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Effects of robotic gait training after stroke: a meta-analysis

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1 **Effects of robotic gait training after stroke: a meta-analysis**

2

3

4 **ABSTRACT**

5 **Background.** Robotic devices are often used in rehabilitation and might be efficient to
6 improve walking capacity after stroke.

7 **Objective.** First to investigate the effects of robot-assisted gait training after stroke and
8 second to explain the observed heterogeneity of results in previous meta-analyses.

9 **Methods.** All randomized controlled trials investigating exoskeletons or end-effector devices
10 in adult patients with stroke were searched in databases (MEDLINE, EMBASE, CENTRAL,
11 CINAHL, OPENGREY, OPENSIGLE, PEDRO, WEB OF SCIENCE, CLINICAL TRIALS,
12 conference proceedings) from inception to November 2019, as were bibliographies of
13 previous meta-analyses, independently by 2 reviewers. The following variables collected
14 before and after the rehabilitation program were gait speed, gait endurance, Berg Balance
15 Scale (BBS), Functional Ambulation Classification (FAC) and Timed Up and Go scores. We
16 also extracted data on randomization method, blinding of outcome assessors, drop-outs,
17 intention (or not) to treat, country, number of participants, disease duration, mean age,
18 features of interventions, and date of outcomes assessment.

19 **Results.** We included 33 studies involving 1466 participants. On analysis by subgroups of
20 intervention, as compared with physiotherapy alone, physiotherapy combined with body-
21 weight support training and robot-assisted gait training conferred greater improvement in gait
22 speed (+0.09 m/s, 95% confidence interval [CI] 0.03 to 0.15; p= 0.002), FAC scores (+0.51,
23 95% CI 0.07 to 0.95; p=0.022) and BBS scores (+4.16, 95% CI 2.60 to 5.71; p=0.000). A
24 meta-regression analysis suggested that these results were underestimated by the attrition bias
25 of studies.

1 **Conclusions.** Robot-assisted gait training combined with physiotherapy and body-weight
2 support training seems an efficient intervention for gait recovery after stroke.

3

4 **Keywords.** stroke; robot-assisted gait training; exoskeleton; end-effector; gait; walking;
5 rehabilitation.

6

7

8 **Introduction**

9 Stroke is one of the most frequently occurring diseases worldwide and leads to permanent
10 disability [1]; restoring walking ability is an important goal of post-stroke rehabilitation [2].
11 Cohort studies showed that 22% of stroke patients do not regain any walking function [3].
12 Among the many methods for gait training after stroke, robotic devices have the ability to
13 provide “repetitive task training” (RTT). According to moderate-quality evidence, RTT can
14 improve walking distance and functional ambulation after stroke [4]. Walking speed is higher
15 during robot-assisted gait training (RAGT) than conventional gait training, so patients repeat
16 more gait cycles [5]. Besides, the exoskeletons and end-effectors of RAGT create force fields
17 to “guide” the person toward a successful trajectory and also promote variability in training,
18 which is a necessary constraint for successful human action learning according to studies of
19 pediatric neurodevelopment [6–8]. Constraints on walking speed and various gait parameters
20 can be varied with control within the training, and RAGT enables possibilities of “bottom-up”
21 rehabilitation interventions such as complete assistance or assistance-as-needed resistance [9].
22 RAGT can also be combined with “top-down” rehabilitation techniques such as transcranial
23 direct current stimulation (tDCS), virtual reality (VR) and biofeedback. Moreover, robotic
24 assistance reduces the physical burden for therapists because they no longer need to manually
25 place the paretic limbs or assist in trunk movements [10].

1 Walking recovery after stroke occurs mainly during the first 10 weeks, and recovery
2 capacities are directly linked to degrees of initial severity [11]. The theory of “critical
3 rehabilitation period” has grown with the Biernaskie et al. studies [12,13] demonstrating
4 clinical improvements after experimental stroke in rats when rehabilitation was initiated
5 within a 5- or 14-day period after stroke but not within a 30-day period after stroke. In this
6 context, robotic devices seem to be a solution to provide “task-specific” rehabilitation earlier
7 and more intensively than with conventional methods.

8 Several studies have investigated the effects of automated electromechanical and RAGT
9 devices on post-stroke gait improvement, but none used the same instructions or the same
10 rehabilitation intervention [14]. In a recent meta-analysis, Mehrholz et al. (2017) concluded
11 that stroke patients who received electromechanical-assisted gait training combined with
12 physiotherapy were more likely to achieve independent walking than those with gait training
13 alone [15]. More specifically, patients with subacute stroke and those who are not able to
14 walk before rehabilitation are expected to benefit more from electromechanical devices than
15 patients with chronic stroke. However, this meta-analysis was limited by the use of the very
16 wide term “electromechanical device,” which included a variety of robotic devices such as
17 exoskeletons, end-effector devices, seated rehabilitation robots, ankle robots, motorized
18 walkers, robotic assistance with functional electric stimulation, etc. These various devices and
19 associated interventions stimulate different aspects of neurorehabilitation, and the
20 heterogeneity of the reported results in this meta-analysis could be linked to the heterogeneity
21 of interventions.

22 In this systematic review, our objective was to conduct meta-analyses to investigate the
23 effects of RAGT on gait after stroke. Especially, we focused on exoskeletons and end-effector
24 devices and compared the efficiency of combinations of interventions such as conventional
25 therapy (CT), CT associated with body-weight support training (BWST) and RAGT

1 [CT+BWST+RAGT], CT associated with BWST, RAGT and functional electrical stimulation
2 (FES) [CT+BWST+RAGT+FES], and BWST and RAGT without any CT [BWST+RAGT].
3 In addition, we performed meta-regressions to evaluate the impact of age, time since stroke,
4 intensity of rehabilitation, stroke severity and risk of bias on the heterogeneity of results.

5

6 **Methods**

7 *Search strategy and selection criteria*

8 This systematic review and meta-analyses were conducted according to the Preferred
9 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and by use
10 of a predefined research protocol. Databases (MEDLINE, Embase, Central, CINAHL,
11 Opengrey, Opensigle, Pedro, Web of Science, Clinical Trials) were searched from inception
12 to November 2017 and updated to November 2019, as were conference proceedings and
13 bibliographies of previous meta-analyses and scoping reviews. A full description of the search
14 strategy is in supplementary data (E-component 1). All randomized controlled trials (RCTs)
15 comparing the efficiency of RAGT with exoskeletons or end-effector robots versus CT to
16 improve walking after stroke and that met the following criteria were included: studies
17 including patients of both sexes > 18 years old, with lower-extremity hemiparesis and limited
18 walking ability after ischemic or hemorrhagic stroke, and having sufficient abilities to
19 understand the exercises to be performed during the interventions. All trials with other
20 electromechanical devices than exoskeletons or end-effectors were excluded. There was no
21 language restriction, and we translated with professional or electronic translators papers in
22 languages other than English, Spanish and French. We tried to contact authors and trial
23 coordinators whenever necessary.

24 Two reviewers (G.M. and H.C.) independently screened titles and abstracts manually for
25 potential eligibility and assessed eligibility for inclusion based on full-text screening.

1 Doubtful records were discussed (G.M and H.C.) with an independent third reviewer (P.D.).
2 The study selection process was recorded with a PRISMA flow chart.

3

4 *Definition of interventions*

5 The goal of this study was to evaluate the effect of RAGT, but studies often used robotic
6 rehabilitation combined with other devices/approaches. Therefore, we classified the different
7 types of interventions according to following categories:

- 8 • RAGT: robot-driven exoskeleton orthoses or end-effector devices fitting the legs and
9 simulating the phases of gait. Patients' legs are guided by the robotic device according to a
10 preprogrammed gait pattern. The process of gait training is automated and controlled by a
11 computer. This category includes exoskeletons such as the Lokomat®, Ekso Bionic leg®,
12 Hybrid-Assistive-Locomotion® (HAL), H2®, etc., as well as end-effector machines such
13 as the GT trainer®.
- 14 • CT: locomotor training via a repetitive execution of walking movements manually guided
15 by a physiotherapist. Guiding principles for this approach can be summarized as the
16 rehabilitation of the lost function by guiding the patient through the expected lower-limb
17 movement trajectory and thereby “teaching” neural circuits governing locomotion in the
18 spinal cord to walk via somatosensory, cognitive, and motor systems. The rules of motor
19 learning such as diversification, repetition, and task-oriented strategies are applied. No
20 electromechanical device is used. Only treadmills, tilt-tables, canes and walkers were
21 allowed.
- 22 • BWST: method promoted for stroke patients by Hesse et al. [16] consisting of a gait re-
23 training overground or on a treadmill, with part of the body weight unloaded. Patients can
24 walk with 60% to 100% of their body weight. BWST enhances automatic walking

1 processes and endurance. Many robotic devices are used in conjunction with a harness to
2 unload patients' weight. In this case, we classified the intervention as BWST+RAGT.

- 3 • Biofeedback: use of detection and restitution support to give a quantitative feedback from
4 a physiological process. It can be audio, sensory or visual feedback and gives the patient
5 real-time control of their movements. It was considered a component of the rehabilitation
6 program when mentioned.
- 7 • tDCS: a non-invasive neurostimulation method whereby very low levels of constant
8 current are delivered to specifically targeted areas of the brain. Sham-tDCS is a method of
9 blinding participants, a form of placebo stimulation.
- 10 • FES: a method of delivering an electrical current to a nerve or a muscle through the skin
11 to obtain a muscle contraction useful for walking. It aims to assist functional movement.
12 Electrical impulses are used to reduce the motor deficit or muscle overactivity.
- 13 • VR: systems that use VR headsets or multi-projected environments to generate realistic
14 images, sounds and other sensations that simulate a user's physical presence in a virtual
15 environment. A person using VR equipment is able to look around the artificial world,
16 move around in it, and interact with virtual features or items.

17 18 ***Data collection and extraction***

19 Data were extracted from reports of selected trials for which full texts were obtained. One
20 reviewer (G.M.) extracted data from each study according to a predefined data extraction
21 form. A second independent reviewer (H.C.) checked the results and characteristics of all
22 studies. A third reviewer (P.D.) was used to achieve consensus in cases of disagreement.

23 Regarding studies that were not trials with 2 parallel-arm comparison, only the first part of
24 cross-over studies (before crossing) were included, and for 3-arm studies, 3 different
25 comparisons were proposed: group A versus B, group A versus C and group B versus C.

1 The following information was extracted for each study included in the review: number of
2 drop-outs, intention-to-treat analysis, randomization, country, number of participants, age of
3 participants, time since stroke, side of stroke, type of stroke (ischemic/hemorrhagic),
4 inclusion and exclusion criteria, period and intensity of rehabilitation, type of intervention,
5 assessment period, outcomes.

6 Intensity of intervention was expressed in "total minutes" of rehabilitation.

7 The most frequently outcomes assessed were gait speed (self-selected gait speed), Functional
8 Ambulation Classification (FAC), Berg Balance Scale (BBS), gait endurance and Timed Up
9 and Go (TUG).

10 The distribution of FAC, BBS, TUG, gait speed and gait endurance outcomes are presented as
11 quantitative continuous measures: FAC: 0 to 5 arbitrary units (AU); gait speed: 0 to 3 m/s;
12 gait endurance: 0 to 800 m; TUG: 0 to 100 sec; BBS: 0 to 56 AU. Standard deviations (SD)
13 were converted by using the Alpha method ($SD_{speed} = SD_{time} \times (\text{distance} / \text{total test}$
14 $\text{duration}^2)$). The few data collected as medians were converted to means after confirming the
15 normality of the distribution. Considering the quartiles' normal distribution, we hypothesized
16 that a median is approximately equal to the mean, and SD was calculated as the mean of
17 $(\text{quartile 3} - \text{median})/0.674$ and $(\text{quartile 1} - \text{median})/0.674$ [17].

