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Review

Effects of robotic gait training after stroke: A meta-analysis☆

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A B S T R A C T

Background: Robotic devices are often used in rehabilitation and might be efficient to improve walking capacity after stroke.
Objective: First to investigate the effects of robot-assisted gait training after stroke and second to explain the observed heterogeneity of results in previous meta-analyses.
Methods: All randomized controlled trials investigating exoskeletons or end-effector devices in adult patients with stroke were searched in databases (MEDLINE, EMBASE, CENTRAL, CINAHL, OPENGREY, OPENSIGLE, PEDRO, WEB OF SCIENCE, CLINICAL TRIALS, conference proceedings) from inception to November 2019, as were bibliographies of previous meta-analyses, independently by 2 reviewers. The following variables collected before and after the rehabilitation program were gait speed, gait endurance, Berg Balance Scale (BBS), Functional Ambulation Classification (FAC) and Timed Up and Go scores. We also extracted data on randomization method, blinding of outcome assessors, drop-outs, intention (or not) to treat, country, number of participants, disease duration, mean age, features of interventions, and date of outcomes assessment.
Results: We included 33 studies involving 1466 participants. On analysis by subgroups of intervention, as compared with physiotherapy alone, physiotherapy combined with body-weight support training and robot-assisted gait training conferred greater improvement in gait speed (+0.09 m/s, 95% confidence interval [CI] 0.03 to 0.15; $p = 0.002$), FAC scores (+0.51, 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 meta-regression analysis suggested that these results were underestimated by the attrition bias of studies.
Conclusions: Robot-assisted gait training combined with physiotherapy and body-weight support training seems an efficient intervention for gait recovery after stroke.
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1. Introduction

Stroke is one of the most frequently occurring diseases worldwide and leads to permanent disability [1]; restoring walking ability is an important goal of post-stroke rehabilitation [2]. Cohort studies showed that 22% of stroke patients do not regain any walking function [3]. Among the many methods for gait training after stroke, robotic devices have the ability to provide "repetitive task training" (RTT). According to moderate-quality evidence, RTT can improve walking distance and functional ambulation after stroke [4]. Walking speed is higher during robot-assisted gait training (RAGT) than conventional gait training, so patients repeat more gait cycles [5]. Besides, the exoskeletons and end-effectors of RAGT create force fields to "guide" the person toward a successful trajectory and also promote variability in training, which is a necessary constraint for successful human action learning according to studies of pediatric neurodevelopment [6–8]. Constraints on walking speed and various gait parameters can be varied with control within the training, and

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RAGT enables possibilities of "bottom-up" rehabilitation interventions such as complete assistance or assistance-as-needed resistance [9]. RAGT can also be combined with "top-down" rehabilitation techniques such as transcranial direct current stimulation (tDCS), virtual reality (VR) and biofeedback. Moreover, robotic assistance reduces the physical burden for therapists because they no longer need to manually place the paretic limbs or assist in trunk movements [10].

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

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

In this systematic review, our objective was to conduct meta-analyses to investigate the effects of RAGT on gait after stroke. Especially, we focused on exoskeletons and end-effector devices and compared the efficiency of combinations of interventions such as conventional therapy (CT), CT associated with body-weight support training (BWST) and RAGT [CT + BWST + RAGT], CT associated with BWST, RAGT and functional electrical stimulation (FES) [CT + BWST + RAGT + FES], and BWST and RAGT without any CT [BWST + RAGT]. In addition, we performed meta-regressions to evaluate the impact of age, time since stroke, intensity of rehabilitation, stroke severity and risk of bias on the heterogeneity of results.

2. Methods

2.1. Search strategy and selection criteria

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

Two reviewers (G.M. and H.C.) independently screened titles and abstracts manually for potential eligibility and assessed eligibility for inclusion based on full-text screening. Doubtful records were discussed (G.M and H.C.) with an independent third reviewer (P.D.). The study selection process was recorded with a PRISMA flow chart.

2.2. Definition of interventions

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

- RAGT: robot-driven exoskeleton orthoses or end-effector devices fitting the legs and simulating the phases of gait. Patients' legs are guided by the robotic device according to a preprogrammed gait pattern. The process of gait training is automated and controlled by a computer. This category includes exoskeletons such as the Lokomat®, Ekso Bionic leg®, Hybrid-Asssitive-Locomotion® (HAL), H2®, etc., as well as end-effector machines such as the GT trainer®;
- CT: locomotor training via a repetitive execution of walking movements manually guided by a physiotherapist. Guiding principles for this approach can be summarized as the rehabilitation of the lost function by guiding the patient through the expected lower-limb movement trajectory and thereby "teaching" neural circuits governing locomotion in the spinal cord to walk via somatosensory, cognitive, and motor systems. The rules of motor learning such as diversification, repetition, and task-oriented strategies are applied. No electromechanical device is used. Only treadmills, tilt-tables, canes and walkers were allowed;
- BWST: method promoted for stroke patients by Hesse et al. [16] consisting of a gait re-training overground or on a treadmill, with part of the body weight unloaded. Patients can walk with 60% to 100% of their body weight. BWST enhances automatic walking processes and endurance. Many robotic devices are used in conjunction with a harness to unload patients' weight. In this case, we classified the intervention as BWST + RAGT;
- Biofeedback: use of detection and restitution support to give a quantitative feedback from a physiological process. It can be audio, sensory or visual feedback and gives the patient real-time control of their movements. It was considered a component of the rehabilitation program when mentioned;
- tDCS: a non-invasive neurostimulation method whereby very low levels of constant current are delivered to specifically targeted areas of the brain. Sham-tDCS is a method of blinding participants, a form of placebo stimulation;
- FES: a method of delivering an electrical current to a nerve or a muscle through the skin to obtain a muscle contraction useful for walking. It aims to assist functional movement. Electrical impulsions are used to reduce the motor deficit or muscle overactivity;

- VR: systems that use VR headsets or multi-projected environments to generate realistic images, sounds and other sensations that simulate a user's physical presence in a virtual environment. A person using VR equipment is able to look around the artificial world, move around in it, and interact with virtual features or items.

2.3. Data collection and extraction

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

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

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

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

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

The distribution of FAC, BBS, TUG, gait speed and gait endurance outcomes are presented as quantitative continuous measures:

- FAC: 0 to 5 arbitrary units (AU);
- gait speed: 0 to 3 m/s;
- gait endurance: 0 to 800 m;
- TUG: 0 to 100 sec;
- BBS: 0 to 56 AU.

