Multiple Sclerosis and Related Disorders 41 (2020) 102034

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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https://doi.org/10.1016/j.msard.2020.102034
Received 26 June 2019; Received in revised form 12 January 2020; Accepted 29 February 2020

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 (QOL) (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 disease-modifying 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® (Hocoma, Zurich, Switzerland) to control the kinematics of the pelvis and knees and the end-effector approach using Gait Trainer GTII® (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 decision-making 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

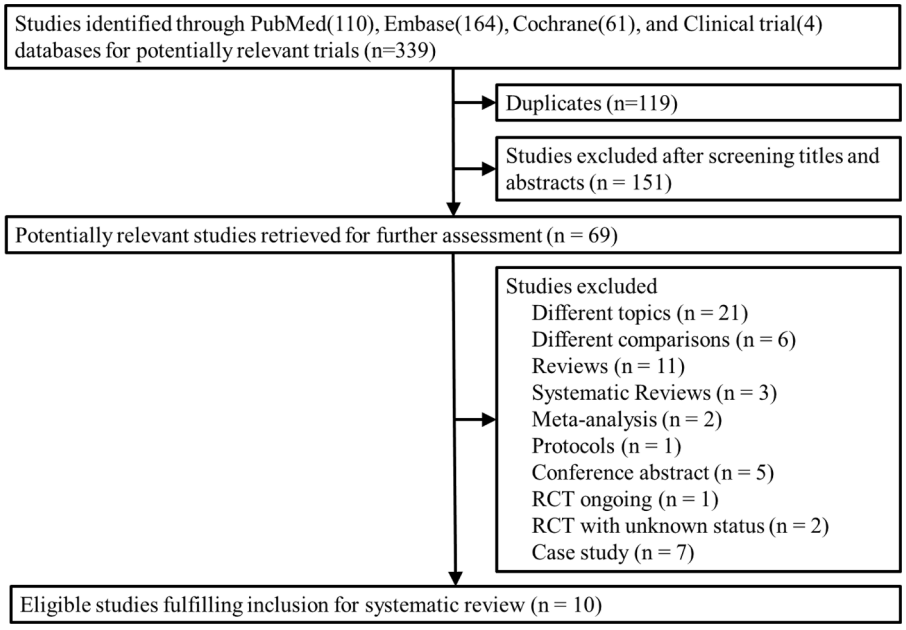

Fig. 1. Flowchart of study selection process.

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)	I: 36 (33% [a]) C: 36 (31%)	I: 56 ± 11 C: 55 ± 11	I: RAGT (Lokomat[d]), 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[e] 1 h/session × 12 session/4 wks C: Assisted over-ground walking with habitual walking device, speed based on tolerance, 1 h/session (30 min for walking) + exercise [e] 1 h/session × 12 sessions/4 wks	T25FW, 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 (EDSS: 6–7.5) and MMSE score ≥ 24	I: 21 (52.4%) C:22 (45.5%)	I: 47.00 ± 11.17 C: 49.86 ± 8.21	I: RAGT (Gait Trainer GTII®[b]), 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[c]), 3 sessions/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).	I: 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 strengthening (10 min), motor coordination, gait, and 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)
Gandolfi (2014), Italy	Age 30–60 y, diagnosis of MS (RR, SP), MMSE ≥ 24, able to maintain standing position without aids (at least 1 min), walk independently (at least 15 min), no concomitant neurological or orthopedic 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[c]	I: RAGT (Gait Trainer GTII®). 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.) followed by 10 passive lower limb joint mobilizations and stretching exercises. Total: 50 min/session, 2 sessions/wk × 6 wks 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 III) within a 5-min period. Total: 50 min/session, 2 sessions/wk × 6 wks	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 km/h; as training progressed, training parameters were adjusted according to subject performance. 1 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 exercises were optionally added.)	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), Israel	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)	I: 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: Gait and dynamic balance exercises, standing from sitting training and walking ± walking aids. 30 min/session, 2–3 sessions/wk × 4wks	10MWT, 6MWT, TUG, BBS, EDSS, FIM, RAND-36 scales
Vaney (2012), Switzerland	Age ≥ 18 y, diagnosis of MS by McDonald criteria, men and nonpregnant women (EDSS: 3–6.5), able to walk 14 *m* ± assistive devices	I: 26 (not provided) C: 23 (not provided)	I: 54.22 ± 11.28 C: 58.23 ± 9.42	I: RAGT (Lokomat), speed depending on observation of gait and changed randomly to simulate normal gait. First session: 50% of BWS, adapted on observation of the gait. 30 min/session, × 9 sessions C: Over-ground walking training. Walk for 30 min in the gym room or sometimes outside on uneven ground ± walking aids 30 min/session, × 9 sessions	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 ≥ 18 y, diagnosis of MS by McDonald criteria (PP, SP, RR) with gait 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 × 3 wks C: BWSTT. 40 min/session, 2 sessions/wk × 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 ability to walk 25 ft without assistance	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	Diagnosis of MS with a 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 × 3 wks C: CWT, walking over ground ± walking aids with assistance of physical therapists. 30 min/session, 5 sessions/wk × 3 weeks	Walking velocity (20-m timed walking), 6MWT, stride length, knee-extensor strength, EBI, subjective walking safety (VAS), overall satisfaction with RAGT (VAS)

PP: Primary progressive; SP: secondary progressive; RR: relapse-remitting; BWS: body weight support; EDS: expanded disability status scale; MMSE: Mini-Mental State Examination; 2MWT: 2-min walking test; FAC: Functional Ambulatory Category; RMI: Rivermead Mobility Index; mBI: modified Barthel Index; MS: multiple sclerosis; RAGT: robot-assisted gait training; CWT: conventional walking training; EDSS: Expanded Disability Status Scale; FSS: Fatigue Severity Scale; VAS: visual analog scale; 10MWT: Ten-Meter Walk Test; 6MWT: 6-min walk test; TUG: Timed up and go test; BBS: Berg Balance Scale; PHQ-9: Patient Health Questionnaire; SF-36: Short Form 36 SF-36; ABC: Activities-Specific Balance Confidence Scale; SOT: Sensory Organization Balance Test; SA: stabilometric assessment; MSQOL-54: Multiple Sclerosis Quality of Life-54; SIBT: sensory integration balance training; FIM: functional independence measure, RAND-36 scales: Hebrew version of the Medical Outcomes Study Short-Form 36; MSQLI: comprising a well-established general HRQoL measure, the 36-Item Short Form Health Survey (SF-36) from the Medical Outcomes Study (MOS), and nine symptom-based scales that represent areas of specific concern to individuals with MS; MS Quality of Life Inventory; LS: general life satisfaction; BWSTT: body-weight-supported treadmill training (Individuals walk on a treadmill while a portion of their body weight is supported by a parachute-style harness linked to an overhead pulley system.); MET: metabolic equivalents; T25FW: timed 25-foot walk; DST: double support time; SLR, step length ratio; EBI: Extended Barthel Index; WEIMuS: Würzburger Erschöpfungsinventar bei Multipler Sklerose; MSIS-29: MS impact scale-29; MSWS-12: MS walking scale-12. Age is presented as mean ± SD or mean (range).

[a] (): % male.

[b] Patients stood with the feet on the motor-driven footplates and were supported by a harness and practiced gait-like movements. The electromechanical device applies an inverse control approach with end point trajectories' control (end effector).

[c] Static exercises on the parallel bars for lower limb movement and control; exercises for trunk and pelvis control; exercises for balance and coordination.

[d] Every patient wore a harness attached to a system that provided body weight support, and walked on a treadmill with the help of Lokomat. Legs were guided based on a physiological gait pattern.

[e] Exercise: lower limb and core stretching exercise.

Table 2
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[c]	Low risk	Low risk	Some concerns
Straudi (2015)	Low risk	Some concerns[b]	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[a]	Some concerns[b]	Low risk	Some concerns[e]	Low risk	High risk
Schwartz (2012)	Low risk	Some concerns[b]	Some concerns[d]	Low risk	Low risk	Some concerns
Vaney (2012)	Low risk	Low risk	Low risk	Some concerns[e]	Low risk	Some concerns
Lauren (2011)	Some concerns[a]	Low risk	Low risk	Some concerns[e]	Some concerns[f]	High risk
Lo (2008)	Some concerns[a]	Low risk	Low risk	Some concerns[e]	Low risk	Some concerns
Beer (2008)	Low risk	Low risk	Low risk	Low risk	Some concerns[g]	Some concerns

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

[a] No information of allocation concealment.

[b] Patients and personnel were not blinded and with unclear information of co-intervention.

[c] 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.

[d] 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.

[e] Lack of information on outcome assessor blinding.

[f] Outcome data reported as only mean without standard deviation.

[g] Outcome data reported as median and interquartile range.