18

19 *Statistical analysis and study quality*

20 After data extraction was completed, the possibility of a meta-analysis was determined. A
21 meta-analysis was conducted if at least 3 studies used the same combination of interventions
22 and same outcomes. Then, a meta-analysis by subgroups was conducted according to the
23 types of comparison: [CT] vs [CT+BWST+RAGT], [CT] vs [BWST+RAGT],
24 [CT+BWST+RAGT] vs [CT+BWST+RAGT+FES], and [BWST] vs [BWST+RAGT].
25 Biofeedback or VR techniques were indicated by the expression "±add" in the interventions,

1 and their effects were not sufficiently quantifiable to be analyzed in meta-analysis. Subgroup
2 analyses were conducted according to the Cochrane Handbook for Systematic Reviews of
3 Interventions [18].

4 The effect of each intervention was assessed for each outcome by the pooled mean difference
5 (MD), corresponding to the difference in mean values before and after treatment. Thus, the
6 pooled mean difference for each outcome and each intervention with corresponding 95%
7 confidence intervals (CIs) was calculated using a random-effects model to account for within-
8 and between-study variance.

9 In case of missing data, we tried to contact the authors of the included studies.

10 The median of correlation factors “r” for all included studies was calculated for each
11 outcome, and forest plots based on median “r” were created. Sensitivity analyses were
12 performed for significant results with correlation factor “r” (difference before/after
13 intervention dispersion) from -1, -0.5, 0, +0.5, +1, by comparing the results in the analysis.

14 The heterogeneity of the studies was measured with the I^2 statistic ($I^2 < 25\%$, 25–50% and
15 $> 50\%$ represents low, medium and high heterogeneity, respectively). To identify possible
16 sources of any high heterogeneity, meta-regression models were conducted with the Metafor
17 meta-analysis package for R software [19] and including the following covariates: age, time
18 since stroke, intensity of rehabilitation, stroke severity and risks of bias.

19 To assess the quality of included studies, two review authors (G.M. and H.C.) independently
20 used the "Cochrane risk of bias assessment tool" as described in Chapter 8 of the Cochrane
21 Handbook for Systematic Reviews of Interventions [18]. Any disagreement was resolved by
22 consultation with a third review author (P.D.).

23 Publication bias was assessed by funnel plots.

24

1 **Results**

2 *Included studies and main characteristics*

3 Of 936 identified articles, 161 were selected for full-text screening (Fig. 1); 54 studies met
4 inclusion criteria and were included in the qualitative synthesis. In total, 21 studies were
5 excluded from the meta-analyses for 2 reasons: 9 articles presented a lack of data that could
6 not be retrieved from authors after several contact requests and 12 studies evaluated
7 combinations of interventions that were different from the predefined sub-groups of meta-
8 analysis. Thus, only 33 studies compared similar combinations of interventions and provided
9 enough outcome information to be included in the quantitative synthesis analysis. These 33
10 studies represented a total of 1466 participants.

11 The mean age in the 54 included studies ranged from 45.4 years [20] to 76.8 years [21].
12 Approximately 68% of patients had an ischemic stroke and 53% a right hemisphere lesion.
13 The mean time since stroke was heterogeneous, ranging from 16.1 days [22] to 4575 days
14 [23]. The least intense rehabilitation was 10 sessions for 200 min in total [24] and the most
15 intense was 96 sessions for 4320 min in total [25]. We found no homogeneity in the intensity
16 of rehabilitation, but most studies with significant results proposed rehabilitation programs
17 over 800 to 1200 min by arm: 45 to 60 min a day, 5 days a week for 4 weeks.

18 The main characteristics of the 33 included studies for meta-analysis, classified into 4
19 subgroups, are presented in Tables 1-4. Outcomes were immediately assessed after
20 rehabilitation programs. We did not have sufficient data to evaluate effects during follow-up.

21

22 *Risk of bias in included studies*

23 A detailed list of biases for each study is shown in Figure 2. In total, 36 studies had adequate
24 random sequence generation, and 18 did not give enough information. Regarding “selection”
25 bias, 30 studies had adequate allocation concealment, 19 did not give enough information and

1 5 described risky allocation concealment. Overall, 34 studies reported a blinded outcome
2 assessment, 10 did not give enough information and 10 declared non-blinding assessments.
3 Finally, 23 studies described complete outcome data, 16 did not give enough information and
4 15 reported incomplete data. For most studies, reporting bias was not mentioned because the
5 protocol was not described. Of the 54 studies, only 3 provided enough information to be
6 considered at low risk.

7

8 **Effect of interventions: analyses by subgroups**

9 Main results of meta-analyses by subgroups are presented in Table 5.

10

11 *Group 1: Comparison of effectiveness of [CT±add] vs [CT+BWST+RAGT±add]. The term*
12 *"add" means interventions used in complement to rehabilitation programs (e.g.,*
13 *biofeedback, VR).*

14

15 Funnel plots are presented in E-component 2 for all these group analyses, demonstrating no
16 publication bias.

17

18 *Gait speed*

19 In this analysis, 500 patients from 11 trials were included (Fig. 3A). For the same
20 rehabilitation intensity, the pooled mean difference for gait speed was +0.09 m/s (95% CI:
21 0.03 to 0.15); p=0.002; level of heterogeneity I²=79.2%, r=0.5. The sensitivity analysis
22 showed constant significance: for r=-1, the pooled mean value was +0.10 m/s (95% CI: 0.03
23 to 0.16), p=0.003; for r=-0.5 pooled mean value was +0.10 m/s (95% CI: 0.03 to 0.16),
24 p=0.002; for r=0, the pooled mean value was +0.09 m/s (95% CI: 0.03 to 0.15), p=0.002; for

1 $r=0.5$, the pooled mean value was $+0.09$ m/s (95% CI: 0.03 to 0.15), $p=0.002$; for $r=1$, the
2 pooled mean value was $+0.09$ m/s (95% CI: 0.03 to 0.14), $p=0.001$.

3 Meta-regressions showed that the quality study attrition explained 98.4% of the heterogeneity
4 and the square root of estimated τ^2 value was 0.01. Thus, a meta-analysis of 6 selected
5 studies (304 patients) with low risk of attrition bias was performed, showing an improvement
6 of $+0.12$ m/s (95% CI: 0.09 to 0.16); $p=0.000$; level of heterogeneity $I^2=0.1\%$, $r=0.5$ (Fig.
7 4A).

8

9 *Gait endurance*

10 In this analysis, 213 patients from 3 trials were included (Fig. 3B). We found no significant
11 difference for gait endurance: $+22.73$ m per 6 min (95% CI: -16.90 to 62.35); $p=0.261$; level
12 of heterogeneity $I^2=34.9\%$, $r=0.5$.

13

14 *Functional Ambulation Classification*

15 In this analysis, 639 patients from 12 trials were included (Fig. 3C). For the same
16 rehabilitation intensity, the pooled mean difference for FAC scores was $+0.51$ AU (95% CI:
17 0.07 to 0.95); $p=0.022$; level of heterogeneity $I^2=71.3\%$, $r=0$. The sensitivity analysis showed
18 constant significance: for $r=-1$, the pooled mean value was $+0.53$ AU (95% CI: 0.06 to 1.00),
19 $p=0.027$; for $r=-0.5$, the pooled mean value was $+0.52$ AU (95% CI: 0.07 to 0.97), $p=0.025$;
20 for $r=0$, the pooled mean value was $+0.51$ AU (95% CI: 0.07 to 0.95), $p=0.022$; for $r=0.5$,
21 pooled mean value was $+0.50$ AU (95% CI: 0.08 to 0.92), $p=0.019$; for $r=1$, the pooled mean
22 value was $+0.48$ AU (95% CI: 0.09 to 0.88), $p=0.017$.

23 Meta-regressions showed that the quality study attrition explained 61.6% of heterogeneity and
24 the square root of estimated τ^2 value was 0.39. Thus, a meta-analysis of 5 selected studies

1 (276 patients) with low risk of attrition bias was conducted, showing an improvement of
2 +1.13 AU (95% CI: 0.73 to 1.54); $p < 0.000$; level of heterogeneity $I^2 = 19.5\%$, $r = 0$ (Fig. 4B).

4 *Berg Balance Scale*

5 In this analysis, 230 patients from 6 trials were included (Fig. 3D). For the same rehabilitation
6 intensity, the pooled mean difference for BBS scores was +4.16 AU (95% CI: 2.60 to 5.71);
7 $p = 0.000$; level of heterogeneity $I^2 = 2.7\%$, $r = 0.5$. However, the sensitivity analysis did not
8 show constant significance: for $r = -1$, the pooled mean value was +4.44 AU (95% CI: 3.13 to
9 5.75), $p = 0.000$; for $r = -0.5$, the pooled mean value was +4.42 AU (95% CI: 3.12 to 5.72),
10 $p = 0.000$; for $r = 0$, the pooled mean value was +4.38 AU (95% CI: 3.09 to 5.67), $p = 0.000$; for
11 $r = 0.5$, pooled mean value was +4.16 AU (95% CI: 2.60 to 5.71), $p = 0.000$; for $r = 1$, the pooled
12 mean value was 2.09 AU (95% CI: -1.37 to 5.54), $p = 0.237$.

13 Meta-regressions showed that the quality study attrition explained 100% of the heterogeneity
14 and the square root of estimated τ^2 value was 0.00. Because of only 2 studies with low risk
15 of attrition bias, a meta-analysis was not conducted.

17 *Timed Up and Go*

18 In this analysis, 77 patients from 3 trials were included (Fig. 3E) and no significant difference
19 was found. The pooled mean difference for TUG was +3.20 sec (95% CI: -2.58 to 8.98);
20 $p = 0.277$; level of heterogeneity $I^2 = 91.6\%$, $r = 0.5$.

22 ***Group 2: Comparison of effectiveness of [CT±add] vs [BWST+RAGT±add]. The term***
23 ***"add" means interventions used as a complement to rehabilitation programs (e.g.***
24 ***biofeedback, sham-tDCS).***

25

1 Funnel plots are presented in E-component 3 for all of these group analyses, demonstrating no
2 publication bias.

3

4 *Gait speed*

5 In this analysis, 184 patients from 7 trials were included (Fig. 5A) and no significant
6 difference was found. The pooled mean difference for gait speed was -0.04 m/s (95% CI: -
7 0.12 to 0.04); $p=0.331$ level of heterogeneity $I^2=83.4%$, $r=0.5$.

8

9 *Gait endurance*

10 In this analysis, 182 patients from 6 trials were included (Fig. 5B) and no significant
11 difference was found. The pooled mean difference for gait endurance was -23.39 m per 6 min
12 (95% CI: -65.56 to 18.77); $p=0.277$; level of heterogeneity $I^2=92.7%$, $r=0.5$.

13

14 *Functional Ambulation Classification*

15 In this analysis, 107 patients from 3 trials were included (Fig. 5C) and no significant
16 difference was found. The pooled mean difference for FAC was 0.00 AU (95% CI: -0.10 to
17 0.10); $p=0.954$; level of heterogeneity $I^2=0%$, $r=0$.

18

19 *Berg Balance Scale*

20 In this analysis, 117 patients from 3 trials were included (Fig. 5D) and no significant
21 difference was found. The pooled mean difference for BBS scores was +0.10 AU (95% CI: -
22 1.42 to 1.62); $p=0.900$; level of heterogeneity $I^2=48.4%$, $r=0.5$.

23

1 ***Group 3: Comparison of effectiveness of [CT+BWST+RAGT] vs [CT+BWST+RAGT+FES]***

2

3 Funnel plots are presented in E-component 4 for all of these group analyses, demonstrating no
4 publication bias.

5

6 ***Gait speed***

7 In this analysis, 113 patients from 4 trials were included (Fig. 6A) and no significant
8 difference was found. The pooled mean difference for Gait speed was +0.06 m/s (95% CI: -
9 0.03 to 0.16); p=0.232; level of heterogeneity I²=0%, r=0.5.

