Heterogeneity: Tau² =	0.12; C	hi <b>²</b> = 6.0	6, df=	3 (P = 0	.11); I≧=	= 51%				
Test for overall effect:	Z = 0.33	3 (P = 0.1	74)							
0.4.0.01						L 114 A				
2.4.3 Changes from t	Dasiine t	to postt	reatme	ent (sev	ere disa	ability)				
Schwartz 2012	6.5	9.1	12	3.2	8	16	24.5%	0.38 [-0.38, 1.13]	2011	
Straudi 2015	-2.66	13.79	27	3.96	10.5	25	35.6%	-0.53 [-1.08, 0.02]	2015	
Straudi 2019	-1.3	24.59	34	6.3	31.81	30	39.9%	-0.27 [-0.76, 0.23]	2019	
Subtotal (95% CI)			13			1	100.0%	-0.20 [-0.66, 0.26]		
Heterogeneity: Tau <sup>2</sup> =	0.07; C	hi² = 3.6	2, df =	2 (P = 0	.16); I <b>≊</b> =	= 45%				
Test for overall effect:	∠ = 0.88	5 (P = 0.3	39)							
										-2 -1 0 1 2
										Favours [CWT] Favours [RAGT]

Fig. A.12. Forest plot of changes in ambulation capability after Lokomat-based RAGT.

	F	RAGT			CWT			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
2.5.1 Changes from b	asline	to post	treatm	nent						
Vaney 2012	8.69	6.86	26	5.95	4.89	23	27.3%	0.45 [-0.12, 1.02]	2011	
Straudi 2013	1.2	1.31	8	0.6	1.54	8	9.0%	0.40 [-0.60, 1.39]	2013	
Straudi 2015	0.23	1.05	25	0.01	1.15	23	27.4%	0.20 [-0.37, 0.76]	2015	
Straudi 2019 Subtotal (95% CI)	0.4	0.95	34 93	0.2	1.1	30 84	36.4%	0.19 [-0.30, 0.69]	2019	•
Heterogeneity: Tau <sup>2</sup> =	0.00.0	$hi^2 = 0$	50 df:	= 3 (P =	n anv	I <sup>2</sup> = 0%	1001070	0120 [ 0102; 0100]		-
Test for overall effect:	Z = 1.86	6 (P = 0	.00, ur - ).06)		0.00),	1 - 0 /0				
			,							
2.5.2 posttreatment 3	3 month	s follo	w-up							
Straudi 2013	0.5	1.59	8	0.5	1.51	8	12.5%	0.00 [-0.98, 0.98]	2013	
Straudi 2015	-0.18	0.87	25	-0.18	1.16	23	37.6%	0.00 [-0.57, 0.57]	2015	<b>_</b>
Straudi 2019	0.1	0.95	34	0	1.14	30	49.9%	0.09 [-0.40, 0.59]	2019	
Subtotal (95% CI)			67			61	100.0%	0.05 [-0.30, 0.39]		-
Heterogeneity: Tau² =	0.00; C	hi² = 0.	.07, df=	= 2 (P =	0.96);	I <sup>2</sup> = 0%				
Test for overall effect:	Z = 0.27	7 (P = 0	).79)							
2.5.3 Changes from b	asline	to post	treatm	nent (se	vere d	isabilit	v)			
Straudi 2015	0.23	1.05	25	0.01	1.15	23	42.9%	0.20 (-0.37, 0.76)	2015	
Straudi 2019	0.4	0.95	34	0.2	1.1	30	57.1%	0.19 [-0.30, 0.69]	2019	
Subtotal (95% CI)			59			53	100.0%	0.19 [-0.18, 0.57]		<b>*</b>
Heterogeneity: Tau <sup>2</sup> =	0.00; C	hi² = 0.	.00, df=	= 1 (P =	0.99);	l <sup>2</sup> = 0%				
Test for overall effect:	Z = 1.03	8 (P = 0	).30)							
2.5.4 Changes from b	asline	to post	treatm	nent (mi	ld-mo	derate	diasabilit	(V)		
Vanev 2012	8.69	6.86	26	5.95	4.89	23	75.3%	0.45 (-0.12, 1.02)	2011	+- <b>B</b>
Straudi 2013	1.2	1.31	8	0.6	1.54	8	24.7%	0.40 [-0.60, 1.39]	2013	
Subtotal (95% CI)			34			31	100.0%	0.44 [-0.06, 0.93]		-
Heterogeneity: Tau <sup>2</sup> =	0.00; C	hi <b>=</b> 0.	.01, df=	= 1 (P =	0.93);	I <sup>2</sup> = 0%				
Test for overall effect:	Z = 1.73	3 (P = 0	).08)							
										-2 -1 0 1 2
										Favours [CWT] Favours [RAGT]