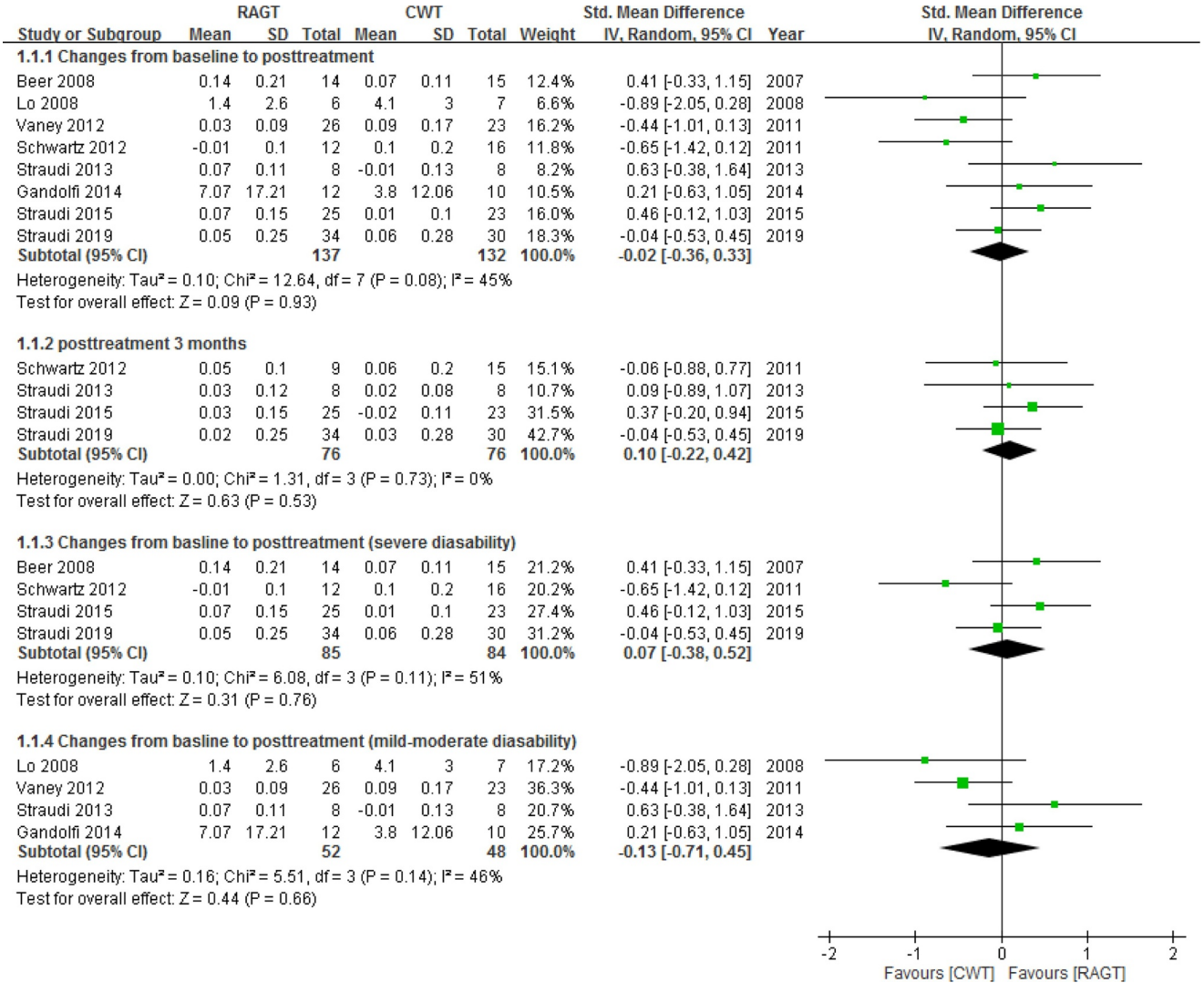

Fig. 2. Forest plot of changes in gait speed after RAGT.

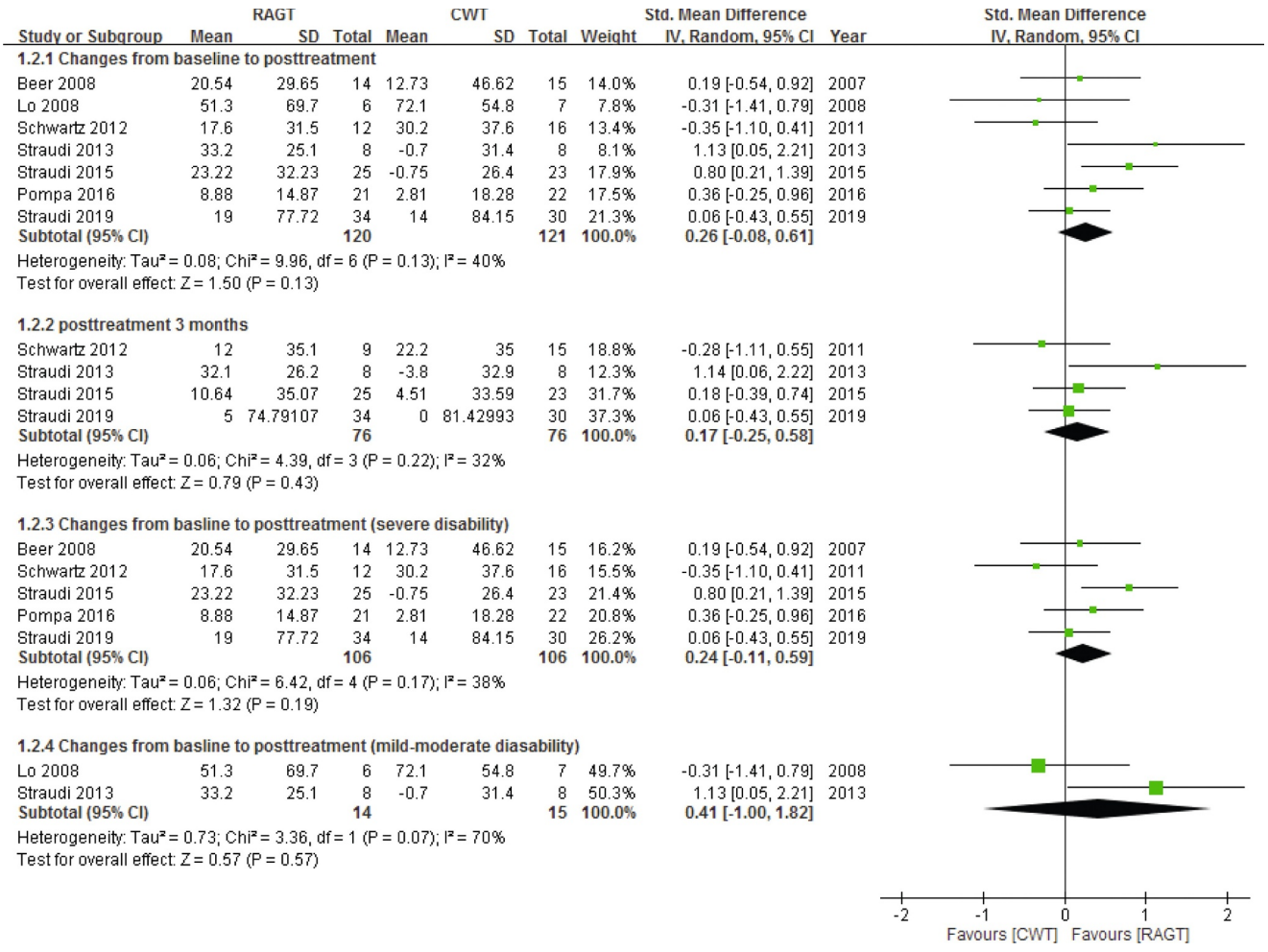

Fig. 3. Forest plot of changes in gait endurance after RAGT.

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-for-bias 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 6-camera 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

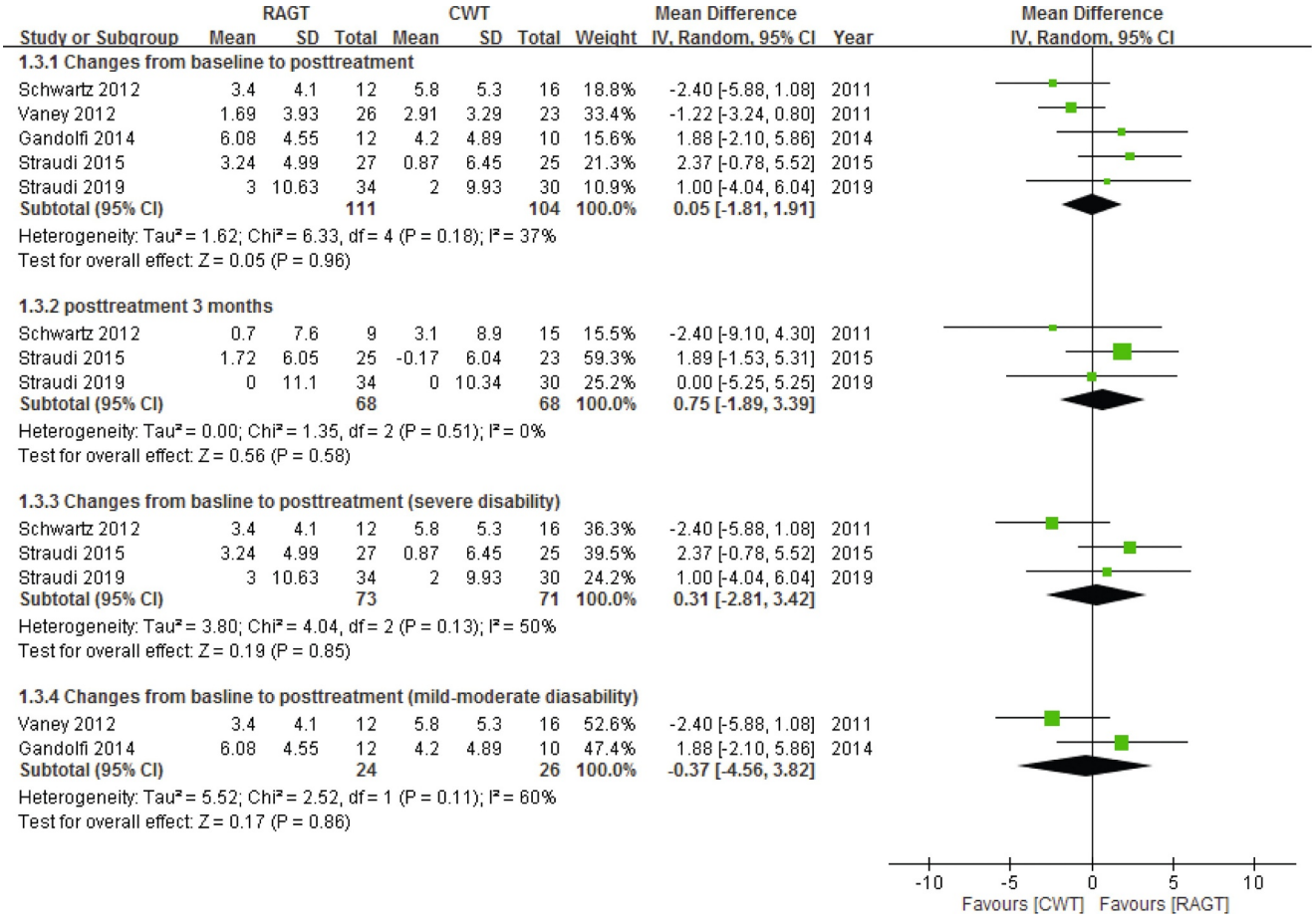

Fig. 4. Forest plot of changes in balance after RAGT.

