Efficacy of physiotherapy interventions late after stroke: a meta-analysis

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ABSTRACT

Objective Physiotherapy is usually provided only in the first few months after stroke, while its effectiveness and appropriateness in the chronic phase are uncertain. The authors conducted a systematic review and meta-analysis of randomised clinical trials (RCT) to evaluate the efficacy of physiotherapy interventions on motor and functional outcomes late after stroke.

Methods The authors searched published studies where participants were randomised to an active physiotherapy intervention, compared with placebo or no intervention, at least 6 months after stroke. The outcome was a change in mobility and activities of daily living (ADL) independence. The quality of the trials was evaluated using the PEDro scale. Findings were summarised across studies as effect size (ES) or, whenever possible, weighted mean difference (WMD) with 95% CI in random effects models.

Results Fifteen RCT were included, enrolling 700 participants with follow-up data. The meta-analysis of primary outcomes from the original studies showed a significant effect of the intervention (ES 0.29, 95% CI 0.14 to 0.45). The efficacy of the intervention was particularly evident when short- and long-distance walking were considered as separate outcomes, with WMD of 0.05 m/s (95% CI 0.008 to 0.088) and 20 m (95% CI 3.6 to 36.0), respectively. Also, ADL improvement was greater, though non-significantly, in the intervention group. No significant heterogeneity was found.

Interpretation A variety of physiotherapy interventions improve functional outcomes, even when applied late after stroke. These findings challenge the concept of a plateau in functional recovery of patients who had experienced stroke and should be valued in planning community rehabilitation services.

INTRODUCTION

Beside being the third leading cause of death, stroke is the main cause of severe disability in the ageing populations of industrialised countries.[1] The dynamics of the disabling process after stroke is complex. Although most stroke survivors show some neurological recovery in the initial postacute phase, usually within the first 3 months,[2] improvement may continue well beyond this time. As many as 40% to 60% of patients will recover functional independence in the domains of mobility and ADL from 3 months to 10 years after a stroke[2] and at a widely variable pace.[3] Conversely, once a given level of independence is reached, it can be hardly maintained long term, as functional status generally tends to deteriorate slowly over time.[4 5]

In general, rehabilitation services are designed without fully taking into account the complexity in functional evolution of stroke survivors. Although a variety of in-hospital or out-of-hospital multidisciplinary interventions may be proposed to promote motor function recovery,[6] physiotherapy usually is deemed appropriate only within weeks or a few months after stroke.[7] Thus, it is unusual that patients with 'chronic' stroke are offered any form of rehabilitation.[4] This is due to the limited availability of resources as well as to the paucity of high-quality evidence of the efficacy of late rehabilitation. In view of scarce and inconclusive findings from RCT, the concept prevails that there is a limit to late functional recovery after a stroke, and doubts are cast upon the effectiveness of late motor rehabilitation interventions. As a result, evidence-based practice guidelines generally agree that stroke survivors with persistent disabilities should be periodically assessed for further possible interventions, whereas agreement is scarce on the strength of recommendations on late rehabilitation.[6 8–11]

The present systematic review and meta-analysis of RCT was performed to evaluate the efficacy of motor rehabilitation and physiotherapy interventions conducted late after stroke.

METHODS

In accordance with the meta-analysis of randomised controlled trials (QUOROM) statement,[12] we conducted an extensive search for published RCT performed at least 6 months after stroke onset, enrolling five or more adults in each group, randomised to an active physiotherapy intervention aimed either at improving mobility and ADL independence or at controlling treatment (placebo or no intervention). Active treatment had to be represented by conventional rehabilitation (including neuromuscular interventions, practising functional activities, muscle strengthening and application of assistive equipments), and had to be provided or supervised by qualified physiotherapists (alone or within a multidisciplinary team). This selection focused on physiotherapy interventions that are considered standard practice in stroke rehabilitation,[13–15] excluding techniques which are highly innovative (eg, robotic therapy) or poorly used in most community-based rehabilitation services (eg, treadmill training with partial body weight support). Because we focused on outcomes represented by functional abilities mostly involving lower extremities, we also excluded studies where active treatment targeted upper extremities (eg, constraint induced movement therapy).

