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Subacute stroke physical rehabilitation evidence in activities of daily living outcomes

A systematic review of meta-analyses of randomized controlled trials

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Abstract

Background: Stroke is a leading cause of disabilities worldwide. One of the key disciplines in stroke rehabilitation is physical therapy which is primarily aimed at restoring and maintaining activities of daily living (ADL). Several meta-analyses have found different interventions improving functional capacity and reducing disability.

Objectives: To systematically evaluate existing evidence, from published systematic reviews of meta-analyses, of subacute physical rehabilitation interventions in (ADLs) for stroke patients.

Methods: Umbrella review on meta-analyses of RCTs ADLs in MEDLINE, Web of Science, Scopus, Cochrane, and Google Scholar up to April 2018. Two reviewers independently applied inclusion criteria to select potential systematic reviews of meta-analyses of randomized controlled trials (RCTs) of physical rehabilitation interventions (during subacute phase) reporting results in ADLs. Two reviewers independently extracted name of the 1st author, year of publication, physical intervention, outcome(s), total number of participants, and number of studies from each eligible meta-analysis. The number of subjects (intervention and control), ADL outcome, and effect sizes were extracted from each study.

Results: Fifty-five meta-analyses on 21 subacute rehabilitation interventions presented in 30 different publications involving a total of 314 RCTs for 13,787 subjects were identified. Standardized mean differences (SMDs), 95% confidence intervals (fixed and random effects models), 95% prediction intervals, and statistical heterogeneity (I^2 and Q test) were calculated. Virtual reality, constraint-induced movement, augmented exercises therapy, and transcranial direct current stimulation interventions resulted statistically significant ($P<.05$) with moderate improvements ($0.5 \leq \text{SMD} \leq 0.8$) and no heterogeneity ($I^2=0\%$). Moxibustion, Tai Chi, and acupuncture presented best improvements ($\text{SMD}>0.8$) but with considerable heterogeneity ($I2>75\%$). Only acupuncture reached “suggestive” level of evidence.

Conclusion: Despite the range of interventions available for stroke rehabilitation in subacute phase, there is lack of high-quality evidence in meta-analyses, highlighting the need of further research reporting ADL outcomes.

Abbreviations: ADLs = activities of daily living, AMSTAR = assessment of multiple systematic reviews, CI = confidence interval, CIM = constraint-induced movement, FES = functional electrical stimulation, GBD = global burden of disease, MD = mean difference, PI = prediction interval, PICOS = population, intervention, comparison, outcome, study design, RCT = randomized controlled trial, rPMS = repetitive peripheral magnetic stimulation, rTMS = repetitive transcranial magnetic stimulation, RTT = repetitive task training, SMD = standard mean difference, tDCS = transcranial direct current stimulation.

Keywords: activities of daily living, meta-analysis, rehabilitation, stroke, subacute interventions, umbrella review

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1. Introduction

Stroke is the 2nd cause of mortality and the 3rd cause of long-term disability worldwide with 33 million stroke survivors.[1] Mortality is declining, yet prevalence is stable, meaning there are more survivors with long-term disability.[2] Using Global Burden of Disease incidence rates, between 2015 and 2035, it is projected that the number of stroke survivors in the European Union will rise from 3,718,785 in 2015 to 4,631,050 in 2035, an increase of 25%.[3] In the United States, approximately every 40 seconds someone experiences a stroke, as death rates have declined, stroke has become the leading cause of long-term disability.[4]

Interdisciplinary complex rehabilitation interventions are assumed to represent the mainstay of poststroke care.[5] One of the key disciplines in interdisciplinary stroke rehabilitation is physical therapy which is primarily aimed at restoring and maintaining activities of daily living (ADL).[6] In this work, we consider physical therapy as “therapeutic modalities frequently used in physical therapy specialty by physical therapists or physiotherapists to promote, maintain, or restore the physical and physiological well-being of an individual” (Mesh, MEDLINE

Subject Heading). Although stroke patients at an early stage depend on a stroke unit in the acute hospital, their functional recovery and long-term health status are more affected by subacute (1–6 months) rehabilitation hospital.[7]

Several meta-analyses have found different interventions improving functional capacity and reducing disability.[7] A recent umbrella review[8] summarizes the effects of exercise therapy on functional capacity in patients considering 22 different chronic diseases. Eighty-five meta-analyses were included, nevertheless only 11 of them reported outcomes on stroke of which 5 refer to ADLs, in our work we aim to update (only 6 of the 11 studies are dated after 2013) and extend that body of knowledge.

Veerbeek and colleagues[9] retrieved randomized controlled trials (RCTs) regarding physical therapy in stroke. In their analysis, most database searches (90%) were performed by mid-2011. In this work, we aim to link interventions specifically to ADLs and include new therapeutic approaches in which physical exercise is combined with innovative treatments enhancing neuroplasticity, such as transcranial direct current stimulation[10] or repetitive peripheral magnetic stimulation.[11]

A nonspecific systemic inflammatory response occurs after both ischemic and hemorrhagic stroke, either as part of the process of brain damage or in response to complications such as deep venous thrombosis.[12] Inflammation may be important both before, in predisposing to a stroke, and afterwards, where it takes part in the mechanisms of cerebral injury and repair.[13,14] Clinically, the susceptibility of the patients to stroke and the subsequent prognosis are influenced by such inflammatory processes.[15–17] As stroke patients with systemic inflammation have been reported to exhibit clinically poorer outcomes,[18] in this work, we will report mentions to inflammatory processes in the identified meta-analyses.