Fig. A.13. Forest plot of changes in fatigue after Lokomat-based RAGT.



Fig. A.14. Forest plot of changes in spasticity after Lokomat-based RAGT.

# (Fig. 7 and Fig. A.4, respectively).

In the "mild to moderate disability" subgroup, comparable improvement between RAGT and CWT in any of the outcomes being evaluated was observed (Figs. 2–4, 6, Figs. A.1–A.3).

# 3.6. Sensitivity analysis

When we only included studies in which Lokomat was used, we found that RAGT was as effective as CWT in all outcome while lost its superiority in improving fatigue, spasticity and global mobility (Fig. A.9–A.24) whether immediately after or 3 months after the intervention.

# 3.7. Side effects

Four RCTs (including three trials) reported no adverse effect during RAGT treatment (Lo and Triche, 2008; Schwartz et al., 2012; Straudi et al., 2019; Wier et al., 2011). One RCT reported a patient developing ankle sprain (not related to the interventions) one day before final outcome assessment and some patients with minor bruising

from the straps (Vaney et al., 2012). Another trial reported two dropouts in the RAGT group owing to skin irritation over the knee and lower leg caused by the fixation belt, which later underwent full recovery (Beer et al., 2008). The other four RCTs (Gandolfi et al., 2014; Pompa et al., 2017; Straudi et al., 2013, 2016) provided no information about side effects; however, one of these trials reported that RAGT is a safe and well-tolerated therapy (Straudi et al., 2013).

# 4. Discussion

To the best of our knowledge, this is the most updated systematic review and meta-analysis involving 312 patients to specifically evaluate the efficacy of RAGT in MS. The results demonstrated that RAGT was not only as effective as CWT in improving walking performance and several functional outcomes but also more beneficial to improving perceived fatigue and spasticity, especially in patients with severe disability due to MS. A possible reason for the limited superiority of RAGT over CWT in some outcome is the insufficient total net walking time (240–360 min) in the RCTs included in our meta-analysis, which is shorter than the net walking time in the RCTs focusing on other diseases

	F	RAGT		(	CWT			Std. Mean Difference		Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI			
2.7.1 Changes from baseline to posttreatment													
Schwartz 2012	1.98	8.6	12	9.5	15.5	16	18.5%	-0.56 [-1.33, 0.20]	2011				
Straudi 2015	1.67	7.74	27	1.84	6.77	25	36.6%	-0.02 [-0.57, 0.52]	2015				
Straudi 2019	1	6.66	34	2	8.9	30	44.9%	-0.13 [-0.62, 0.36]	2019				
Subtotal (95% CI)			73			71	100.0%	-0.17 [-0.50, 0.16]		-			
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.31, df = 2 (P = 0.52); l <sup>2</sup> = 0%													
Test for overall effect:	Z = 1.01	(P = 0	1.31)										
2.7.2 posttreatment 3	s month	S											
Schwartz 2012	-3.9	15.3	9	-0.34	16	15	18.5%	-0.22 [-1.05, 0.61]	2011				
Straudi 2015	5.11	16.6	25	1.04	6.24	23	35.9%	0.31 [-0.26, 0.88]	2015				
Straudi 2019	-1	7.33	34	1	8.9	30	45.6%	-0.24 [-0.74, 0.25]	2019				
Subtotal (95% CI)			68			68	100.0%	-0.04 [-0.41, 0.33]		-			
Heterogeneity: Tau² =	0.02; C	hi <b>²</b> = 2.	32, df=	= 2 (P =	0.31);	$ ^{2} = 14^{\circ}$	%						
Test for overall effect:	Z = 0.20	) (P = 0	1.84)										
273 Changos from k	aclino f	to nost	troatm	ont lea	voro d	icabilit	2						
Z.r.J Changes non it	4 00	o posi	40	ienii (se	vere u	1500111	<b>3)</b>	0.0014.00.0.001	2044				
Schwanz 2012	1.98	8.6	12	9.5	15.5	16	18.5%	-0.56 [-1.33, 0.20]	2011				
Straudi 2015	1.67	1.74	21	1.84	0.11	25	30.0%	-0.02 [-0.57, 0.52]	2015				
Straudi 2019 Subtotal (05% CI)	1	0.00	34	2	8.9	30	44.9%	-0.13 [-0.02, 0.36]	2019	-			
Subtotal (95% Cl)	0.00.0	6.7 - A	10	200-	0.500.	17 - 000	100.0%	-0.17 [-0.50, 0.10]					
Heterogeneity, rau-=	0.00, C	nr= 1.	31, ur=	= 2 (P =	0.52);	1-= 0%							
Test for overall effect:	∠ = 1.01	(P=0	1.31)										
										-2 -1 0 1 2			
										Favours [CWT] Favours [RAGT]			