10

11 ***Berg Balance Scale***

12 In this analysis, 83 patients from 3 trials were included (Fig. 6B) and no significant difference
13 was found. The pooled mean difference for BBS scores was +0.55 AU (95% CI: -3.88 to
14 4.98); p=0.808; level of heterogeneity I²=0%, r=0.5.

15

16 ***Group 4: Comparison of effectiveness of [BWST±add] vs [BWST+RAGT±add]. The term***
17 ***"add" means interventions used in complement to rehabilitation programs (e.g.,***
18 ***biofeedback or FES).***

19

20 Funnel plots are presented in E-component 5 for all of these group analyses, demonstrating no
21 publication bias.

22

1 *Gait speed*

2 In this analysis, 53 patients from 3 trials were included (Fig. 7) and no significant difference
3 was found. The pooled mean difference for gait speed was +0.04 m/s (95% CI: -0.13 to 0.22);
4 $p=0.630$; level of heterogeneity $I^2=0\%$, $r=0.5$.

5

6 **Discussion**

7 For the same rehabilitation intensity, the pooled mean results showed that the association
8 [CT+BWST+RAGT] was more efficient than [CT] alone, according to the change in gait
9 speed (+0.09 m/s), FAC scores (+0.51 AU) and BBS scores (+4.16 AU). The pooled mean
10 results could be underestimated based on attrition bias that was the source of much of the
11 heterogeneity, as shown by meta-regressions. Therefore, the calculated effect of interventions
12 was likely lower than the real central effect. Calculated meta-analyses of selected studies with
13 low risk of attrition bias indicated an improvement of +0.12 m/s for gait speed and +1.13 for
14 FAC scores. This is all the more remarkable given that the significant differences were
15 confirmed by sensitivity analyses.

16 The relevance of an improvement in gait speed of 0.09 m/s depends both on the Minimal
17 Detectable Change (MDC90) and the Minimal Clinically Important Difference (MCID) for
18 gait speed. Fulk et al. [26] calculated 2 MDC90 values for gait speed according to the level of
19 dependence at the start of rehabilitation. MDC90 was 0.07 m/s for individuals who required
20 physical assistance to walk at the start of rehabilitation (mean [SD] gait speed at start 0.26
21 [0.18] m/s) and was 0.36 m/s for those who could walk without physical assistance at the start
22 of rehabilitation (mean gait speed at start 0.56 [0.30] m/s). Bohannon et al. [27] calculated a
23 MCID of 0.13 m/s as a reduction in assistance required (definitions compatible with the
24 Functional Independence Measure) and the mean gait speed of their cohort of 21 stroke
25 patients at the start of rehabilitation was 0.18 (0.18) m/s. Tilson et al. [28] measured a MCID

1 of 0.16 m/s as an improvement of one category of modified Rankin Scale, and the mean gait
2 speed of their cohort of 283 patients at the start of rehabilitation was 0.18 (0.16) m/s. Fulk et
3 al. [29] calculated 2 different MCID values: one MCID of 0.175 m/s as the perception of “an
4 important change in walking ability” estimated by the patient and one MCID of 0.190 m/s as
5 the perception of “an important change in walking ability” estimated by the physical therapist
6 (evaluated by Global Rating of Change). Their cohort of 44 stroke patients walked at a mean
7 gait speed of 0.56 (0.22) m/s at the start of rehabilitation. Given that these most common
8 findings about MDC90 and MCID walking speed after stroke and taking into account that the
9 range of patients included in our meta-analyses was very broad, our findings suggest a
10 clinically relevant improvement in gait speed. Besides, the combination [CT+BWST+RAGT]
11 should be effective for the most severely affected patients.

12 We may explain the relevant synergy of physiotherapy and robotic devices by the ability to
13 offer global training from the start. Usually, CT is conducted according to the following steps
14 [30]: 1) trunk stability is re-trained by using increasing levels of difficulty during standing, 2)
15 the ability to stand is re-trained by standing up in active safety systems, and 3) gait re-training
16 starts when the patient acquired enough trunk and standing force. RAGT helps overcome the
17 initial rehabilitation steps and compensate for the patient’s postural weakness by using lumbar
18 straps attached to the device and motorized joint control assistance. RAGT offers task-
19 specific training from the start of intensive rehabilitation. Thus, our findings complement the
20 conclusions of the Mehrholz et al. meta-analyses [15] and can explain the absence of a
21 significant difference for meta-analyses that compared the effects of a rehabilitation program
22 combining BWST+RAGT without CT to one with CT. Certainly, CT adds important “task-
23 specific” techniques of rehabilitation, such as balance training, sit-to-stand working or
24 stability of belts training for the recovery of walking.

1 Otherwise, if adding FES to a rehabilitation program combining [CT+BWST+RAGT] was
2 not associated with a significant difference, meta-analyses were probably not powerful
3 enough: only 114 patients were included in the largest study, and no comparable intensities of
4 rehabilitation/disease durations could be used for comparison.

5 According to meta-regressions in all meta-analyses subgroups, the effectiveness of the
6 intervention did not depend on rehabilitation intensity, stroke severity, age of patients or time
7 since stroke, in contrast to Craig et al. [31] who found an association between gait
8 impairments during post-stroke recovery and age, severity of paresis and decrease in leg
9 strength. Mehrholz et al. [15] also found that electromechanical assisted training would be
10 more effective for acute stroke. Morone et al. [32] supported this assumption. The authors
11 compared 2 groups: one group of “low motricity” (severe deficiency) and one of “high
12 motricity” (less severe deficiency) and found that the robot rehabilitation program
13 significantly benefited more the “low motricity” patients (improvement of FAC scores: +1.80
14 AU, 95% CI: 0.93 to 2.67) than the “high motricity” patients (improvement of FAC scores:
15 +0.5 AU, 95% CI: -0.43 to 1.43). We suggest that even if meta-regressions did not identify
16 severity of stroke as a key factor associated with better benefit from RAGT rehabilitation, the
17 severity of the impairments is likely a factor associated with the gait outcome. In addition, the
18 absence of significant results in meta-regressions evaluating the impact of rehabilitation
19 intensity, age, or time since stroke on RAGT rehabilitation outcomes could be explained by
20 the inadequacy of large and homogeneous cohorts for a proper comparison.

21 To minimize the publication bias, all accessible electronic databases were searched, including
22 the grey literature, and the authors of identified studies were contacted whenever necessary
23 (but unsuccessfully). Nevertheless, only studies with complete outcome assessments were
24 included, and studies/abstracts that did not give any information about potential bias were
25 excluded. Finally, our findings were balanced with positive and negative results about robotic

1 rehabilitation, as confirmed by the well-balanced aspect of the funnel plot, which reinforces
2 the low publication bias of this review.

3 The overall quality of studies was good to moderate [33]. Therefore, the findings should be
4 interpreted with caution, although most of the risks likely came from attrition bias, as shown
5 by meta-regressions. This highlights the importance of paying attention to attrition bias,
6 which can more easily be prevented than blinding bias, which is a well-known problem in
7 rehabilitation.

8 Beyond the biases of included studies (assessed with the Cochrane Risk of Bias tool [18]),
9 some factors caution the interpretation of the meta-analysis results: the inaccuracy of outcome
10 conversions (median values were converted to mean values), a possible influence of
11 interventions pooled in “add” items (no mean values to consider them), a possible inaccuracy
12 of rehabilitation intensity, the heterogeneity between rehabilitation protocols (not the same
13 devices, intensity, and motion), the heterogeneity between trial designs (2 arms, 3 arms,
14 parallel-group, cross-over groups, selection criteria), the heterogeneity between characteristics
15 of patients, and the use of outcomes collected from primary or secondary outcomes depending
16 on the studies.

17 Since October 2017, 3 meta-analyses have evaluated the effects of RAGT on gait recovery
18 after stroke, but they did not provide the same information as our meta-analyses. Zheng et al.
19 [34] evaluated the efficiency of RAGT for balance. Outcomes were BBS, Fugl-Meyer
20 Balance assessment scores and TUG. Their search stopped in March 2018. The authors found
21 a positive impact of RAGT on balance after stroke. Asiri et al. [35] evaluated the efficiency of
22 RAGT on gait speed but excluded end-effectors. Thus, the authors conducted a meta-analysis
23 of only 4 trials. They found that the effect of RAGT to improve walking speed was
24 significantly inferior than CT. Results were heterogeneous without any explanation. Their
25 search stopped in 2017 (no details). Bruni et al. [36] evaluated efficiency of RAGT by

1 distinguishing end-effectors and exoskeletons but did not specify rehabilitation protocols in
2 combination with RAGT. Outcomes were gait speed, gait endurance, TUG and FAC.
3 Although their results were heterogeneous, stroke patients who received [CT+BWST+RAGT]
4 were more likely to reach better gait speed results than those who received [CT]. Their search
5 stopped in June 2015.

6

7 **Conclusion**

8 These present findings suggest that the use of RAGT associated with CT and BWST would
9 improve the efficiency of walking rehabilitation after stroke, with significant gait speed, FAC
10 and BBS improvements. These meta-analyses explained part of the heterogeneity of the
11 Mehrholz et al. 2017 meta-analyses [37] by performing subgroup analyses and meta-
12 regressions. Efficiency evidence is not yet strong enough to recommend the use of FES in
13 combination with robots. More research with tight training protocols is required to define new
14 rehabilitation programs with exoskeletons/end-effector devices such as balance training and
15 sit-to-stand training. In addition, simplified ways of using these devices must be developed
16 before they can be used more by rehabilitation specialists.

17 We suggest some recommendations for future research work: 1) rehabilitation programs
18 should be conducted with a minimum intensity of 1200 min (minimum 1 hr a day, 5 days per
19 week, for 4 weeks) and a minimum of 50 patients per arm should be included for good
20 statistical power; and 2) more sensitive rating scales than FAC or gait speed should be used,
21 such as ABILICO [38], permitting a 3-D evaluation.

22 We suggest some recommendations for engineers: 1) robotic devices should propose more
23 complex training than “walking straight” training, given that variability is a necessary
24 constraint for successful rehabilitation; and 2) the role of robotic devices should be to create

1 movement environments and provide personal and environmental constraints that elicit and
2 support self-produced functional actions.

3 Advice can also be given to clinicians according to the MDC90 for gait speed and the MCID
4 for gait speed: RAGT seems more relevant for the most dependent patients, especially those
5 walking under 0.20 m/s (self-selected walking speed) and who need human assistance to
6 walk.

7

8 **Conflict of interest.** None declared.