We performed an electronic search of original papers, published in English or Italian, indexed in MEDLINE, PEDro, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINHAL, ISI Web of Science, and EMBASE, with no temporal limits up to January 2010, using the following combination of keywords: (stroke OR cerebrovascular accident OR cerebrovascular disorders) AND (rehabilitation OR physical therapy OR physiotherapy OR occupational therapy OR exercise OR exercise therapy OR training) AND (randomised controlled trial OR meta-analysis). To ensure retrieval of all potentially relevant RCT, we scanned reference lists of pertinent articles and performed a handsearch of major journals. Reference lists of articles retrieved were evaluated for relevant publications. Setting, duration of intervention and of follow-up were recorded but not used as selection criteria. Full texts of all articles judged to be of possible interest on the basis of title and abstract were retrieved. Two reviewers (FF, MDB) independently evaluated the studies selected for final inclusion; disagreement was resolved by consensus.

The outcome of the study was the difference between groups at the end of the treatment period in mobility and ADL independence, measured with previously validated tools. Relevant data were extracted using a standard data-recording spreadsheet, including characteristics of the population involved (age, gender, time elapsed from stroke), sample size, number of participants completing the study, characteristics of the intervention (therapeutic approach, setting, duration and professionals involved), primary and secondary objectives, results related to all the outcomes assessed and other characteristics useful for quality evaluation (see below). Where information was not available in the published material, details were requested from the authors.

The PEDro database,[16] which scores published RCT on rehabilitation, was consulted for quality evaluation. The PEDro score, developed by the Centre for Evidence-Based Physiotherapy, has been shown to be reliable[17] and particularly useful for assessing the quality of studies in stroke rehabilitation.[18] Criteria for quality assessment are represented by randomness and concealment of allocation, baseline comparability between groups, blinding of participants, therapists, and assessors, adequacy of follow-up assessments, intention-to-treat analysis, between-group comparisons, point estimates and variability. The total PEDro score ranges from 0 (poor quality) to 10 (excellent quality); a score of 6 is conventionally considered as a threshold to identify high-quality studies.[16] The same criteria were applied to evaluate the quality of the two most recent studies,[19 20] not found in the PEDro database.

Analytic procedures

To obtain the same data format for as many outcome measures as possible, preliminary data manipulation was performed as follows. In one study,[21] mean and pooled standard deviation (SD) were calculated to create a single intervention group from data originally divided into three experimental groups, which differed only in the specific care setting (outpatient, home and mixed). Missing SD values for the end of treatment Functional Independence Measure (FIM) scale were substituted with baseline values in one study[22] or were calculated from reported standard error of the mean in another.[20] Finally, mean and SD data were obtained directly from the authors of a study,[23] where most outcome data had been originally reported as median and interquartile range. Original values of outcome measures which decrease with improving performance were reverted into corresponding negative values.[24 25]

Three studies, in which a crossover design was used,[24 26 27] were analysed as parallel group RCT, by calculating effects before the point of crossover. In one study,[19] data pertinent to the present meta-analysis were represented only by those collected in one of three intervention arms and to controls.

A variety of different outcome measures were found, sometimes also in the same study, within the broad category of mobility and ADL independence. The primary outcome of each original study was chosen as the primary measure of interest of this meta-analysis. When a primary outcome had not been explicitly declared, the first outcome reported in the area of mobility and ADL independence was selected. Due to variability of outcome measures, standardised ES and 95% CI were calculated for this outcome, using Cohen's d estimator, as the difference between post-test values in the intervention and control groups, divided by the pooled SD. A second set of comparisons was performed, by separately pooling measures of ADL independence, short-distance walking (SDW) (usually 10 m), and long-distance walking (LDW) (6 min walking). For the first of these comparisons, ES was calculated, whereas for SDW and LDW WMD and 95% CI, as clinically meaningful outcome measures, were compared between intervention and control groups. For this purpose, the original SDW measure units were converted into metres per second as a common unit; a study[21] which reported SDW speed in terms of relative velocity was excluded from this specific analysis. Results were pooled across studies with DerSimonian–Laird random effects models,[28] anticipating possible heterogeneous effects among different treatment strategies.

StatsDirect (version 2.7.2; StatsDirect, Sale, UK) was used to perform the statistical analysis. A p value <0.05 was assumed to represent a significant result.

RESULTS

Of 200 titles retrieved, 121 were excluded because they did not meet the inclusion criteria. Of the remaining 79 titles, 76 were found in full text and were evaluated by two independent investigators, who eventually included only 15 studies,[19–27 29–34] fulfilling the selection criteria. The two main causes of exclusion were when stroke onset was less than 6 months before enrolment and if experimental interventions were not coherent with our inclusion criteria (figure 1).

