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Review

Robot-Assisted Therapy for Upper Extremity Motor Impairment After Stroke: A Systematic Review and Meta-Analysis

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Abstract

Objective. The purpose of this study was to review the effects of robot-assisted therapy (RT) for improving poststroke upper extremity motor impairment.

Methods. The PubMed, Embase, Medline, and Web of Science databases were searched from inception to April 8, 2020. Randomized controlled trials that were conducted to evaluate the effects of RT on upper extremity motor impairment poststroke and that used Fugl-Meyer assessment for upper extremity scores as an outcome were included. Two authors independently screened articles, extracted data, and assessed the methodological quality of the included studies using the Physiotherapy Evidence Database (PEDro) scale. A random-effects meta-analysis was performed to pool the effect sizes across the studies.

Results. Forty-one randomized controlled trials with 1916 stroke patients were included. Compared with dose-matched conventional rehabilitation, RT significantly improved the Fugl-Meyer assessment for upper extremity scores of the patients with stroke, with a small effect size (Hedges $g = 0.25$; 95% CI, 0.11-0.38; $I^2 = 45.9\%$). The subgroup analysis revealed that the effects of unilateral RT, but not that of bilateral RT, were superior to conventional rehabilitation (Hedges $g = 0.32$; 95% CI, 0.15-0.50; $I^2 = 55.9\%$). Regarding the type of robot devices, the effects of the end effector device (Hedges $g = 0.22$; 95% CI, 0.09–0.36; $I^2 = 35.4\%$), but not the exoskeleton device, were superior to conventional rehabilitation. Regarding the stroke stage, the between-group difference (ie, RT vs convention rehabilitation) was significant only for people with late subacute or chronic stroke (Hedges $g = 0.33$; 95% CI, 0.16-0.50; $I^2 = 34.2\%$).

Conclusion. RT might be superior to conventional rehabilitation in improving upper extremity motor impairment in people after stroke with notable upper extremity hemiplegia and limited potential for spontaneous recovery.

Keywords: Stroke, Upper Extremity, Unilateral/Bilateral Robot-Assisted Therapy, Meta-Analysis, Randomized Controlled Trial

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Introduction

Stroke is one of the most common causes of adult-onset neurological disability.[1] According to the Global Burden of Disease study in 2016,[2] stroke is one of the leading causes of the loss of disability-adjusted life-years worldwide. Upper extremity hemiplegia is the most common and stable symptom of stroke survivors.[3] Physical therapy and occupational therapy interventions delivered by therapists are the mainstream rehabilitation treatments for poststroke upper extremity motor impairment. Various rehabilitation approaches focusing on upper extremity motor rehabilitation, such as constraint-induced movement training, task-oriented training, mental practice, and mirror therapy, have been widely applied in clinical practice.[3] Robot-assisted therapy (RT) has been developed as an approach for hemiplegia rehabilitation in the upper extremities in recent decades.[4] RT is defined as "an electronic computer-controlled system that can be used with a device to assist in functional rehabilitation of humans; these can be divided into therapeutic and assistive robots."[5] Compared with conventional therapist-led rehabilitation, RT can provide high-intensity, repetitive, and highly reproducible motor training to facilitate the restoration of hemiplegic upper extremity function and neuroplasticity after stroke.[6,7]

Therapeutic robots can be broadly categorized into end effector and exoskeleton devices. An end effector device is a tool that interacts with the environment and connects to the individual at a solitary point, whereas an exoskeleton device is connected to the individual at multiple points that match the joint axes.[8] In clinical practice, RT is used on the paretic arm only or both arms and is therefore referred to as unilateral robot-assisted therapy (URT) or bilateral robot-assisted therapy (BRT), respectively. URT aims to train the hemiplegic arm through repeated active or passive exercise. Turner et al[9] reported that URT was associated with the activation of the ipsilesional primary motor cortex in stroke patients, consequently facilitating the recovery of upper extremity motor impairment. BRT aims to train both arms, with the most impaired arm mimicking the unimpaired or less impaired arm to perform synchronous movements assisted by the robot device.[10] Studies have also examined the usefulness of bilateral asymmetrical movements for stroke rehabilitation, although these are seldom practiced with robotic devices.

Some researchers postulate that bilateral arm training is superior to unilateral arm training in improving hemiplegic arm function. Indeed, some studies with functional magnetic resonance imaging[11,12] showed that the effect of bilateral arm training may be superior to that of unilateral arm training in terms of activating the ipsilesional primary motor cortex and supplementary motor area, thus rebalancing the abnormal interhemispheric transcallosal inhibition caused by stroke. Such movement also improves interlimb coordination and enhances intra- and interhemisphere coupling. With the support of the bilateral recovery theory, BRT has been developed and applied in several clinical studies with stroke patients.[13–15]

Previous reviews investigated the effects of RT in upper extremity motor rehabilitation. A review conducted by Veerbeek et al[16] in 2016 showed that RT significantly improved Fugl-Meyer assessment for upper extremity (FMA-UE) scores, and subgroup analyses revealed that the type of robot device, stroke stage, and the type of control therapy may impact the effect size. Similar results were found in a Cochrane review conducted by Mehrholz et al,[17] in which high-level evidence was found to support the effects of electromechanical and RT for improving hemiplegic arm functions, as measured with the FMA-UE scores, in stroke patients. However, neither review included statistical comparisons between the different subgroups. Another meta-analysis by Zhang et al[18] was also published on this topic; however, various outcome measurements may lead to high heterogeneity among their analyses. Because a substantial number of studies have been published in this area, it is time to conduct detailed subgroup analyses with appropriate statistical comparisons to examine the potential influence of the patient characteristics and the interventional methodology on the treatment effect.

Thus, the objective of the present review was to answer the following questions: (1) Does RT have a superior effect on the improvement of upper extremity motor impairment in stroke patients compared with the conventional, therapist-led rehabilitation training, in terms of short-term (immediately after intervention) or long-term (follow-up) outcomes? (2) Is there any difference in effects between BRT and URT? (3) Could the patient characteristics such as stroke stage or the baseline level of upper extremity motor impairment measured with the FMA-UE scores[19,20] influence the effect size associated with the treatment? Finally, (4) could the type of robot device (e.g., end effector or exoskeleton) influence the effect sizes associated with the treatment? By answering these questions, this review aims to provide an overall picture of the currently available evidence regarding the clinical application of RT in poststroke upper extremity rehabilitation.