9

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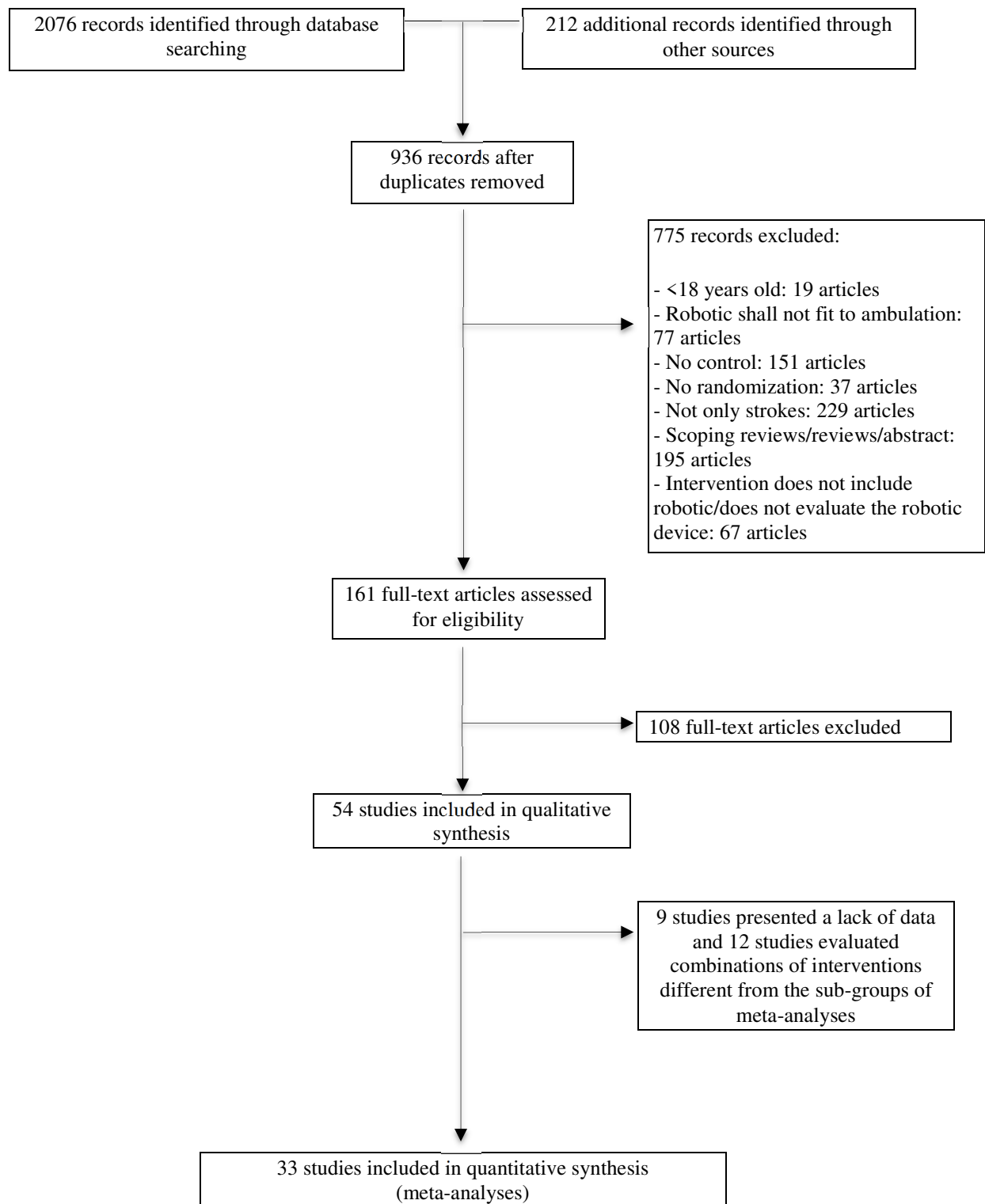
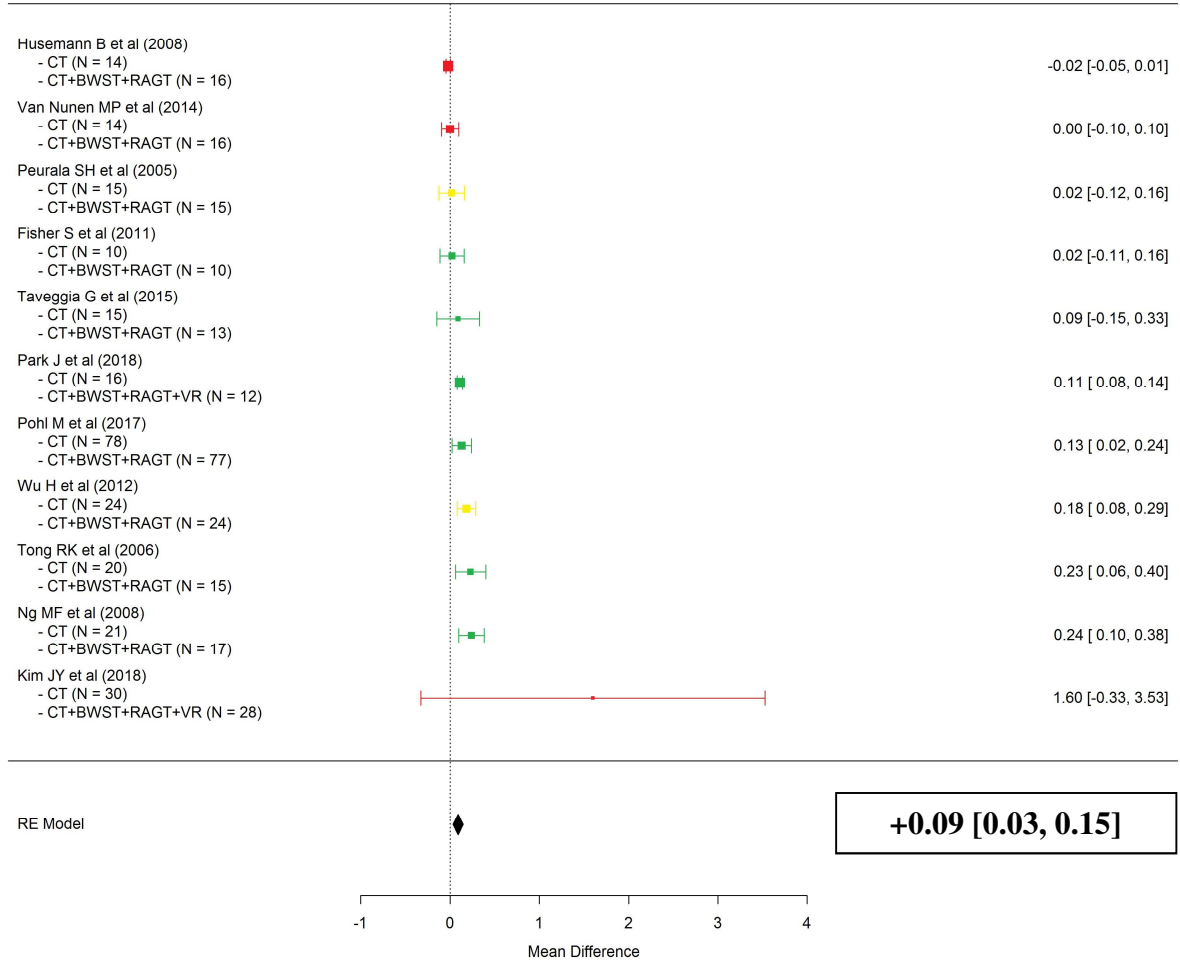


Figure 1. Study flow chart.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)
Bae YH et al 2014	?	+	+	?	?
Bang DH et al 2016	+	+	+	+	?
Belas dos santos et al 2018	?	?	+	+	?
Bergmann et al 2018	+	+	+	+	?
Buesing C et al 2015	+	+	+	+	?
Calabro et al 2018	?	+	+	+	+
Calabrò RS et al 2017	?	+	+	+	?
Chang WH et al 2012	?	+	+	+	?
Cho DY et al 2015	?	+	+	+	?
Chua J et al 2016	+	+	+	+	?
Danzl MM et al 2013	?	+	+	+	?
Dias D et al 2007	+	+	+	+	?
Fisher S et al 2011	+	?	+	+	?
Geroin C et al 2011	+	+	+	+	?
Han EY et al 2016	?	?	+	+	?
Hidler J et al 2009	+	?	+	+	?
Hornby TG et al 2008	+	+	+	+	?
Husemann B et al 2007	+	+	+	+	?
Jung KH et al 2008	+	+	?	?	?
Kang TW et al 2018	+	+	+	+	?
Kelley CP et al 2013	+	+	+	?	?
Kim JY et al 2018	+	?	?	+	?
Kim SY et al 2015	?	?	+	+	?
Kim YH et al 2019	+	+	+	+	?
Mayr A et al 2007	+	?	+	+	?
Mayr A et al 2018	+	+	+	?	?
Morone G et al 2012	+	+	+	+	?
Morone G et al 2018	+	+	+	+	?
Nam YG et al 2018	+	+	?	+	?
Ng MF et al 2008	+	?	+	+	?
Noser E et al 2012	?	?	+	?	?
Ochi M et al 2015	+	+	+	+	?
Park J et al 2019	?	?	?	+	?
Peurala SH et al 2005	+	+	+	?	?
Picelli A et al 2017	+	+	+	+	?
Picelli A et al, 2015	+	+	+	+	?
Pohl M et al 2007	+	+	+	+	?
Richards CL et al 2004	?	?	+	+	?
Rodrigues TA et al 2017	?	+	+	?	?
Schwartz I et al 2009	?	?	+	+	?
Sczesny-Kaiser et al 2019	+	+	+	?	?
Seo HG et al 2017	+	?	+	+	?
Srivastava et al 2016	?	?	?	?	?
Stein J et al 2014	?	?	+	+	?
Taveggia G et al 2015	+	+	+	+	?
Tomida K et al 2019	+	?	?	+	?
Tong RK et al 2006	+	+	+	+	?
Van Nunen MP et al 2014	?	?	+	+	?
Watanabe H et al, 2017	+	+	?	+	?
Werner C et al 2002	+	+	+	+	?
Westlake KP et al 2009	+	+	?	?	?
Wu H et al 2012	+	?	?	?	?
Wu M et al 2014	?	?	?	?	?
Yun et al 2018	+	+	+	?	?

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. ● = low risk of bias, ? = unclear risk of bias, ● = high risk of bias