To the best of our knowledge, no attempts of reviewing the existing literature through an umbrella review in stroke rehabilitation has been conducted. Umbrella review offers the possibility to analyze the strength of evidence and extent of potential biases in the association between physical interventions in subacute rehabilitation and ADL outcomes.

2. Methods

2.1. Literature search

According to the Joanna Briggs Institute Umbrella Review Methodology,[19] literature search was conducted independently by 2 reviewers (AGR, DSP) in MEDLINE (2000 through April 2018), Web of Science (through April 2018), Scopus (through April 2018), Cochrane database of systematic reviews, and Google Scholar (up to mid-April 2018). The search strategy included combinations of multiple search terms for 2 themes: Stroke and interventions (rehabilitation). The keywords used to search for studies for this review are listed in Appendix Search strategy, http://links.lww.com/MD/C839. All meta-analyses registered in these databases that reported a systematic electronic search of literature for a defined period of time were included. Bibliographies of identified articles and manual search of relevant journals for additional references was conducted. The most updated or complete publication was used when more than an article was present for a single study. In addition, separate meta-analyses on multiple outcomes presented in a single article were assessed separately. Gray literature search was conducted using different internet search engines and websites: such as Google Scholar.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria, established by using the PICOS (Population, Intervention, Comparison, Outcome, Study Design)[19] strategy presented in Appendix - Supplementary Table 1, http://links.lww.com/MD/C839.

Study design: meta-analyses (quantitative analysis) of RCTs in subacute rehabilitation phase (1–6 months after onset).

Study population: stroke patients in subacute rehabilitation phase >18 years.

Outcomes: ADL outcome scales, regarded as continuous scaled, where usually higher scores indicate a good outcome, for example, functional independence measure,[20] Barthel index,[21] modified Rankin scale,[22] Frenchay activities index,[23] Rivermead ADL Assessment,[24] Katz index of independence in ADL,[25] motor activity log,[26] and modified Barthel index.[27] Eligible articles were required to be meta-analyses of RCTs, have outcome measures related to ADLs, compare physical therapy with no treatment or usual care, have adult participants, as defined by the Cochrane Collaboration,[28] and have stroke patients as defined by World Health Organization.[29] Meta-analyses were excluded if intervention did not clearly take place during subacute rehabilitation phase (considering the following criteria as in related research[30] acute: <1 month after stroke, subacute: 1 to 6 months after stroke and chronic: more than 6 months after stroke), they did not report the number of studies or participants in experimental or control groups, they assessed postsurgical recovery or site-specific musculoskeletal conditions such as patellofemoral pain syndrome (although physical therapy may be a standard treatment). We excluded meta-analyses that did not present study-specific data (effect size and 95% confidence intervals [CIs]).

2.3. Data extraction

We extracted the name of the 1st author, year of publication, physical intervention, ADL outcome(s), and number of studies from each eligible meta-analysis. From each individual study in a meta-analysis, we extracted the 1st author, year of publication, total number of subjects assigned to the intervention and to the control groups, mean value and standard deviation of ADL outcome, and maximally adjusted effect size measurements (mean difference [MD] or standardized MD [SMD]) along with the corresponding 95% CI. Two investigators (AGR, DSP) independently searched the literature, assessed the eligibility of the retrieved papers, and extracted the data using a standard pro-form. Disagreements were resolved by consensus with a third senior investigator (EOS or JMT).

2.4. Assessment of methodological quality of included studies

Both reviewers independently assessed the methodological quality of each review, using the AMSTAR (Assessment of Multiple Systematic Reviews) appraisal tool.[31] Disagreements were resolved by consensus with a 3rd senior investigator (EOS or JMT) (see Appendix Supplementary Table 3, http://links.lww.com/MD/C839 for details).

2.5. Data analysis

Estimation of summary effect: The summary effect size and its CIs by 95% were estimated using both fixed effects and random effects models for each meta-analysis,[32] by using the Cochrane Collaboration's Review Manager V.5.3.

Assessment of heterogeneity: Heterogeneity between studies was assessed with Cochran *Q* test[33] and the I^2 statistic.[34] For interpreting I^2, we follow related research criteria[34]: $I^2=0\%$ no heterogeneity, $I^2=25\%$ low heterogeneity and when I^2 exceeds 50% or 75%, the heterogeneity is considered substantial or considerable, respectively.

Estimation of prediction intervals: For the summary random effects, we estimated the 95% prediction interval (PI),[35] we therefore can report the range of effects across study settings, providing a more complete picture for clinical practice.

Grading the evidence: For each rehabilitation intervention, the data were analyzed qualitatively based on the SMDs of each included meta-analysis. The SMDs were evaluated using forest plot and graded as small (SMD < 0.5), moderate (SMD 0.5–0.8), and large (SMD > 0.8) effect sizes.[36] The significance of the results ($P<.05$) was judged based on the 95% CIs of the SMDs.

Publication bias: Studies published in peer-reviewed journals are much more likely to report statistically significant results than are studies that report a nonsignificant conclusion, especially for smaller studies. Publication bias is assessed checking for asymmetry in funnel plots.[37]

This study was approved by Institut Guttmann Local Ethics Committee.

2.6. Patient involvement

No patients were involved in setting the research question or outcome measures, nor were they involved in developing plans for design or implementation of the study.

3. Results

3.1. Literature review

The search retrieved 251 published systematic reviews evaluating rehabilitation interventions. Of these, 88 reviews met the abstract inclusion criteria and were selected for closer scrutiny. Full texts of these articles were retrieved and both reviewers performed the final selection. Overall, 11 reviews published in Cochrane Library database and 19 published in other academic journals were included. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) of the study selection process is provided in Figure 1.