Methods

Data Sources and Search Terms

This review was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21] Two authors (J.W. and H.C.) independently searched the PubMed, Embase, Medline, and Web of Science databases to identify any randomized controlled trials (RCTs) about the effects of RT on the rehabilitation of upper extremity motor impairment in patients with stroke. Studies were collected from inception up to April 8, 2020. In each database, the search was conducted using a combination of the keywords: "stroke OR hemiplegic OR paresis OR cerebrovascular disorder OR cerebrovascular accident" AND "upper limb OR upper extremity OR arm OR forearm OR hand OR shoulder OR elbow" AND "robot-assisted OR robotics OR exoskeleton OR robotic aided OR robot assisted OR robotic device" AND "randomized controlled trial OR controlled trial." These terms were searched for in the whole article. Any disagreement was settled by discussion with the third author (J.Z.). The detailed search strategy is presented in Supplementary Table 1.

Study Selection

Studies that met all of the following criteria were included in this review: (1) studies designed as an RCT with either a crossover or parallel design; (2) studies with participants who were adults (aged over 18 years) diagnosed as having a unilateral hemispheric stroke; (3) studies that used a robot-assisted device for intervention; (4) studies with at least 1 control group in which participants received dose-matched conventional physical/occupational therapy led by therapists (the experimental and control groups had equal treatment times); and (5) studies that used the FMA-UE scores to assess hemiplegic upper extremity impairment, which is the most widely used primary outcome of patients with poststroke upper extremity motor impairment.[22] We restricted the outcome of interest to hemiplegic upper extremity impairment because it could reduce the potential heterogeneity during the subgroup analyses and statistical comparisons among different subgroups.

Studies that met any of the following criteria were excluded from this review: (1) studies published as conference abstracts, conference proceedings, or research protocols; (2) studies in which the reported data were insufficient for effect size calculation; (3) studies that used similar robot devices for intervention in both groups, except for those that compared BRT and URT, or end effector and exoskeleton devices; (4) studies that combined RT with other interventional modalities such as functional electrical stimulation, transcutaneous electrical nerve stimulation, or noninvasive brain stimulation; (5) studies that were not published in the English language (the English language restriction did not significantly affect the results of the meta-analysis, as demonstrated in a previous study[23]); and (6) non-RCTs or single-group pre/post-repeated-measures studies.

Data Extraction

After identifying the relevant studies, 2 authors (J.W. and H.C.) independently extracted the following information from each article: (1) the first author and publication year; (2) the characteristics of the participants (eg, age, time since stroke, and baseline motor impairment level); (3) the intervention in both groups, including the involved body parts in the RT (U = unilateral arm, B = bilateral arm), the joints involved in the RT (ie, whole upper extremity, shoulder/elbow, or forearm/wrist/hand), type of robot device (ie, exoskeleton or end effector robotic device), and intervention duration; and (4) the short- and long-term outcome data, including the mean and SD for each group. When the SDs were not available, estimates were made based on the sample size, median, interquartile range,[24–27] 95% CI,[20,28] SE,[29,30] and correlation coefficient (r).[13–15,31–41] For calculating the SD of the change in scores, we initially used a r of 0.8. Subsequently, different levels of r (0.3 and 0.5) were replaced in the calculation to examine the robustness of our results as a sensitivity analysis.[42] Any disagreement was settled by discussion with the third author (J.Z.).

Quality Assessment

The methodological quality of the included studies was independently assessed by 2 authors using the Physiotherapy Evidence Database (PEDro) scale. The items in the PEDro scale include random allocation, concealment of allocation, baseline equivalence, blinding procedure, intention-to-treat analysis, adequate follow-up, between-group statistical analysis, measurement of data variability, and point estimates. A PEDro score greater than or equal to 6 indicated good methodological quality.[43] We removed studies with a PEDro score less than 6 after every primary meta-analysis to test the robustness of the results, as another sensitivity analysis.

Data Synthesis and Analysis

Stata version 15.0 software (StataCorp LLC., College Station, TX, USA) was used for the meta-analysis, and Comprehensive Meta-Analysis version 3.0 software (Biostat, Englewood, NJ, USA) was used for the statistical analysis, including meta-regression and the Q test for the between-subgroup variance. The Hedges g was used to calculate the effect size, because it could correct the potential bias caused by studies with small sample size. A random-effects meta-analysis was performed because of the obvious clinical and methodological heterogeneity among the included studies.[44] Between-study heterogeneity was examined using the Higgins I^2 statistic. Studies with an I^2 of 25%-50% were considered to have low heterogeneity, and those with an I^2 of 50% to 75% and greater than 75% were considered as having moderate and high levels of heterogeneity, respectively.[45] Publication bias was assessed using funnel plots and Egger tests. Subgroup analyses were used to examine the moderating effects of the RT design (ie, URT vs BRT), type of robot device (ie, end effector vs exoskeleton), stroke stage (ie, <3 months vs ≥3 months, or <6 months vs ≥6 months),[46] and baseline severity of arm hemiplegia (ie, mildly impaired: FMA-UE score >50; moderately impaired: FMA-UE score 18-50; and severely impaired: FMA-UE score < 18).[19,20] After the subgroup analyses, we further performed a Q test based on the analysis of variance to test the between-subgroup portion of the variance.[47] The potential dose-dependent effect of the RT was assessed using a univariable meta-regression. In the meta-regression, we treated the total training time, the number of training sessions, and average training time per session as the independent variables, and effect size as the dependent variable. Because the dose is likely to be an important modulator of the treatment effects, we further included significant dose parameters and categorical variables in the multivariable meta-regression model, when appropriate. The statistical threshold was set at $P < .05$ (2-tailed), with the exception that a threshold of $P < .1$ (2-tailed) was used for the Egger test.[48]

Role of the Funding Source

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Results

Study Selection

The search resulted in 1018 citations. After removing duplicates, 548 records were screened, of which 356 citations were excluded for the following reasons: the studies were irrelevant (n = 233); the studies were reviews or meta-analyses (n = 29); the studies focused on infants, children, or adolescents (n = 19); technical papers (n = 64); or the studies enrolled healthy individuals exclusively (n = 11). The remaining 192 articles were subjected to full-text screening, of which 151 were removed for the following reasons: RCTs applied similar RTs in both the experiment and control groups (n = 17); the studies were not designed as RCTs (n = 44); the reported data for the meta-analysis were insufficient (n = 7); the studies were conference abstracts or study protocols (n = 19); the studies did not use FMA-UE scores as the outcome (n = 15); the studies compared brain-computer interface–guided/electronic-based/electromyography-driven RT with pure RT (n = 36); or the studies did not use a dose-matched conventional rehabilitation as the control or used different conventional rehabilitations in the experiment and control groups (n = 13). Finally, 41 studies with 1916 stroke patients satisfied the inclusion criteria and were included in the present systematic review. Supplementary Figure 1 shows the flowchart of the study selection, and the characteristics of the included studies are presented in Supplementary Table 2. The methodological quality of the included studies is presented in Supplementary Table 3.