Standard deviations (SD) were converted by using the Alpha method (SDspeed = SDtime $\times$ (distance/total test duration^2). The few data collected as medians were converted to means after confirming the normality of the distribution. Considering the quartiles' normal distribution, we hypothesized that a median is approximately equal to the mean, and SD was calculated as the mean of (quartile 3–median)/0.674 and (quartile 1–median)/0.674 [17].

2.4. Statistical analysis and study quality

After data extraction was completed, the possibility of a meta-analysis was determined. A meta-analysis was conducted if at least 3 studies used the same combination of interventions and same outcomes. Then, a meta-analysis by subgroups was conducted according to the types of comparison: [CT] vs [CT + BWST + RAGT], [CT] vs [BWST + RAGT], [CT + BWST + RAGT] vs [CT + BWST + RAGT + FES], and [BWST] vs [BWST + RAGT]. Biofeedback or VR techniques were indicated by the expression " $\pm$ add" in the interventions, and their effects were not sufficiently quantifiable to be analyzed in meta-analysis. Subgroup analyses were conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [18].

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

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

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

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

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

Publication bias was assessed by funnel plots.

3. Results

3.1. Included studies and main characteristics

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

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

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

3.2. Risk of bias in included studies

A detailed list of biases for each study is shown in Fig. 2. In total, 36 studies had adequate random sequence generation, and 18 did not give enough information. Regarding "selection" bias, 30 studies

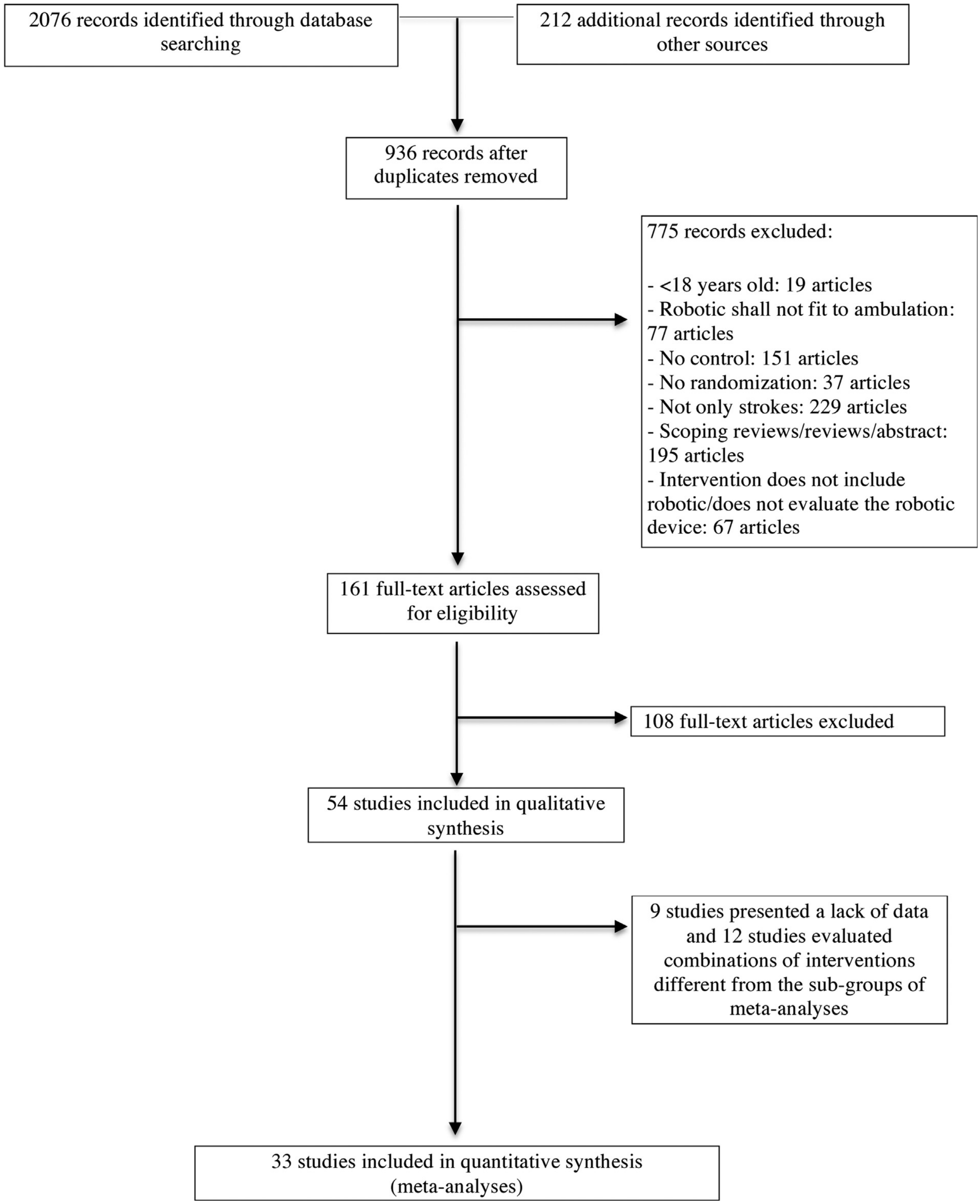

Fig. 1. Study flow chart.

had adequate allocation concealment, 19 did not give enough information and 5 described risky allocation concealment. Overall, 34 studies reported a blinded outcome assessment, 10 did not give enough information and 10 declared non-blinding assessments. Finally, 23 studies described complete outcome data, 16 did not give enough information and 15 reported incomplete data. For most studies, reporting bias was not mentioned because the protocol was not described. Of the 54 studies, only 3 provided enough information to be considered at low risk.

3.3. Effect of interventions: analyses by subgroups

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

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
Taveggia 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.

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

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

3.3.1.1. Gait speed. In this analysis, 500 patients from 11 trials were included (Fig. 3A). For the same rehabilitation intensity, the pooled mean difference for gait speed was +0.09 m/s (95% CI: 0.03 to 0.15); $p = 0.002$; level of heterogeneity $I^2 = 79.2\%$, $r = 0.5$. The sensitivity analysis showed constant significance: for $r = -1$, the pooled mean value was +0.10 m/s (95% CI: 0.03 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), $p = 0.002$; for $r = 0$, the pooled mean value was +0.09 m/s (95% CI: 0.03 to 0.15), $p = 0.002$; for $r = 0.5$, the pooled mean value was +0.09 m/s (95% CI: 0.03 to 0.15), $p = 0.002$; for $r = 1$, the pooled mean value was +0.09 m/s (95% CI: 0.03 to 0.14), $p = 0.001$.

Meta-regressions showed that the quality study attrition explained 98.4% of the heterogeneity and the square root of estimated tau^2 value was 0.01. Thus, a meta-analysis of 6 selected studies (304 patients) with low risk of attrition bias was performed, showing an improvement 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. 4A).