Participants

The sample size of selected trials ranged from 13 to 170 participants, totalling 730 randomised participants, 700 of whom were reassessed at follow-up. The proportion of participants reassessed at follow-up was similar (p=0.506) between active treatment (n=370, 96%) and controls (n=330, 95%). All studies except one[21] detailed demographic and clinical characteristics of the sample. Age was 40 years or above (weighted mean age: 70.3 years), and 59% of participants were males. The proportion of the side affected was comparable between treatment groups. Major comorbidities and, in particular, other neuromuscular and skeletal diseases or dementia were exclusion criteria in all RCT but two.[19–26 29–32 34] Eleven studies[19 21 22 25–27 29–31 33 34] did not include participants with severe cognitive or sensory deficits, and four[21 32–34] specified that participants had to be clinically stable. Stroke occurred at least 6 months before enrolment in five studies,[20 25 29–31] 9 months in one study[26] and at least 12 months in the others[19 21–24 27 32–34] (weighted mean: 4 years).

Baseline functional level ranged widely. Authors, with one exception,[19] specified various functional inclusion criteria: moderate to severe disability,[22–24 27] being able to walk

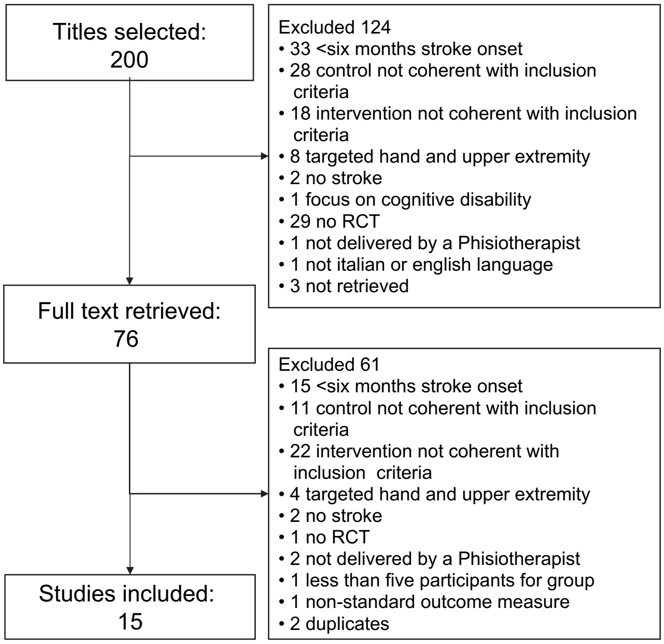


Figure 1 Literature search flow chart and main exclusion criteria.

without[34] or else with or without assistive devices,[20 21 25 26 29 30 32 33] a minimum walking capacity (15 min[26 32] or a given distance[25 29 30 33 34]), minimum[34] or maximum[30] walking speed, a minimum activity tolerance of 45 min.[26 29 31] Most studies allowed classifying participants at baseline according to Perry's Ambulation Classification[35]: 15.4% of participants were household ambulators, 60.7% were limited community ambulators, and 15.6% were full community ambulators, whereas this classification could not be obtained for the remaining 8.3%, whose functional level was of severe to moderate disability as an inclusion criterion.[22 27]

As reported in nine out of 15 articles, studies differed for duration and kind of off-protocol treatment delivered. Three RCT specified that all[21 22] or 13 out of 19[27] participants had received inpatient rehabilitation in the acute phase. One study reported that 50 out of 63 participants had received inpatient rehabilitation after the initial hospital stay, and 41 had outpatient rehabilitation after discharge home.[32] In two articles, participants had completed rehabilitation;[20 30] three studies required the absence of physical therapy treatments 4–6 months before enrolment,[22 23 27] and three others clarified that no other type of rehabilitation was delivered in the period of the study.[21 25 33]

Intervention

The duration of a single treatment session ranged between 10 and 120 min. The intervention lasted from 4 to 26 weeks (with a frequency from less than one to five sessions per week) and was delivered at home in three cases,[19 24 27] in an outpatient setting in 10 cases[20 22 25 26 29–34] (three of which were in groups of eight to 12 participants[20 22 32]), and in a mixed outpatient and home-based setting in the remaining two[21 23] (table 1).