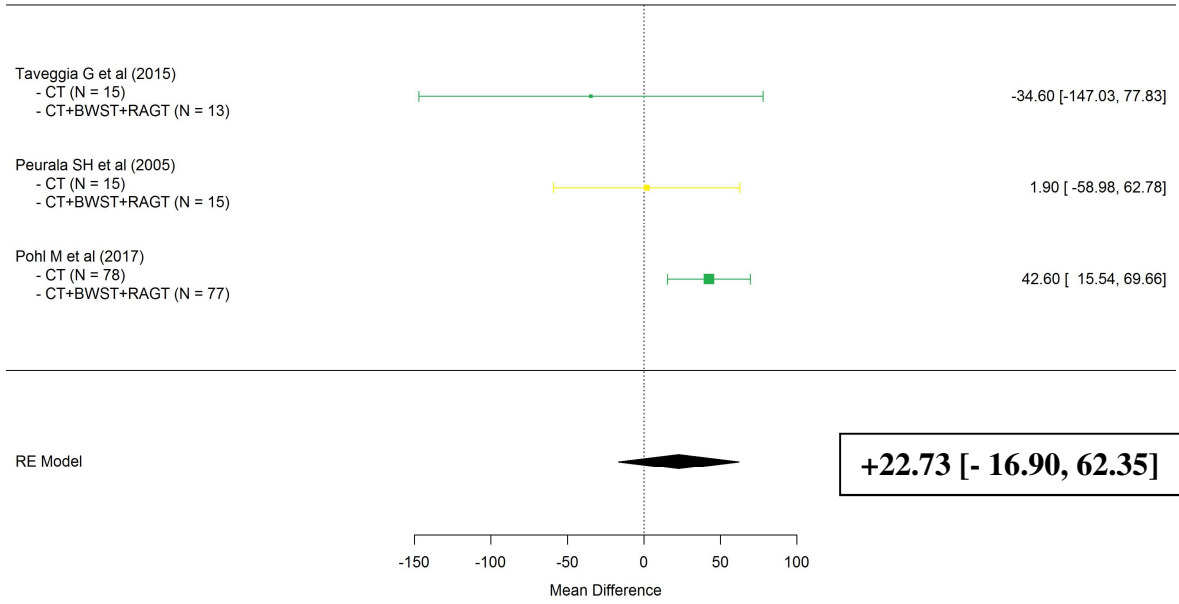


Level of heterogeneity $I^2=79.22%$, $r = 0.5$

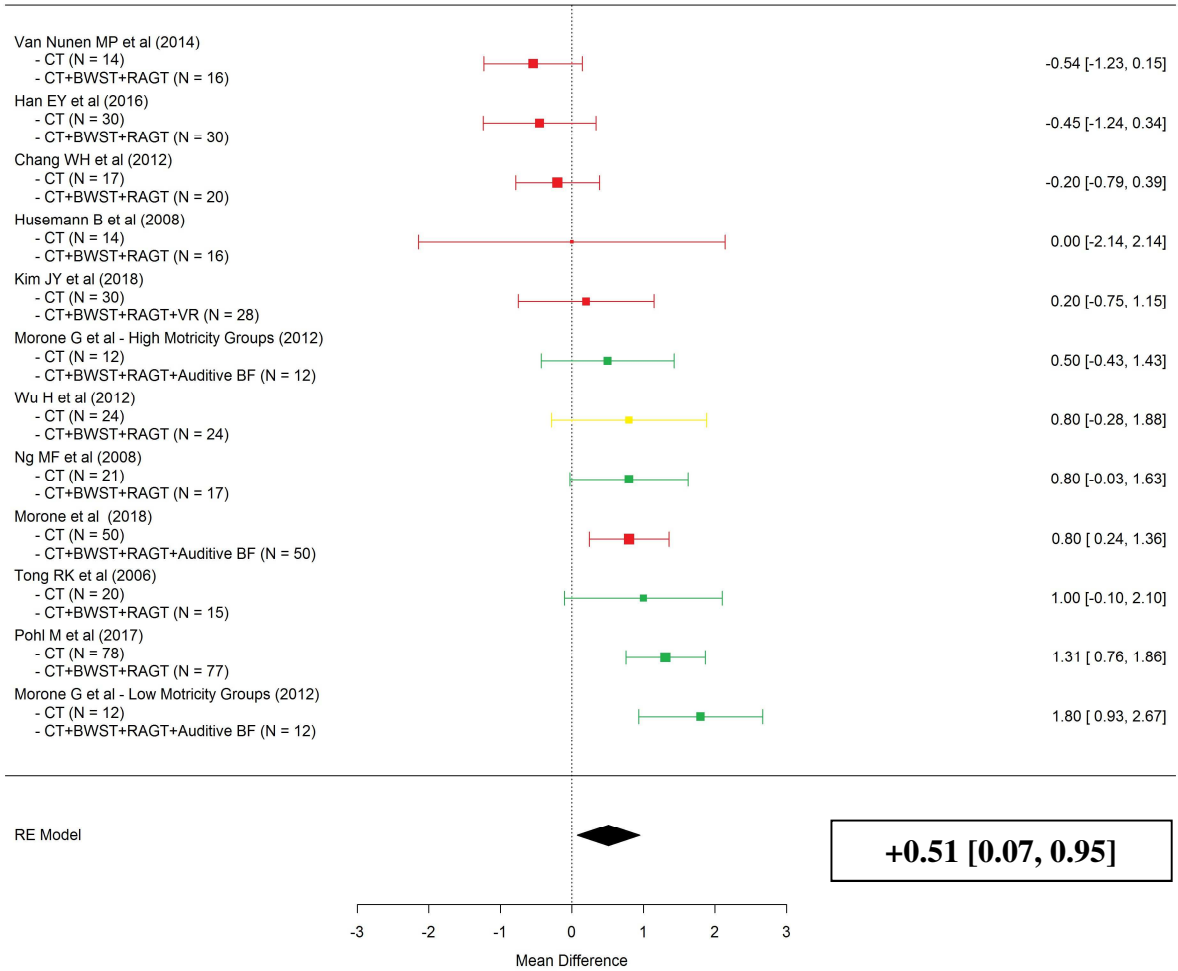
Meta-regression: 98.36% of heterogeneity was explained by the quality study attrition.

3B

Gait endurance - CT+add vs CT+BWST+RAGT+add

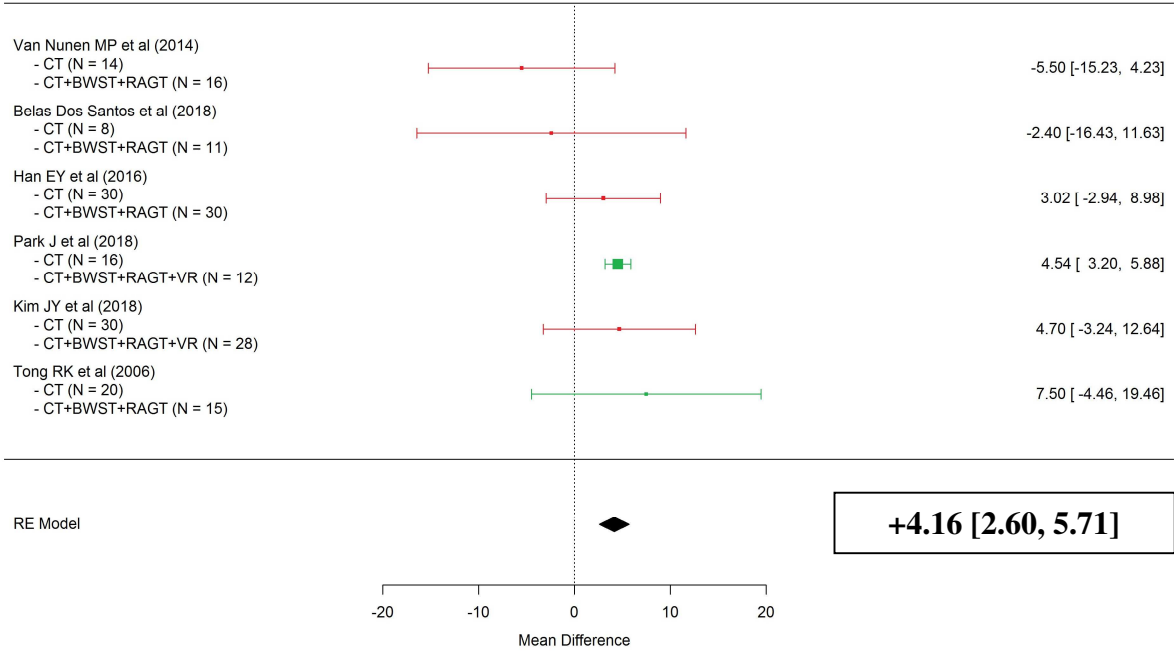


Level of heterogeneity $I^2=34,90\%$, $r = 0.5$



Level of heterogeneity $I^2=71.34%$, $r = 0$
 Meta-regression: 61.58% of heterogeneity was explained by the quality study attrition.

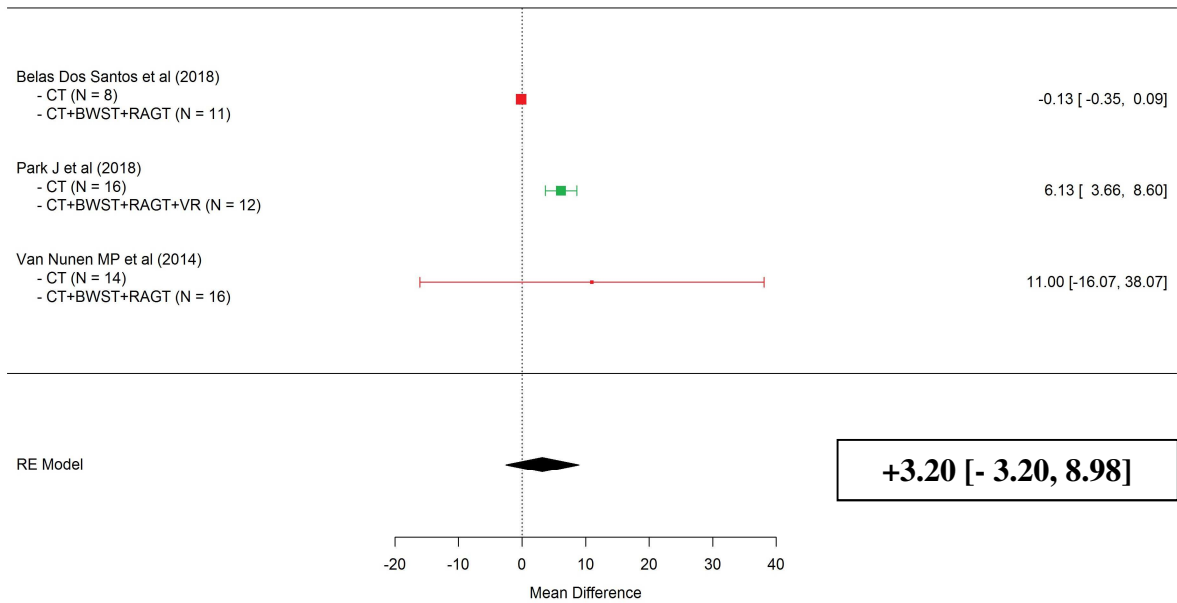
BBS - CT+add vs CT+BWST+RAGT+add



Level of heterogeneity $I^2=2.68\%$, $r = 0.5$
 Meta-regression: 100.00% of heterogeneity was explained by the quality study attrition.