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

3.3.1.3. Functional Ambulation Classification. In this analysis, 639 patients from 12 trials were included (Fig. 3C). For the same rehabilitation intensity, the pooled mean difference for FAC scores was +0.51 AU (95% CI: 0.07 to 0.95); $p = 0.022$; level of heterogeneity $I^2 = 71.3\%$, $r = 0$. The sensitivity analysis showed constant significance: for $r = -1$, the pooled mean value was +0.53 AU (95% CI: 0.06 to 1.00), $p = 0.027$; for $r = -0.5$, the pooled mean value was +0.52 AU (95% CI: 0.07 to 0.97), $p = 0.025$; for $r = 0$, the pooled mean value was +0.51 AU (95% CI: 0.07 to 0.95), $p = 0.022$;

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 + auditive 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 ± 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)
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.

for $r = 0.5$, pooled mean value was +0.50 AU (95% CI: 0.08 to 0.92), $p = 0.019$; for $r = 1$, the pooled mean value was +0.48 AU (95% CI: 0.09 to 0.88), $p = 0.017$.

Meta-regressions showed that the quality study attrition explained 61.6% of heterogeneity and the square root of estimated tau^2 value was 0.39. Thus, a meta-analysis of 5 selected studies (276 patients) with low risk of attrition bias was conducted, showing an improvement of +1.13 AU (95% CI: 0.73 to 1.54); $p < 0.000$; level of heterogeneity $I^2 = 19.5\%$, $r = 0$ (Fig. 4B).

3.3.1.4. Berg Balance Scale. In this analysis, 230 patients from 6 trials were included (Fig. 3D). For the same rehabilitation

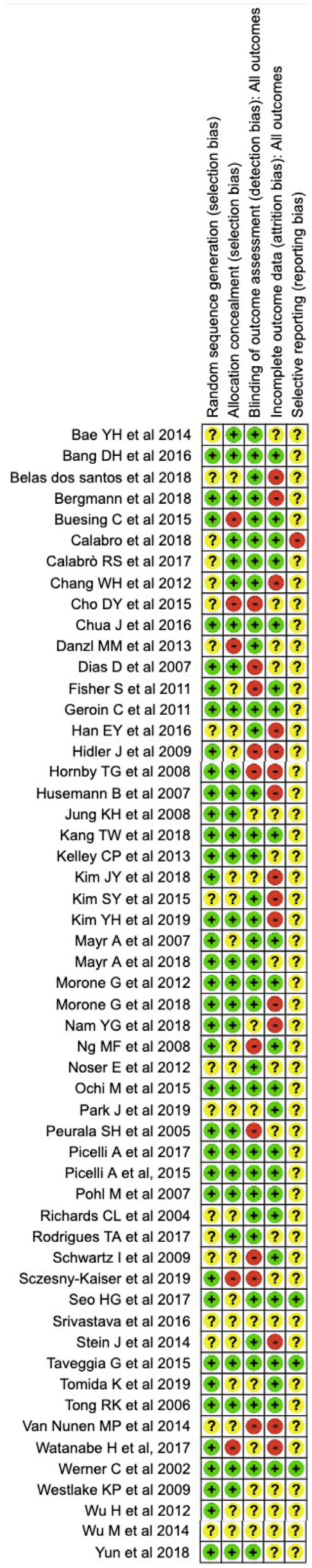

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. + = low risk of bias, ? = unclear risk of bias, − = high risk of bias.

intensity, the pooled mean difference for BBS scores was +4.16 AU (95% CI: 2.60 to 5.71); $p = 0.000$; level of heterogeneity $I^2 = 2.7\%$, $r = 0.5$. However, the sensitivity analysis did not show constant significance: for $r = -1$, the pooled mean value was +4.44 AU (95% CI: 3.13 to 5.75), $p = 0.000$; for $r = -0.5$, the pooled mean value was +4.42 AU (95% CI: 3.12 to 5.72), $p = 0.000$; for $r = 0$, the pooled mean value was +4.38 AU (95% CI: 3.09 to 5.67), $p = 0.000$; for $r = 0.5$, pooled mean value was +4.16 AU (95% CI: 2.60 to 5.71), $p = 0.000$; for $r = 1$, the pooled mean value was 2.09 AU (95% CI: −1.37 to 5.54), $p = 0.237$.

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

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

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

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

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

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

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

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

3.3.3. Group 3: comparison of effectiveness of [CT + BWST + RAGT] vs [CT + BWST + RAGT + FES]

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

3.3.3.1. Gait speed. In this analysis, 113 patients from 4 trials were included (Fig. 6A) and no significant difference was found. The pooled mean difference for Gait speed was +0.06 m/s (95% CI: −0.03 to 0.16); $p = 0.232$; level of heterogeneity $I^2 = 0\%$, $r = 0.5$.

3.3.3.2. Berg Balance Scale. In this analysis, 83 patients from 3 trials were included (Fig. 6B) and no significant difference was found. The pooled mean difference for BBS scores was +0.55 AU (95% CI: −3.88 to 4.98); $p = 0.808$; level of heterogeneity $I^2 = 0\%$, $r = 0.5$.

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

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

3.3.3.3. Gait speed. In this analysis, 53 patients from 3 trials were included (Fig. 7) and no significant difference was found. The

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. *: p-value < 0.05.

pooled mean difference for gait speed was +0.04 m/s (95% CI: −0.13 to 0.22); $p = 0.630$; level of heterogeneity $I^2 = 0\%$, $r = 0.5$.

4. Discussion

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

The relevance of an improvement in gait speed of 0.09 m/s depends both on the Minimal Detectable Change (MDC90) and the Minimal Clinically Important Difference (MCID) for gait speed. Fulk et al. [26] calculated 2 MDC90 values for gait speed according to the level of dependence at the start of rehabilitation. MDC90 was 0.07 m/s for individuals who required physical assistance to walk at the start of rehabilitation (mean [SD] gait speed at start 0.26 [0.18] m/s) and was 0.36 m/s for those who could walk without physical assistance at the start of rehabilitation (mean gait speed at start 0.56 [0.30] m/s). Bohannon et al. [27] calculated a MCID of 0.13 m/s as a reduction in assistance required (definitions compatible with the Functional Independence Measure) and the mean gait speed of their cohort of 21 stroke patients at the start of rehabilitation was 0.18 (0.18) m/s. Tilson et al. [28] measured a MCID of 0.16 m/s as an improvement of one category of modified Rankin Scale, and the mean gait speed of their cohort of 283 patients at the start of rehabilitation was 0.18 (0.16) m/s. Fulk et al. [29] calculated 2 different MCID values: one MCID of 0.175 m/s as the perception of "an important change in walking ability" estimated by the patient and one MCID of 0.190 m/s as the perception of "an important change in walking ability" estimated by the physical therapist (evaluated by Global Rating of Change). Their cohort of 44 stroke patients walked at a mean gait speed of 0.56 (0.22) m/s at the start of rehabilitation. Given that these most common findings about MDC90 and MCID walking speed after stroke and taking into account that the range of patients included in our meta-analyses was very broad, our findings suggest a clinically relevant improvement in gait speed. Besides, the combination [CT + BWST + RAGT] should be effective for the most severely affected patients.