Meta-Analysis

Among the included studies, 34 compared the effect of RT and dose-matched conventional rehabilitation[14,15,20,24,26–28,30–41,49–62] (except in 1 study, the duration in the control group seemed to be longer than that in the RT group[63]). Three studies had 3 groups, namely, the BRT, URT, and dose-matched conventional rehabilitation, and we therefore divided the comparisons into 2 units of analysis.[13,25,64] Two studies compared the effect of the sequential use of BRT and URT with that of dose-matched conventional rehabilitation.[29,65] One study had 4 groups, namely, the combined URT and BRT, URT, BRT, and dose-matched conventional rehabilitation and therefore, the comparisons were divided into 3 units of analysis.[66] One study directly compared the effects of BRT and dose-matched URT without conventional rehabilitation.[67]

Seventeen studies were included to estimate both the short-term effects immediately after the intervention and the long-term retention effects at follow-up (mean [SD] = 22.0 [7.4] weeks). When a study had several follow-up time points, the longest one was selected,[24,26,27,29,30,34,39–41,50,51,53–55,59,65,66] and 24 studies only estimated the short-term effects immediately after the intervention.[13–15,20,25,28,31–33,35–38,49,52,56–58,60–64,67] A statistically significant difference was observed in favor of RT over conventional rehabilitation immediately after the training (n = 1906; Hedges $g = 0.25$; 95% CI, 0.11–0.38; $P < .001$; $I^2 = 45.9\%$) (Fig. 1) but not at the follow-up assessment (n = 897; Hedges $g = 0.16$; 95% CI, −0.03 to 0.34; $P = .092$; $I^2 = 26.9\%$) (Supplementary Figure 2). No evidence of publication bias was found in the retention effects ($P = .31$) among the included studies, but we found a publication bias immediately after intervention ($P = .04$), as suggested by the Egger test (Supplementary Figures 3 and 4).

Meta-Regression With Dose Parameters

In the meta-regression with dose parameters, total training time, number of training sessions, and average training time per session were not significantly associated with the effect sizes in the short term ($P = .127$, .717, and .079, respectively) and long term ($P = .878$, .978, and .093, respectively).

Subgroup Meta-Analysis

This study then analyzed 5 subgroups based on the type of RT (i.e., URT, BRT, or combined URT and BRT), stroke stage (using either 3 or 6 months as the cutoff value), baseline motor impairment level (ie, moderate to severe or mild to moderate), type of robot device (ie, end effector or exoskeleton), and trained part (ie, proximal or distal joints). Owing to the limited number of studies with follow-up assessments, the subgroup analyses were performed on the basis of the effects immediately after RT.

Comparison of URT/BRT With Conventional Rehabilitation

In total, 33 units of analysis compared URT with conventional rehabilitation, 14 units of analysis compared BRT with conventional rehabilitation, and 3 units of analysis compared combined URT and BRT with conventional rehabilitation. The results indicated that URT was superior to conventional rehabilitation (n = 1548; Hedges $g = 0.32$; 95% CI, 0.15–0.50; $P < .001$; $I^2 = 55.9\%$).[13,20,24–28,30,31,35,36,38–40,49–64,66] When BRT was compared with conventional rehabilitation, the overall effect was not significant (n = 312; Hedges $g = 0.07$; 95% CI, −0.15 to 0.28; $P = .542$; $I^2 = 0\%$).[13–15,25,32–34,37,41,64,66] Combined URT and BRT was also not superior to conventional rehabilitation (n = 80; Hedges $g = 0.22$; 95% CI, −0.71 to 1.15; $P = .645$; $I^2 = 74.5\%$) (Fig. 1).[29,65,66] No statistically significant difference was detected by the Q test when either 2 subgroups (ie, URT and BRT) ($Q = 2.46$; $P = .12$) or 3 subgroups (ie, URT, BRT, and URT plus BRT) ($Q = 2.48$; $P = .29$) were compared.

Comparison of URT and BRT

Five studies directly compared the effects of BRT with those of URT.[13,25,64,66,67] The results showed that URT was better than BRT in terms of improved FMA-UE scores (n = 68; Hedges $g = -0.53$; 95% CI, −1.02 to −0.04; $P = .035$; $I^2 = 0\%$) (Fig. 2).

Influence of Stroke Stage

The subgroup analysis based on 35 studies revealed that RT significantly improved the FMA-UE scores in patients who had had a stroke at least 3 months before the assessment (n = 809; Hedges $g = 0.33$; 95% CI, 0.16–0.50; $P < .001$; $I^2 = 34.2\%$)[13–15,20,25,27,30,32,33,36,38,41,49–52,54–57,59,63–65] but not in those who had had a stroke less than 3 months before (n = 457; Hedges $g = 0.21$; 95% CI, −0.12 to 0.54; $P = .220$; $I^2 = 64.8\%$) (Fig. 3).[24,26,29,31,34,35,40,53,58,60,61] Similarly, when using 6 months as the cutoff, RT significantly improved the FMA-UE scores in patients who had had a stroke at least 6 months before the assessment (n = 826; Hedges $g = 0.26$; 95% CI, 0.12–0.41; $P < .001$; $I^2 = 2.3\%$)[13–15,20,25,27,30,32,33,36,38,41,49–52,56,57,59,64,65] but not in those who had had a stroke less than 6 months before (n = 518; Hedges $g = 0.17$; 95% CI, −0.08 to 0.42; $P = .177$; $I^2 = 53.2\%$).[24,26,28,29,31,34,35,37,40,53,58,60,61,66] However, no statistically significant difference between the subgroups was detected by the Q test when either 3 months ($P = .473$) or 6 months ($P = .471$) was used as the cutoff.