In Appendix Excluded, http://links.lww.com/MD/C839, we present a list of a selection of excluded publications, all dated ≥2015 and most of them addressing interventions already included in the final selection that had to be left out for the reasons presented in Figure 1.

3.2. Description of meta-analyses

A total of 55 meta-analyses on 21 subacute rehabilitation interventions presented in 30 different publications[1,10,11,38–65] (Table 1) involving a total of 314 RCTs were included in this umbrella review. Meta-analyses included a median of 5 studies (ranging from 1 to 19). Robotic training and CIM (constraint induced movement) are the interventions with the highest number of meta-analyses (10 each), followed by Acupuncture and transcranial direct current stimulation (tDCS) with 6 and 5, respectively, then modified CIM and Virtual Reality with 3, the rest of interventions have been studied in 1 or 2 meta analyses.

The total number of subjects in the included RCTs was 13,787 (7167 cases and 6,620 controls) and the median number of participants was 171 (range: 30–1136). In Appendix Supplementary Table 1, http://links.lww.com/MD/C839, we present for each intervention the total number of cases and controls, almost 80% of subjects have participated in 7 of the 21 interventions (acupuncture, robotic, CIM, tDCS, moxibustion, repetitive task training [RTT], and mirror therapy).

For results that were not presented as SMD in the original meta-analysis, the Cochrane Collaboration's Review Manager V.5.3 was used to convert the outcomes to SMD to allow visual comparison of the results in a forest plot (presented in Supplementary Material, http://links.lww.com/MD/C839 along with forest plots for fixed and random effect sizes for all 55 meta-analyses).

3.3. Summary effect size

The evaluation of the level of significance for both random and fixed effect calculations, the number of studies, sample size (cases and controls), the 95% PI and heterogeneity (I^2 and *Q* test level of significance) are reported in Table 1 for the resulting 55 meta-analyses, grouped by rehabilitation interventions. Thirty of the 55 meta-analyses (54%) reported nominally statistically significant findings ($P<.05$) in both fixed and random effect sizes denoted with † in Table 1. Sixteen (77%) of the 21 interventions reported statistically significant results in both fixed and random effects in at least 1 meta-analysis.

Bilateral training, imagery training, repetitive transcranial magnetic stimulation (rTMS), repetitive peripheral magnetic stimulation (rPMS), and Nintendo Wii training did not report statistically significant results in any of their meta-analyses. Based only on the fixed effects model, 44 meta-analyses (80%) gave nominally statistically significant findings ($P<.05$). Wii, bilateral training, and rPMS did not report statistically significant results in any of their meta-analyses. Thirty-one meta-analyses (57%) gave a nominally significant findings based on the random effects model. Wii, bilateral training, imagery, rTMS, and rPMS did not report statistically significant results in any of their meta-analyses. Only Wii, bilateral training, and rPMS did not report statistically significant results neither in random nor in fixed effects models. At a stricter threshold of $P<.001$, 27 (49%) and 13 (24%) meta-analyses produced significant summary results using the fixed and random effects models, respectively. At $P<10^{-6}$, 23 (42%) and 6 (11%) meta-analyses were significant, respectively. In general, the magnitude of the observed summary estimates were small to moderate with 30% of the estimates yielding an effect size >0.8 as shown in Figure 2.

Negative effects summaries were reported in 4 meta-analyses from 3 interventions (acupuncture [2], CIM [1], and rPMS [1]).

3.4. Heterogeneity between studies

Q test was significant at $P\leq 0.10$ in 24 of the 55 meta-analyses (44%). Eleven meta-analyses (20%) showed no heterogeneity ($I^2=0\%$) for several interventions (robotic, Wii, tDCS, CIM, mCIM, virtual reality, RTT, bilateral, and augmented). Thirteen meta-analyses (24%) showed low heterogeneity ($I^2<50\%$) in robotic, tDCS, acupuncture, CIM, virtual reality, functional electrical stimulation (FES), RTT, mirror therapy, and circuit interventions. Substantial heterogeneity ($50\%\leq I^2\leq 75\%$) is present in 11 (20%) meta-analyses addressing 5 interventions (robotic, tDCS, CIM, mCIM, Tai Chi). Considerable heteroge-