We may explain the relevant synergy of physiotherapy and robotic devices by the ability to offer global training from the start. Usually, CT is conducted according to the following steps [30]:

- trunk stability is re-trained by using increasing levels of difficulty during standing;
- the ability to stand is re-trained by standing up in active safety systems;
- gait re-training starts when the patient acquired enough trunk and standing force.

RAGT helps overcome the initial rehabilitation steps and compensate for the patient's postural weakness by using lumbar straps attached to the device and motorized joint control assistance. RAGT offers task-specific training from the start of intensive rehabilitation. Thus, our findings complement the conclusions of the Mehrholz et al. meta-analyses [15] and can explain the absence of a significant difference for meta-analyses that compared the effects of a rehabilitation program combining BWST + RAGT without CT to one with CT. Certainly, CT adds important "task-specific" techniques of rehabilitation, such as balance training, sit-to-stand working or stability of belts training for the recovery of walking.

Otherwise, if adding FES to a rehabilitation program combining [CT + BWST + RAGT] was not associated with a significant difference, meta-analyses were probably not powerful enough: only

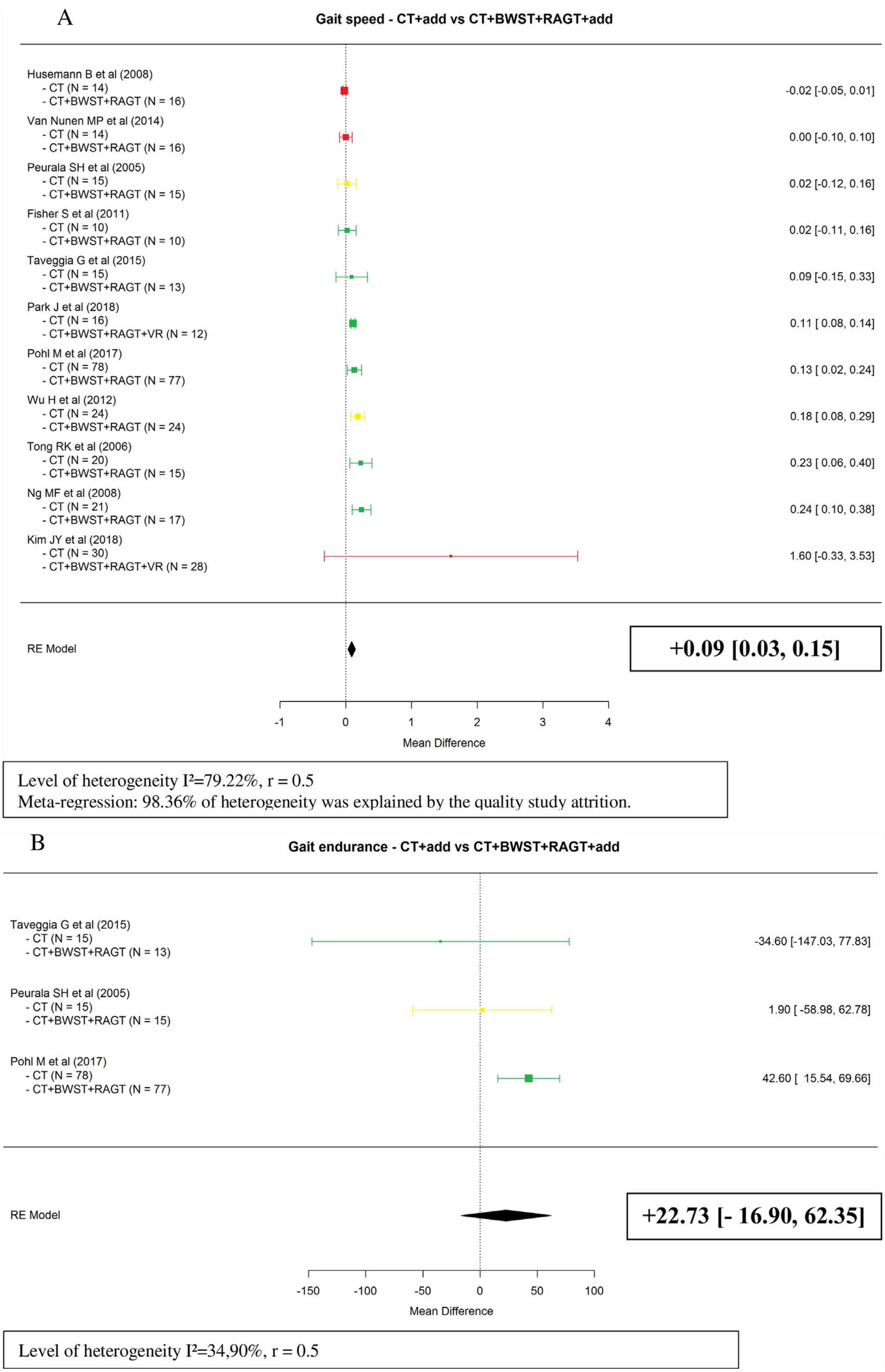

Fig. 3. Forest plots and outcomes for comparison of [CT ± add] vs [CT + BWST + RAGT ± add]. A. Gait speed, B. Gait endurance, C. Functional Ambulation Classification (FAC), D. Berg Balance Scale (BBS), E. Timed Up And Go (TUG). Colors on figures correspond to the quality of attrition: green is “low risk”, 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.