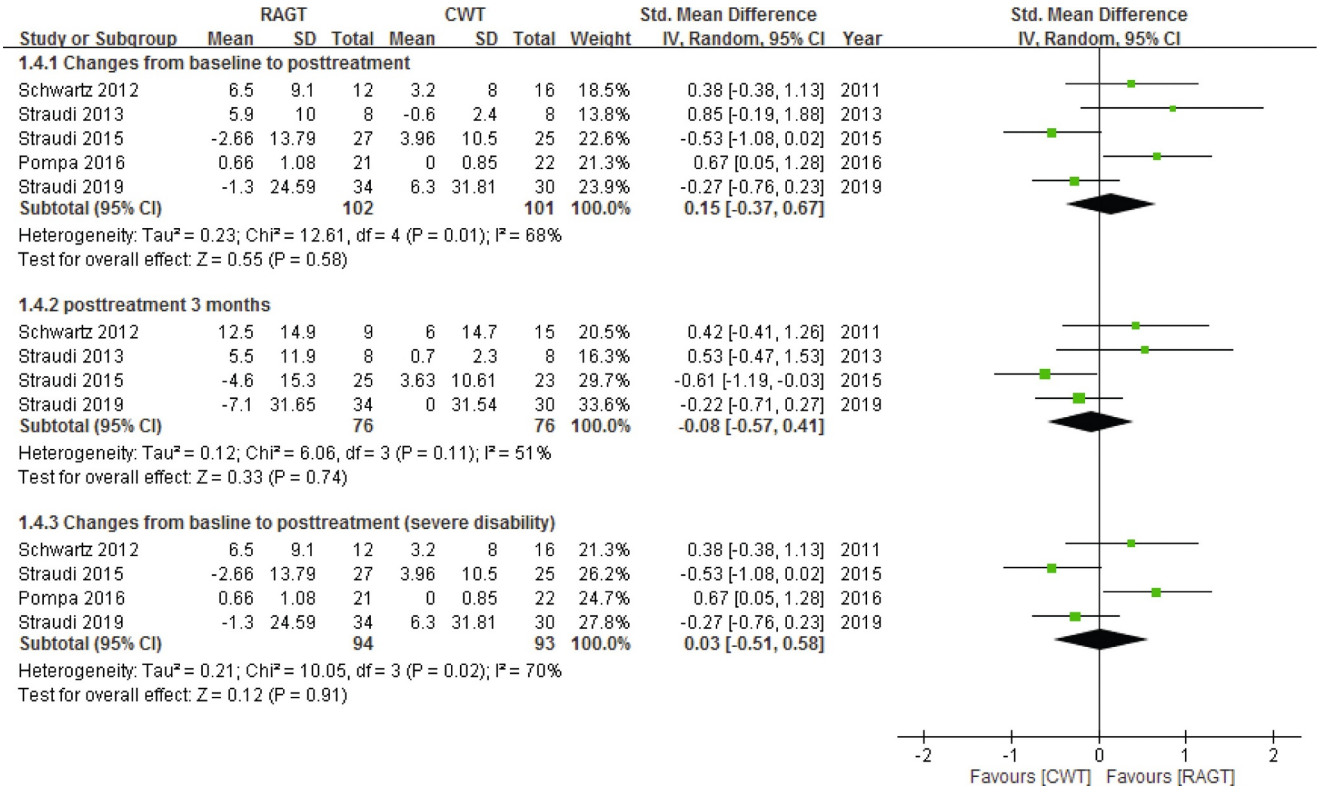

Fig. 5. Forest plot of changes in ambulation capability after RAGT.

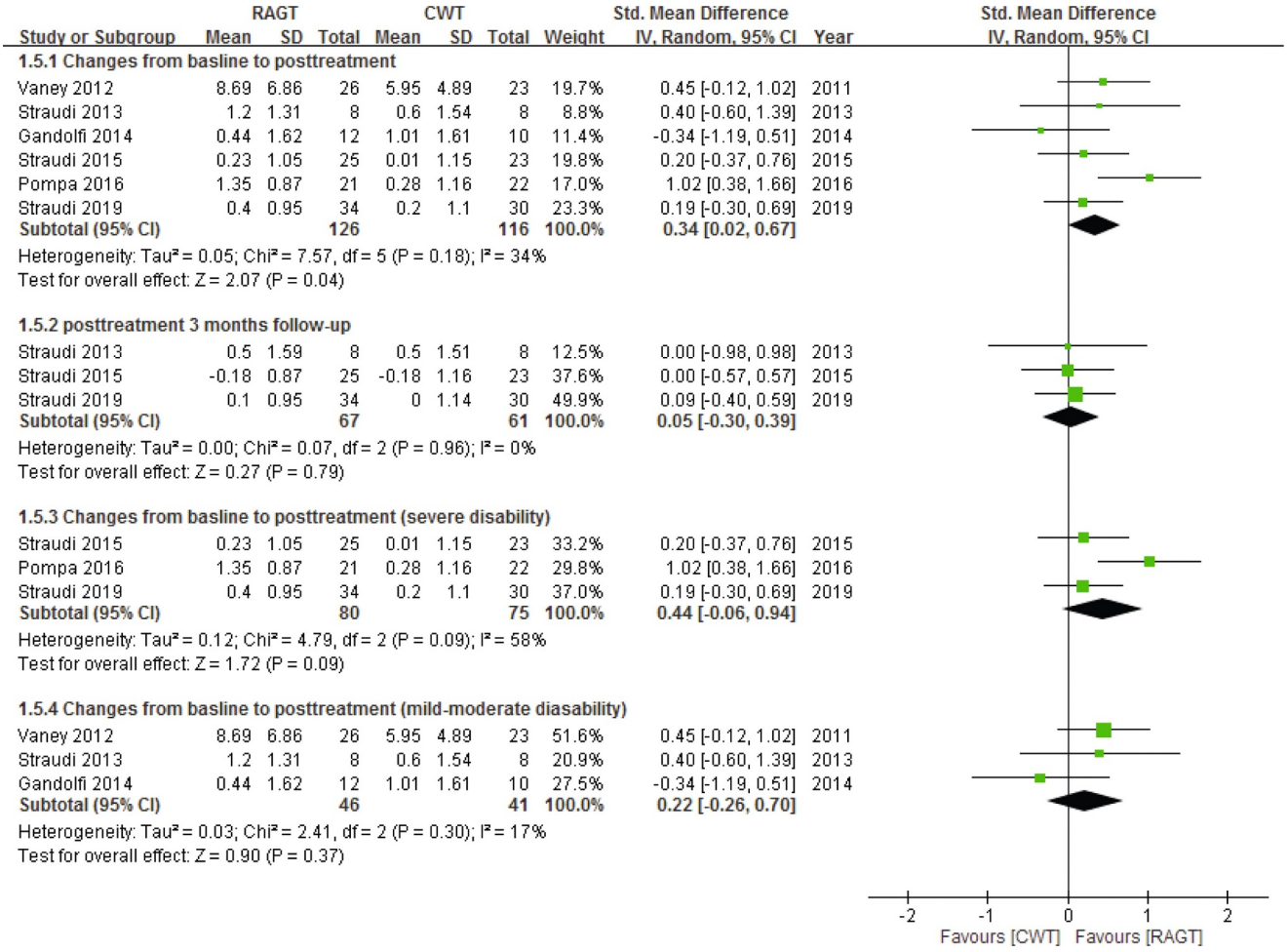

Fig. 6. Forest plot of changes in fatigue after RAGT.

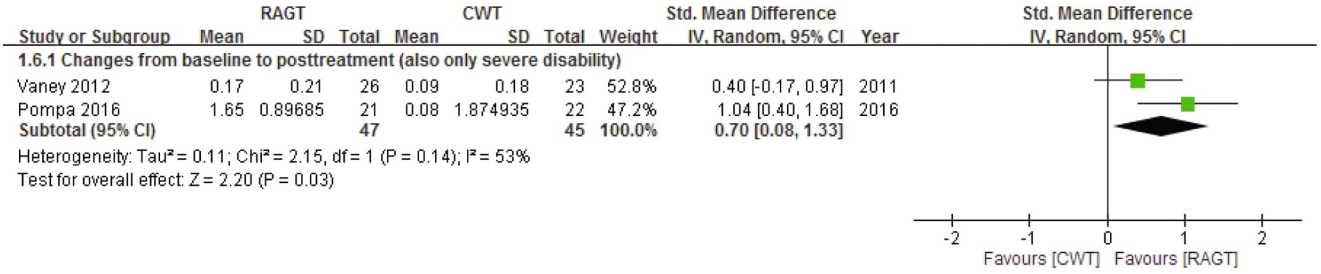

Fig. 7. Forest plot of changes in spasticity after RAGT.

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).

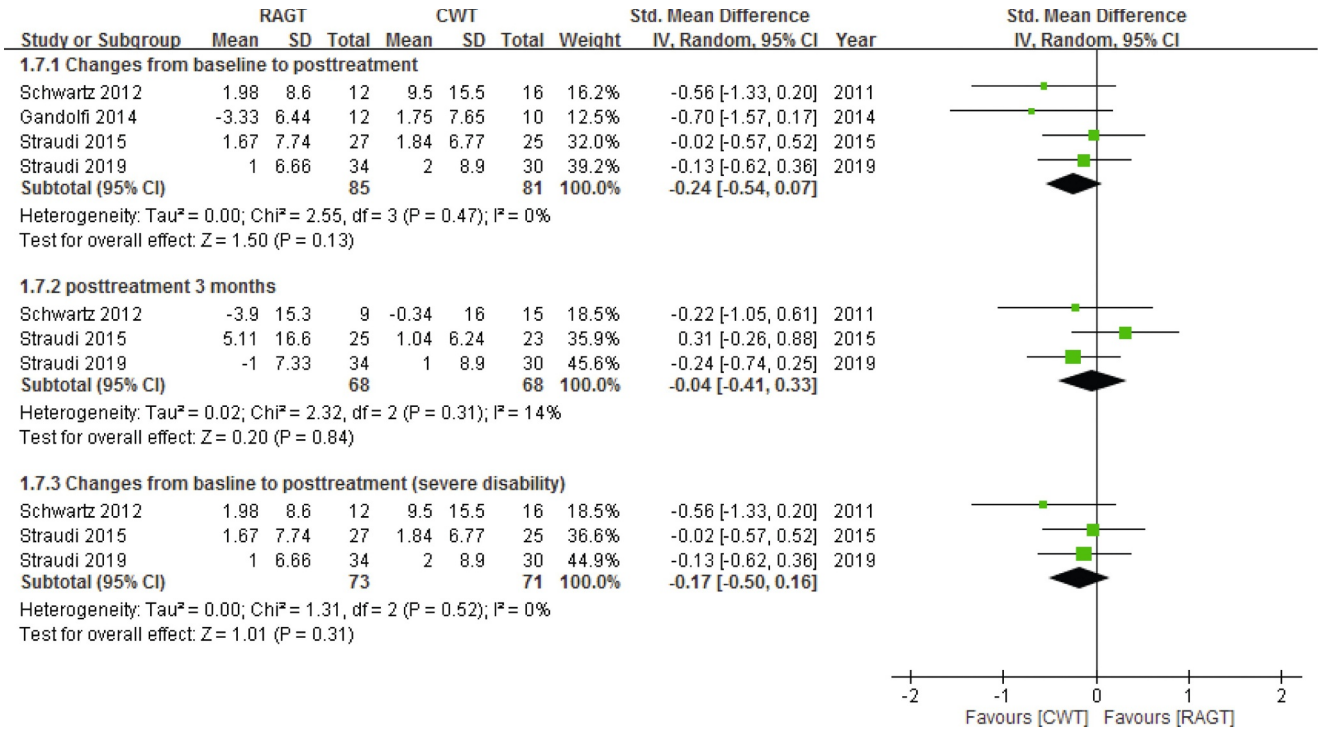

Fig. 8. Forest plot of changes in physical QOL after RAGT.