In most studies, conventional therapeutic approaches (neuromuscular interventions, practising functional activities, muscle strengthening and application of assistive equipments) were combined, with the aim of improving mobility or independence. As illustrated in studies, or specified by authors on request,[29 31 34] active intervention was practised or supervised by physical therapists, alone, within a multidisciplinary staff (which might include occupational therapists, exercise physiologists or instructors), or in collaboration with the family (table 1).

Outcome measures

A variety of outcome measures had been used in the original studies (table 1). The FIM–motor scale[22] and the Rivermead Mobility Index[23] were indicated as primary outcomes. First mobility or ADL independence outcome measures reported were the Barthel Index,[27] the Timed-Up-and-Go-Test,[25] SDW speed,[19–21 24 26 29 30 33 34] and the 6 min walking test (6MWT).[31 32] Overall, four studies had measures of ADL independence,[22–24 27] whereas measures of walking ability, either on SDW or LDW, were reported in 13,[19–21 23–26 29–34] out of 15 studies, of which six[19 20 25 30 31 33] had both SDW and LDW measures.

Quality evaluation

Following PEDro criteria,[16] trials selected for this meta-analysis had a quality score ranging from three to eight (mean 6.3). Randomisation was concealed in seven trials;[19 20 23 30 32–34] assessors were blinded in all studies but two,[19 20 22–25 27 29–34] whereas both participants and therapists could never be blinded to group assignment. All studies except one[26] reported baseline data by randomisation group. Based on the original description, analysis was by intention to treat in six cases.[19 20 29 31 32] One article[22] was not accurate in reporting variability of follow-up data (table 2).

Meta-analysis

The meta-analysis of all outcome measures showed a pooled ES of 0.29 (95% CI 0.14 to 0.45; $p<0.001$) in favour of the intervention, with no heterogeneity (figure 2).

In terms of ADL independence, a trend in favour of the intervention did not reach statistical significance, with a pooled ES of 0.08 (95% CI −0.21 to 0.37; $p=0.583$) and no heterogeneity (figure 3).

Active treatment significantly improved both SDW and LDW ability, as shown by WMD of 0.05 m/s (95% CI 0.008 to 0.088; $p=0.017$) (figure 4) and 20 m (95% CI 3.6 to 36.0; $p=0.017$) (figure 5), respectively, with no significant heterogeneity. These figures represented an 8% gain over baseline values of SDW and LDW.

DISCUSSION

This study provides evidence, drawn from systematic search and meta-analysis of RCT, that a variety of conventional motor rehabilitation and physiotherapy interventions, applied late after stroke, improve motor and functional outcomes, compared with no treatment or placebo. Specifically, SDW and LDW ability improved substantially.

Systematic reviews show that organised multidisciplinary care and rehabilitation are effective in the early phase of a stroke, improving survival and independence, and reducing length of hospital stay and need for institutionalisation.[36–39] A meta-analysis of RCT demonstrates that therapy-based rehabilitation services, targeting community-dwelling patients within 1 year of stroke, improve ADL independence and reduce the risk of further functional deterioration.[40] Another meta-analysis of RCT[41] reports that augmented exercise therapy time of at least 16 h within the first 6 months after stroke obtains a measurable improvement in ADL and, to a lesser degree, in instrumental ADL and gait speed. A Cochrane systematic review reports that, compared with no treatment or placebo, a mix of conventional rehabilitation approaches significantly improves the recovery of