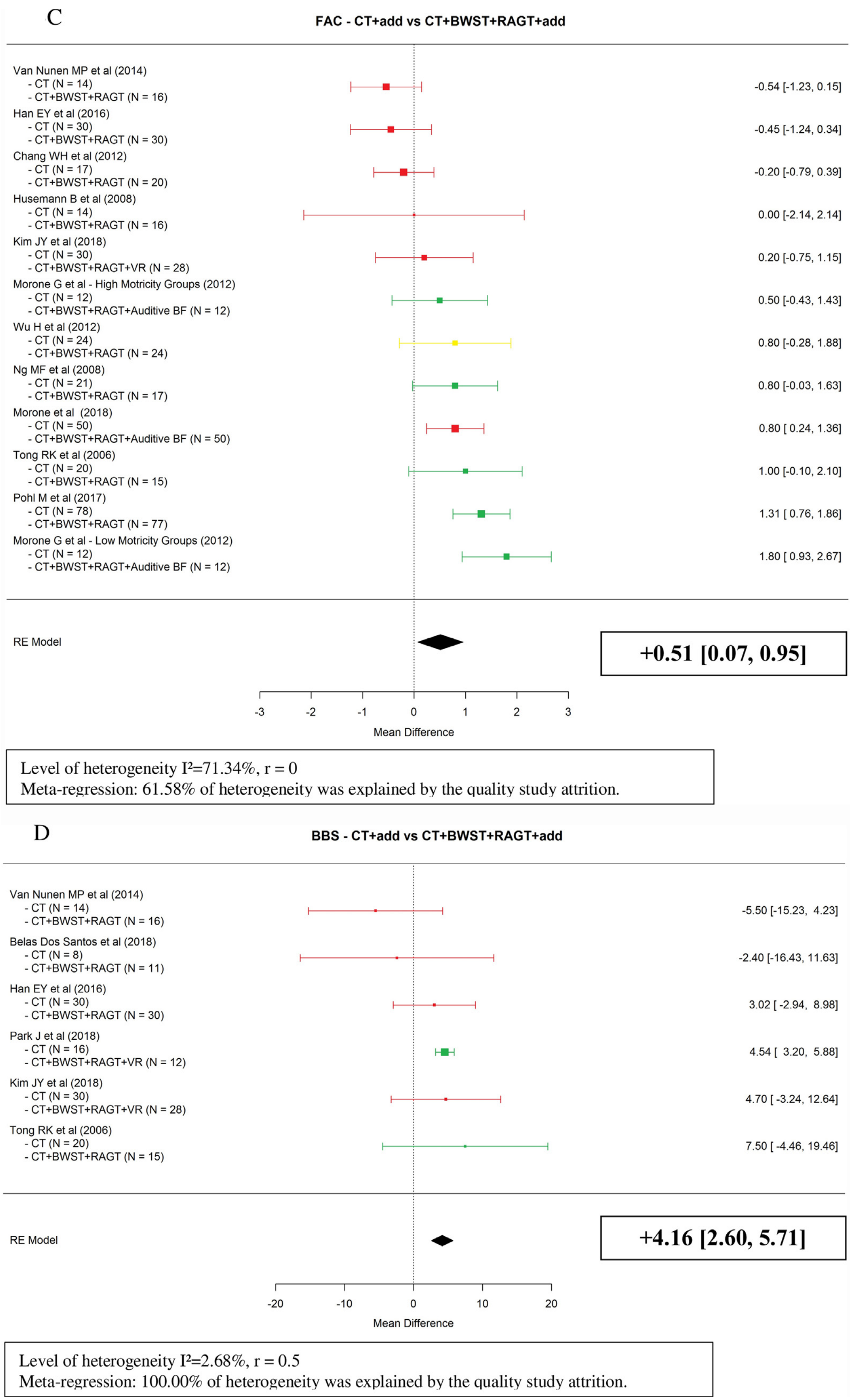

Fig. 3. (*Continued*).

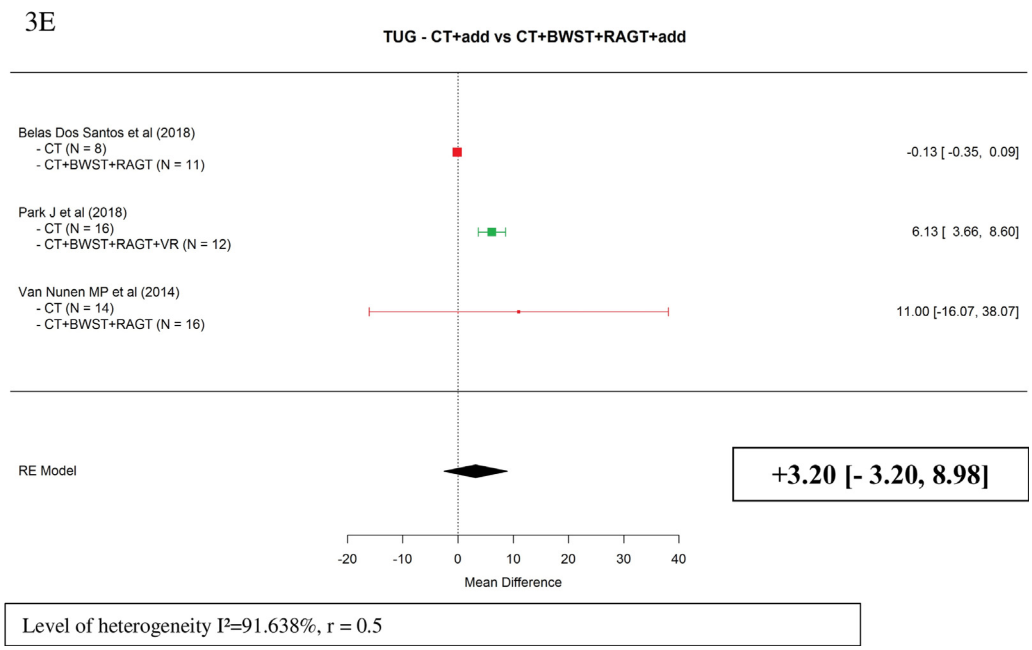

Fig. 3. (*Continued*).

114 patients were included in the largest study, and no comparable intensities of rehabilitation/disease durations could be used for comparison.

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

To minimize the publication bias, all accessible electronic databases were searched, including the grey literature, and the authors of identified studies were contacted whenever necessary (but unsuccessfully). Nevertheless, only studies with complete outcome assessments were included, and studies/abstracts that did not give any information about potential bias were excluded. Finally, our findings were balanced with positive and negative results about robotic rehabilitation, as confirmed by the well-balanced aspect of the funnel plot, which reinforces the low publication bias of this review.