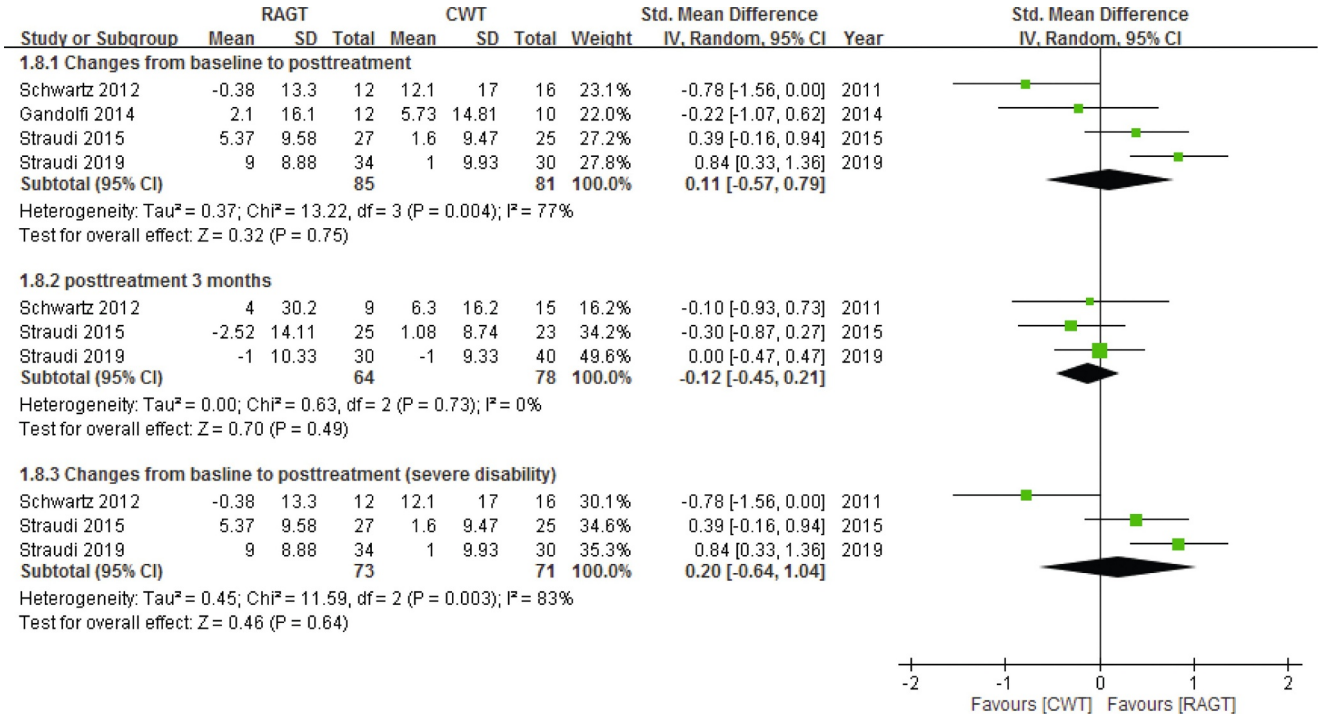

Fig. 9. Forest plot of changes in mental QOL after RAGT.

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

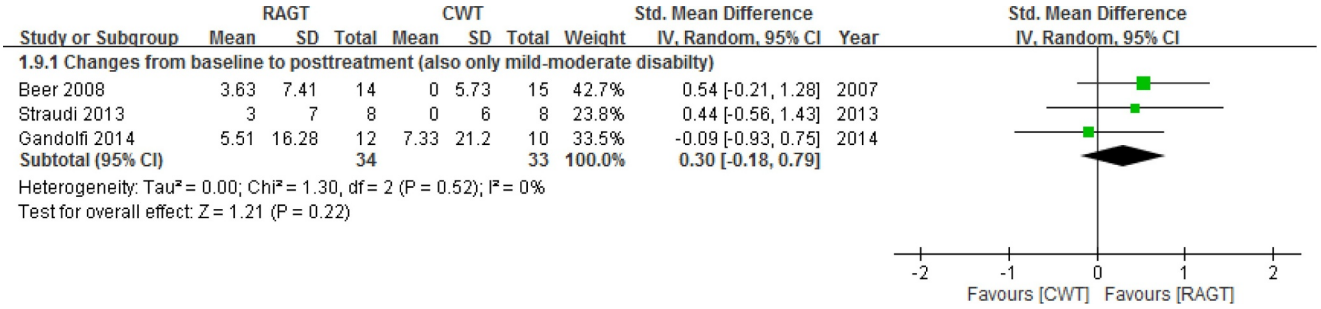

Fig. A.1. Forest plot of changes in stride strength after RAGT.

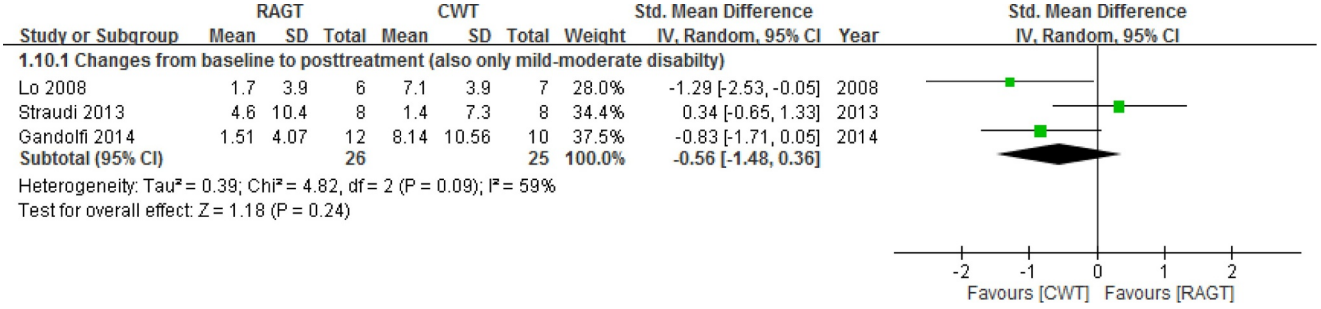

Fig. A.2. Forest plot of changes in double support time after RAGT.

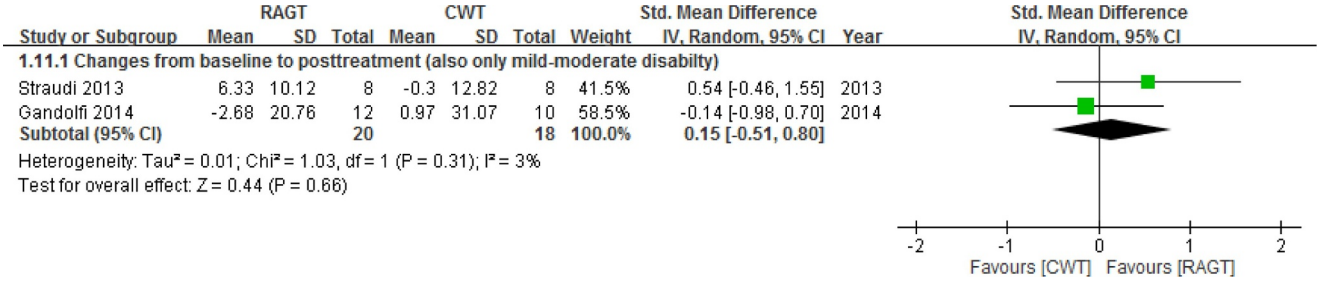

Fig. A.3. Forest plot of changes in cadence after RAGT.

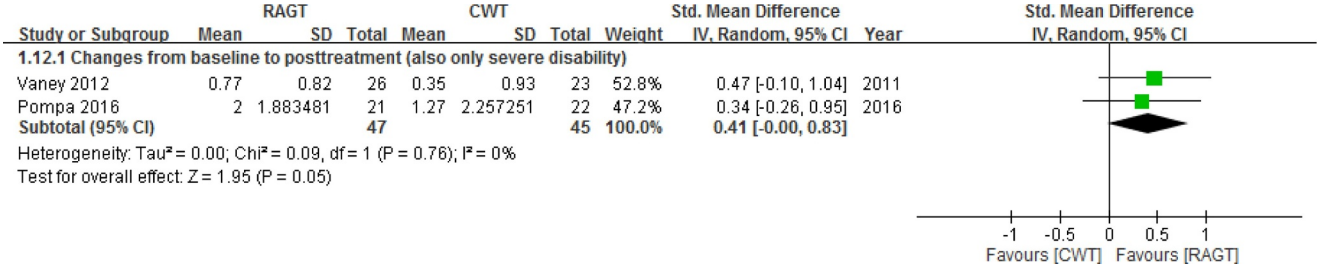

Fig. A.4. Forest plot of changes in global mobility after RAGT.

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

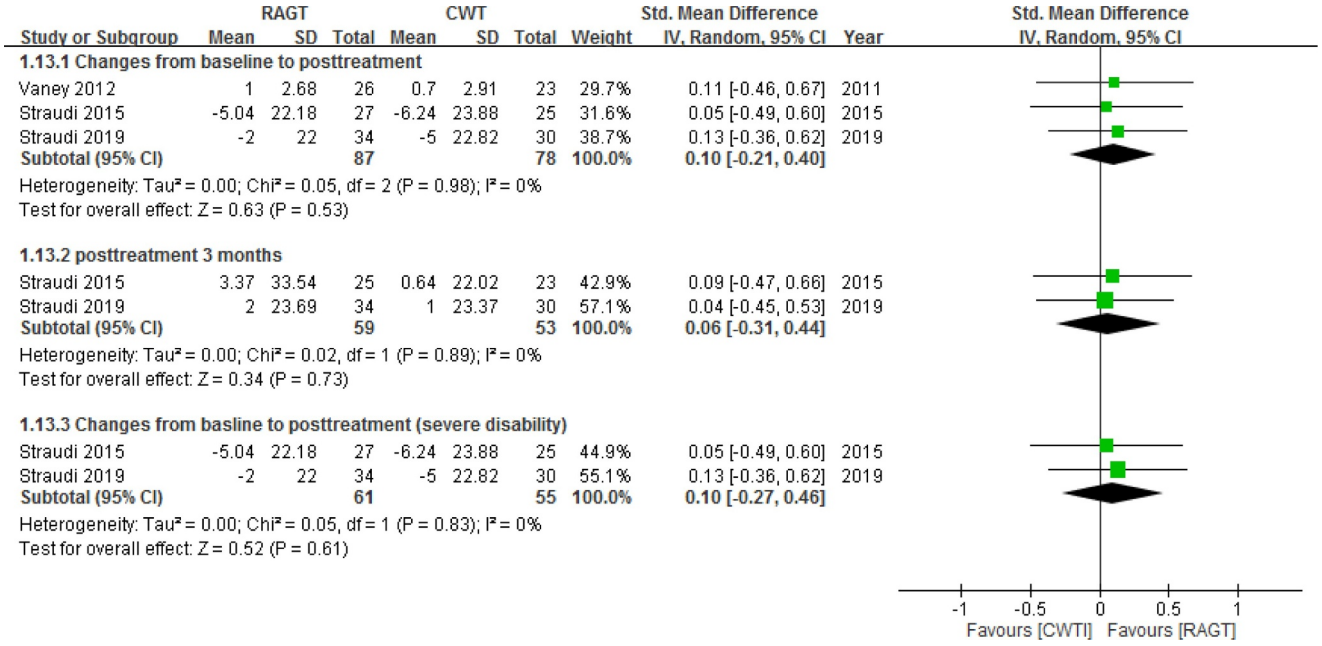

Fig. A.5. Forest plot of changes in pain after RAGT.