Influence of Baseline Motor Impairment Level

We found that RT significantly improved the FMA-UE scores in the patients with moderate to severe motor impairment, compared with the control (n = 1295; Hedges $g = 0.27$; 95% CI, 0.08–0.46; $P = .004$; $I^2 = 53.0\%$).[24–26,29–31,34–36,38,39,49–57,59,61,64–66] However, no significant between-group difference (RT vs control) was identified in the patients with mild to moderate motor impairment (n = 316; Hedges $g = 0.19$; 95% CI, −0.01 to 0.40; $P = .063$; $I^2 = 0\%$)

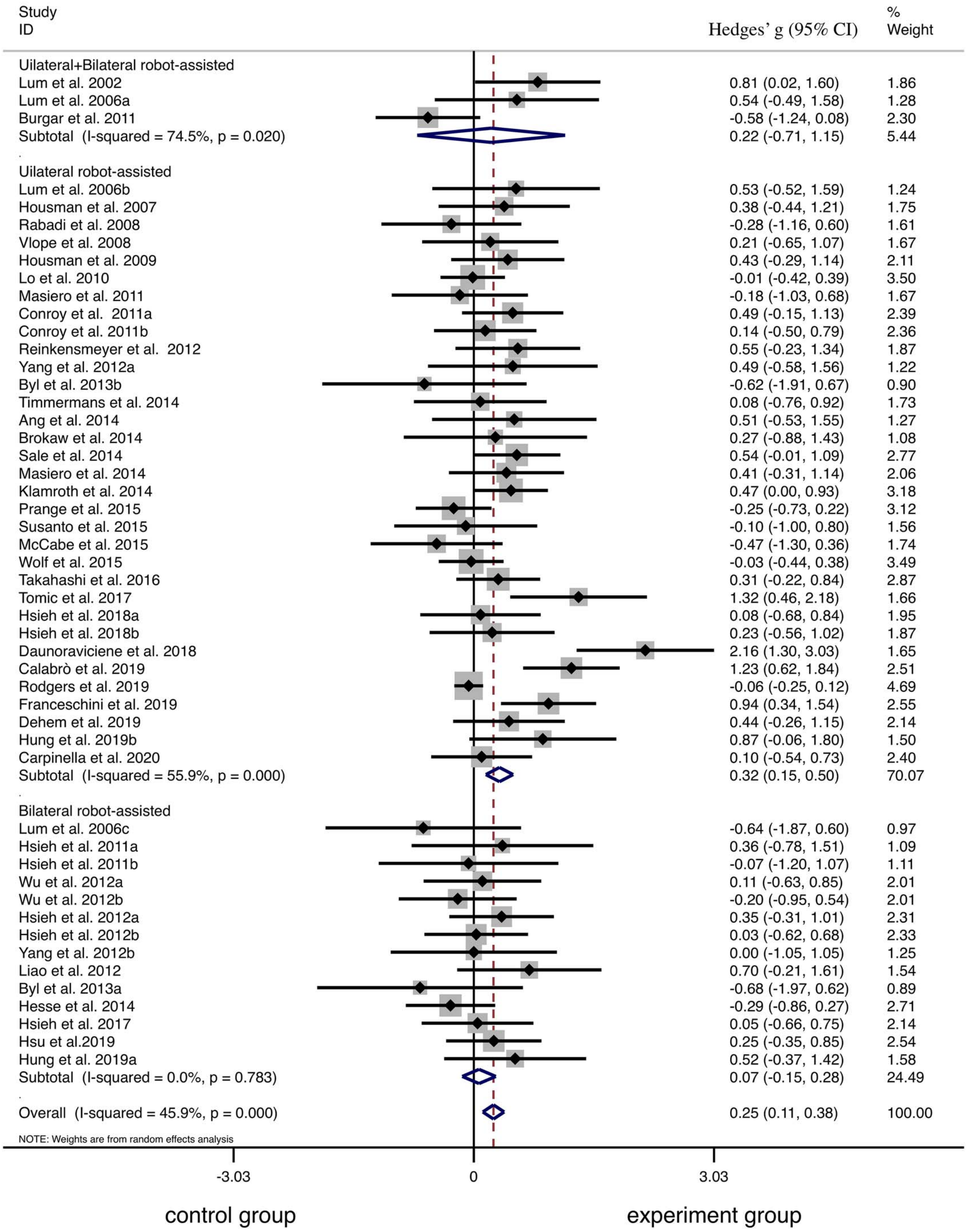

Figure 1. Meta-analysis of short-term changes in FMA-UE score between RT and the control group, URT and the control group, BRT and the control group, and combined URT and BRT and the control group. BRT = bilateral robot-assisted therapy; FMA-UE = Fugl-Meyer assessment for upper extremity; RT = robot-assisted therapy; URT = unilateral robot-assisted therapy.

(Fig. 4).[13–15,20,27,32,33,41,60] Moreover, no statistically significant difference among the subgroups was detected by the *Q* test ($Q = 0.24$; $P = .889$).

Influence of the Type of Robot Device

We found that end effector robots (n = 1605; Hedges $g = 0.22$; 95% CI, 0.09–0.36; $P = .001$; $I^2 = 35.4\%$) [13–15,20,24–41,50,52,53,55,60–62,65,66] but not exoskeleton robots (n = 301; Hedges $g = 0.31$; 95% CI, −0.14 to 0.76; $P = .171$; $I^2 = 68.9\%$)[49,51,54,56–59,63,64] were superior to conventional rehabilitation in terms of improving the FMA-UE scores (Fig. 5). However, no statistically significant difference between the subgroups was detected by the *Q* test ($Q = 0.25$; $P = .616$).