Fig. A.15. Forest plot of changes in physical QOL after Lokomat-based RAGT.

	RAGT CWT							Std. Mean Difference		Std. Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI			
2.8.1 Changes from baseline to posttreatment													
Schwartz 2012	-0.38	13.3	12	12.1	17	16	30.1%	-0.78 [-1.56, 0.00]	2011				
Straudi 2015	5.37	9.58	27	1.6	9.47	25	34.6%	0.39 [-0.16, 0.94]	2015				
Straudi 2019 Subtotal (95% CI)	9	8.88	34 73	1	9.93	30 71	35.3% 100.0%	0.84 [0.33, 1.36] 0.20 [-0.64, 1.04]	2019				
Heterogeneity: Tau <sup>2</sup> = 0.45; Chi <sup>2</sup> = 11.59, df = 2 (P = 0.003); l <sup>2</sup> = 83%													
Test for overall effect: Z = 0.46 (P = 0.64)													
202													
2.8.2 posttreatment .	s month	S											
Schwartz 2012	4	30.2	9	6.3	16.2	15	16.2%	-0.10 [-0.93, 0.73]	2011				
Straudi 2015	-2.52	14.11	25	1.08	8.74	23	34.2%	-0.30 [-0.87, 0.27]	2015				
Straudi 2019	-1	10.33	30	-1	9.33	40	49.6%	0.00 [-0.47, 0.47]	2019				
Subtotal (95% CI)			04			18	100.0%	-0.12 [-0.45, 0.21]					
Heterogeneity: Tau* =	0.00; C	hr = 0.6	3, df =	2 (P = 0	.73); P	'= 0%							
l est for overall effect:	Z = 0.70	$\Gamma(P=0.)$	49)										
2.8.3 Changes from t	oasline t	o postt	reatme	nt (sev	ere dis	sability	)						
Schwartz 2012	-0.38	13.3	12	12.1	17	16	30.1%	-0.78 [-1.56, 0.00]	2011				
Straudi 2015	5.37	9.58	27	1.6	9.47	25	34.6%	0.39 [-0.16, 0.94]	2015	+-			
Straudi 2019	9	8.88	34	1	9.93	30	35.3%	0.84 [0.33, 1.36]	2019				
Subtotal (95% CI)			73			71	100.0%	0.20 [-0.64, 1.04]					
Heterogeneity: Tau <sup>2</sup> =	0.45; C	hi² = 11.	59, df=	= 2 (P =	0.003)	); <b>I</b> ≊ = 83	3%						
Test for overall effect:	Z = 0.48	i (P = 0.)	64)										
										+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$			
										Eavours [CWT] Eavours [RAGT]			
										. Liveno [orright around [resol]			

Fig. A.16. Forest plot of changes in mental QOL after Lokomat-based RAGT.

such as stroke (mostly 600 min) (Cho et al., 2018), SCI (mostly 720 min) (Nam et al., 2017), or Parkinson disease (mostly > 360 min) (Alwardat et al., 2018). Our results differed from a previous systematic review/meta-analysis (including 7 trials) investigating merely gait-related outcomes (Xie et al., 2017). The previous study showed that RAGT significantly improved gait endurance when compared with that of CWT at the end of the treatment. Our study including 10 RCTs showed that RAGT was only comparable to CWT in improving gait performance but superior to CWT in reducing fatigue and spasticity in the group receiving RAGT. However, both studies expressed reservations about recommending patients with MS to receive RAGT as the primary rehabilitation intervention.