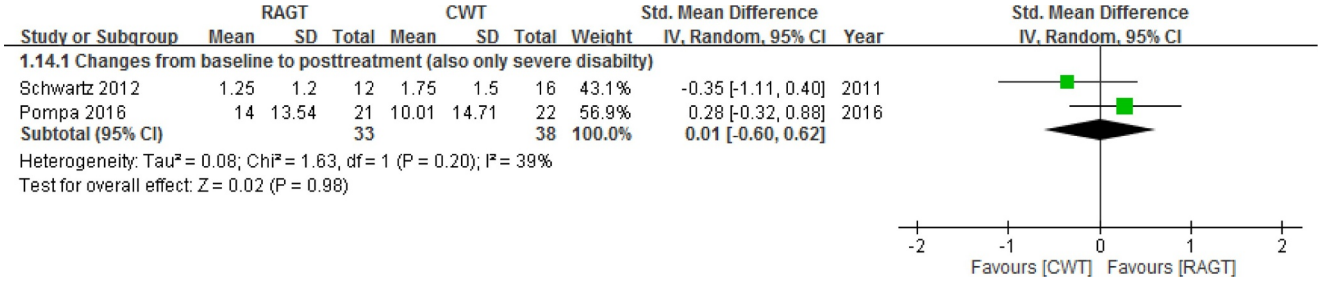

Fig. A.6. Forest plot of changes in ADL after RAGT.

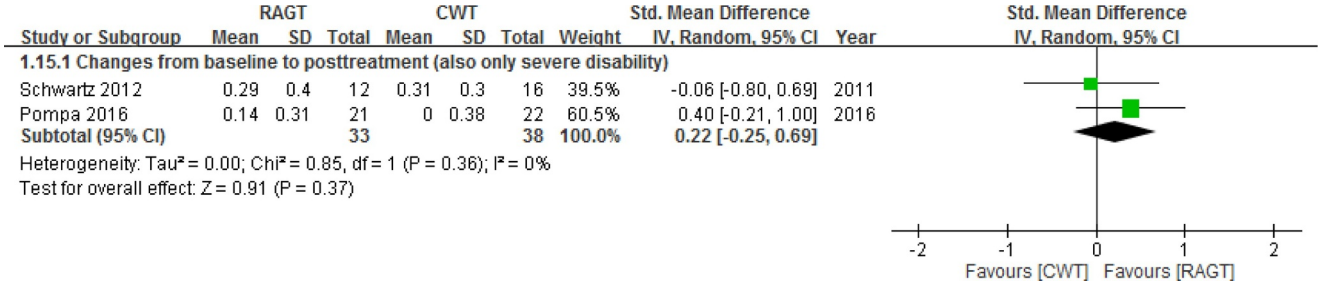

Fig. A.7. Forest plot of changes in EDSS after RAGT.

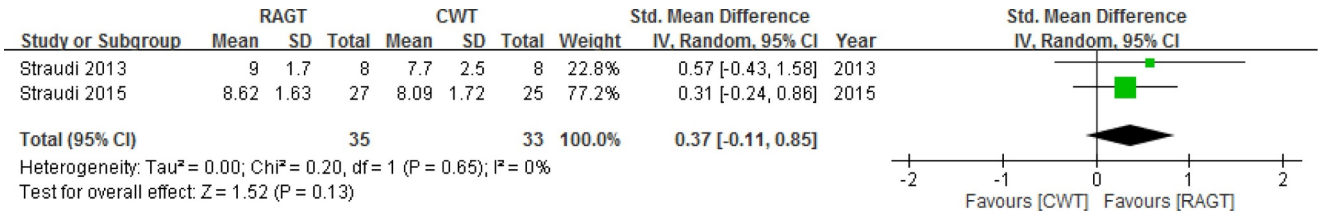

Fig. A.8. Forest plot of treatment acceptance after RAGT.

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

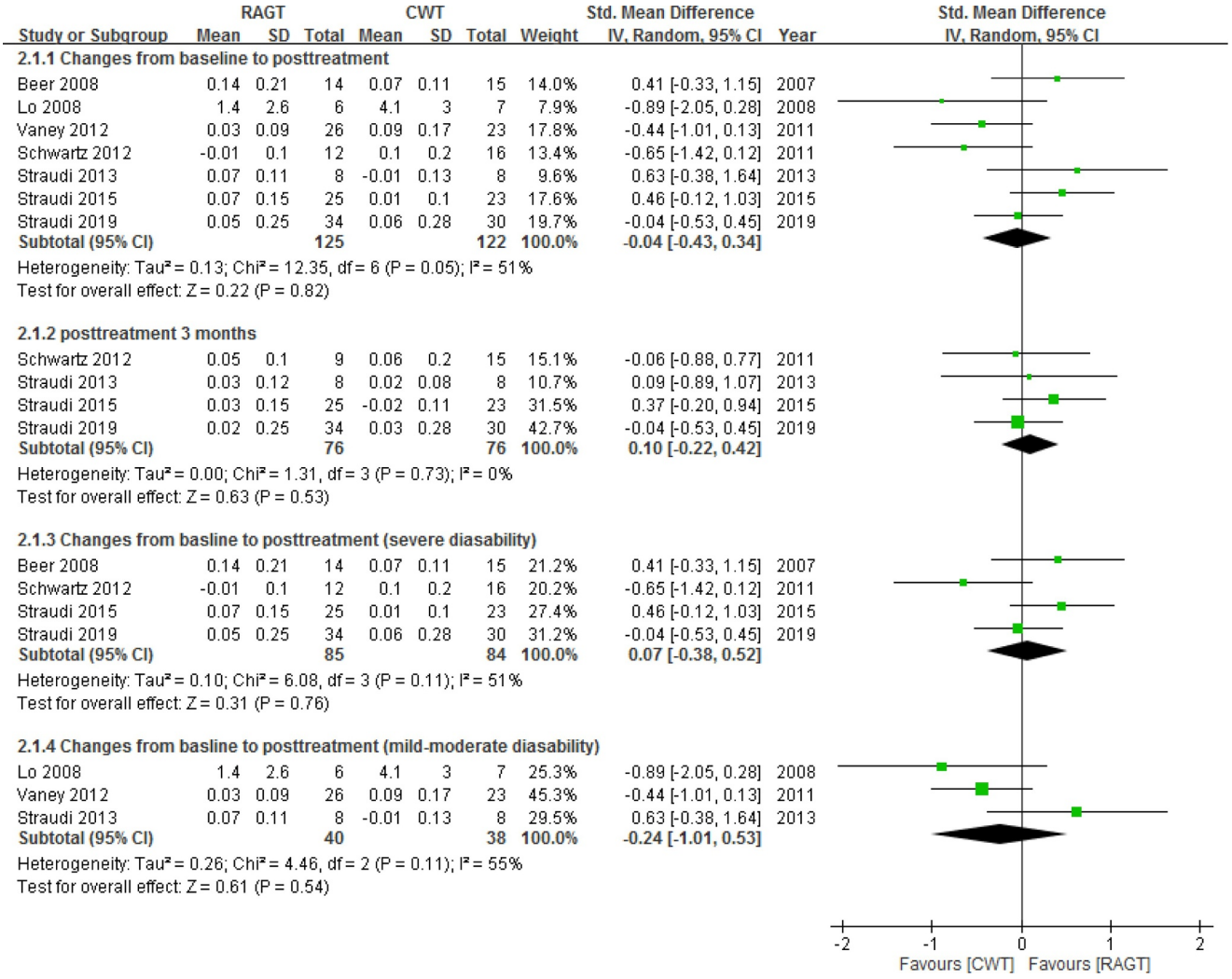

Fig. A.9. Forest plot of changes in gait speed after Lokomat-based RAGT.