Influence of the Trained Part

The subgroup analysis based on 30 studies revealed that shoulder/elbow robotics (n = 1097; Hedges $g = 0.27$; 95% CI,

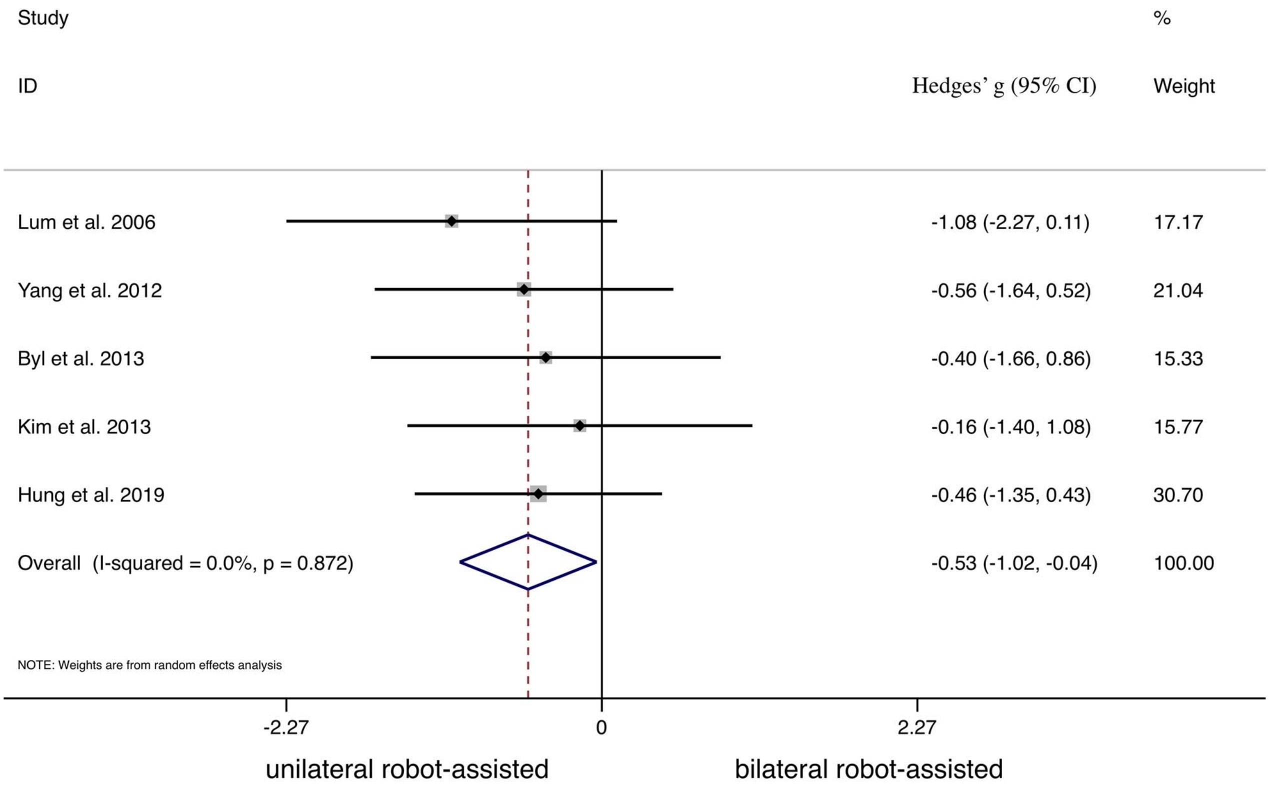

Figure 2. Meta-analysis of changes in FMA-UE score between URT and BRT. BRT = bilateral robot-assisted therapy; FMA-UE = Fugl-Meyer assessment for upper extremity; URT = unilateral robot-assisted therapy.

0.05–0.50; $P = .018$; $I^2 = 61.9\%$)[24,26,29–31,35,36,38,39,50–53,54,58,60–62,65,66] and forearm/wrist/hand robotics (n = 417; Hedges $g = 0.19$; 95% CI, 0.01–0.37; $P = .042$; $I^2 = 0.0\%$)[13–15,25,28,32,33,37,40,41,55,59] were superior to conventional rehabilitation in terms of improving the FMA-UE scores (Fig. 6). However, no statistically significant difference between the subgroups was detected in the Q test ($Q = 0.10$; $P = .755$).

Sensitivity Analyses

The results of the sensitivity analysis are presented in Supplementary Table 4. The overall results of the analysis were robust when different levels of correlation coefficients were used to estimate the SD of the change scores, except the results of the 2-subgroup analyses (ie, URT vs BRT, and proximal joints vs distal joints). An additional sensitivity analysis was performed on the basis of the methodological quality of the included studies as measured with the PEDro scale. The overall results of the analysis were robust when only high-quality (PEDro score ≥6) studies were included.

Discussion

This review suggests that RT was superior to conventional rehabilitation in terms of improving upper extremity motor impairment as assessed using the FMA-UE scores. A subsequent subgroup analysis revealed that URT, but not BRT, was superior to conventional rehabilitation, with a small effect size. Furthermore, URT seemed to be better than BRT in improving upper extremity motor impairment based on the meta-analysis of the 5 studies with direct comparisons. End effector robots, but not exoskeleton robots, seemed to be more useful for improving upper limb motor impairment after stroke than conventional rehabilitation. The subgroup analysis also revealed that the superiority of RT was more obvious when it was applied to patients with a limited potential for spontaneous biological recovery after stroke and patients with moderate to severe upper extremity motor impairment, although the statistical comparison did not reach significance in all the subgroup comparisons.

Learned nonuse is a common phenomenon whereby the movement of the hemiplegic arm is suppressed because of stroke, resulting in failure to use the hemiplegic arm during daily activities.[68] Along with the suppression of neural activities in the affected hemisphere, the unaffected hemisphere becomes overactivated, which leads to an interhemispheric asymmetry; however, this phenomenon could be overcome with appropriate behavioral training.[69] URT can be used to address learned nonuse by delivering high-intensity, repetitive training. Repetitive and high-intensity movement of the hemiplegic arm results in the reorganization of the affected motor cortex and consequently rebalances the interhemispheric asymmetry caused by unilateral stroke.[70–72] The results of this meta-analysis were in line with this theory and suggest that URT is an effective intervention for improving the upper extremity motor function of stroke patients. In addition, the theory on the recovery of bilateral hemispheric interaction after stroke suggests that bilateral arm training is potentially more effective than unilateral arm training in upper extremity rehabilitation. The underlying mechanisms may include the activation of the ipsilateral non-cross