Early in 2001, Colombo et al. compared the effects of manually assisted locomotor training with RAGT in patients with paraplegia (Colombo et al., 2001). They concluded that RAGT is more reproducible with the ability to test and thus optimize the biomechanical gait pattern, whereas manual-assisted training often requires a longer time for therapists to be specialized to offer optimal training. Another advantage of RAGT is that participants can receive more intense training sessions when the training is performed at a higher speed with a prolonged







Fig. A.18. Forest plot of changes in double support time after Lokomat-based RAGT.







Fig. A.20. Forest plot of changes in global mobility after Lokomat-based RAGT.

duration. Further, therapists can reduce their burden from repetitive physical work via RAGT. As a result, we are anticipating more studies assessing the satisfaction of RAGT among practitioners.

Our meta-analysis showed significantly less fatigue and spasticity and better global mobility in RAGT group than CWT group. Most RCTs included in our study used the Lokomat-based RAGT with exoskeleton, while 2 RCTs used RAGT with end-effector device (Gait Trainer GTII\*) (Gandolfi et al., 2014; Pompa et al., 2017). After sensitivity analysis of only including the Lokomat-based system, RAGT did not show the superiority than CWT. A previous study suggested that an end-effector robotic device is less constrictive or assistive to the pelvis and allows patients to vary their gait pattern more freely than the exoskeleton approach through voluntary contraction of major proximal leg muscles during gait training (Morone et al., 2014). This might explain the benefits regarding fatigue, spasticity and global mobility of RAGT mainly contributing from the trials using end-effector device. Recently, a novel RAGT system characterized by a hybrid of end-effector and exoskeleton was reported to be safe, feasible, and potentially beneficial to patients with stroke (Lin et al., 2017). We are looking forward to the effect of this innovative system on MS as it provides the advantages of both Lokomat and Gait Trainer GTII.

Besides, Calabrò et al. had applied Lokomat-based RAGT equipped with virtual reality (VR) system in MS patients with walking disabilities as compared to RAGT without VR. That RCT showed comparable efficacy in motor function (Berg Balance Scale and TUG) between RAGT with VR and RAGT without VR. Furthermore, RAGT with VR yielded additional effect on psychological outcomes (greater positive attitude and problem-solving ability) rather than purely RAGT. The contribution of VR to RAGT effects may depend on the improvement in either attention/motivation/motor learning (as the immediate feedback to performance) or mood (Calabro et al., 2017). In the future, combined RAGT with VR may be another valuable management in patients with



Fig. A.21. Forest plot of changes in pain after Lokomat-based RAGT.



Fig. A.22. Forest plot of changes in ADL after Lokomat-based RAGT.



Fig. A.23. Forest plot of changes in EDSS after Lokomat-based RAGT.

	F	RAGT			CWT			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
Straudi 2013	9	1.7	8	7.7	2.5	8	15.9%	1.30 [-0.79, 3.39]	2013	
Straudi 2015	8.62	1.63	27	8.09	1.72	25	84.1%	0.53 [-0.38, 1.44]	2015	
<b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.00; C Z = 1.53	hi² = 0. } (P = (	<mark>35</mark> .44, df= ).13)	= 1 (P =	0.51);	<mark>33</mark>  ² = 0%	100.0%	0.65 [-0.18, 1.49]		
			,							Favours [CW1] Favours [RAG1]

Fig. A.24. Forest plot of treatment acceptance after Lokomat-based RAGT.