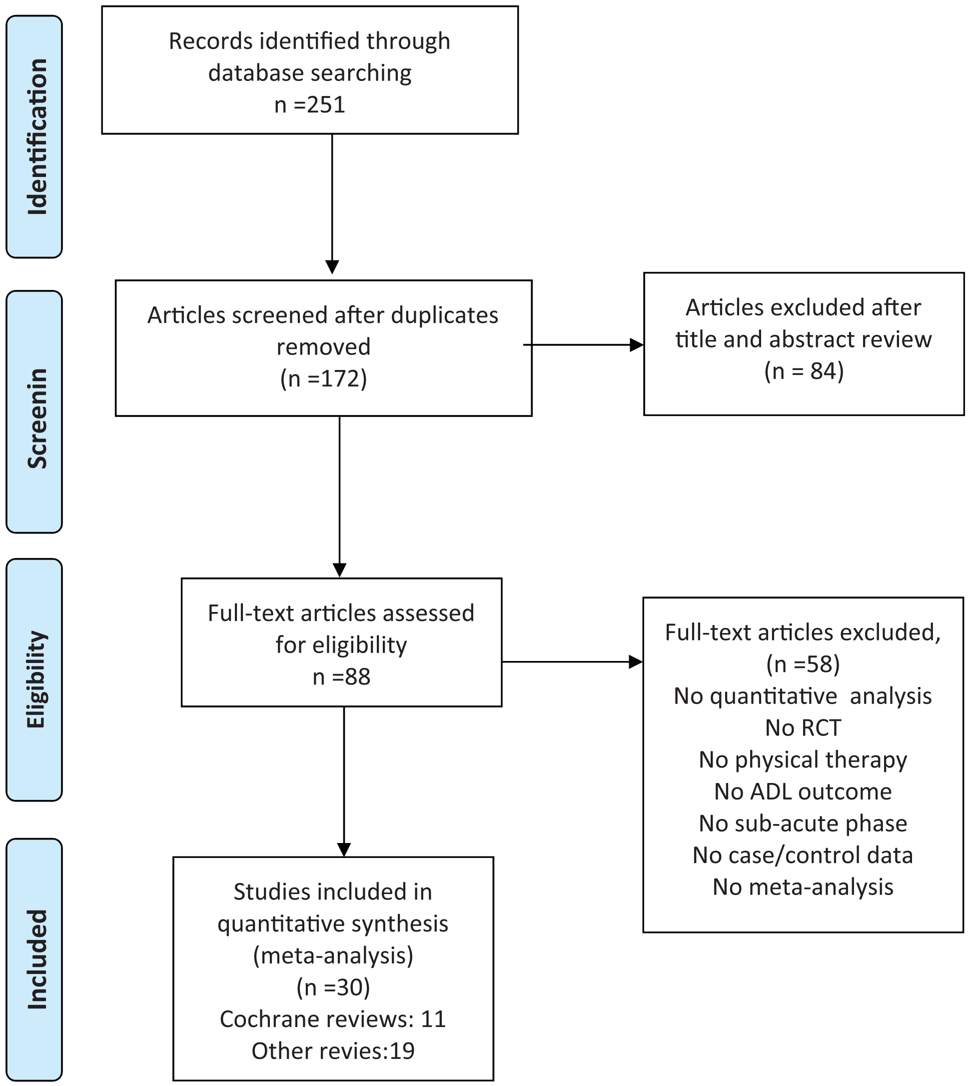

Figure 1. PRISMA Flow diagram of the study selection process.[19]

neity ($I^2 > 75$) is shown in 15 (27%) meta-analyses in 8 interventions (robotic, moxibustion, acupuncture, CIM, imagery, ElectroAcu, Tai Chi, rTMS). Table 2 shows the number of statistical significant studies at the 4 levels of heterogeneity of small (SMD < 0.5), moderate (SMD 0.5–0.8), and large (SMD > 0.8) effect sizes.

3.5. Assessment of methodological quality of included studies (AMSTAR)

Twenty-nine (94%) of the included publications are rated *high quality* (mean value 9.61, see Appendix Supplementary Table 3, http://links.lww.com/MD/C839). All meta-analyses provided an "a priori" design, performed a literature search in at least 2 electronic databases, reported duplicate study selection and made it possible to replicate the literature search, but 20% did not report the inclusion of grey literature, 7% did not report conflict of interest, and 20% did not assess the scientific quality of the included studies. Appendix Supplementary Table 4, http://links.lww.com/MD/C839, shows top rated interventions: circuit, FES, hydrotherapy, mirror therapy, rPMS, rTMS, tCDS, and virtual reality.

3.6. Prediction intervals

We calculated 95% PI, as presented in Table 1; the null value was excluded in only 10 meta-analyses (from a total of 55).

Figure 3 shows the forest plot of the meta-analyses with significant ($P < .05$) summary fixed and random effects with random effects 95% PI excluding null value, along with the number of studies (treatments and controls) implemented in *forest plot* R package.[66]

In Appendix Supplementary Figure 1, http://links.lww.com/MD/C839, we included the funnel plots (all of them presenting visually acceptable symmetry) for the 4 meta-analyses with more than 1 study from Figure 3 to visually assess symmetry (these funnel plots are extracted from Supplementary Material, http://links.lww.com/MD/C839, where we present all funnel plots for all selected meta-analyses).

For publications with $P < .05$ and number of studies ≥9,

Table 1

Summary effect calculations, studies, sample size (cases and controls), 95% prediction interval (PI) and heterogeneity.