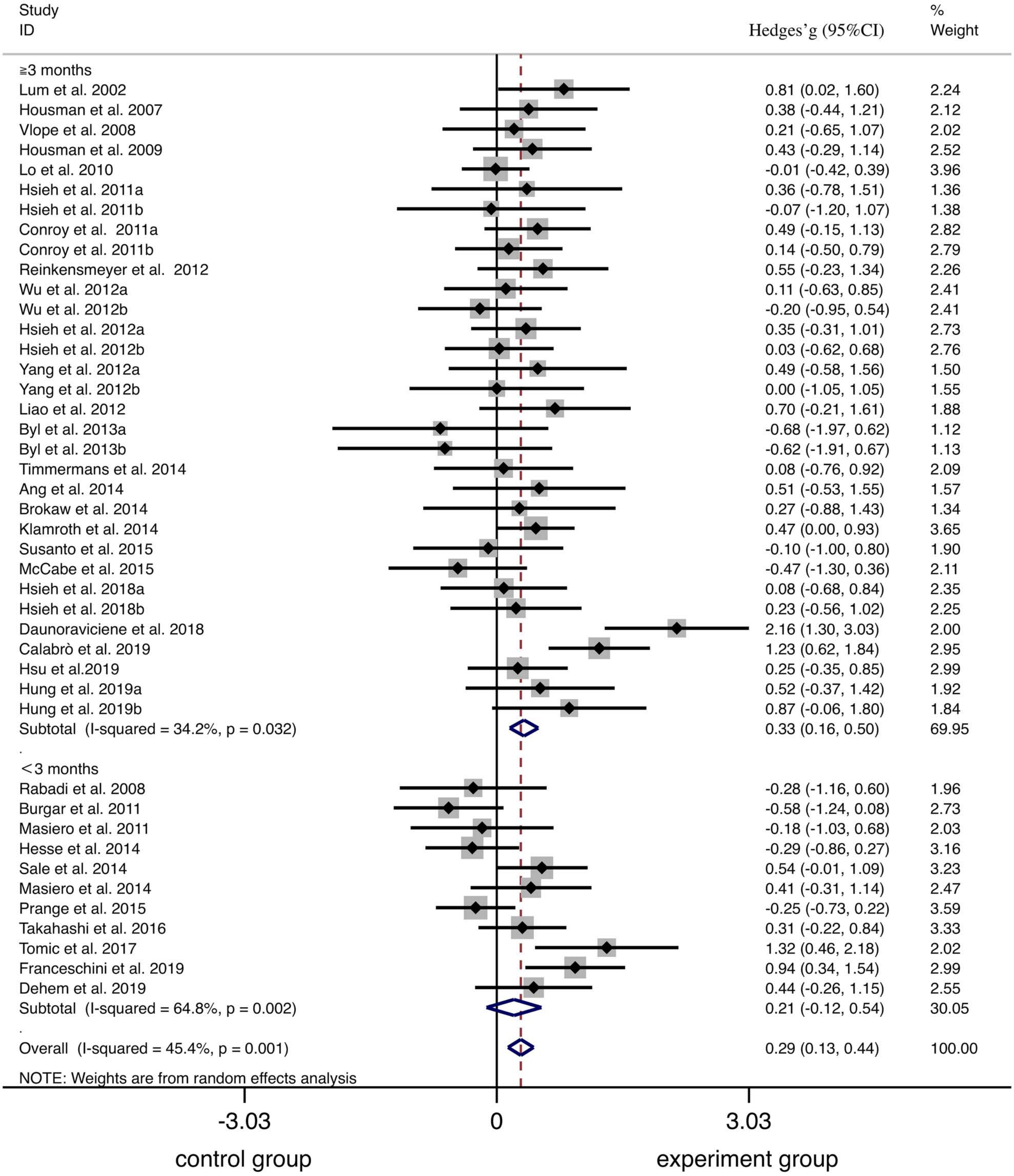

Figure 3. Meta-analysis of changes in FMA-UE score between RT and control groups in the different stages of stroke. FMA-UE = Fugl-Meyer assessment for upper extremity; RT = robot-assisted therapy.

corticospinal pathway. Bilateral arm training may be better than unilateral arm training in terms of increasing the excitability of the ipsilesional motor cortex and transcallosal inhibition from the ipsilesional to the contralesional motor cortex, which results in the rebalance of interhemispheric activities in stroke patients.[11,12] However, in our review, we found that the effect of BRT was not superior to conventional rehabilitation. A potential reason for this finding may be the limited number of studies/the units of analysis (n = 11/n = 14) that used BRT. In addition, BRT can be varied according to symmetrical, asynchronous, and cooperative training modes with bilateral arms, compared with URT, which is important for neurological recovery. However, the included studies applied bilateral synchronous movements during BRT.