# MS.

Our review has some limitations. First, most studies did not clearly report the allocation concealment (Beer et al., 2008; Gandolfi et al., 2014; Lo and Triche, 2008; Schwartz et al., 2012; Straudi et al., 2013, 2016; Straudi et al., 2019; Wier et al., 2011). Second, most studies only blinded the outcome assessors, and four studies provided insufficient information on blinding (Lo and Triche, 2008; Schwartz et al., 2012; Straudi et al., 2013; Wier et al., 2011). Considering that some outcomes such as fatigue, QOL, and pain were subjective parameters, the above shortcomings may introduce allocation bias, performance bias, and detection bias. Third, there were still a few dropouts owing to MS relapse, personal or family reasons, difficulty in transportation, or other

medical complications in some trials; some patients were lost to followup without a clear reason. Either per-protocol analysis or intention-totreat analysis was applied, which may have introduced attrition bias. Fourth, heterogeneity of the baseline characteristics of participants (RR, PP, SP), training protocols (6–15 sessions over 3–6 weeks), and methods used in both RAGT and CWT (BWSTT, over-ground walking, SIBT) groups was found in the RCTs included in the present study. Fifth, the participants in some studies also received a standardized rehabilitation program or maintained their normal physical activities, whereas in other studies, this information was not provided. Those activities may act as confounding factors for clarifying the separate roles of RAGT and CWT.

Despite these limitations, the present study was the most updated and largest systematic review and meta-analysis to provide the most relevant available evidence on whether RAGT confers further benefits to CWT besides motor function outcomes. In addition, this is the first study to perform subgroup analysis according to different levels of disability of patients with MS.

In conclusion, our data indicated that at the end of the treatment, RAGT is comparable to CWT in improving walking performance, QOL, pain, and ADL. RAGT was even significantly superior to CWT in improving perceived fatigue and spasticity. Comparable effectiveness between these two interventions was also found after 3 months of followup. Moreover, RAGT is safe, well tolerated for individuals with MS and less demanding for physical therapists, so it could be considered in patients with MS. However, further larger-scale, better-designed RCTs with a longer training duration and more studies evaluating the satisfaction of RAGT are warranted.

# **Funding sources**

This work is supported by a research grant from Taipei Medical University (grant No. TMU106-AE1-B45). The sponsoring organization was not involved in the study design, data analysis, or interpretation.

# CRediT authorship contribution statement

**Shu-Wei Yeh:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing original draft. **Li-Fong Lin:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing - original draft. **Ka-Wai Tam:** Supervision, Writing - review & editing, Funding acquisition. **Ching-Piao Tsai:** Resources, Software. **Chien-Hsiung Hong:** Formal analysis, Supervision, Validation, Writing - original draft, Data curation, Formal analysis. **Yi-Chun Kuan:** Formal analysis, Supervision, Validation, Data curation, Writing - review & editing, Funding acquisition.

# **Declarations of Competing Interest**

None.

# Acknowledgments

This manuscript was edited by Wallace Academic Editing. This study was supported by. Taipei Medical University and the Center for Evidence-Based Health Care, a department of Medical Research in Shuang Ho Hospital.

# References

Alwardat, M., Etoom, M., Al Dajah, S., Schirinzi, T., Di Lazzaro, G., Sinibaldi Salimei, P., Biagio Mercuri, N., Pisani, A., 2018. Effectiveness of robot-assisted gait training on motor impairments in people with Parkinson's disease: a systematic review and metaanalysis. Int. J. Rehab. Res. Internationale Zeitschrift fur Rehabilitationsforschung. Revue Internationale de Recherches de Readaptation 41 (4), 287–296.