Intervention	Publication	Studies (cases/controls)	Fixed effects (*P*)	Random effects (*P*)	PI (95%)	I^2 (P^*)
Robotic*	Mehrholz et al (2015)[38]	6 (94/101)	0.49 [0.20, 0.78] (.001)	0.49 [0.20, 0.78] (.001)	[0.02, 0.96]	0 (.55)
	Mehrholz et al (2015)[38]	12 (272/250)	0.39 [0.21, 0.58] (<.00001)	0.32 [−0.05, 0.68] (.09)	[−1.16, 1.8]	73 (<.0001)
	Norouzi et al (2012)[39]	3 (55/51)	0.96 [0.55, 1.38] (<.00001)	0.81 [−0.07, 1.70] (.07)	[−4.24, 5.86]	77 (.01)
	Norouzi et al (2012)[39]	3 (32/30)	0.02 [−0.49, 0.53] (.95)	0.00 [−0.62, 0.62] (1.00)	[−2.77, 2.77]	31 (.23)
	Veerbeek et al (2017)[1]	17 (234/193)	0.33 [0.13, 0.53] (.001)	0.27 [−0.05, 0.59] (.09)	[−0.98, 1.52]	56 (.002)
	Veerbeek et al (2017)[1]	14 (184/146)	0.35 [0.12, 0.58] (.003)	0.24 [−0.17, 0.65] (.25)	[−1.37, 1.85]	64 (.0005)
	Veerbeek et al (2017)[1]	17 (234/193)	0.33 [0.13, 0.33] (.001)	0.27 [−0.05, 0.59] (.09)	[−0.98, 1.52]	56 (.002)
	Veerbeek et al (2017)[1]	13 (185/146)	0.34 [0.11, 0.57] (.004)	0.22 [−0.20, 0.65] (.30)	[−1.45, 1.89]	67 (.0003)
	Veerbeek et al (2017)[1]	12 (158/121)	0.08 [−0.16, 0.33] (.51)	0.04 [−0.27, 0.35] (.80)	[−0.84, 0.92]	32 (.13)
†	Veerbeek et al (2017)[1]	5 (76/72)	0.82 [0.48, 1.17] (<.00001)	0.85 [0.32, 1.38] (.002)	[−0.98, 2.68]	54 (.07)
Sling	Chen et al (2016)[40]	1 (40/40)	0.24 [−0.20, 0.68] (.29)	0.24 [−0.20, 0.68] (.29)	NA	NA
†	Chen et al (2016)[40]	1 (48/48)	1.12 [0.69, 1.55] (.00001)	1.12 [0.69, 1.55] (.00001)	NA	NA
Wii	Cheok et al (2015)[41]	2 (20/17)	0.27 [−0.38, 0.93] (.41)	0.27 [−0.38, 0.93] (0.41)	[−8.23, 8.77]	0 (.75)
tDCS	Elsner et al (2016)[10]	9 (232/164)	0.24 [0.03, 0.44] (.02)	0.24 [0.03, 0.44] (.02)	[−0.05, 0.53]	0 (.52)
	Triccas et al (2015)[42]	5 (129/71)	0.24 [−0.06, 0.54] (.11)	0.32 [−0.08, 0.72] (.12)	[−0.85, 1.49]	33 (.20)
	Triccas et al (2015)[42]	3 (102/76)	0.19 [−0.12, 0.50] (.23)	0.54 [−0.27, 1.34] (.19)	[−3.93, 5.01]	70 (.04)
†	Triccas et al (2015)[42]	3 (65/65)	0.38 [0.03, 0.73] (.03)	0.38 [0.02, 0.74] (.04)	[−0.92, 1.68]	5 (.35)
†	Banchetti et al (2017)[43]	3 (37/52)	0.51 [0.07, 0.95] (.02)	0.51 [0.07, 0.95] (.02)	[−0.88, 1.9]	0 (.39)
Moxibustion†	Han et al (2018)[44]	14 (459/434)	0.90 [0.76, 1.04] (<.00001)	1.07 [0.64, 1.50] (<.00001)	[−0.95, 3.09]	88 (<.00001)
Acupuncture	Lee et al (2013)[45]	2 (75/75)	−0.17 [−0.49, 0.15] (.31)	−0.16 [−0.50, 0.18] (.34)	[−5.26, 4.94]	10 (.29)
†	Lee et al (2013)[45]	2 (62/61)	0.78 [0.41, 1.15] (<.00001)	0.78 [0.40, 1.17] (<.00001)	[−4.83, 6.39]	7 (.30)
	Lee et al (2013)[38]	2 (75/75)	1.29 [0.92, 1.66] (<.00001)	1.34 [−0.56, 3.25] (.17)	[−40.98, 43.66]	96 (<.00001)
†	Li et al (2014)[46]	12 (574/562)	0.81 [0.68, 0.94] (<.00001)	1.36 [0.71, 2.01] (<.00001)	[−1.56, 4.28]	95 (<.00001)
†	Yang et al (2016)[47]	9 (309/307)	1.20 [1.01, 1.30] (<.00001)	1.27 [0.54, 2.00] (.0007)	[−1.88, 4.42]	94 (<.00001)
†	Peng et al (2018)[48]	6 (347/345)	0.97 [0.81, 1.14] (<.00001)	1.31 [0.57, 2.05] (.005)	[−1.76, 4.38]	76.7 (<.0001)
CIM	Corbetta et al (2010)[49]	9 (151/127)	0.18 [−0.06, 0.42] (.14)	0.21 [−0.08, 0.50] (.16)	[−0.55, 0.97]	31 (.18)
	Peurala et al (2012)[50]	2 (116/115)	1.27 [0.98, 1.55] (<.00001)	0.98 [0.01, 1.94] (.05)	[−19.58, 21.54]	83 (.02)
	Peurala et al (2012)[50]	2 (29/27)	1.78 [1.10, 2.47] (<.00001)	3.75 [−1.05, 8.55] (.13)	[−101.79, 109.3]	91 (.0007)
	Peurala et al (2012)[50]	5 (77/94)	0.59 [0.27, 0.91] (.0003)	0.59 [0.17, 1.00] (.006)	[−0.69, 1.87]	41 (.15)
	Peurala et al (2012)[50]	2 (116/115)	1.16 [0.87, 1.44] (<.00001)	0.87 [-0.07, 1.81] (.07)	[−19.01, 20.75]	82 (.02)
†	Peurala et al (2012)[50]	1 (20/20)	0.82 [0.17, 1.46] (.01)	0.82 [0.17, 1.46] (.01)	NA	NA

(*continued*)

Table 1
(continued).