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

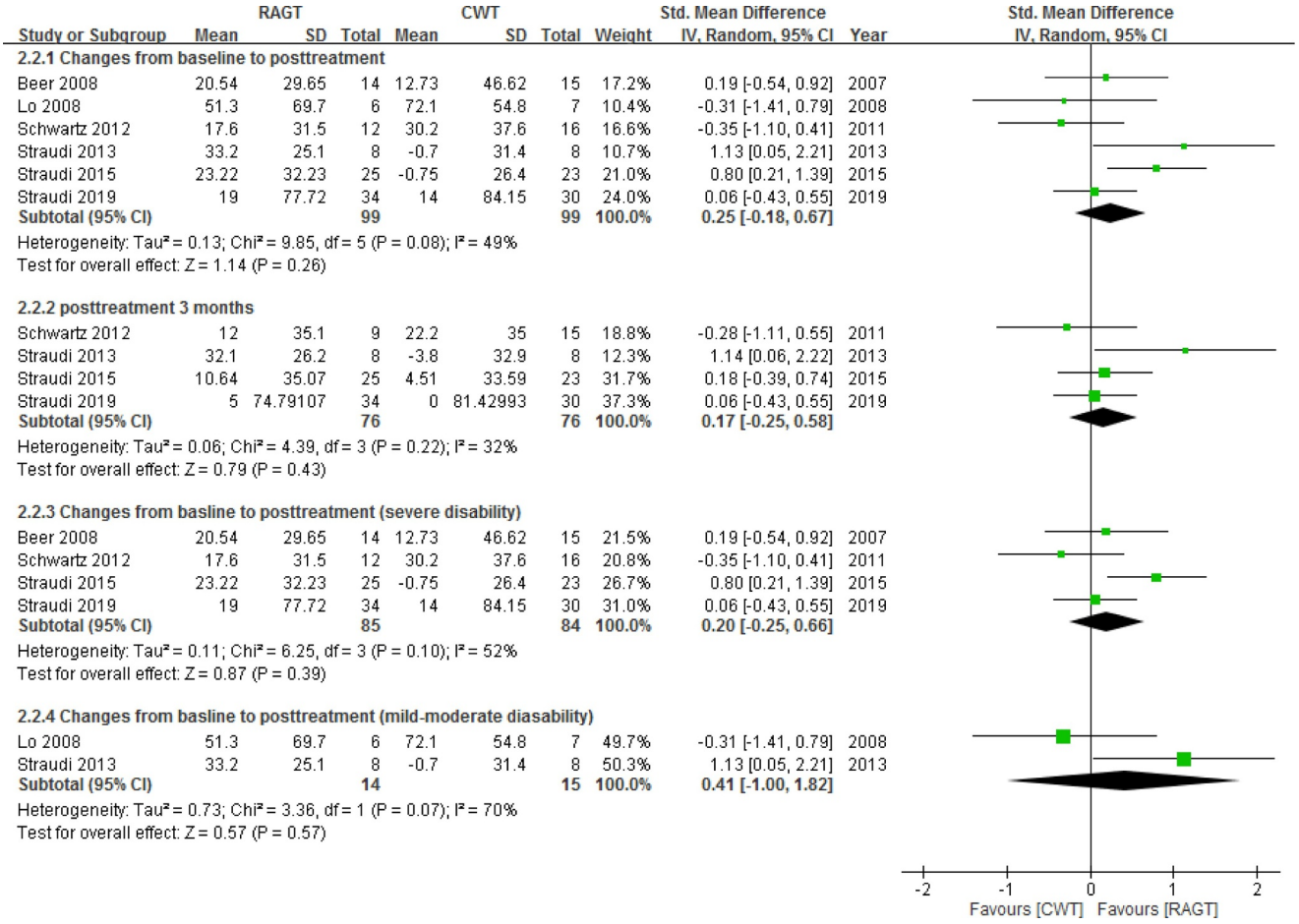

Fig. A.10. Forest plot of changes in gait endurance after Lokomat-based RAGT.

(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^2 = 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 follow-up)

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

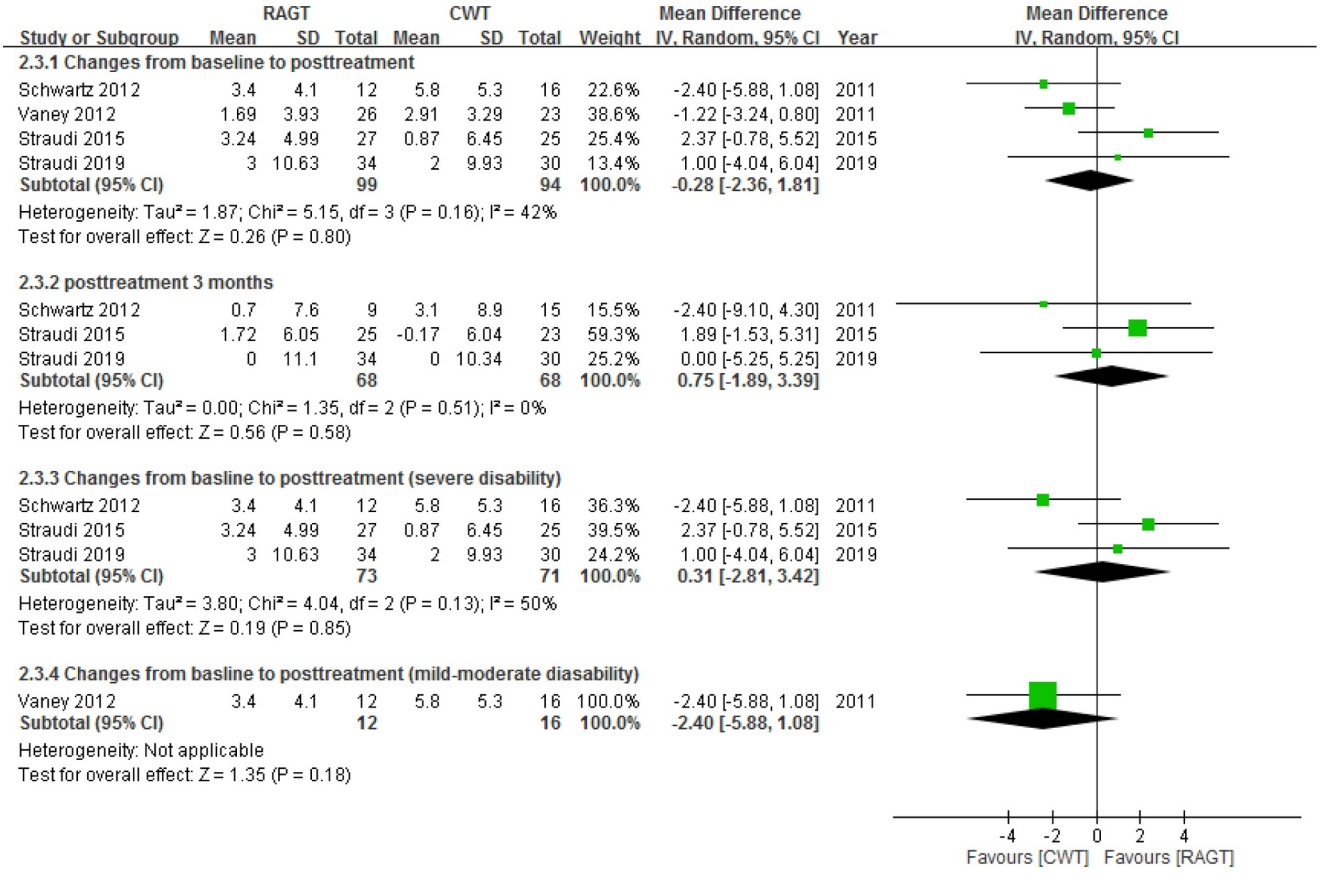

Fig. A.11. Forest plot of changes in balance after Lokomat-based RAGT.

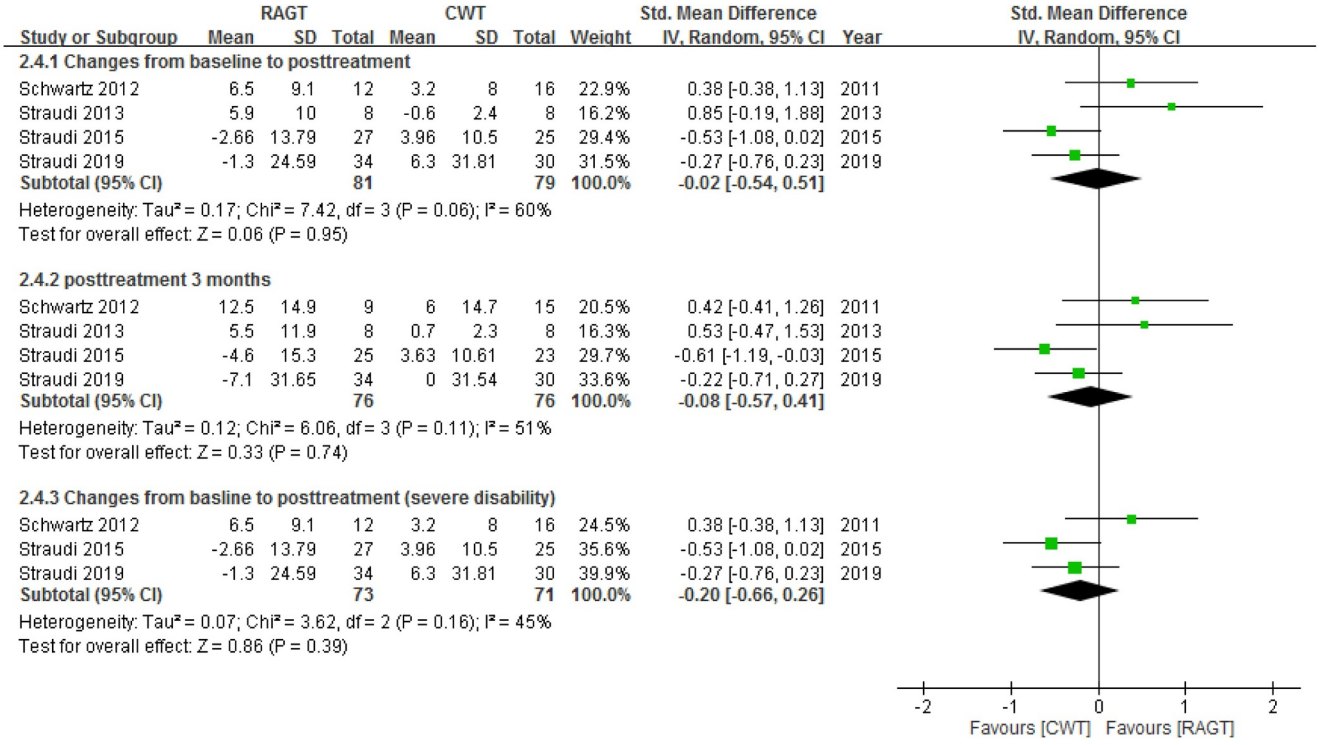

Fig. A.12. Forest plot of changes in ambulation capability after Lokomat-based RAGT.