Table 1 Characteristics of the studies included

Study, year	No of participants with follow-up data		Age (years)*		Gender male/female		Treatment		Main outcome†	Duration (weeks)	No of treatment sessions	Total duration of treatment (h)	Providers	Setting
	Int	Ctr	Int	Ctr	Int	Ctr	Int	Ctr						
Wall and Turnbull,[21] 1987	15	5	45–70		NA		NI	Untreated	SDW normalised by stature	26	52	52	PT and family (spouse or companion)	Mixed (outpatient, home)
Wade *et al*,[24] 1992	48	41	72.3 (9.7)	72.0 (10.6)	27/22	20/25	FA NI AE	Untreated	SDW	13	Mean 4, range 1–11	NA	PT	Home
Werner and Kessler,[22] 1996	28	12	66 (13)	59 (9)	14/14	5/7	NI MS	Untreated	FIM-mm	12	48	96	Multidisciplinary staff (PT+OT)	Outpatient‡
Teixeira-Salmela *et al*,[26]1999	6	7	65.8 (10.2)	69.4 (8.8)	1/5	6/1	MS FA	Untreated	SDW	10	30	30–45	Multidisciplinary staff (PT+EP)	Outpatient
Kim *et al*,[29] 2001	10	10	60.4 (9.5)	61.9 (7.5)	7/3	7/3	MS	Passive range of motion	SDW	6	18	13.5	PT	Outpatient
Green *et al*,[23] 2002	81	80	71.5 (8.7)	73.5 (8.3)	49/36	46/39	FA NI	Untreated	RMI	3–13 contacts	Median 3, range 0–22 (five participants were evaluated, but were not treated)	NA. Individual treatment duration averaged 44 min	PT	Mixed (outpatient, home)
Ada *et al*,[30] 2003	13	14	66 (11)	66 (11)	9/4	10/4	NI	Sham home exercise programme	SDW	4	12	6	PT	Outpatient
Lin *et al*,[27] 2004	9	10	61.4 (11.2)	62.8 (9.4)	7/2	6/4	NI FA	Untreated	BI	10	10	10	PT	Home
Ouellette *et al*,[31] 2004	21	21	65.8 (2.5)	66.1 (2.1)	28/14		MS	Range of motion and upper body flexibility exercises	6MWT	12	36	NA	PT	Outpatient
Pang *et al*,[32] 2005	32	31	65.8 (9.1)	64.7 (8.4)	19/13	18/13	MS NI	Seated upper extremity exercises	6MWT	19	57	57	Multidisciplinary staff (PT+TO +EI)	Outpatient‡
Yang *et al*,[33] 2006	24	24	56.8 (10.2)	60.0 (10.4)	16/8	16/8	MS NI	Untreated	SDW	4	12	6	PT	Outpatient
Yang *et al*,[34] 2007	13	12	59.5 (11.8)	59.2 (12)	7/6	7/5	NI	Untreated	SDW	4	12	6	PT	
Flasbjer,[23] 2008	15	9	61 (5)	60 (5)	9/6	5/4	MS	Usual daily activities	TUG	10	20	NA	PT	Outpatient
Ng and Hui-Chan,[19] 2009	25	29	56.9 (8.6)	55.5 (8)	20/5	20/9	NI	Untreated	SDW	4	20	NA	PT	Home
Mudge *et al*,[20] 2009	31	27	76 (39–89)	71 (44–86)	19/12	13/14	NI	Social and educational sessions	SDW	4	12	10–12	PT	Outpatient‡

*Data are reported as mean (SD) or range.
†Main outcome was represented by the primary outcome, when explicitly declared, or by the first mobility and ADL independence outcome reported.
‡In groups of eight to 12 persons.
6MWT, 6 min walk test; AE, application of assistive equipments; BI, Barthel Index; Ctr, control group; EI, exercise instructor; EP, exercise physiologist; FA, practising functional activities; FIM-mm, functional independence measures—motor measure; Int, intervention group; MS, muscle strengthening; NA, not available; NI, neuromuscular interventions; OT, occupational therapist; PT, physiotherapist; RMI, Rivermead Mobility Index; SDW, short-distance walk; TUG, timed up and go test.

Table 2 PEDro quality score of the studies included

	Wall and Turnbull[21]	Wade *et al*[24]	Werner and Kessler[22]	Teixeira-Salmela *et al*[26]	Kim *et al*[29]	Green *et al*[23]	Ada *et al*[30]	Lin *et al*[27]	Ouellette *et al*[31]	Pang *et al*[32]	Yang *et al*[33]	Yang *et al*[34]	Flansbjer *et al*[25]	Ng and Hui-Chan[19]	Mudge *et al*[20]
Random allocation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concealment of allocation						✓	✓			✓	✓	✓		✓	✓
Comparability of groups at baseline	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Blinding of patients															
Blinding of therapists															
Blinding of assessors		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adequacy of follow-up		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Analysis by intention to treat					✓	✓			✓	✓				✓	✓
Between-group statistical comparisons	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Reports of point estimates and measures of variability	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PEDro score (/10)	4	6	4	3	7	8	7	6	7	8	7	7	6	8	7

postural control and lower-limb function following stroke, thus enhancing independence.[42] Finally, an RCT reports that older patients who had had a stroke benefit on a short-term basis from a higher intensity of community-based rehabilitation, especially in the domains of social participation and health-related quality of life.[43]

Solid scientific evidence supports the practice of physiotherapy early after a stroke, while evidence is more controversial