Intervention	Publication	Studies (cases/controls)	Fixed effects (P)	Random effects (P)	PI (95%)	I^2 (P^*)
†	Peurala et al (2012)[50]	5 (77/94)	0.67 [0.35, 0.99] (<.00001)	0.68 [0.18, 1.18] (.007)	[−1.05, 2.41]	58 (.05)
	Peurala et al (2012)[50]	1 (18/12)	−0.53 [−1.27, 0.21] (.16)	−0.53 [−1.27, 0.21] (.16)	NA	NA
	Peurala et al (2012)[50]	4 (69/46)	0.07 [−0.33, 0.47] (<.00001)	−0.30 [−1.51, 0.91] (.63)	[−5.74, 5.14]	88 (<.0001)
†	Peurala et al (2012)[50]	4 (51/71)	0.50 [0.13, 0.87] (.008)	0.50 [0.13, 0.87] (.008)	[−2.47, 3.47]	0 (.91)
mCIM†	Shi et al (2011)[51]	3 (45/43)	0.45 [0.03, 0.88] (.04)	0.45 [0.03, 0.88] (.04)	[−0.89, 1.79]	0 (.80)
†	Shi et al (2011)[51]	6 (87/86)	0.73 [0.41, 1.05] (<.00001)	0.79 [0.22, 1.37] (.007)	[−1.17, 2.75]	64 (.02)
†	Shi et al (2011)[51]	6 (87/86)	0.81 [0.49, 1.13] (<.00001)	0.86 [0.36, 1.37] (.0007)	[−0.77, 2.49]	54 (.05)
VR†	Laver et al (2012)[52]	3 (60/41)	0.81 [0.39, 1.22] (.0002)	0.81 [0.39, 1.22] (.0002)	[−0.5, 2.12]	0 (.55)
†	Laver et al (2015)[53]	8 (136/117)	0.43 [0.18, 0.69] (.0009)	0.43 [0.18, 0.69] (.0001)	[0.06, 0.8]	2 (.41)
†	Laver et al (2015)[53]	8 (80/73)	0.44 [0.11, 0.76] (.009)	0.44 [0.11, 0.76] (.009)	[−0.03, 0.91]	0 (.57)
FES†	Eraifej et al (2017)[54]	5 (32/33)	1.23 [0.65, 1.80] (<.00001)	1.24 [0.46, 2.03] (.002)	[−1.21, 3.69]	43 (.14)
RTT†	French et al (2010)[55]	5 (175/150)	0.29 [0.07, 0.51] (.01)	0.28 [0.01, 0.55] (.04)	[−0.49, 1.05]	30 (.22)
†	French et al (2016)[56]	9 (273/254)	0.28 [0.10, 0.45] (.002)	0.28 [0.10, 0.45] (.002)	[0.03, 0.53]	0 (.47)
Bilateral	Lee et al (2017)[57]	2 (61/56)	0.26 [−0.10, 0.63] (.16)	0.26 [−0.10, 0.63] (.16)	[−4.48, 5]	0 (.54)
Augmented†	Veerbeek et al (2011)[58]	2 (66/72)	0.54 [0.20, 0.88] (.002)	0.54 [0.20, 0.88] (.002)	[−3.87, 4.95]	0 (.60)
Imagery	Fernandes et al (2017)[59]	5 (81/81)	0.50 [0.17, 0.83] (.003)	0.67 [−0.20, 1.54] (.13)	[−2.89, 4.23]	85 (<.0001)
ElectroAcu†	Cai et al (2017)[60]	7 (262/260)	0.73 [0.55, 0.91] (<.00001)	0.80 [0.41, 1.20] (<.00001)	[−0.72, 2.32]	78 (<.00001)
Tai Chi†	Lyu et al (2018)[61]	7 (199/192)	1.29 [1.06, 1.52] (<.00001)	1.44 [0.78, 2.09] (.0001)	[−1.22, 4.1]	88 (<.00001)
†	Lyu et al (2018)[61]	2 (81/85)	0.92 [0.60, 1.25] (<.00001)	0.97 [0.47, 1.47] (.0001)	[−8.38, 10.32]	54 (.14)
Hydrotherapy†	Mehrholz et al (2011)[62]	1 (16/15)	1.90 [1.03, 2.76] (<.00001)	1.90 [1.03, 2.76] (<.00001)	NA	NA
Mirror therapy†	Thieme et al (2018)[63]	19 (333/289)	0.46 [0.30, 0.63] (<.00001)	0.48 [0.30, 0.65] (<.00001)	[0.07, 0.89]	15 (.27)
rTMS	Hao et al (2013)[64]	2 (93/90)	0.91 [0.58, 1.24] (<.00001)	1.90 [−1.04, 4.84] (.21)	[−63.68, 67.48]	98 (<.00001)
Circuit†	English et al (2017)[65]	2 (147/149)	0.32 [0.09, 0.55] (.006)	0.30 [0.03, 0.58] (.03)	[−4.08, 4.68]	17 (.27)
rPMS	Momosaki et al (2017)[11]	1 (31/32)	−0.11 [−0.60, 0.38] (.66)	−0.11 [−0.60, 0.38] (.66)	[0.02, 0.96]	NA

Several lines for the same publication mean different meta-analyses reported in the same publication (e.g., in Verbeek 2017 RT-UL groups were divided into 5 subgroups: shoulder/elbow, whole arm [shoulder/elbow/wrist and/or hand], elbow, elbow/wrist/hand, wrist/hand and hand).
FES = functional electrical stimulation; mCIM = modified constraint induced movement; NA = not applicable; tDCS = transcranial direct current stimulation; VR = virtual reality; RTT = repetitive task training; rTMS = repetitive transcranial magnetic stimulation; rPMS = repetitive peripheral magnetic stimulation; wii = Nintendo wii.
* *P*-value of the *Q* test.
† Statistically significant findings ($P < .05$).