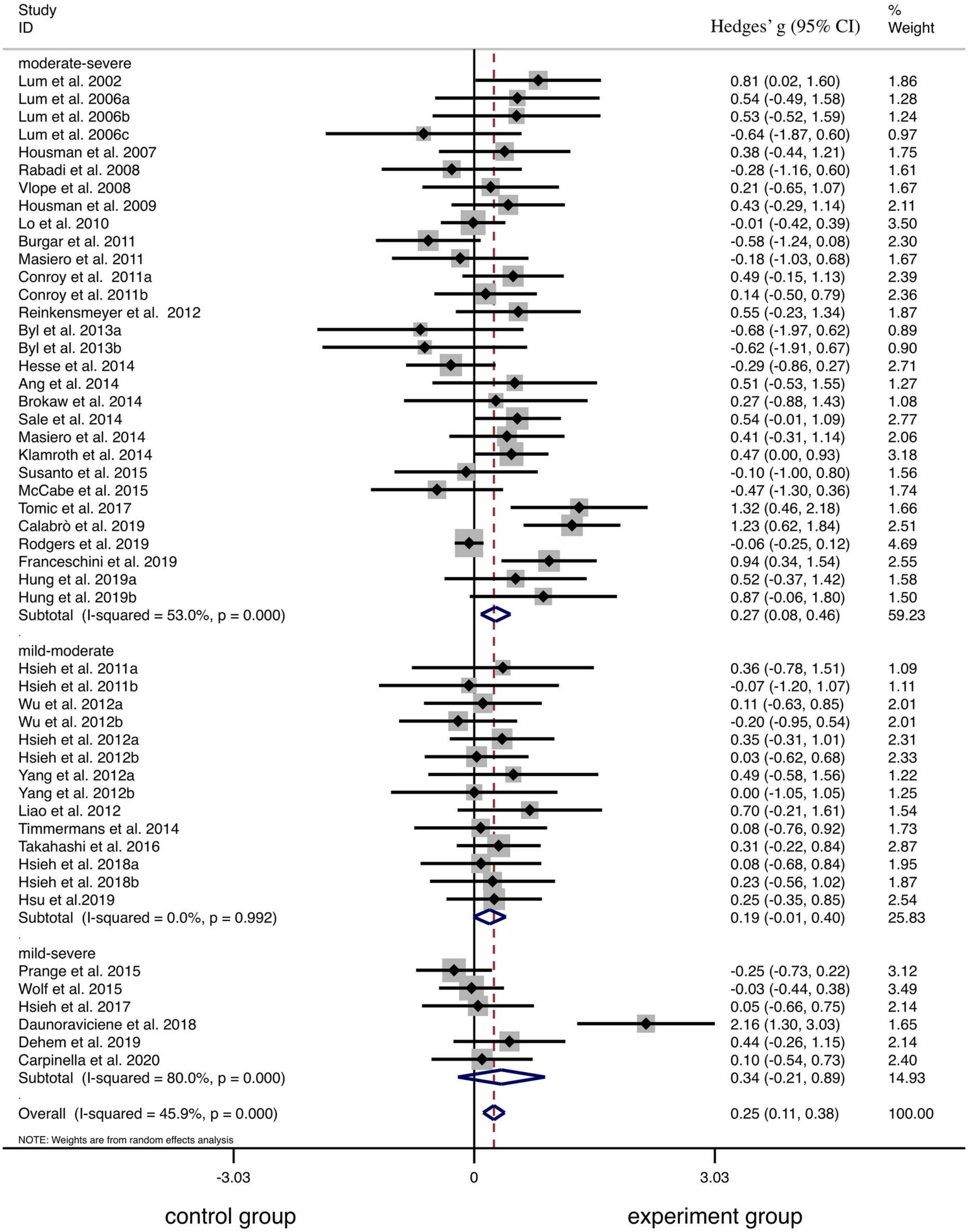

Figure 4. Meta-analysis of changes in FMA-UE score between RT and control groups according to upper extremity motor impairment level. FMA-UE = Fugl-Meyer assessment for upper extremity; RT = robot-assisted therapy.

Thus, whether BRT may provide benefits to stroke patients with ipsilesional upper extremity dysfunction, which occurs in approximately one-third of stroke survivors, is unclear.[73] Further studies are needed to investigate these points.

In terms of disease stage, the results of this meta-analysis were consistent with those of a previous meta-analysis by Zhang et al[18] in that RT led to significant improvement in FMA-UE scores compared with the dose-matched conventional rehabilitation in chronic stroke patients. Spontaneous biological recovery is prominent within the first 3 months after stroke, and it is mostly diminished 6 months after stroke. The nonsignificant results may be due to the

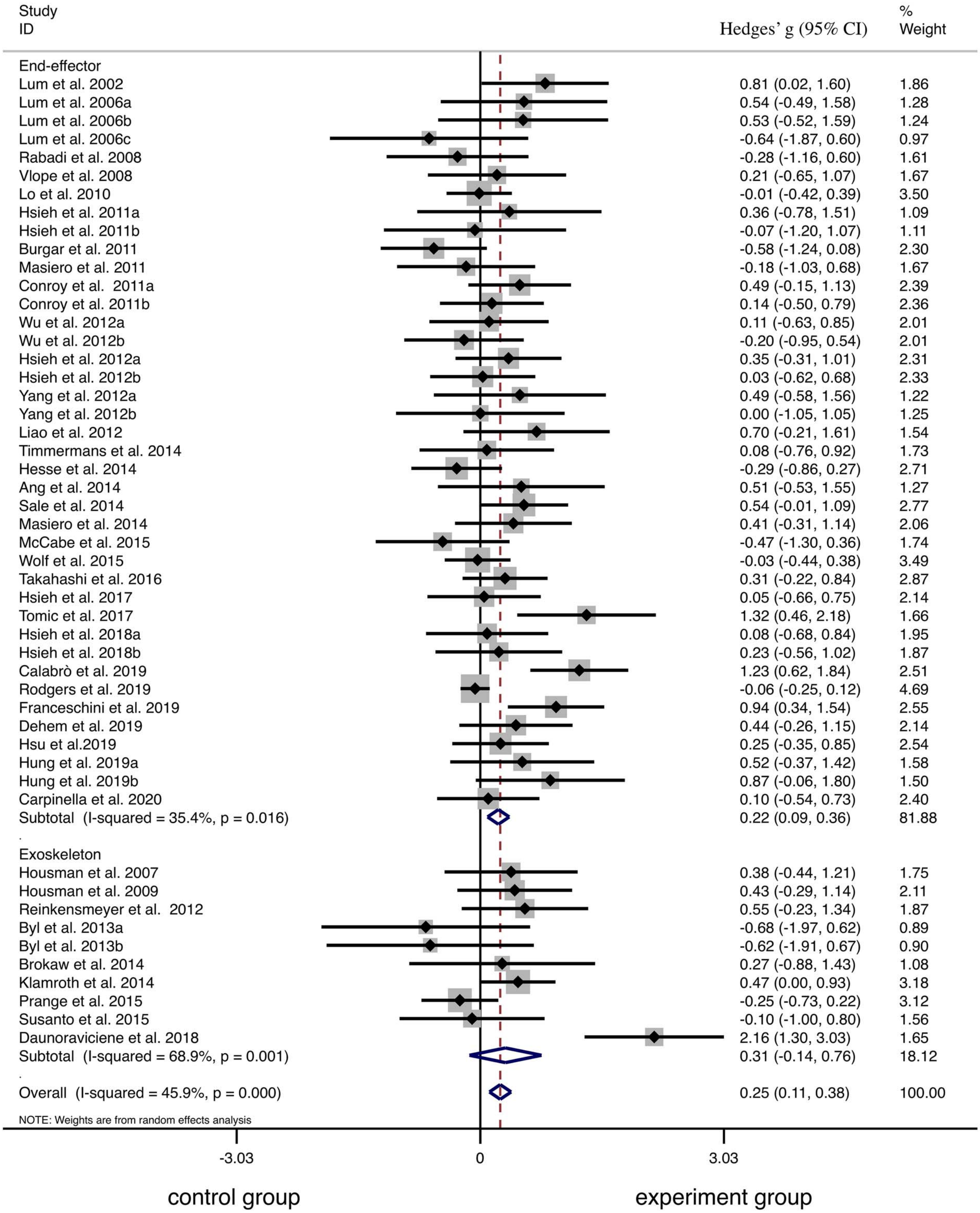

Figure 5. Meta-analysis of changes in FMA-UE score between RT and control groups according to RT device. FMA-UE = Fugl-Meyer assessment for upper extremity; RT = robot-assisted therapy.

strong spontaneous biological recovery in stroke patients in the early stage. This may lead to a similar improvement in upper limb motor function regardless of the type of training provided. Therefore, poststroke patients with limited potential for spontaneous recovery may obtain more benefits from RT than from conventional rehabilitation.