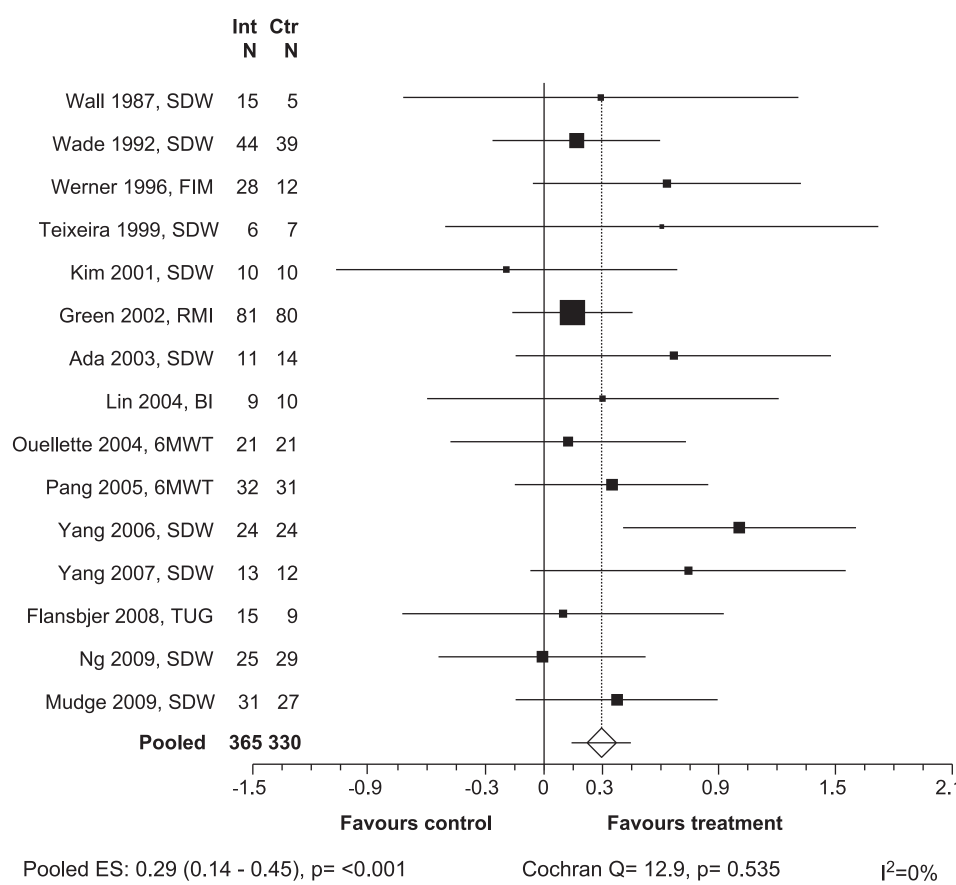


Figure 2 Plot of random effects meta-analysis of effect size for all the outcomes considered. 6MWT, 6 min walking test; BI, Barthel Index; Ctr N, Control group sample size; ES, effect size; FIM, functional independence measure; Int N, intervention group sample size; RMI, Rivermead Mobility Index; SDW, short-distance walk; TUG, timed up-and-go test.

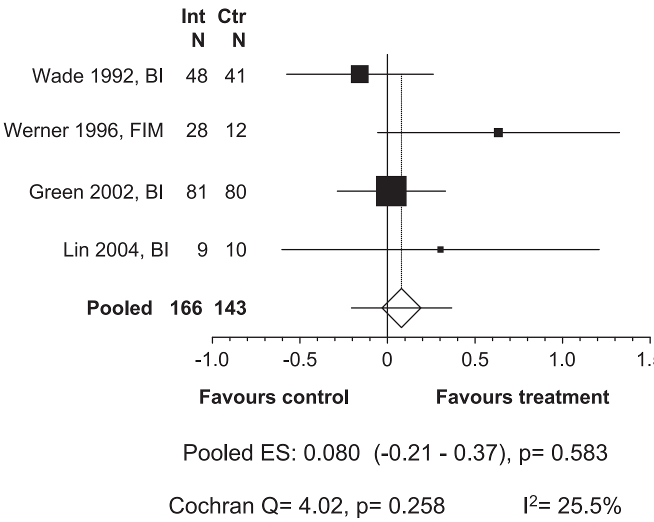


Figure 3 Plot of random effects meta-analysis of effect size for the outcomes of ADL independence. Abbreviations as in figure 2.