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

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

Since October 2017, 3 meta-analyses have evaluated the effects of RAGT on gait recovery after stroke, but they did not provide the same information as our meta-analyses. Zheng et al. [34] evaluated the efficiency of RAGT for balance. Outcomes were BBS, Fugl-Meyer Balance assessment scores and TUG. Their search stopped in March 2018. The authors found a positive impact of RAGT on balance after stroke. Asiri et al. [35] evaluated the efficiency of RAGT on gait speed but excluded end-effectors. Thus, the authors conducted a meta-analysis of only 4 trials. They found that the effect of RAGT to improve walking speed was significantly inferior than CT. Results were heterogeneous without any explanation. Their search stopped in 2017 (no details). Bruni et al. [36] evaluated efficiency of RAGT by distinguishing end-effectors and exoskeletons but did not specify rehabilitation protocols in combination with RAGT. Outcomes were gait speed, gait endurance, TUG and FAC. Although their results were heterogeneous, stroke patients who received [CT + BWST + RAGT] were more likely to reach better gait speed results than those who received [CT]. Their search stopped in June 2015.

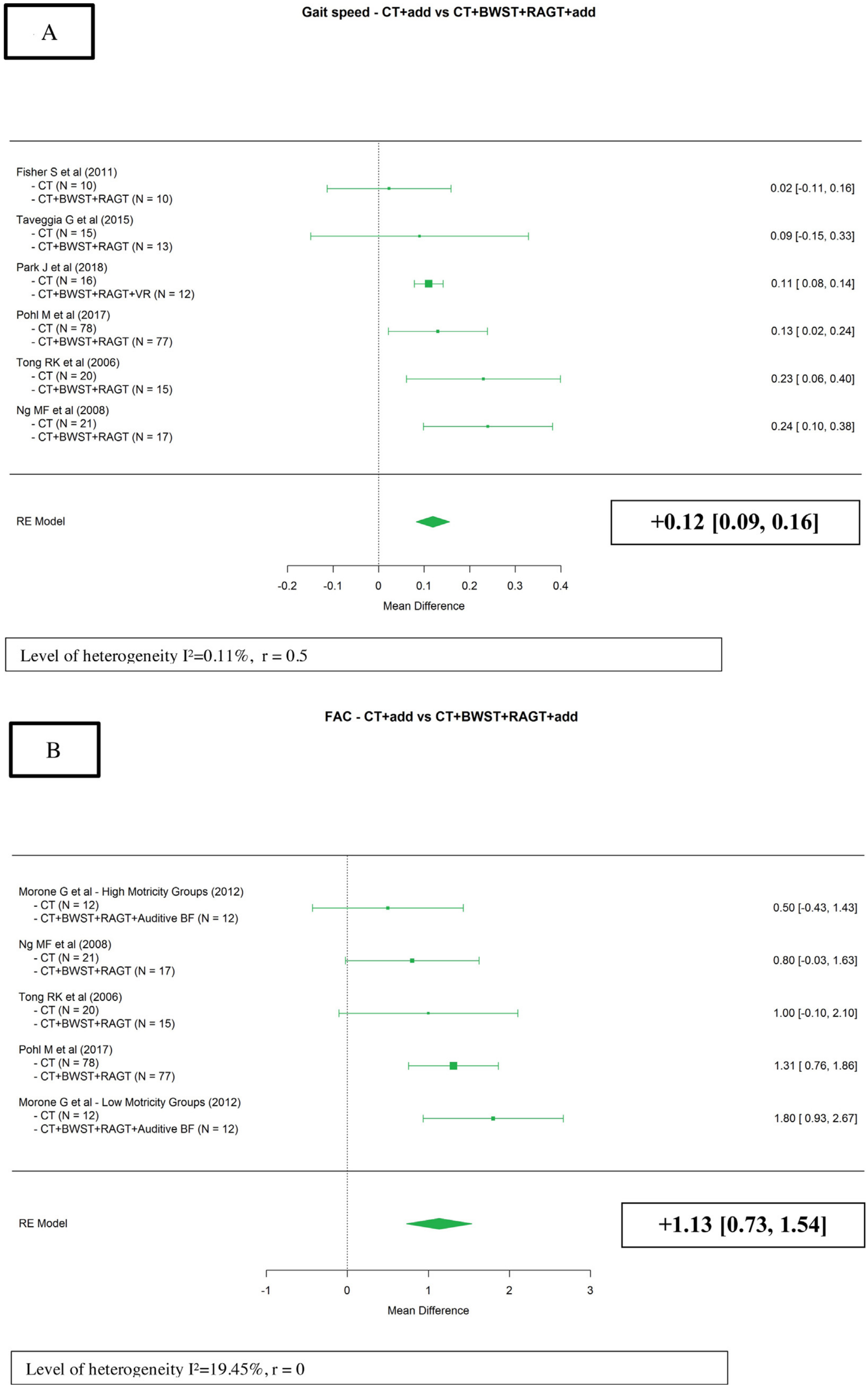

Fig. 4. Forest plots and outcomes for meta-analyses of studies with low risk of attrition bias for comparison of [CT ± add] vs [CT + BWST + RAGT ± add]. A. Gait speed, B. Functional Ambulation Classification (FAC).