With regard to the severity of upper extremity motor impairment in stroke patients, the functional gains associated with RT were higher than those associated with conventional rehabilitation in stroke patients with moderate to severe upper limb impairment. Patients with notable upper limb hemiplegia likely obtain more benefits from RT, where their movements

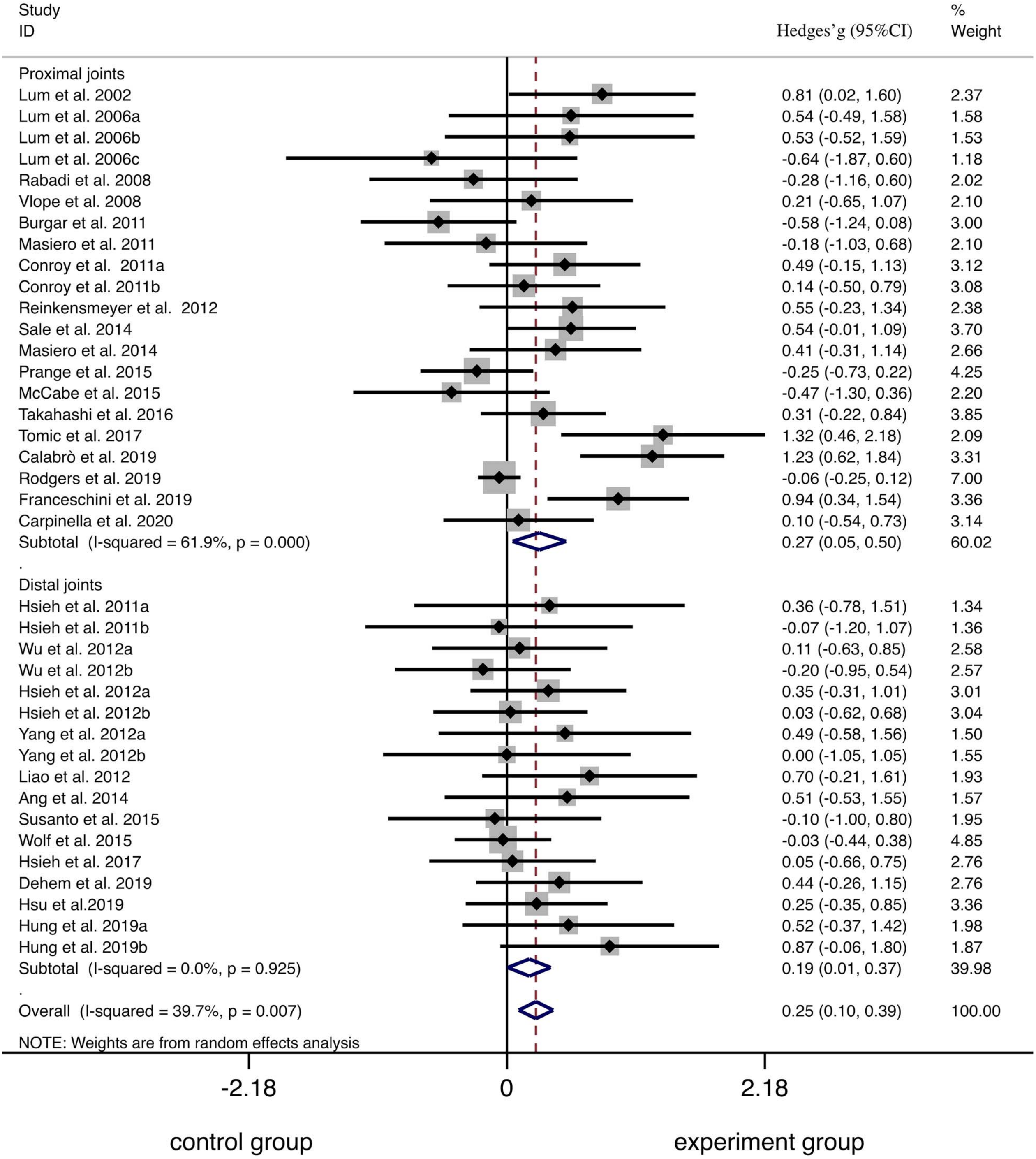

Figure 6. Meta-analysis of changes in FMA-UE score between RT and control groups according to training focus. FMA-UE = Fugl-Meyer assessment for upper extremity; RT = robot-assisted therapy.

can be assisted, than those with mild hemiplegia, who can perform most training tasks without robotic assistance.

We also demonstrated that the application of end effector robots could lead to better outcomes in the restoration of motor impairment after stroke than conventional rehabilitation. End effector robots allow multijoint coordination, which segment the arm movements, and may promote relearning of normal motor patterns of the affected limbs.[74] However, a recent clinical trial by Lee et al[8] reported no interaction effect on FMA-UE scores after training with end effector and exoskeleton robots. Because only 1 study was available for the direct comparison, a meta-analysis could not be performed to determine which type of robot device is potentially superior. Further studies are needed to investigate this point.

Limitations

This study is not free from limitations. First, the present meta-analytic review only focused on the effects of RT on the outcome measures of upper extremity motor impairment to maintain the homogeneity of our meta-analysis and subgroup comparisons. Other important domains such as activities of daily living were not evaluated in the meta-analysis owing to the heterogeneity of the outcome measurements. Second, although this review examined the retention effects, the results should be considered as preliminary due to the differences in the follow-up lengths. Third, all the moderators remained insignificant in the statistical tests by meta-regression and Q test for the between-subgroup variance. Although Q test has taken the weight of each study into account in the calculation, the fact that there are more studies in some subgroups may still influence the statistical comparisons. Also, we were unable to perform further multivariate meta-regression by including all significant modulators, with regards to the statistical insignificance. Therefore, the results of the subgroup analyses should be interpreted with caution. The numerically large effect sizes in the subgroup analyses may help determine the modulators when designing future studies about RT in stroke rehabilitation.

Conclusion

RT is an effective intervention for improving upper extremity motor impairment in stroke patients. The superiority of RT compared with conventional methods might be more obvious when it is applied to stroke patients with notable upper limb hemiplegia and limited potential for spontaneous biological recovery. In addition, URT is likely to be superior to BRT.

Author Contributions

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Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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