- we performed regression analysis with *meta* R package[67] on the number of participants in experimental groups and the year of publication covariates, as in similar previous umbrella reviews.[68] We identified 2 studies [47,63] with *P*-value <.05 for the total participants in experimental group covariate. As shown in Appendix Supplementary Table 5, http://links.lww.com/MD/C839, 2.28% and 8.21%, respectively, of effect size is explained by the number of participants in the experimental group.
- we performed sensitivity analysis with *meta* R package[67] to explain high heterogeneity (publications with $P < .05$ and number of studies ≥9). Therefore, we analyzed Han et al[44] (89%), Li et al[46] (95%), and Yang et al[47] (94%). We obtained our best results for Li et al,[46] when omitting Wu

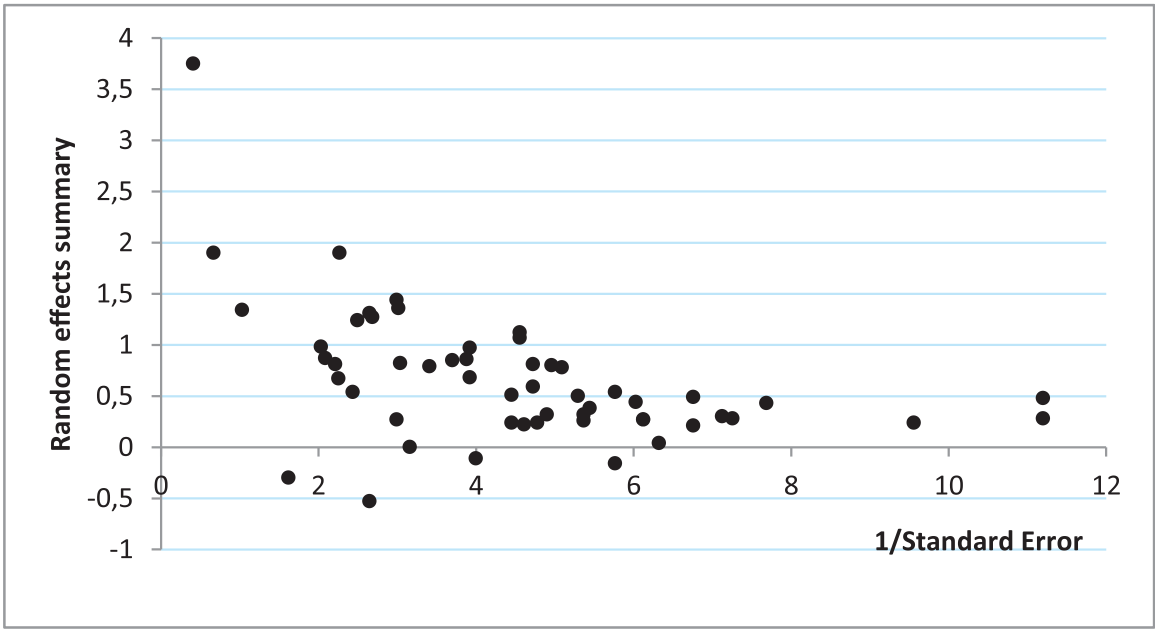

Figure 2. Association of the meta-analysis summary random effects estimate with the inverse of the standard error.

study (2011), heterogeneity declines from 95% to 89%. In the other 2 publications, best reductions are only 1% to 2%.

- we performed subgroup analysis (by using the Cochrane Collaboration's Review Manager V.5.3) on those publications with $P<.05$ and number of studies ≥9 grouping by year of publication. For example, in Thieme et al,[63] we performed subgroup analysis with 3 groups:
  - ˆ Group 1: 2008 to 2012 (6 studies)
  - ˆ Group 2: 2013 to 2014 (7 studies)
  - ˆ Group 3: 2015 to 2018 (6 studies)

Differences could be identified within the 3 periods because of technology evolution in the administration of mirror therapy interventions (e.g., virtual reality technologies). But as shown in page 83 of Supplementary Material, http://links.lww.com/MD/C839, no significant subgroup differences were identified. We proceeded similarly with other publications[44,47] with no significant differences either.

Details of meta-regression, sensitivity, and subgroups analysis are presented in Supplementary Material, http://links.lww.com/MD/C839.

In Appendix Supplementary Figure 2, http://links.lww.com/MD/C839, we included a work design diagram showing our whole analysis process, taking as starting point the outcome of PRISMA flow diagram of the study selection process presented in Figure 1.

Table 2

Summary of the number of studies for small, moderate, and large effect sizes grouped by heterogeneity level for the different intervention.

Intervention	No Heterogeneity 0%	Low < 50%	Substantial 50-75%	Considerable >75%
Robot assisted	6		5	
tDCS	9 / 3	5		
Moxibustion				14
Acupuncture		2		27
CIM	4	5	5	
mCIM	3		6 / 6	
Virtual Reality	3 / 8	8		
FES		5		
RTT	9	5		
Augmented	2			
Electroacu				7
Tai Chi			2	7
Mirror therapy		19		
Circuit		2		