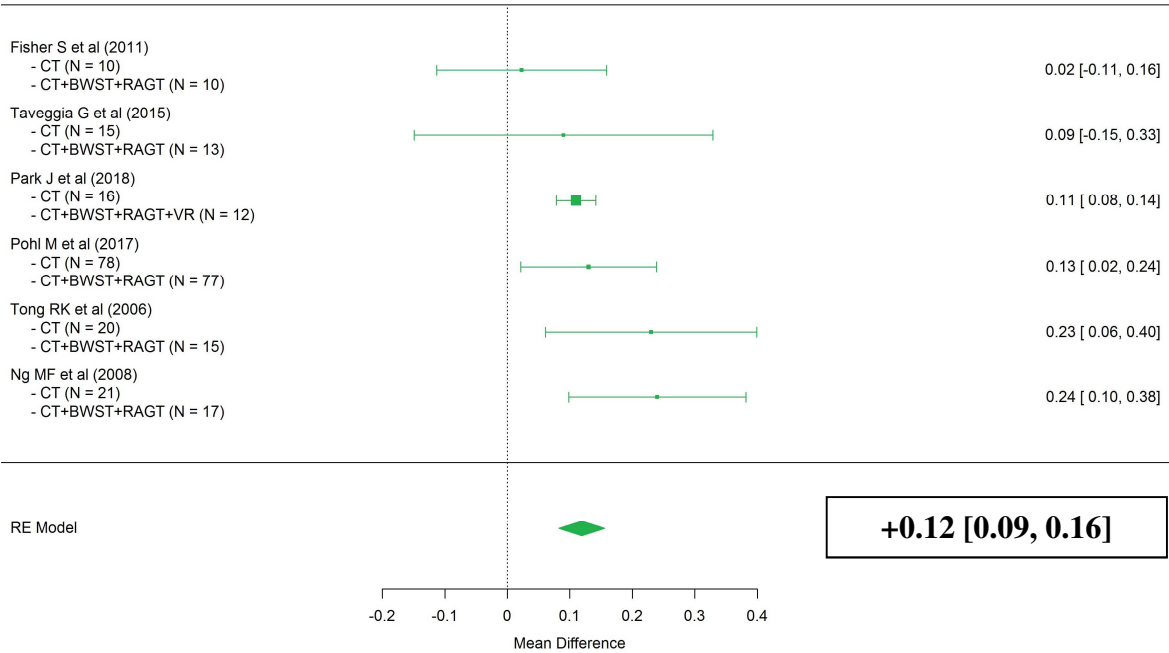
3E

TUG - CT+add vs CT+BWST+RAGT+add



Level of heterogeneity $I^2=91.638\%$, $r = 0.5$

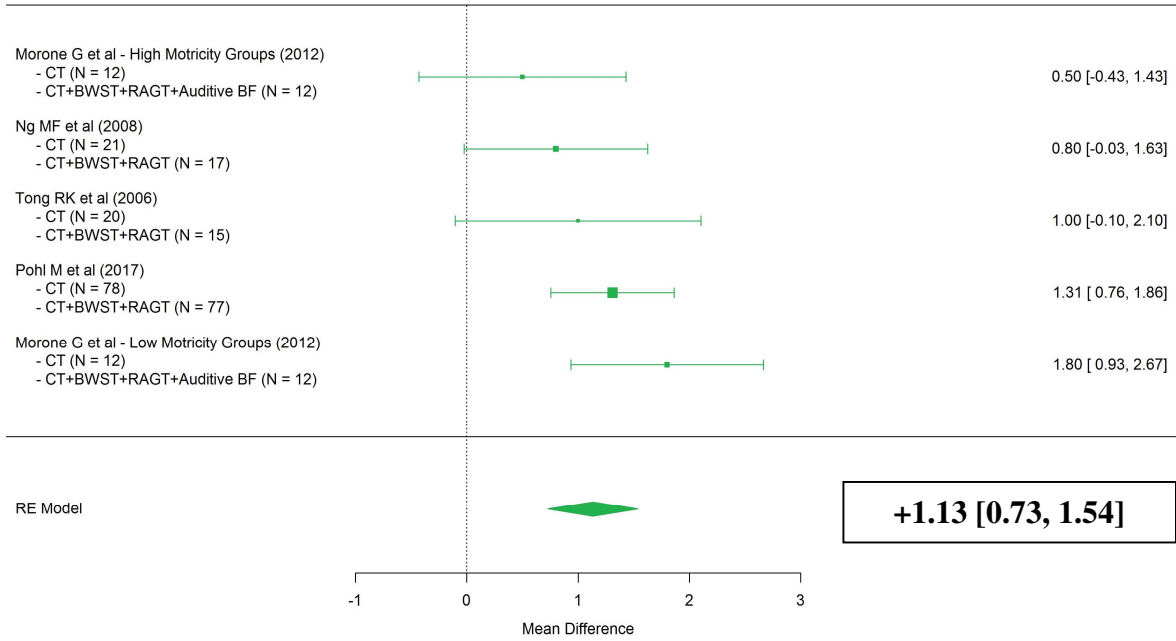
Figure 3. Forest plots and outcomes for comparison of [CT±add] vs [CT+BWST+RAGT±add]. A. Gait speed, B. Gait endurance, C. Functional Ambulation Classification (FAC), D. Berg Balance Scale (BBS), E. Timed Up And Go (TUG). Colors on figures correspond to the quality of attrition: green □ is “low risk”, yellow □ is “unclear risk” and red □ is “high risk”. CT = conventional physiotherapy, BWST = body-weight support training, RAGT = robot-assisted gait training, BF = biofeedback, VR = virtual reality.



Level of heterogeneity $I^2=0.11\%$, $r = 0.5$

4B

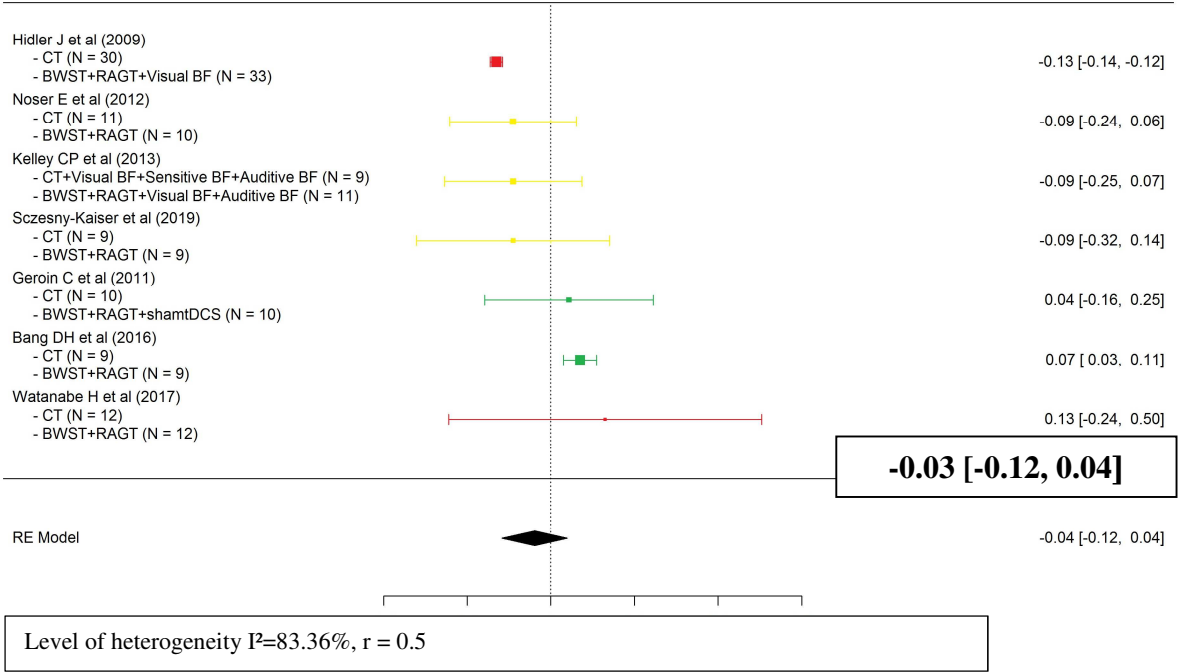
FAC - CT+add vs CT+BWST+RAGT+add



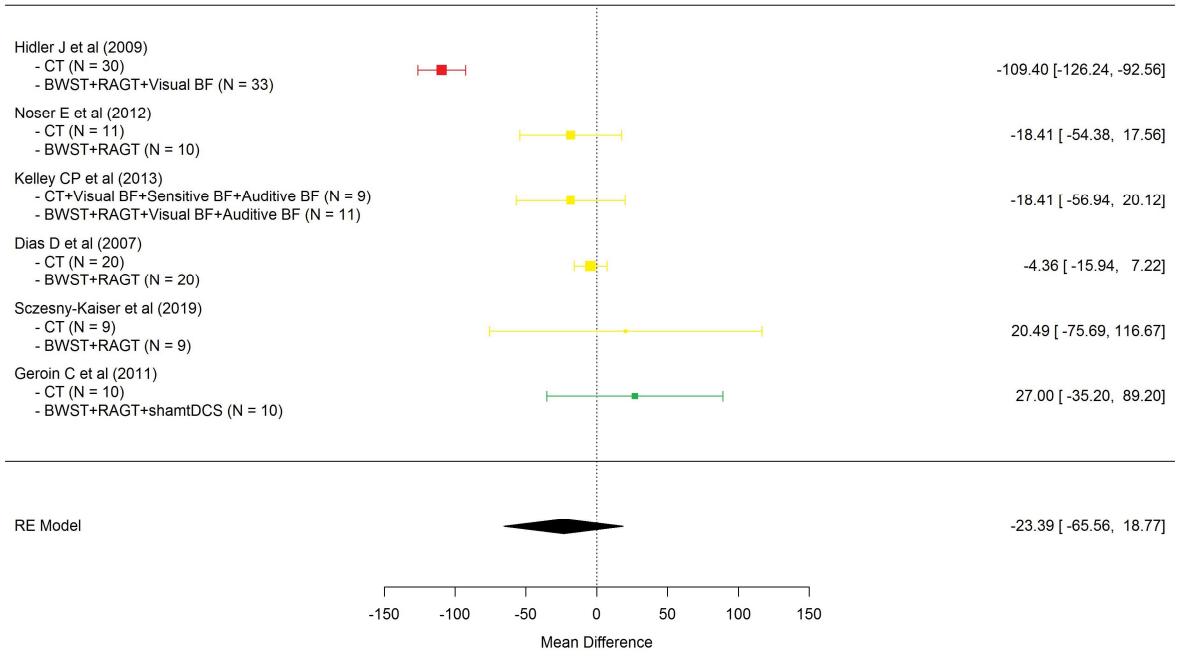
Level of heterogeneity $I^2=19.45%$, $r = 0$

Figure 4. Forest plots and outcomes for meta-analyses of studies with low risk of attrition bias for comparison of [CT±add] vs [CT+BWST+RAGT±add]. A. Gait speed, B. Functional Ambulation Classification (FAC).

Gait speed - CT+add vs BWST+RAGT+add



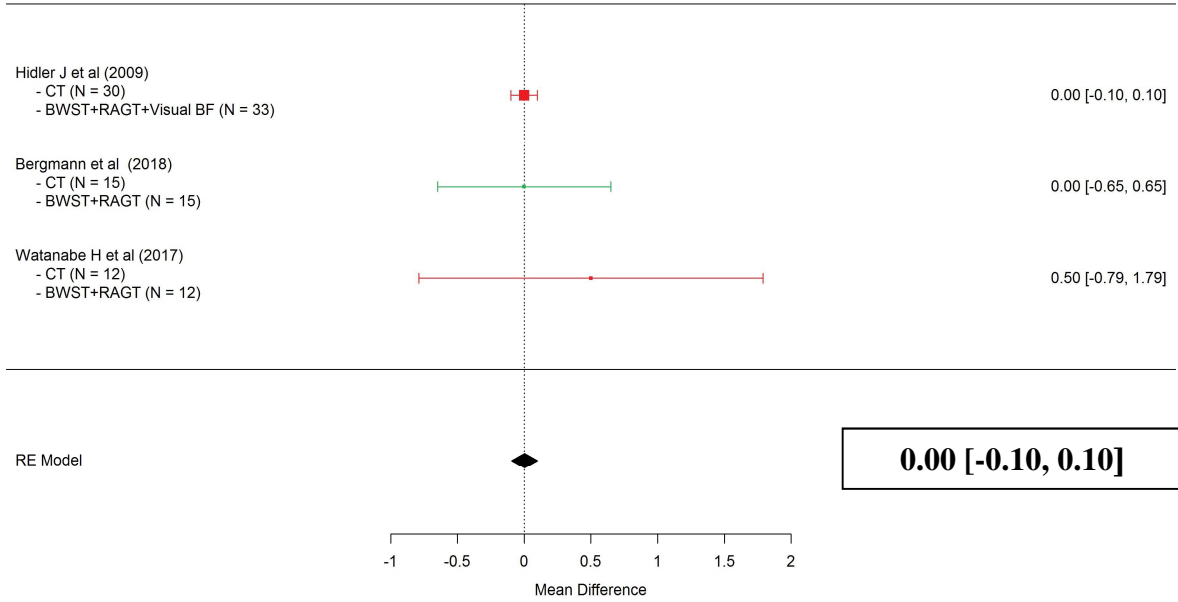
Gait endurance - CT+add vs BWST+RAGT+add



-23.39 [-65.56, 18.77]