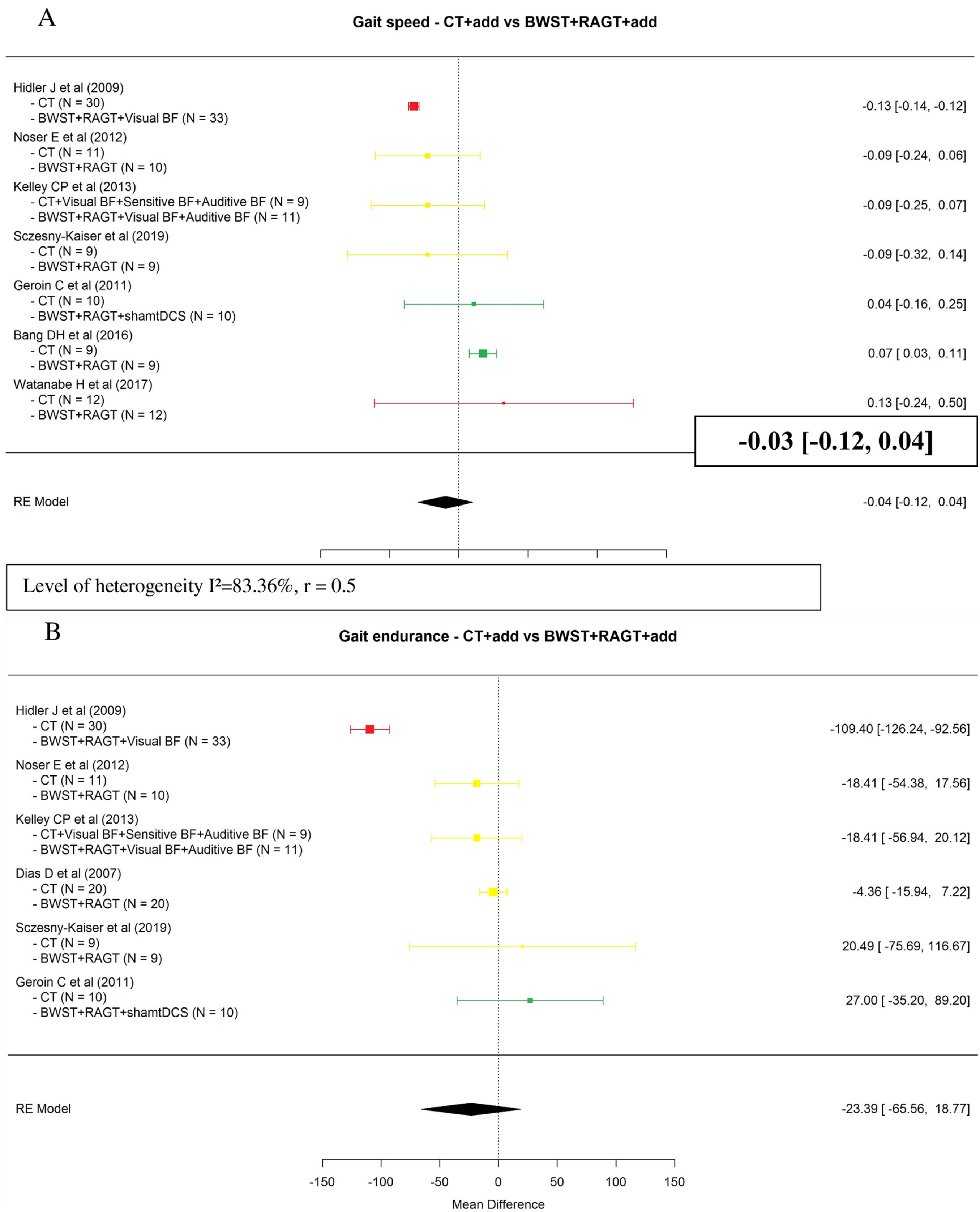

Fig. 5. Forest plots and outcomes for comparison of [CT ± add] vs [BWST + RAGT ± add]. A. Gait speed, B. Gait endurance, C. Functional Ambulation Classification (FAC), D. Berg Balance Scale (BBS). Colors on figures correspond to the quality of attrition: green is "low risk", yellow is "unclear risk"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

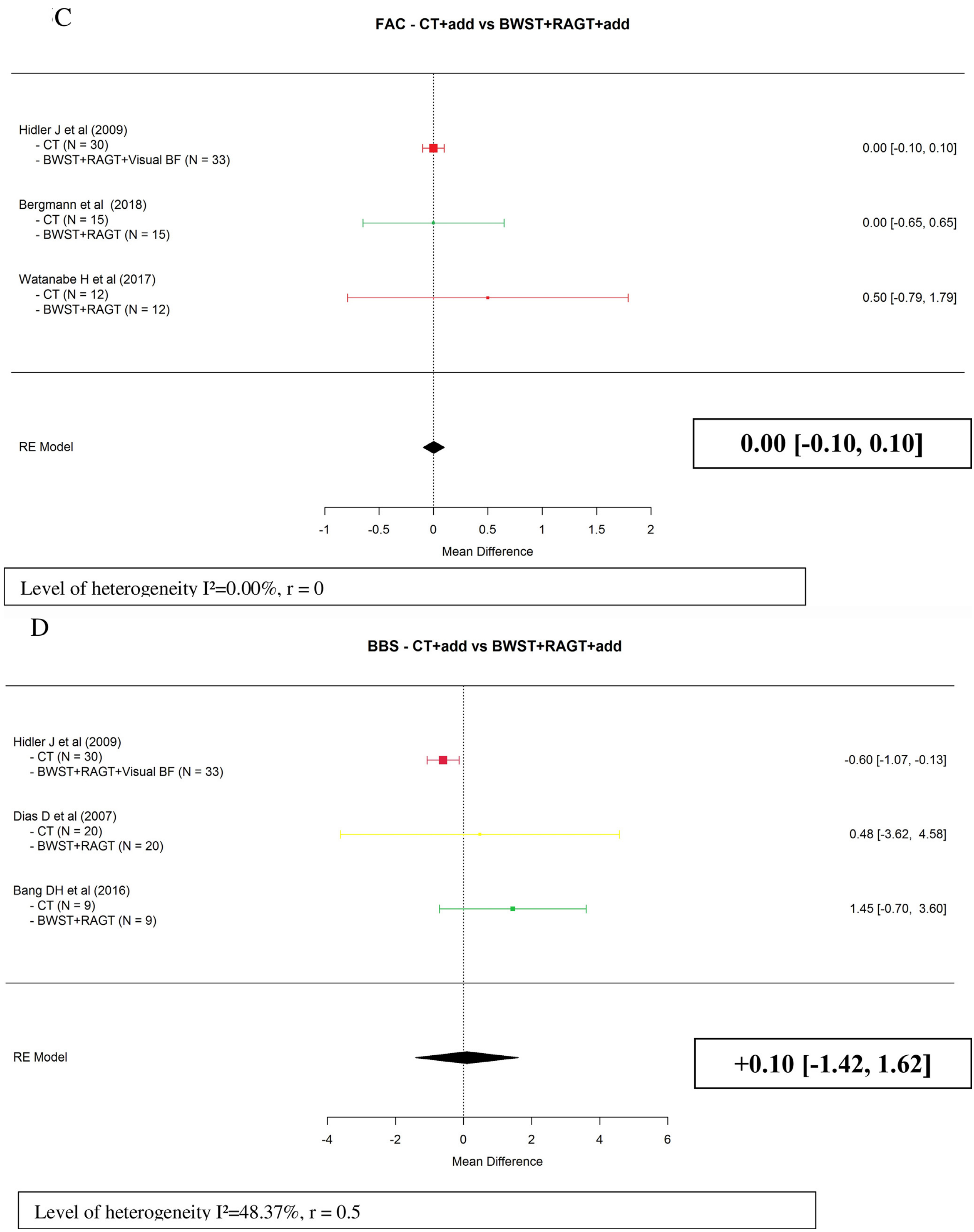

Fig. 5. (*Continued*).