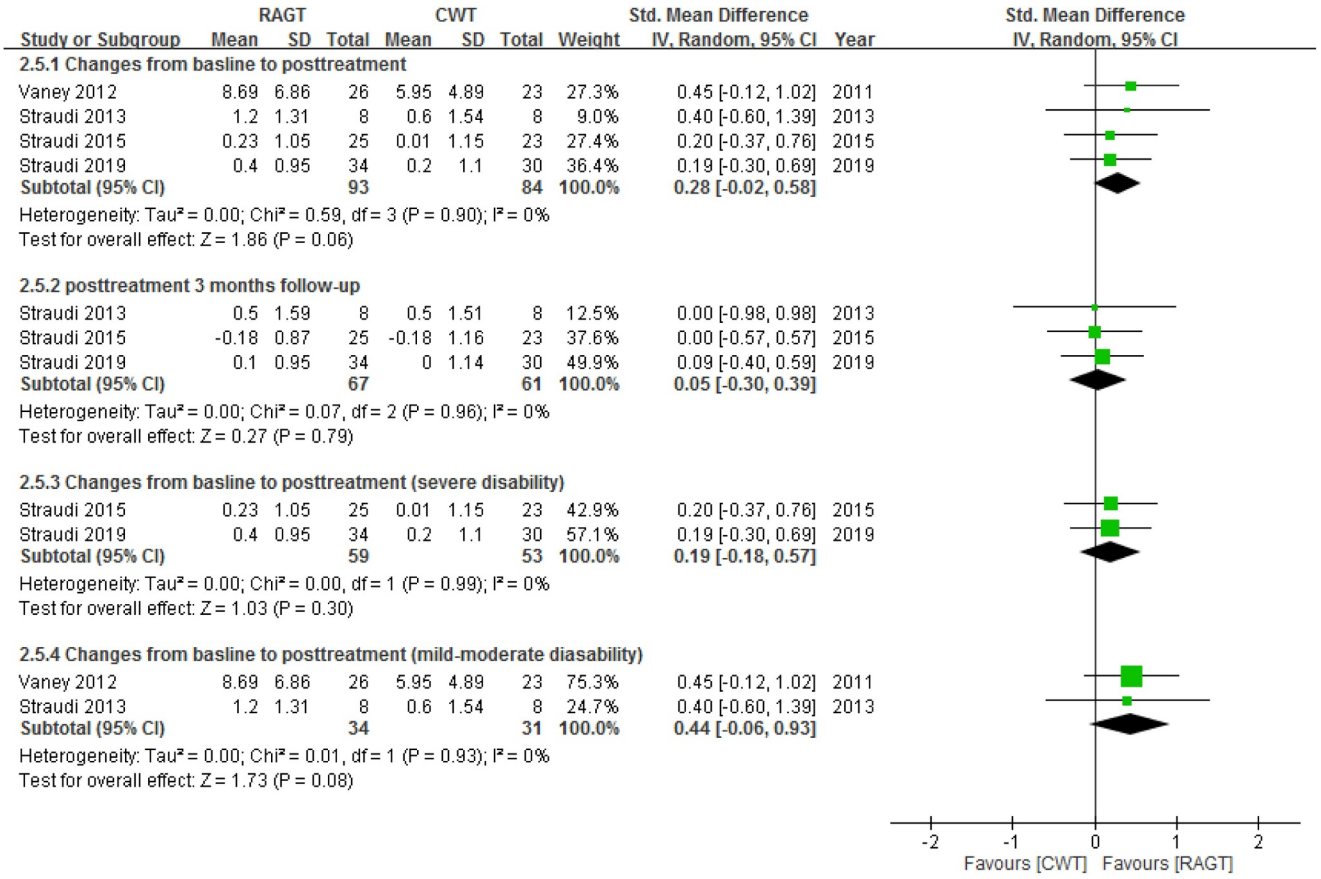

Fig. A.13. Forest plot of changes in fatigue after Lokomat-based RAGT.

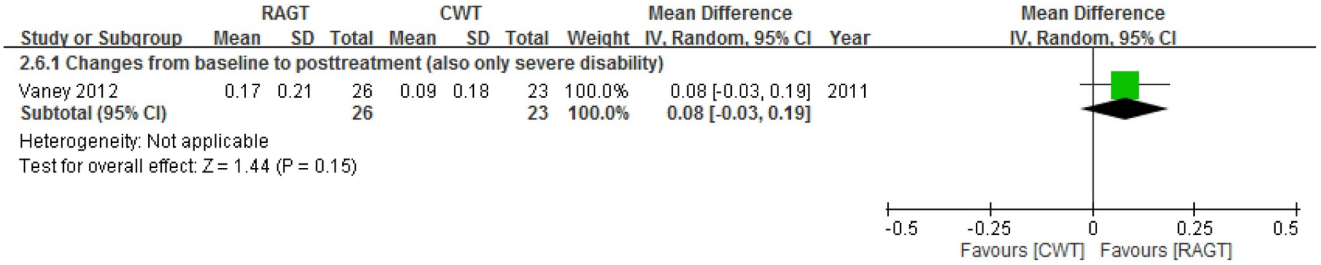

Fig. A.14. Forest plot of changes in spasticity after Lokomat-based RAGT.

(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 drop-outs 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

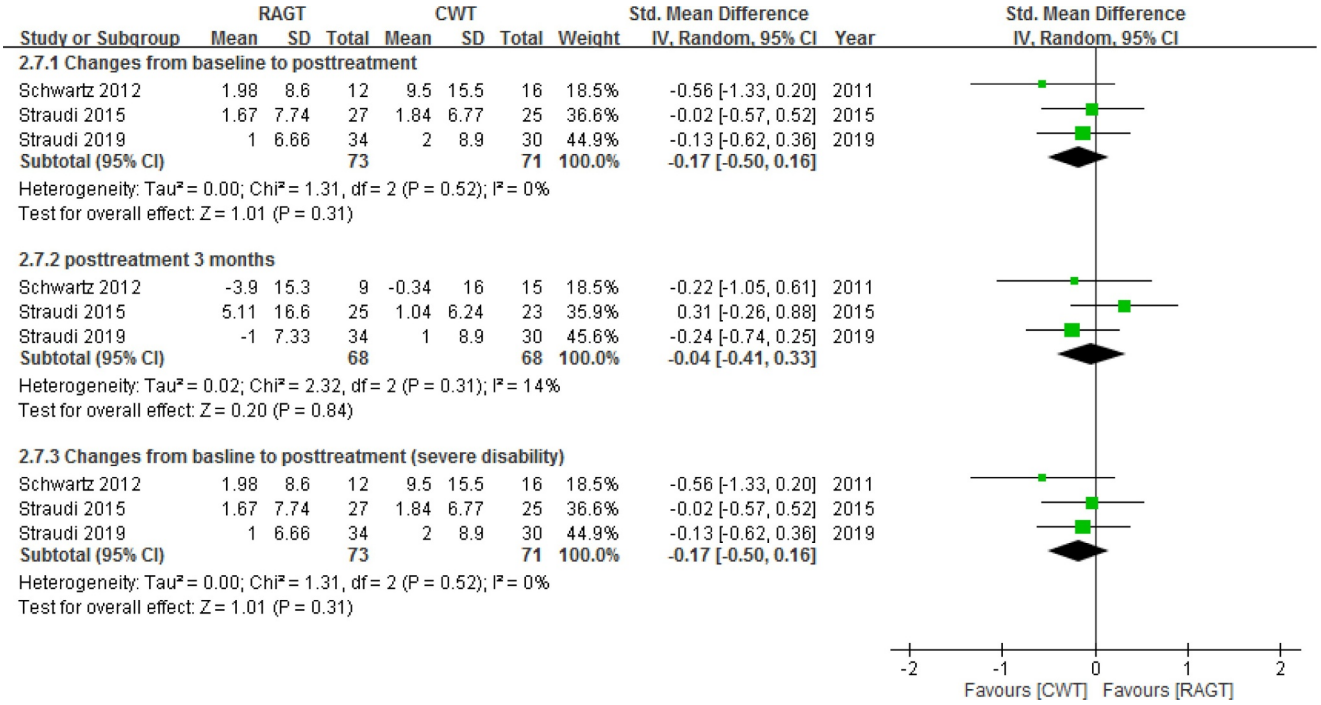

Fig. A.15. Forest plot of changes in physical QOL after Lokomat-based RAGT.

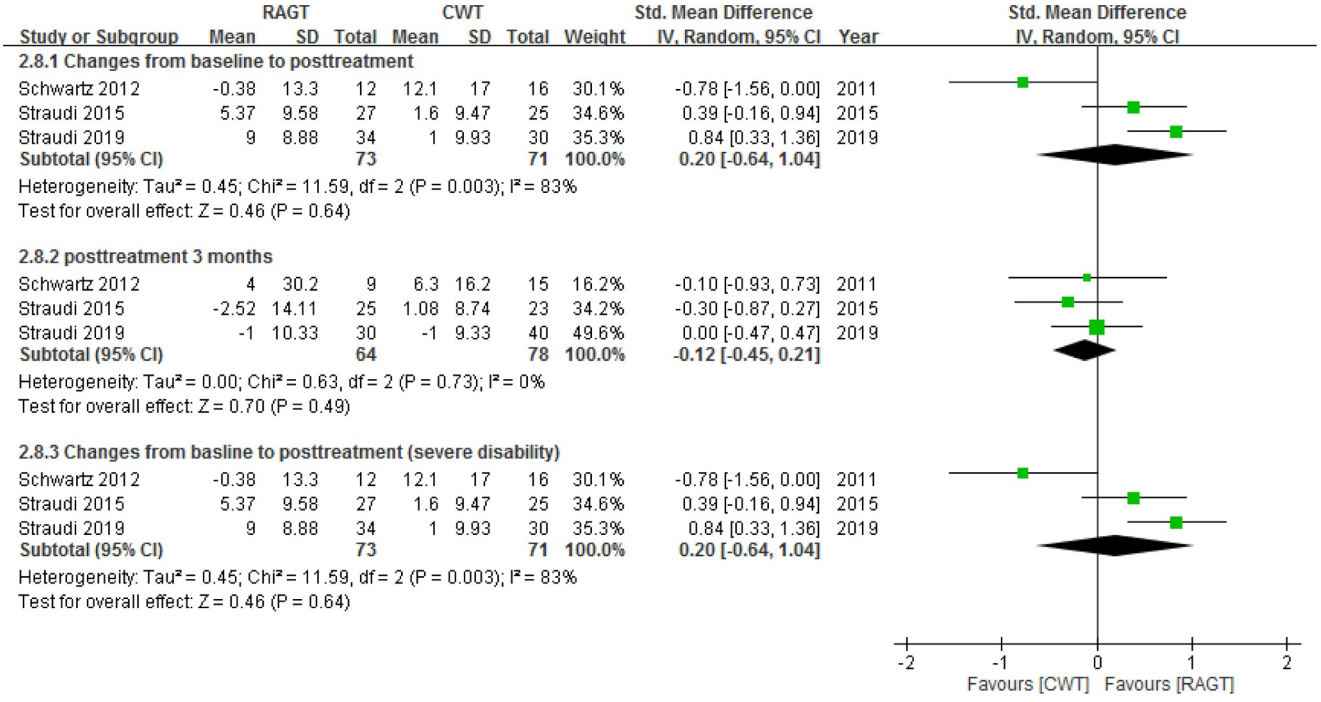

Fig. A.16. Forest plot of changes in mental QOL after Lokomat-based RAGT.

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

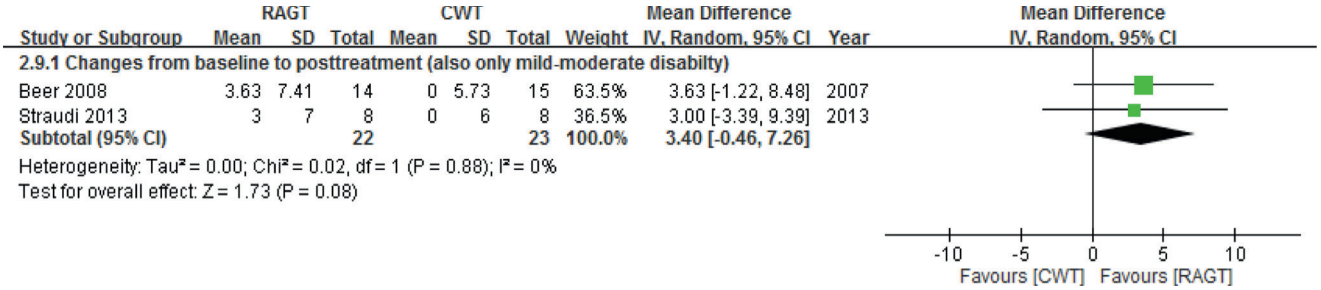

Fig. A.17. Forest plot of changes in stride length after Lokomat-based RAGT.