- Beer, S., Aschbacher, B., Manoglou, D., Gamper, E., Kool, J., Kesselring, J., 2008. Robot-Assisted Gait Training in Multiple sclerosis: a Pilot Randomized Trial 14. Multiple sclerosis (Houndmills, Basingstoke, England, pp. 231–236.
- Benedetti, M.G., Gasparroni, V., Stecchi, S., Zilioli, R., Straudi, S., Piperno, R., 2009. Treadmill exercise in early mutiple sclerosis: a case series study. Eur. J. Phys. Rehabil. Med. 45 (1), 53–59.
- Berg, K.O., Wood-Dauphinee, S.L., Williams, J.I., Maki, B., 1992. Measuring balance in the elderly: validation of an instrument. Can. J. Public Health 83 (2), S7–11 Suppl. Braley, T.J., Chervin, R.D., 2010. Fatigue in multiple sclerosis: mechanisms, evaluation,
- and treatment. Sleep 33 (8), 1061–1067. Calabro, R.S., Russo, M., Naro, A., De Luca, R., Leo, A., Tomasello, P., Molonia, F.,
- Dattola, V., Bramanti, A., Bramanti, P., 2017. Robotic gait training in multiple sclerosis rehabilitation: can virtual reality make the difference? Findings from a randomized controlled trial. J. Neurol. Sci. 377, 25–30.
- Cattaneo, D., De Nuzzo, C., Fascia, T., Macalli, M., Pisoni, I., Cardini, R., 2002. Risks of falls in subjects with multiple sclerosis. Arch. Phys. Med. Rehabil. 83 (6), 864–867.
- Cho, J.E., Yoo, J.S., Kim, K.E., Cho, S.T., Jang, W.S., Cho, K.H., Lee, W.H., 2018. Systematic review of appropriate robotic intervention for gait function in subacute stroke patients. Biomed Res Int 2018, 4085298.
- Colombo, G., Wirz, M., Dietz, V., 2001. Driven gait orthosis for improvement of locomotor training in paraplegic patients. Spinal Cord 39 (5), 252–255.
- Confavreux, C., Vukusic, S., 2006. Natural history of multiple sclerosis: a unifying concept. Brain 129 (Pt 3), 606–616.
- DerSimonian, R., Laird, N., 2015. Meta-analysis in clinical trials revisited. Contemp. Clin. Trials 45 (Pt A), 139–145.
- Feinstein, A., Freeman, J., Lo, A.C., 2015. Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. Lancet Neurol. 14 (2), 194–207.
- Flachenecker, P., König, H., Meissner, H., Müller, G., Rieckmann, P., 2008. Fatigue in multiple sclerosis: validation of the Weimus scale ("Würzburger erschöpfungs-inventar bei multipler sklerose").
- Forlander, D.A., Bohannon, R.W., 1999. Rivermead mobility index: a brief review of research to date. Clin. Rehabil. 13 (2), 97–100.
- Gandolfi, M., Geroin, C., Picelli, A., Munari, D., Waldner, A., Tamburin, S., Marchioretto, F., Smania, N., 2014. Robot-assisted vs. sensory integration training in treating gait and balance dysfunctions in patients with multiple sclerosis: a randomized controlled trial. Front. Hum. Neurosci. 8, 318.
- Gardner, M.B., Holden, M.K., Leikauskas, J.M., Richard, R.L., 1998. Partial body weight support with treadmill locomotion to improve gait after incomplete spinal cord injury: a single-subject experimental design. Phys. Ther. 78 (4), 361–374.
- Gervasoni, E., Cattaneo, D., Jonsdottir, J., 2014. Effect of treadmill training on fatigue in multiple sclerosis: a pilot study. Int. J. Rehab. Res. Internationale Zeitschrift fur Rehabilitationsforschung. Revue Internationale de Recherches de Readaptation 37 (1), 54–60.
- Giesser, B., Beres-Jones, J., Budovitch, A., Herlihy, E., Harkema, S., 2007. Locomotor Training Using Body Weight Support on a Treadmill Improves Mobility in Persons With Multiple Sclerosis: a Pilot Study 13. Multiple sclerosis (Houndmills, Basingstoke, England, pp. 224–231.
- Hesse, S., Konrad, M., Uhlenbrock, D., 1999. Treadmill walking with partial body weight support versus floor walking in hemiparetic subjects. Arch. Phys. Med. Rehabil. 80 (4), 421–427.
- Holden, M.K., Gill, K.M., Magliozzi, M.R., 1986. Gait assessment for neurologically impaired patients. Standards for outcome assessment. Phys. Ther. 66 (10), 1530–1539.
- Hozo, S.P., Djulbegovic, B., Hozo, I., 2005. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 5, 13.
- Keith, R.A., Granger, C.V., Hamilton, B.B., Sherwin, F.S., 1987. The functional independence measure: a new tool for rehabilitation. Adv. Clin. Rehabil. 1, 6–18.
- Kieseier, B.C., Pozzilli, C., 2012. Assessing walking disability in multiple sclerosis. Mult. Scler. J. 18 (7), 914–924.
- Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33 (11), 1444–1452.
- Lewin-Epstein, N., Sagiv-Schifter, T., Shabtai, E.L., Shmueli, A., 1998. Validation of the 36-item short-form health survey (Hebrew version) in the adult population of Israel. Med. Care 36 (9), 1361–1370.
- Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6 (7), e1000100.
- Lin, L.F., Huang, S.W., Chang, K.H., Ouyang, J.H., Liou, T.H., Lin, Y.N., 2017. A novel robotic gait training system (RGTS) may facilitate functional recovery after stroke: a feasibility and safety study. NeuroRehabilitation 41 (2), 453–461.
- Lo, A.C., Triche, E.W., 2008. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. Neurorehabil. Neural Repair 22 (6), 661–671.
- Menz, H.B., Latt, M.D., Tiedemann, A., Mun San Kwan, M., Lord, S.R., 2004. Reliability of the GAITRite walkway system for the quantification of temporo-spatial parameters of gait in young and older people. Gait Posture 20 (1), 20–25.
- Morone, G., Iosa, M., Tamburella, F., Muzzioli, L., Pisotta, I., Moreno, J., L. Pons, J., Paolucci, S., Cincotti, F., Molinari, M., 2014. An EMG pattern comparison of exoskeleton vs. end-effector robotic device for assisted walking training, pp. 563–567.
- Nam, K.Y., Kim, H.J., Kwon, B.S., Park, J.W., Lee, H.J., Yoo, A., 2017. Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review. J. Neuroeng. Rehabil. 14 (1), 24.
- Newman, M.A., Dawes, H., van den Berg, M., Wade, D.T., Burridge, J., Izadi, H., 2007. Can Aerobic Treadmill Training Reduce the Effort of Walking and Fatigue in People with Multiple Sclerosis: a Pilot Study 13. Multiple sclerosis (Houndmills, Basingstoke, England, pp. 113–119.