for physiotherapy interventions applied after 6 months or more from the acute phase. A Cochrane review[44] analysed five RCT with 487 participants that had suffered stroke, at least 75% of whom were recruited 1 year after the event. They were randomised to receive a therapy-based rehabilitation intervention or conventional care. Primary outcome was the proportion of participants who deteriorated or were dependent in ADL at the end of the follow-up. Although no conclusive evidence was found that therapy-based rehabilitation improves ADL independence,[44] the sensitivity to interventions of such a hard outcome is limited. Another recent Cochrane review that investigated the effectiveness of overground gait training for improving overall measures of gait function in people who had suffered a stroke found limited evidence of benefits for variables such as gait speed or 6MWT.[45] Gait speed and mobility measures, such as those considered in the present meta-analysis, have robust metric properties,[46] are more sensitive to change and represent major, clinically relevant endpoints.[47] Notably, in the only included study reporting a favourable effect of active treatment on ADL, the number and cumulative duration of treatment sessions were substantially greater than in other studies.[22] Consequently, we might speculate that, as in early stroke rehabilitation,[41] late rehabilitation effects on ADL may well be a matter of treatment intensity and duration.

Using mobility measures as an outcome, the present meta-analysis shows favourable effects of physiotherapy late after stroke, thus helping to fill an important knowledge gap. However, we are aware of the limitations of the evidence provided, stemming from the small number of participants enrolled, as well as from differences in type, frequency and intensity of interventions delivered and outcomes assessed. All these characteristics usually increase heterogeneity and threaten validity. Nevertheless, no statistical evidence of heterogeneity was detected. Moreover, the rehabilitation interventions applied were similar to those routinely used in clinical practice, and study outcomes were represented by simple, previously validated functional measures. Furthermore, it should be noted that almost all the outcome measures selected have been identified as core measures in stroke rehabilitation.[48] Thus, we believe that the present meta-analysis reflects stroke rehabilitation as practised in most community services. As evaluated according to PEDro methodology,[16] the quality of the studies included was satisfactory: since blinding of participants and therapists cannot be obtained in this kind of trials, the mean score of 6.3 (table 2) should be weighed against a maximum score of only 8, not 10, points obtainable.[49] When strengths and limitations of the RCT contributing to this meta-analysis are carefully balanced, we feel that the findings obtained are valid, clinically meaningful and generalisable.

Figure 4 Plot of random effects meta-analysis of weighted mean differences for the outcomes of short-distance walk. Abbreviations as in figure 2.