Level of heterogeneity $I^2=91.72\%$, $r = 0.5$

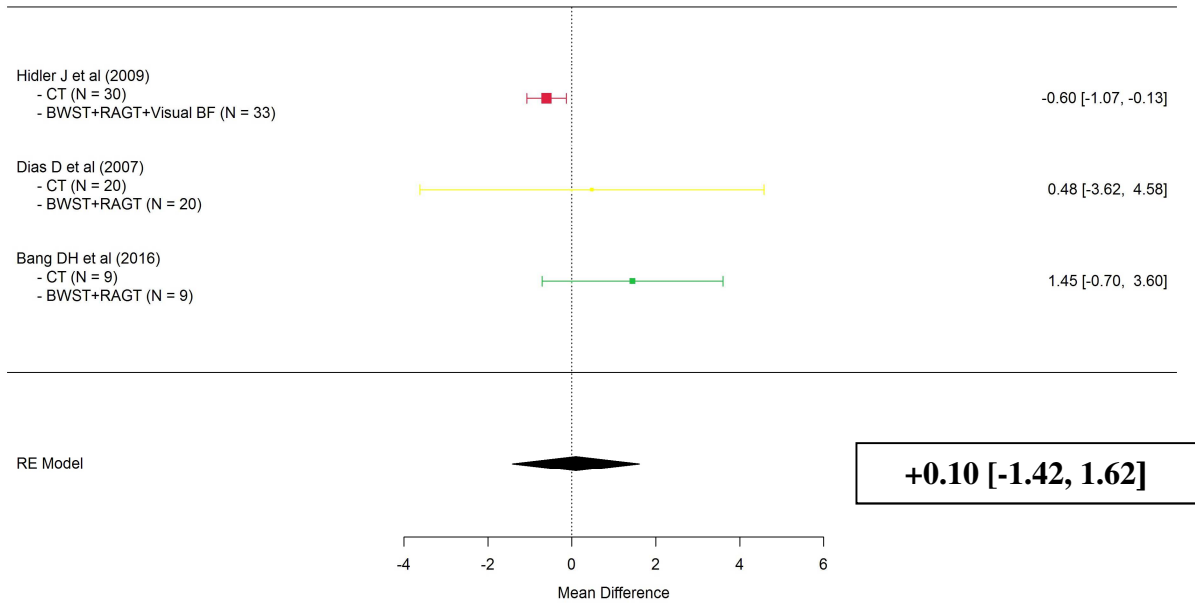
FAC - CT+add vs BWST+RAGT+add



Level of heterogeneity $I^2=0.00\%$, $r = 0$

5D

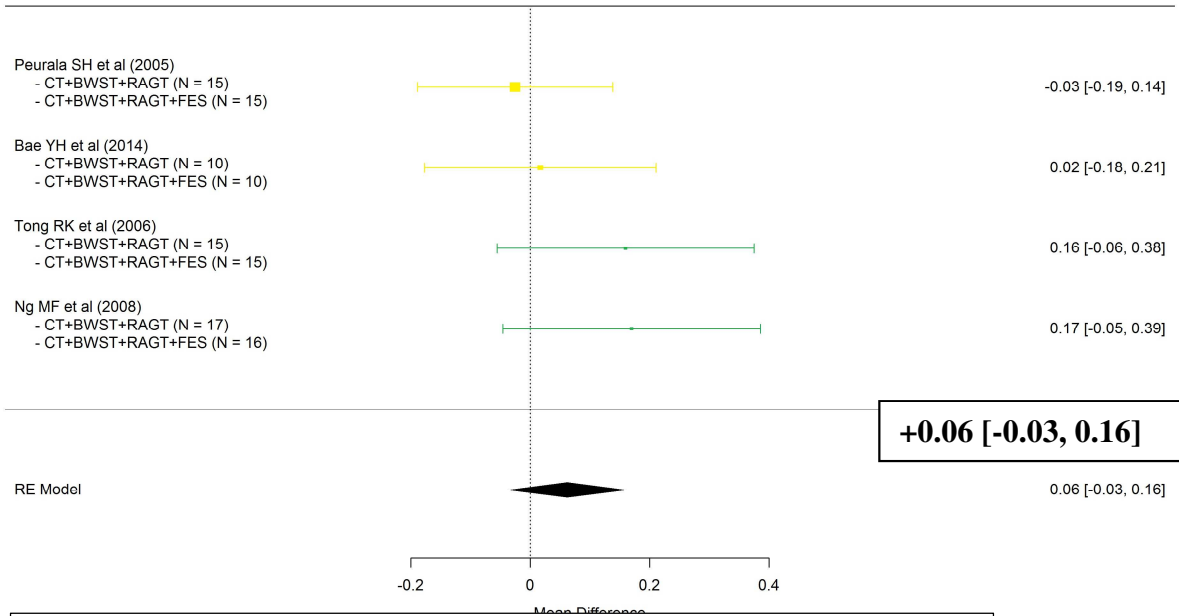
BBS - CT+add vs BWST+RAGT+add



Level of heterogeneity $I^2=48.37%$, $r = 0.5$

Figure 5. Forest plots and outcomes for comparison of [CT±add] vs [BWST+RAGT±add]. A. Gait speed, B. Gait endurance, C. Functional Ambulation Classification (FAC), D. Berg Balance Scale (BBS). Colors on figures correspond to the quality of attrition: green □ is “low risk”, yellow □ is “unclear risk” and red □ is “high risk”.

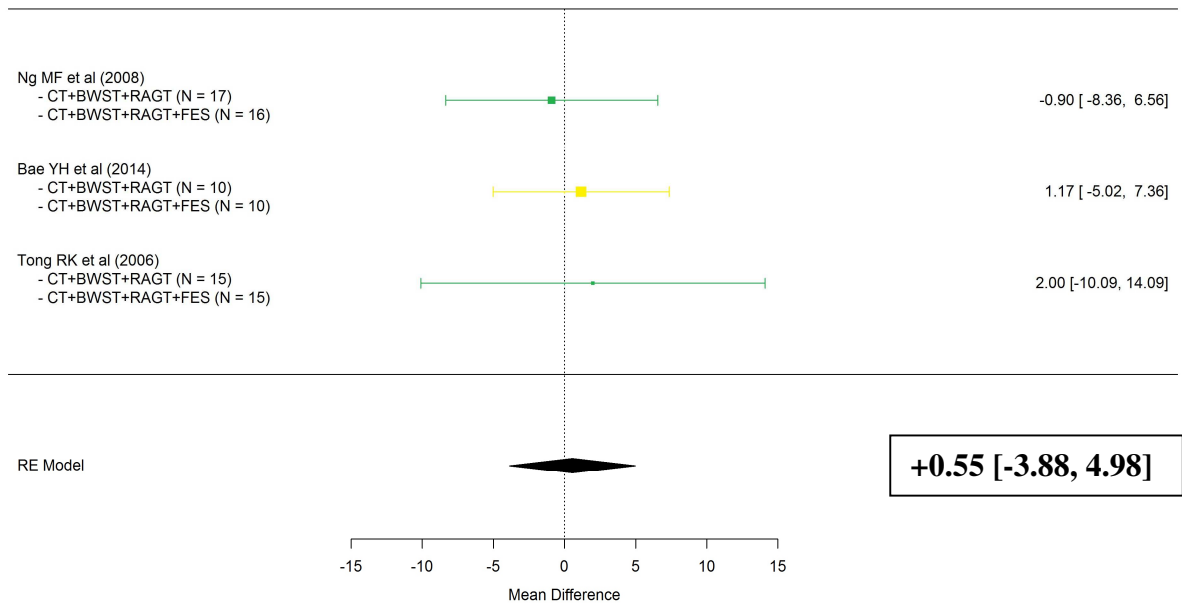
Gait speed - CT+BWST+RAGT vs CT+BWST+RAGT+FES



Level of heterogeneity $I^2=0\%$, $r = 0.5$

6B

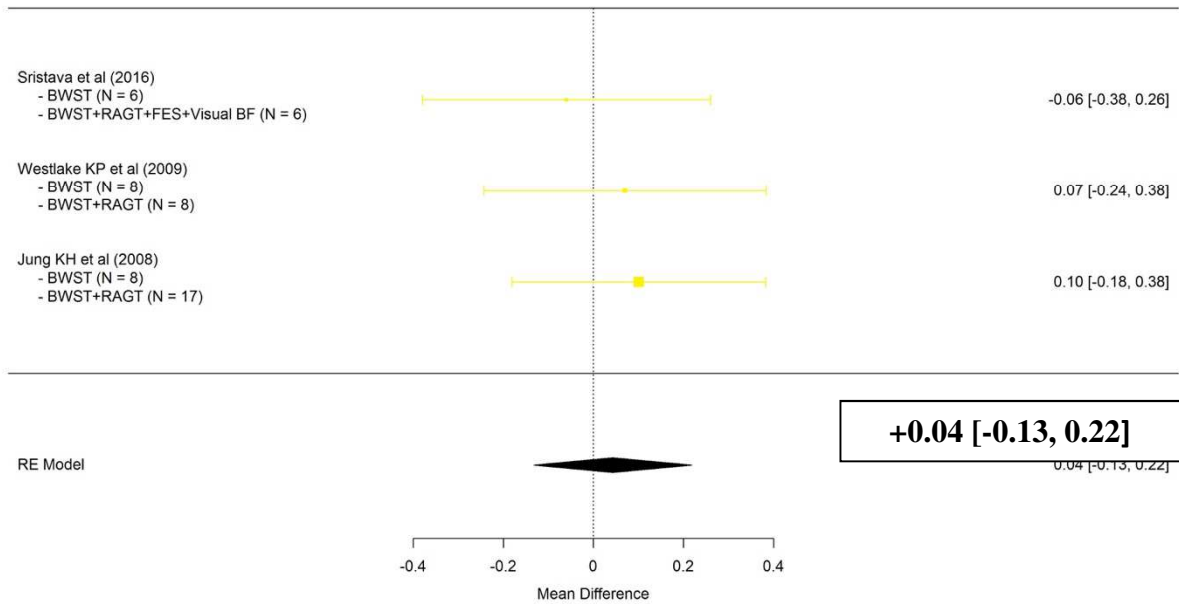
BBS - CT+BWST+RAGT vs CT+BWST+RAGT+FES



Level of heterogeneity $I^2=0\%$, $r = 0.5$

Figure 6. Forest plots and outcomes for comparison of [CT+BWST+RAGT] vs [CT+RAGT+BWST+FES] : A. Gait speed, B. Berg Balance Scale (BBS). Colors on figures correspond to the quality of attrition: green ■ is “low risk”, yellow ■ is “unclear risk” and red ■ is “high risk”.

Gait speed - BWST+add vs BWST+RAGT+add



Level of heterogeneity $I^2=0\%$, $\tau = 0.5$

Figure 7. Forest plots and outcomes for gait speed when comparing [BWST±add] vs [BWST+RAGT±add]. Colors on figures correspond to the quality of attrition: green ■ is “low risk”, yellow ■ is “unclear risk” and red ■ is “high risk”.

Table 1. Main characteristics of studies included in meta-analyses for Group 1: conventional physiotherapy [CT] ±add vs CT + body-weight support training [BWST] + robot-assisted gait training [RAGT] ±add.