Nichols, D.S., 1997. Balance retraining after stroke using force platform biofeedback. Phys. Ther. 77 (5), 553–558.

- Nuyens, G., De Weerdt, W., Ketelaer, P., Feys, H., De Wolf, L., Hantson, L., Nieuwboer, A., Spaepen, A., Carton, H., 1994. Inter-rater reliability of the Ashworth scale in multiple sclerosis.
- P. Jensen, M., Karoly, P., 1992. Self-Report scales and procedures for assessing pain in adults.
- Pilutti, L.A., Lelli, D.A., Paulseth, J.E., Crome, M., Jiang, S., Rathbone, M.P., Hicks, A.L., 2011. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. Arch. Phys. Med. Rehabil. 92 (1), 31–36.
- Podsiadlo, D., Richardson, S., 1991. The timed "Up & go": a test of basic functional mobility for frail elderly persons. J. Am. Geriatr. Soc. 39 (2), 142–148.
- Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., Fujihara, K., Havrdova, E., Hutchinson, M., Kappos, L., Lublin, F.D., Montalban, X., O'Connor, P., Sandberg-Wollheim, M., Thompson, A.J., Waubant, E., Weinshenker, B., Wolinsky, J.S., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69 (2), 292–302.
- Pompa, A., Morone, G., Iosa, M., Pace, L., Catani, S., Casillo, P., Clemenzi, A., Troisi, E., Tonini, A., Paolucci, S., Grasso, M.G., 2017. Does Robot-Assisted Gait Training Improve Ambulation in Highly Disabled Multiple Sclerosis people? A pilot Randomized Control Trial 23. Multiple sclerosis, (Houndmills, Basingstoke, England, pp. 696–703.
- Schwartz, I., Sajin, A., Moreh, E., Fisher, I., Neeb, M., Forest, A., Vaknin-Dembinsky, A., Karusis, D., Meiner, Z., 2012. Robot-Assisted Gait Training in Multiple Sclerosis patients: a Randomized Trial 18. Multiple sclerosis (Houndmills, Basingstoke, England, pp. 881–890.
- Shah, S., Vanclay, F., Cooper, B., 1989. Improving the sensitivity of the Barthel index for stroke rehabilitation. J. Clin. Epidemiol. 42 (8), 703–709.
- Smania, N., Corato, E., Tinazzi, M., Stanzani, C., Fiaschi, A., Girardi, P., Gandolfi, M., 2010. Effect of balance training on postural instability in patients with idiopathic Parkinson's disease. Neurorehabil. Neural Repair 24 (9), 826–834.
- Solari, A., Filippini, G., Mendozzi, L., Ghezzi, A., Cifani, S., Barbieri, E., Baldini, S., Salmaggi, A., Mantia, L.L., Farinotti, M., Caputo, D., Mosconi, P., 1999. Validation of Italian multiple sclerosis quality of life 54 questionnaire. J. Neurol. Neurosurg. Psychiatr. 67 (2), 158–162.
- Sterne, J.A.C., Savovic, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C.J., Cheng, H.Y., Corbett, M.S., Eldridge, S.M., Emberson, J.R., Hernan, M.A., Hopewell, S., Hrobjartsson, A., Junqueira, D.R., Juni, P., Kirkham, J.J., Lasserson, T., Li, T., McAleenan, A., Reeves, B.C., Shepperd, S., Shrier, I., Stewart, L.A., Tilling, K., White, I.R., Whiting, P.F., Higgins, J.P.T., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, 14898 Clinical research ed.