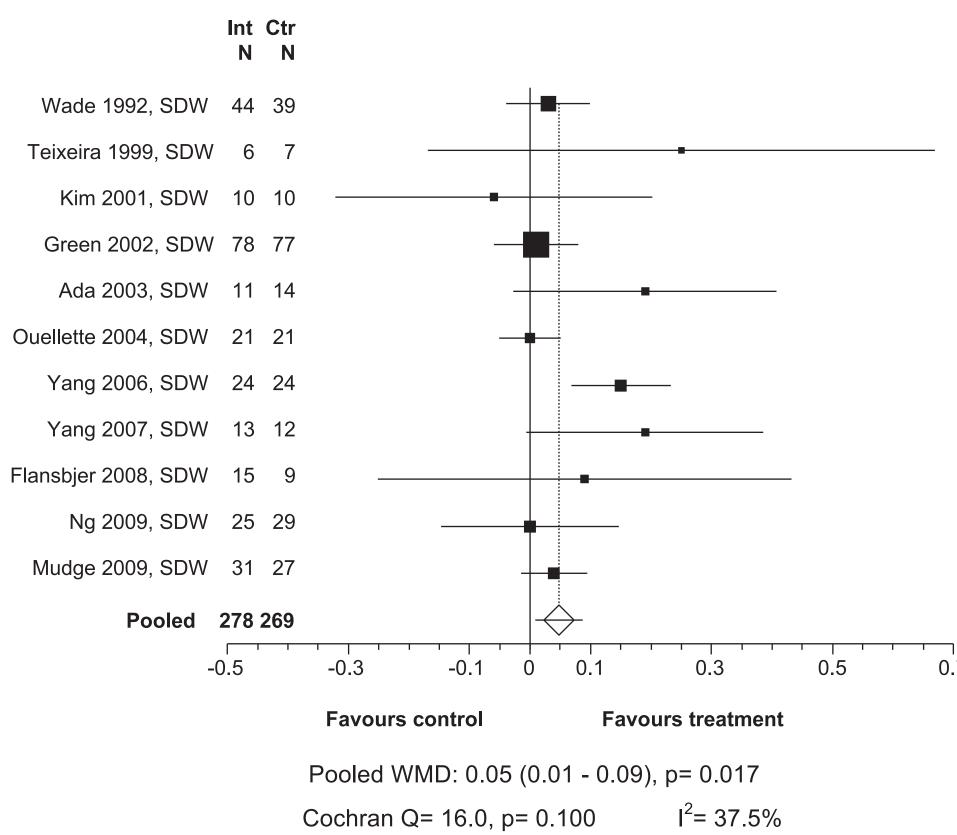
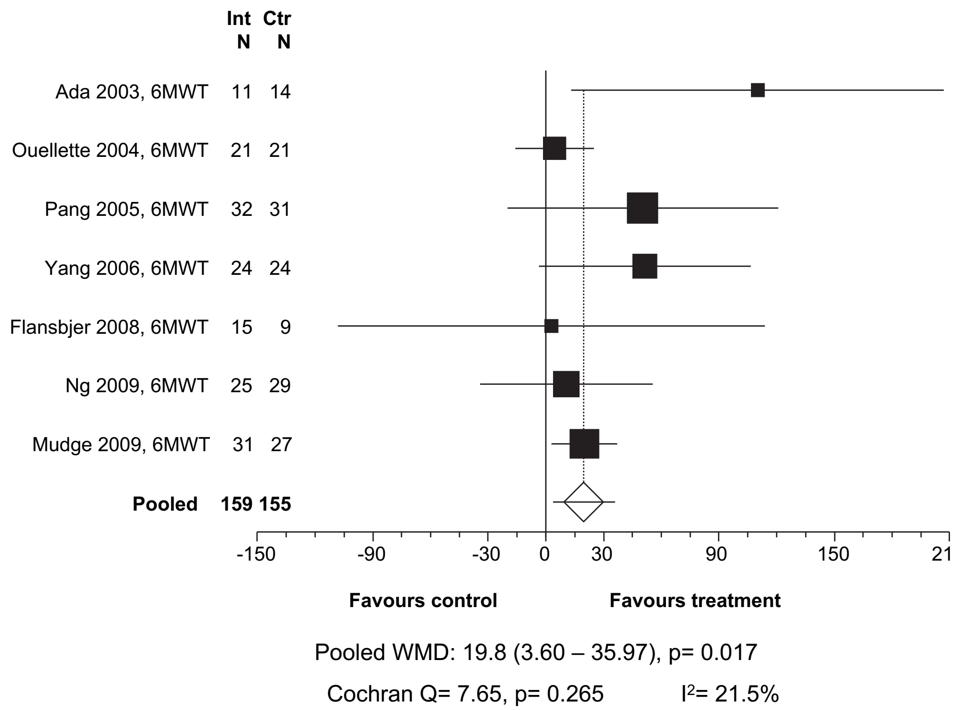


Figure 5 Plot of random effects meta-analysis of weighted mean differences for the outcomes of long-distance walk. Abbreviations as in figure 2.



The clinical and public health implications of this study deserve further attention. In general, rehabilitation services for stroke survivors are available and deliver more intensive interventions in the initial phase after the stroke, gradually decreasing thereafter.[4] Six to 12 months after the acute phase, physical therapy is usually no longer provided, especially when patients appear to reach a plateau and fail to improve further with prolonged treatment.[50] Yet, our findings suggest that a significant functional recovery can be observed after a stroke later than is usually believed. The improvement observed was small, below what is usually considered clinically meaningful,[46] but it possibly challenges the concept itself of a plateau, which might rather stem from the delivery of less intensive therapy.[51]

Before existing practices are definitively changed, further studies are required to corroborate our findings and to clarify areas of uncertainty they cannot solve. First of all, it would be interesting to clarify whether delivering higher doses of physiotherapy, or targeting patients more accurately, would lead to greater improvement. Likewise, the potential economic implications of our results deserve careful consideration and further investigation. Most healthcare systems cannot afford allocation of additional resources to physiotherapy programmes, extended several months to years after stroke onset. However, scientific evidence of clinical efficacy should not be overlooked in the face of pure economic constraints: cost-effectiveness analyses, as well as studies on predictors of recovery, should be performed to help clinicians and politicians make informed decisions on this issue.

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