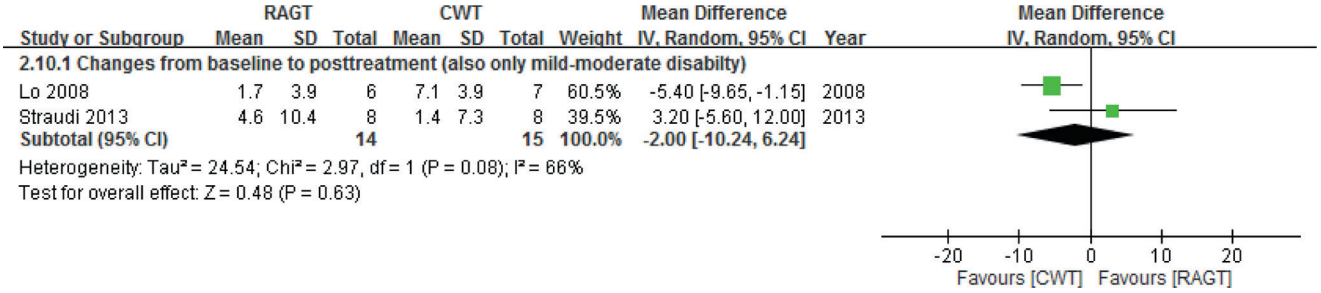

Fig. A.18. Forest plot of changes in double support time after Lokomat-based RAGT.

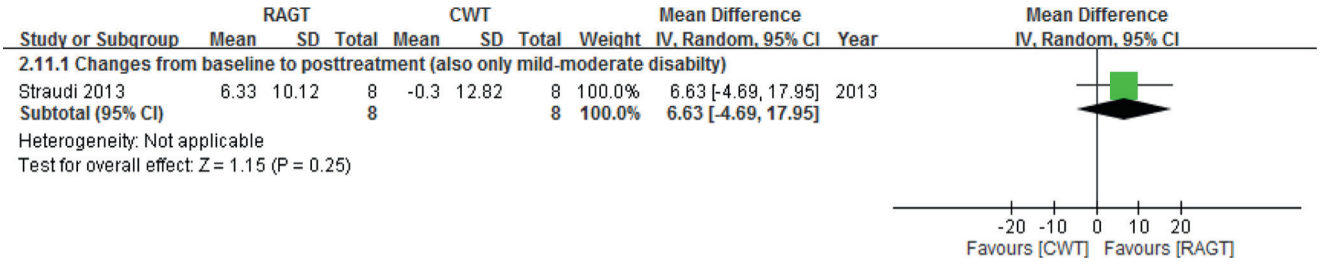

Fig. A.19. Forest plot of changes in cadence after Lokomat-based RAGT.

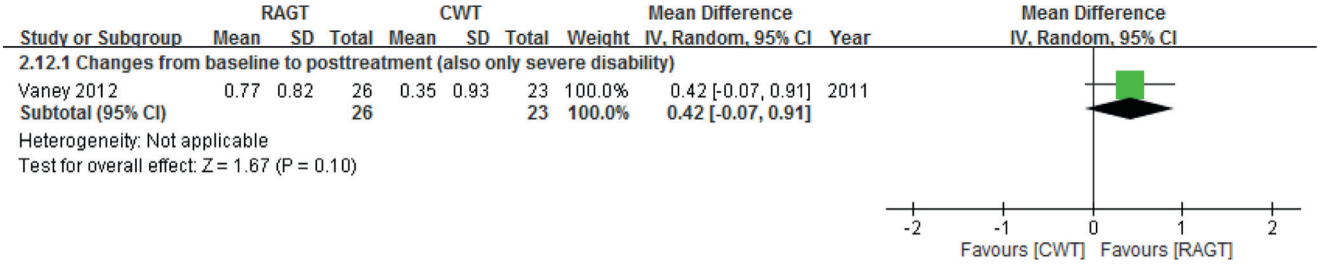

Fig. A.20. Forest plot of changes in global mobility after Lokomat-based RAGT.

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

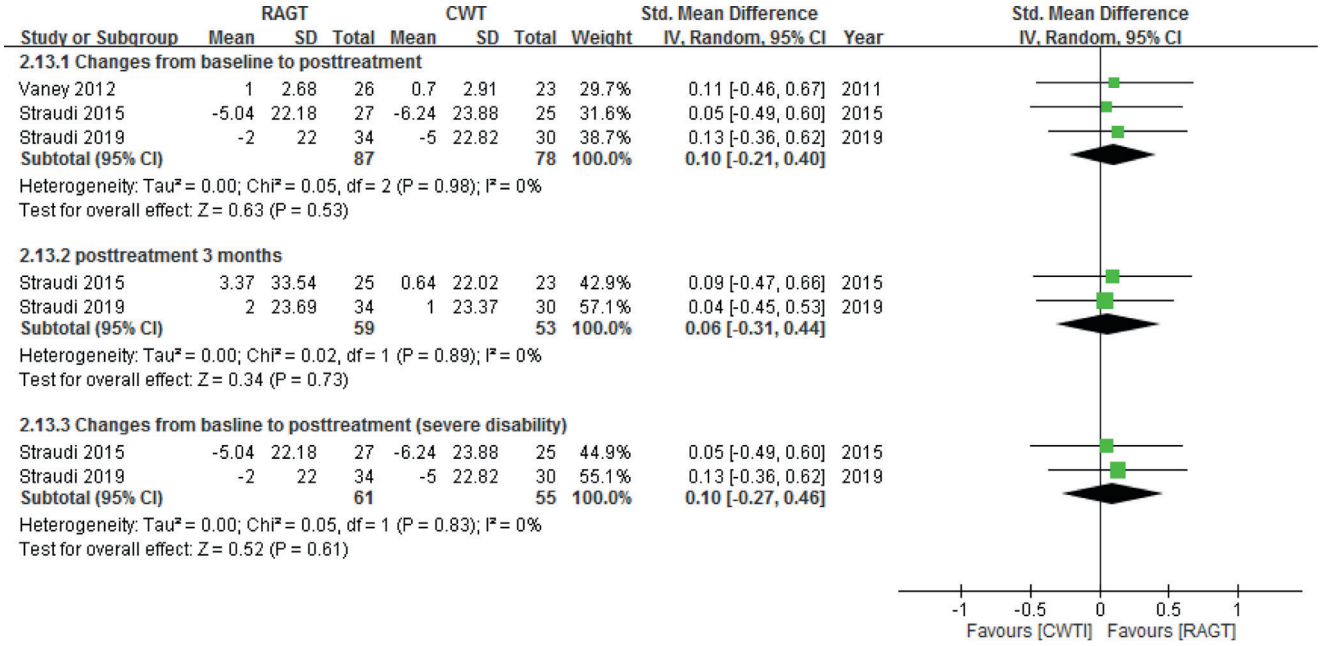

Fig. A.21. Forest plot of changes in pain after Lokomat-based RAGT.

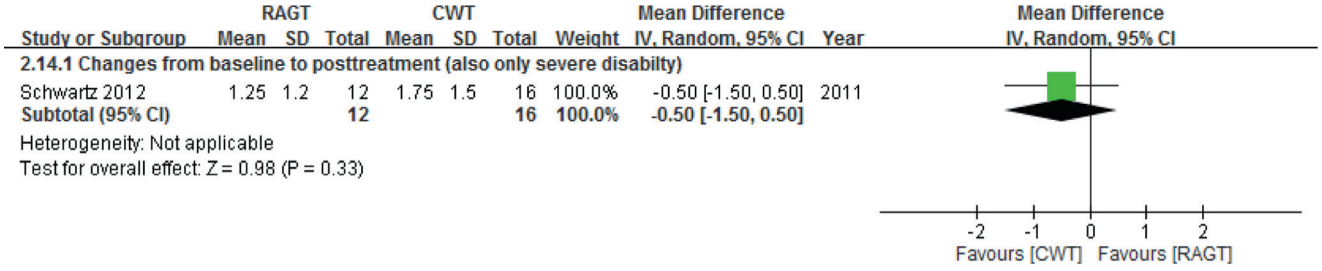

Fig. A.22. Forest plot of changes in ADL after Lokomat-based RAGT.

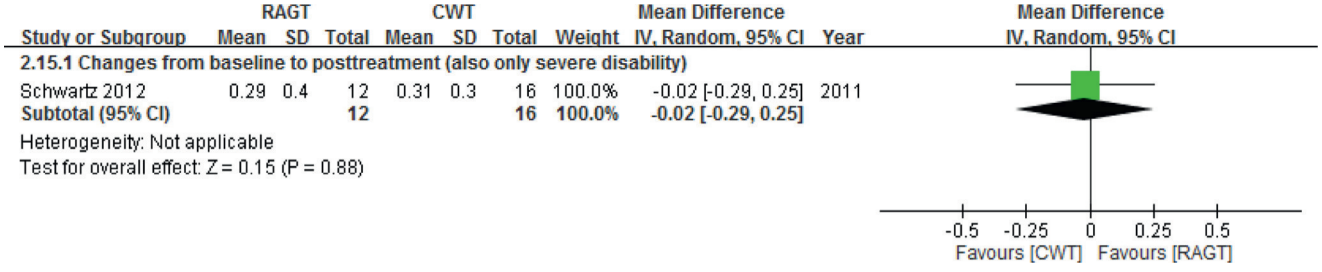

Fig. A.23. Forest plot of changes in EDSS after Lokomat-based RAGT.

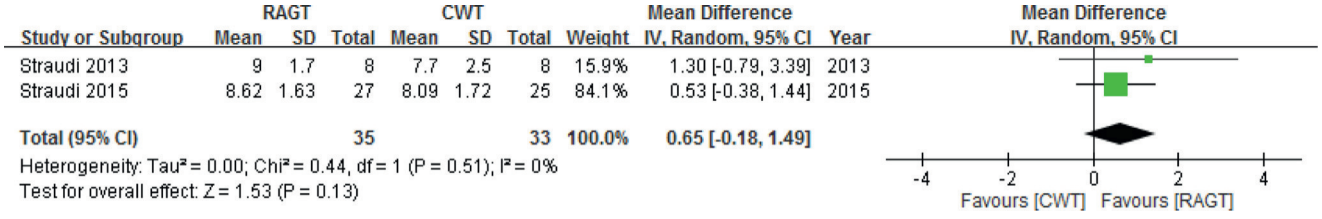

Fig. A.24. Forest plot of treatment acceptance after Lokomat-based RAGT.

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 follow-up without a clear reason. Either per-protocol analysis or intention-to-treat 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 follow-up. 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.

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