- SMD > 0.8
- SMD 0.5 - 0.8
- SMD < 0.5
- No effects

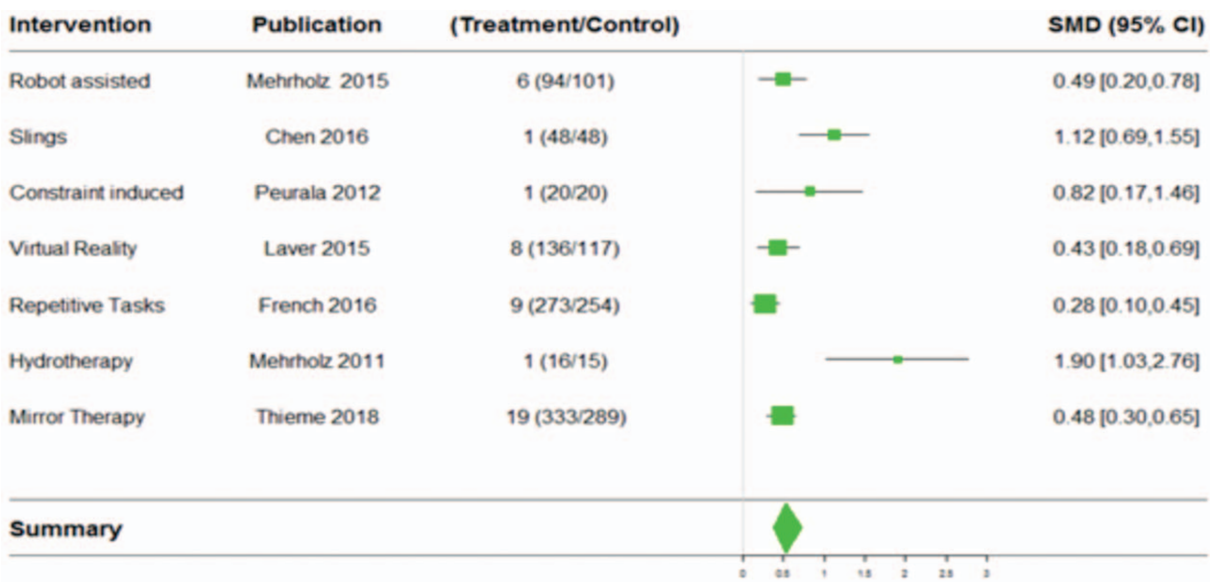

Figure 3. Forest plot for meta-analysis with significant ($P<.05$) summary fixed and random effects with random effects 95% prediction interval excluding null value.

4. Discussion

It is recommended[69] that the 95% PI should be routinely reported to allow more informative inferences in meta-analyses. It presents the expected range of true effects in similar studies, therefore in 95% of cases the true effect of a new study (assessing the impact of a physical intervention in ADLs) will fall within the PI values. In our case, most PIs contain null values, leading us to consider that although therapists' interventions are effective on average to increase performance in ADLs most of them may not be effective because the null value was excluded in only 10 (with 5 of them NA) of the 55 meta-analyses.

Considering recent umbrella reviews in medical field (e.g., Cancer or Parkinson disease)[70] "highly convincing" evidence requires >1000 cases, $P<10^{-6}$ by random effects, 95% PI excluding the null and not large heterogeneity ($I^2<50\%$). "Suggestive" evidence requires >1000 cases and $P<.001$ by random effects. Only acupuncture meta-analysis reached such thresholds, leaving the rest of studies included in this work at the "weak" level, pointing out the need of new RCTs assessing ADLs.

After full-text review of the 30 included studies, we did not find mentions to inflammatory process. Clinical outcomes after stroke are highly variable, and reasons for these variations are often unexplained.[71] Recovery after ischemic or hemorrhagic stroke begins immediately after acute onset, and several different levels of biological responses are involved. Genetic factors also influence many different aspects of brain function and repair, as well as recurrent stroke risk and response to interventions, and can account for unexplained variation in stroke recovery.[71] Up to 30% of ischemic strokes remain unexplained after thorough investigation.[72] Cryptogenic stroke is more common in patients with stroke occurring at a young age, defined as age 55 or less. For example, it has been reported that approximately 1% to 2% of young stroke patients are demonstrated with Fabry disease,[72] a rare inherited disorder of the metabolism, associated with renal, cardiac, and cerebrovascular complications.[73,74] With such a multitude of molecular events being related to recovery, not surprisingly a number of genes have been suggested as important to variability in stroke recovery. Genetic variation in any of these components might influence each individual's capacity for brain plasticity and could explain the variability in motor rehabilitation efficacy.

4.1. Study limitations

We did not publish a protocol for this study. We only included systematic reviews with meta-analysis (we took this approach as in recent reviews related to health).[75]

5. Conclusion

Moxibustion, acupuncture, and Tai Chi not only show large SMD values and large number of participants, but also the highest values of heterogeneity ($I^2>75$), when interventions are grouped according to the four levels of heterogeneity of small (SMD < 0.5), moderate (SMD 0.5–0.8), and large (SMD > 0.8) effect sizes considering the significance of the results ($P<.05$) based on the 95% CIs of the SMDs for both fixed and random effects.

Robot assisted, virtual reality, tDCS, and RTT present small and moderate effect sizes but without heterogeneity ($I^2=0$). The total number of participants in the included RCTs was 13,787 and the median number was 171 with almost 80% of subjects participating in only 7 of the 21 interventions (acupuncture, robotic, CIM, tDCS, moxibustion, RTT, and mirror therapy), meaning that 80% of participants are recruited in only 30% of interventions. Besides, when categorizing our evidence according to state-of-the art thresholds only weak levels of evidence are reached in almost all of the included studies.

Acupuncture as a complementary therapy has increased worldwide and has become widely applied to stroke rehabilitation.[76] Similarly, Tai Chi has been applied in stroke rehabilitation for over 10 years worldwide.[61] Moxibustion has been less studied, being noninvasive it might be more applicable in other cultures.[44] Our results encourage further RCTs into them.

Future research could analyze the excess significance bias, whether observed number of studies with statistically significant results is different from the expected number of them[77] and extend subgroup analyses considering gender and/or age differences.

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