- Straudi, S., Benedetti, M.G., Venturini, E., Manca, M., Foti, C., Basaglia, N., 2013. Does robot-assisted gait training ameliorate gait abnormalities in multiple sclerosis? A pilot randomized-control trial. NeuroRehabilitation 33 (4), 555–563.
- Straudi, S., Fanciullacci, C., Martinuzzi, C., Pavarelli, C., Rossi, B., Chisari, C., Basaglia, N., 2016. The effects of robot-assisted gait training in progressive multiple sclerosis: a randomized controlled trial. Multiple sclerosis (Houndmills, Basingstoke, England) 22(3), 373–384.
- Straudi, S., Manfredini, F., Lamberti, N., Martinuzzi, C., Maietti, E., Basaglia, N., 2019a. Robot-assisted gait training is not superior to intensive overground walking in multiple sclerosis with severe disability (the ragtime study): a randomized controlled trial. Mult. Scler. J 1352458519833901.
- Straudi, S., Manfredini, F., Lamberti, N., Martinuzzi, C., Maietti, E., Basaglia, N., 2019. Robot-Assisted Gait Training is Not Superior to Intensive Overground Walking in Multiple Sclerosis With Severe Disability (the Ragtime study): a Randomized Controlled Trial. Multiple sclerosis (Houndmills, Basingstoke, England), 1352458519833901.
- Thompson, A.J., Baranzini, S.E., Geurts, J., Hemmer, B., Ciccarelli, O., 2018. Multiple Sclerosis. 391. Lancet, London, England, pp. 1622–1636.
- van den Berg, M., Dawes, H., Wade, D.T., Newman, M., Burridge, J., Izadi, H., Sackley, C.M., 2006. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. J. Neurol. Neurosurg. Psychiatr. 77 (4), 531–533.
- Vaney, C., Gattlen, B., Lugon-Moulin, V., Meichtry, A., Hausammann, R., Foinant, D., Anchisi-Bellwald, A.M., Palaci, C., Hilfiker, R., 2012. Robotic-assisted step training (lokomat) not superior to equal intensity of over-ground rehabilitation in patients with multiple sclerosis. Neurorehabil. Neural Repair 26 (3), 212–221.
- Wan, X., Wang, W., Liu, J., Tong, T., 2014. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med. Res. Methodol. 14, 135.
- Ware Jr., J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 30 (6), 473–483.
- Wier, L.M., Hatcher, M.S., Triche, E.W., Lo, A.C., 2011. Effect of robot-assisted versus conventional body-weight-supported treadmill training on quality of life for people with multiple sclerosis. J. Rehabil. Res. Dev. 48 (4), 483–492.
- Wiles, C.M., Newcombe, R.G., Fuller, K.J., Shaw, S., Furnival-Doran, J., Pickersgill, T.P., Morgan, A., 2001. Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. J. Neurol. Neurosurg. Psychiatr. 70 (2), 174–179.
- Xie, X., Sun, H., Zeng, Q., Lu, P., Zhao, Y., Fan, T., Huang, G., 2017. Do patients with multiple sclerosis derive more benefit from robot-assisted gait training compared with conventional walking therapy on motor function? A meta-analysis. Front. Neurol. 8, 260.