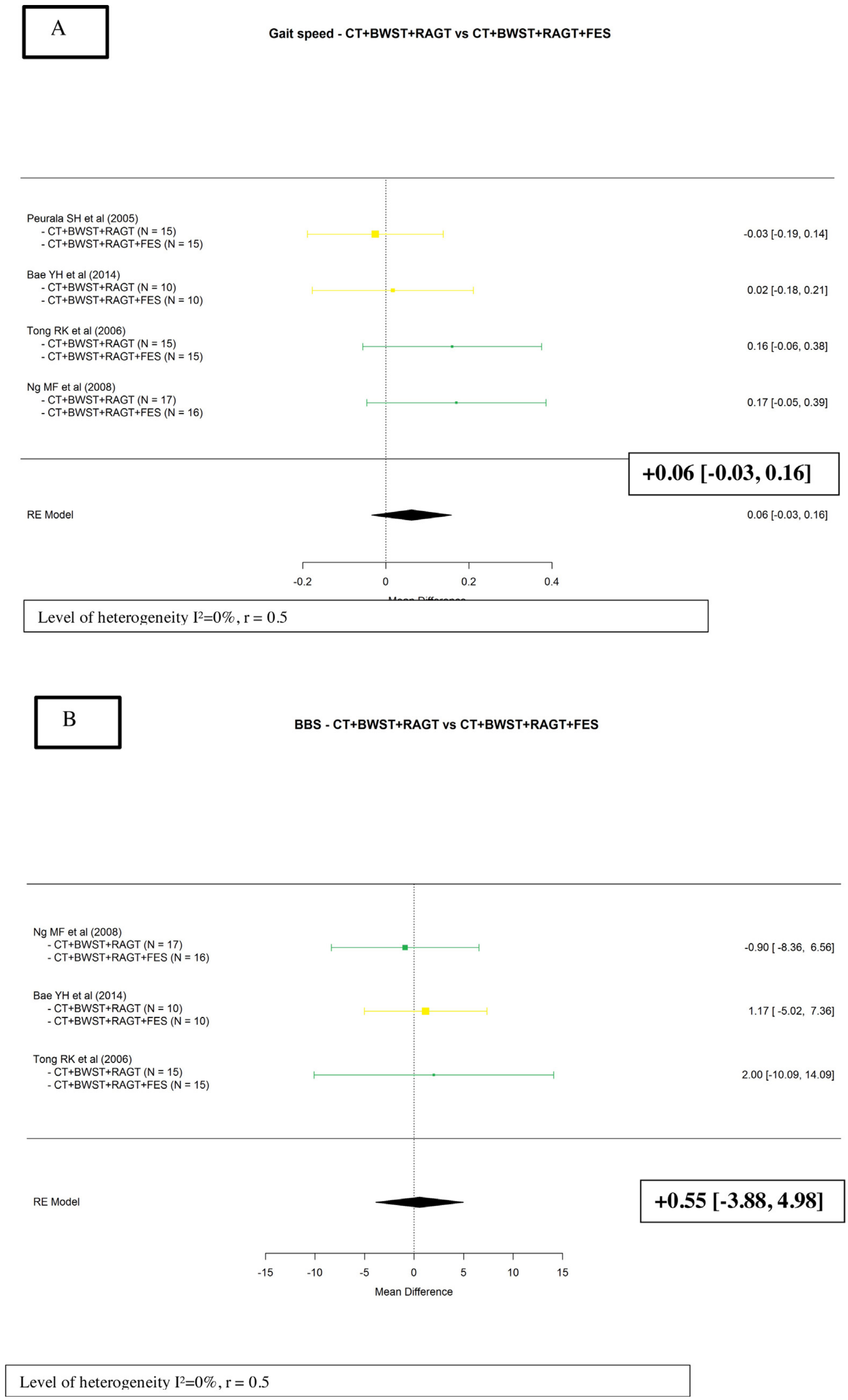

Fig. 6. Forest plots and outcomes for comparison of [CT + BWST + RAGT] vs [CT + RAGT + BWST + FES]: A. Gait speed, B. Berg Balance Scale (BBS). Colors on figures correspond to the quality of attrition: green ■ is "low risk", yellow ■ is "unclear risk" and red ■ is "high risk".

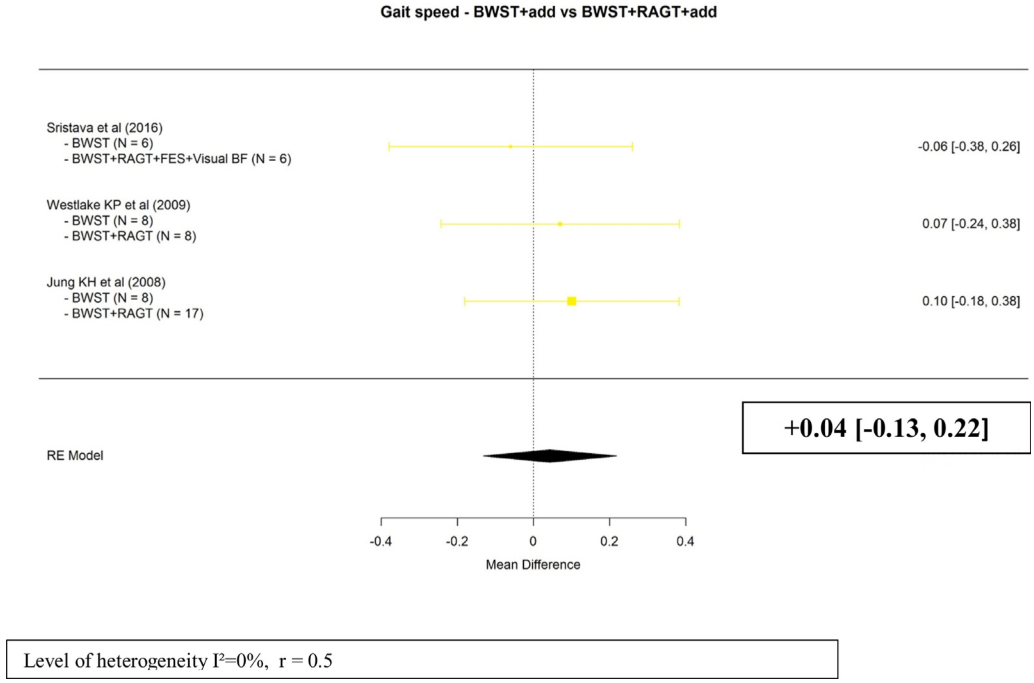

Fig. 7. Forest plots and outcomes for gait speed when comparing [BWST ± add] vs [BWST + RAGT ± add]. Colors on figures correspond to the quality of attrition: green is "low risk", yellow is "unclear risk" and red is "high risk".

5. Conclusion

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

We suggest some recommendations for future research work:

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

We suggest some recommendations for engineers:

- robotic devices should propose more complex training than "walking straight" training, given that variability is a necessary constraint for successful rehabilitation;
- the role of robotic devices should be to create movement environments and provide personal and environmental constraints that elicit and support self-produced functional actions.

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

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2020.02.008.

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