Studies	Intervention	Patients (n)	Age, years mean (SD)	IS (n)	HS (n)	FAC mean (SD)	Gait speed before intervention (m/s) mean (SD)	Time since stroke, days mean (SD)	Intensity of rehabilitation (minutes)	Duration of intervention (weeks)
Belas Dos Santos et al 2018	CT	8	56.4 (11.8)	--	--	--	--	3832.5 (1971.0)	3600	20
	CT+BWST+RAGT	11	44.4 (12.7)	--	--	--	--	1752.0 (335.8)	3600	20
Chang et al 2012	CT	17	59.7 (12.1)	11	6	0.4 (0.5)	--	18.2 (5.0)	1000	2
	CT+BWST+RAGT	20	55.5 (12.0)	12	8	0.5 (0.5)	--	16.1 (4.9)	1000	2
Fisher et al 2011	CT	10	60.0 (14.0)	--	--	--	0.08 (0.07)	81.0 (106.0)	1440	7
	CT+BWST+RAGT	10	60.0 (14.0)	--	--	--	0.06 (0.04)	57.0 (73.0)	1440	7
Han et al 2016	CT	30	63.2 (10.6)	16	10	0.3 (0.5)	--	18.1 (9.8)	2400	4
	CT+BWST+RAGT	30	67.9 (14.9)	17	13	0.1 (0.3)	--	21.6 (7.9)	2400	4
Husemann et al 2008	CT	14	57.0 (11.0)	10	4	0.0 (0.0)	0.12 (0.03)	89.0 (61.0)	1200	4
	CT+BWST+RAGT	16	60.0 (13.0)	12	4	0.0 (0.1)	0.14 (0.02)	79.0 (56.0)	1200	4
Kimet al 2018	CT	30	60.4 (13.2)	18	5	2.9 (1.2)	0.50 (0.50)	78.0 (93.0)	1350	3
	CT+BWST+RAGT+VR	28	57.7 (12.9)	14	11	2.9 (1.2)	0.50 (0.50)	60.0 (72.0)	1350	3

Morone et al 2012 low motricity groups	CT	12	60.2 (9.6)	11	1	0.0 (0.0)	--	20.0 (12.7)	3600	4
	CT+BWST+RAGT+ Auditive Biofeedback	12	55.6 (13.3)	9	3	0.1 (0.3)	--	16.2 (11.3)	3600	4
Morone et al 2012 high motricity groups	CT	12	62.9 (17.4)	12	0	0.4 (0.7)	--	20.0 (15.7)	3600	4
	CT+BWST+RAGT+ Auditive Biofeedback	12	68.3 (9.1)	9	3	0.0 (0.0)	--	21.9 (10.7)	3600	4
Morone et al 2018	CT	50	63.5 (12.9)	43	7	0.2 (0.6)	--	16.5 (11.2)	3600	4
	CT+BWST+RAGT+ VR	50	61.9 (11.9)	38	12	0.3 (0.7)	--	19.3 (14.3)	3600	4
Ng et al 2008	CT	21	73.4 (11.5)	18	3	1.4 (0.7)	0.00 (0.10)	17.5 (8.4)	3000	4
	CT+BWST+RAGT	17	66.6 (11.3)	13	4	1.3 (0.9)	0.00 (0.05)	18.9 (8.4)	3000	4
Park et al 2018	CT	16	57.5 (9.9)	7	9	--	0.35 (0.04)	232.5 (53.1)	1170	6
	CT+BWST+RAGT+ VR	12	55.6 (10.4)	9	3	--	0.34 (0.03)	219.9 (34.5)	1710	6
Peurala et al 2005	CT	15	52.3 (6.8)	8	7	--	0.25 (0.16)	1440.0 (2088.0)	1125	3
	CT+BWST+RAGT	15	51.2 (7.9)	7	8	--	0.25 (0.23)	864.0 (936.0)	1125	3
Pohl et al 2017	CT	78	64.0 (11.6)	63	15	1.2 (1.1)	0.14 (0.19)	31.5 (13.3)	900	4
	CT+BWST+RAGT	77	62.3 (12.0)	61	16	0.9 (0.9)	0.13 (0.17)	29.4 (12.6)	900	4
Tavaglia et al 2015	CT	15	73.0 (7.0)	--	--	--	0.46 (0.26)	39.4 (31.7)	2250	5
	CT+BWST+RAGT	13	71.0 (5.0)	--	--	--	0.27 (0.25)	60.1 (49.5)	2250	5

Tong et al 2006	CT	20	71.4 (14.0)	17	3	1.0 (1.0)	0.00 (0.00)	18.9 (8.4)	2600	4
	CT+BWST+RAGT	15	66.1 (9.9)	11	4	1.0 (0.0)	0.00 (0.00)	18.9 (8.4)	2600	4
Van Nunen et al 2014	CT	14	56.0 (8.7)	10	4	1.0 (0.7)	0.00 (0.17)	67.1 (49.1)	1680	10
	CT+BWST+RAGT	16	50.0 (9.6)	9	7	1.5 (0.7)	0.03 (0.10)	61.6 (28.7)	1680	10
Wu et al 2012	CT	24	49.0 (10.0)	--	--	2.6 (1.2)	0.47 (0.10)	26.0 (8.0)	4320	8
	CT+BWST+RAGT	24	50.0 (12.0)	--	--	2.7 (1.5)	0.48 (0.11)	27.0 (7.0)	4320	8

VR, virtual reality; IS, ischemic stroke; HS, hemorrhagic stroke; FAC, Functional Ambulation Classification

Table 2. Main characteristics of studies included in meta-analyses for Group 2: CT ±add vs BWST + RAGT ±add.

Studies	Intervention	Patients (n)	Age, years mean (SD)	IS (n)	HS (n)	FAC mean (SD)	Gait speed before intervention (m/s) mean (SD)	Time since stroke, days mean (SD)	Intensity of rehabilitation (minutes)	Duration of interventions (weeks)
Bergmann et al 2018	CT	15	71.0 (10.0)	9	6	0.0 (0.0)	--	56.0 (26.6)	600	2
	BWST+RAGT	15	72.0 (9.0)	8	7	0.0 (0.7)	0.58 (0.11)	52.5 (18.2)	600	2
Dias et al 2007	CT	20	68.0 (10.7)	--	--	--	--	1453.5 (885.3)	1000	5
	BWST+RAGT	20	70.3 (7.3)	--	--	--	--	1413.0 (1914.9)	1000	5
Geroin et al 2011	CT	10	61.1 (6.3)	--	--	--	0.38 (0.21)	807.0 (174.0)	500	2
	BWST+RAGT+shamtDCS	10	63.3 (6.4)	--	--	--	0.52 (24)	801.0 (153.0)	500	2
Hidler et al 2009	CT	30	54.6 (9.4)	21	9	3.7 (0.2)	--	138.9 (60.9)	2160	8
	BWST+RAGT+Visual Biofeedback	33	59.9 (11.3)	26	7	3.3 (0.2)	--	110.9 (62.5)	2160	8
Kelley et al 2013	CT+Visual biofeedback+sensitive Biofeedback+auditive Biofeedback	9	64.3 (10.9)	--	--	--	0.18 (0.12)	518.4 (-)	2400	8

	BWST+RAGT+ Visual biofeedback+au ditive Biofeedback	11	66.9 (8.5)	--	--	--	0.20 (0.10)	1335.6 (- -)	2400	8
Noser et al 2012	CT	11	64.3 (10.9)	--	--	--	0.18 (0.12)	1353.6 (- -)	--	9
	BWST+RAGT	10	66.9 (8.5)	--	--	--	0.20 (0.10)	525.0 (- -)	--	9
Sczesny- Kaiser et al 2019	CT	9	63.3 (7.1)	8	1	3.9 (1.53)	0.64 (0.29)	107.1 (111.9)	900	6
	BWST+RAGT	9	63.2 (7.2)	6	3	3.6 (1.12)	0.49 (0.21)	62.4 (31.3)	900	6
Watanabe et al 2017	CT	12	76.8 (13.8)	--	--	2.0 (0.9)	0.45 (0.53)	48.1 (33.3)	240	4
	BWST+RAGT	12	66.9 (16.0)	7	5	2.0 (1.0)	0.56 (0.43)	57.0 (44.3)	240	4

sham-tDCS, sham transcranial direct-current stimulation; IS, ischemic stroke; HS, hemorrhagic stroke; FAC, Functional Ambulation Classification

Table 3. Main characteristics of studies included in meta-analyses for Group 3: CT + BWST + RAGT vs CT + BWST + RAGT + Functional Electrical Stimulation.

Studies	Intervention	Patients (n)	Age, years mean (SD)	IS (n)	HS (n)	FAC mean (SD)	Gait speed before intervention (m/s) mean (SD)	Time since stroke, days mean (SD)	Intensity of rehabilitation (minutes)	Duration of interventions (weeks)
Bae et al 2014	CT+BWST+RAGT	10	52.0 (16.1)	--	--	--	0.37 (0.19)	345.0 (153.0)	450	5
	CT+BWST+RAGT+FES	10	45.4 (19.7)	--	--	--	0.35 (0.20)	294.0 (180.0)	450	5
Ng et al 2008	CT+BWST+RAGT	17	66.6 (11.3)	13	4	1.30 (0.90)	0.00 (0.05)	18.9 (8.4)	3000	4
	CT+BWST+RAGT+FES	16	62.0 (10.0)	11	4	1.30 (0.50)	0.00 (0.00)	16.1 (7.7)	3000	4
Peurala et al 2005	CT+BWST+RAGT	15	51.2 (7.9)	7	8	--	0.25 (0.22)	864.0 (936.0)	1125	3
	CT+BWST+RAGT+FES	15	53.3 (8.9)	10	5	--	0.23 (0.19)	936.0 (864.0)	1125	3
Tong et al 2006	CT+BWST+RAGT	15	66.1 (9.9)	11	4	1.00 (0.00)	0.00 (0.00)	18.9 (8.4)	2600	4
	CT+BSWT+RAGT+FES	15	61.8 (10.8)	11	4	1.00 (0.00)	0.00 (0.00)	16.1 (7.0)	2600	4

IS, ischemic stroke; HS, hemorrhagic stroke; FAC, Functional Ambulation Classification

Table 4. Main characteristics of studies included in meta-analyses for Group 4: BWST \pm add vs BWST + RAGT \pm add.

Studies	Intervention	Patients (n)	Age, years mean (SD)	IS (n)	HS (n)	FAC mean (SD)	Gait speed before intervention (m/s) mean (SD)	Time since stroke, days mean (SD)	Intensity of rehabilitation (minutes)	Duration of interventions (weeks)
Jung et al 2008	BWST	8	54.8 (16.4)	6	2	4.10 (0.60)	0.60 (0.33)	855.0 (363.0)	360	4
	BWST+RAGT	17	48.8 (15.4)	12	5	3.90 (0.90)	0.58 (0.29)	648.0 (684.0)	360	4
Sristava et al 2016	BWST+RAGT	6	58.8 (9.0)	--	--	--	0.57 (0.20)	459.0 (321.0)	600	5
	BWST+RAGT+ FES+ Visual Biofeedback	6	62.7 (11.6)	--	--	--	0.58 (0.30)	1614.0 (1599.0)	600	5
Westlake et al 2009	BWST	8	55.1 (13.6)	5	3	--	0.62 (0.28)	1104.0 (609.0)	360	4
	BWST+RAGT	8	58.6 (16.9)	3	5	--	0.62 (0.31)	1314.0 (804.0)	360	4

IS, ischemic stroke; HS, hemorrhagic stroke; FAC, Functional Ambulation Classification

Table 5. Main results of the meta-analyses in the 4 groups.

Group 1: CT vs CT + BWST+RAGT					
	Number of studies	Patients (n)	Mean difference post-pre	95% CI	p-value
Gait speed (m/s)	11	500	+ 0.09 *	0.03 ; 0.15	0.002
6 min walk test (m)	3	213	+ 22.73	- 16.90 ; 62.35	0.261
FAC (AU)	12	639	+ 0.51 *	0.07; 0.95	0.022
BBS (AU)	6	230	+ 4.16 *	2.60; 5.71	0.000
TUG (s)	3	77	+ 3.20	- 2.58; 8.98	0.277
Group 2: CT vs BWST+RAGT					
	Number of studies	Patients (n)	Mean difference post-pre	95% CI	p-value
Gait speed (m/s)	7	184	- 0.04	- 0.12 ; 0.04	0.331
6 min walk test (m)	6	182	- 23.39	- 65.56 ; 18.77	0.277
FAC (AU)	3	107	0.00	0.10 ; 0.10	0.954
BBS (AU)	3	117	+ 0.10	- 1.42 ; 1.62	0.900

Group 3: CT + BWST+RAGT vs CT + BWST+RAGT+FES

	Number of studies	Patients (n)	Mean difference post-pre	95% CI	p-value
Gait speed (m/s)	4	113	+ 0.06	- 0.03 ; 0.16	0.232
BBS (AU)	3	83	+ 0.55	- 3.88 ; 4.98	0.808

Group 4: BWST vs. BWST+RAGT

	Number of studies	Patients (n)	Mean difference post-pre	95% CI	p-value
Gait speed (m/s)	3	53	+ 0.04	- 0.13 ; 0.22	0.630

95% CI, 95% confidence interval; BBS, Berg Balance Scale; TUG, Time Up and Go; AU, arbitrary unit