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## **Effects of augmented exercise therapy on outcome of gait and gait-related activities in the first 6 months after stroke: a meta-analysis**

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*Stroke*. 2011;42(11):3311-3315

## ABSTRACT

**Background and purpose** The purpose of this study was to determine the effects of augmented exercise therapy on gait, gait-related activities, and (basic and extended) activities of daily living within the first 6 months poststroke.

**Methods** A systematic literature search in electronic databases from 1990 until October 2010 was performed. Randomized controlled trials were included in which the experimental group spent augmented time in lower limb exercise therapy compared with the control group. Outcomes were gait, gait-related activities, and (extended) activities of daily living. Results from individual studies were pooled by calculating the summary effect sizes. Subgroup analyses were applied for a treatment contrast of  $\geq 16$  hours, timing poststroke, type of control intervention, and methodological quality.

**Results** Fourteen (N=725) of 4966 identified studies were included. Pooling resulted in small to moderate significant summary effect sizes in favor of augmented exercise therapy for walking ability, walking speed, and extended activities of daily living. No significant effects were found for basic activities of daily living. Subgroup analysis did not show a significant effect modification.

**Conclusions** Dose-response trials in stroke rehabilitation are heterogeneous. The present meta-analysis suggests that increased time spent on exercise of gait and gait-related activities in the first 6 months poststroke results in significant small to moderate effects in terms of walking ability, walking speed, and extended activities of daily living. High-quality dose-response exercise therapy trials are needed with identical treatment goals but incremental levels of intensity.

## INTRODUCTION

Stroke rehabilitation is characterized by early initiated, intensive, and ongoing training, in which task and context specificity play an important role.<sup>1,2</sup> There is indirect evidence that complex rehabilitation interventions may prevent inactivity-related complications and enhance functional recovery after stroke.<sup>3-7</sup> However, the underlying mechanisms that drive these benefits are still poorly understood.<sup>5</sup> To optimize rehabilitation services for patients with stroke, a better understanding of the dose-response relationship between exercise therapy and functional outcome is needed.<sup>1,2</sup>

A number of systematic reviews have demonstrated that augmented task-specific training defined as either additional time spent in exercise therapy<sup>1,8</sup> or increased number of repetitions<sup>8,9</sup> enhance outcome of gait-related activities, activities of daily living (ADL), and health-related quality of life.<sup>10</sup> French and colleagues' review showed that repetitive task-oriented training resulted in modest improvements of lower limb function but not of upper-limb function.<sup>9</sup> Another meta-analysis suggested that augmented practice of at least 16 hours in the first 6 months poststroke was needed to gain a mean improvement in ADL of 5%.<sup>1</sup> However, the trials were heterogeneous in terms of focus and timing of augmented exercise therapy poststroke.<sup>1,8</sup> To date, there are no clinical trials that explicitly investigated the impact of different doses of exercise therapy in which content, focus, and timing of therapy are controlled in a systematic way.<sup>1,8</sup> Our aim was to investigate the effect of augmented lower limb exercise therapy, exclusive of extensive technical equipment, on gait and gait-related outcomes and basic and extended ADL during the first 6 months after stroke. Subsequently, a sensitivity analysis was applied to investigate if methodological quality influences the found effects and whether a treatment contrast of 16 hours (i.e. approximately 1000 minutes), timing poststroke (<1 month versus ≥1 month, <3 months versus ≥3 months), and the type of control intervention are effect modifiers.

## MATERIALS AND METHODS

### Definitions

We defined exercise therapy as "a regimen or plan of physical activities designed and prescribed for specific therapeutic goals concerning the field of physical or occupational therapy, intended to restore optimal functioning" (Medline Subject Heading). Lower limb exercise therapy consisted of exercise training without the use of extensive technical training facilities. Studies incorporating

specific training strategies or equipment such as circuit class training, treadmill training without body-weight support, fitness training like (ergo meter) cycling without functional electric stimulation, and functional training like standing, reaching, and walking ability such as walking, stair-walking, turning, making transfers, and walking for specified distances were included.<sup>11</sup> Lower limb exercise therapy is referred to as “exercise therapy.”

The phrase “intensity of augmented exercise therapy” refers to the additional amount of minutes that the experimental group spent in exercise therapy during the intervention period when compared with the control group (i.e. “treatment contrast”).<sup>1</sup>

### **Study identification**

PubMed, Ebsco/Cumulative Index of Nursing and Allied Health Literature (CINAHL), Wiley/Cochrane Library, Central Register of Controlled Trials (CENTRAL), Physiotherapy Evidence Database (PEDro), and Cochrane Database of Systematic Reviews (CDSR) were independently searched by J.M.V., M.K., and J.C.F.K. from 1990 to October 18, 2010. Indexing terms and free-text terms were used with synonyms and related terms in the title or abstract. We searched “stroke,” and “exercise” or “physical therapy” or “rehabilitation,” and “randomized controlled trials.” Studies were included when (1) they were designed as a randomized controlled trial; (2) adult patients ( $\geq 18$  years) were recruited within 6 months poststroke; (3) participants in the experimental group spent more time in lower limb exercise therapy when compared with those in the control group; (4) outcomes were defined as gait, gait-related activities, or (basic or extended) ADL; (5) they were of moderate or high methodological quality (see below, Quality Appraisal); and (6) they were published in peer-reviewed journals in the English, French, German, or Dutch language. References of included studies were checked for other potentially relevant studies and experts in the field of stroke were consulted. For the full search strategy, please contact the corresponding author.

### **Quality appraisal**

Two reviewers (J.M.V. and M.K.) independently assessed the methodological quality of included studies using the PEDro scale.<sup>12,13</sup> Interrater reliability on item-level was calculated (Cohen’s K), and consensus was sought in case of disagreement. Based on the total PEDro score, studies were classified as high, moderate, or low-quality randomized controlled trials. A PEDro score of  $\geq 6$  out of 10 indicated high quality, including points for randomization and concealment of the randomization schedule (items 2 and 3), a PEDro score of 4 to 5 of 10 points or  $\geq 6$  of 10 without points on items 2 and 3 indicated moderate quality, and a PEDro score  $\leq 3$  of 10 indicated low quality.

## Analysis

Data from the included studies were independently extracted by 2 assessors (J.M.V. and M.K.). These data concerned the number of patients, outcome measures, and means and standard deviations (SD) of post intervention scores for both the experimental and control groups. In case of missing information, authors were contacted. Subsequently, for each individual study, the standardized mean difference (SMD) with 95% confidence interval (CI) was calculated. For each outcome measure, SMDs were pooled to determine the summary effect size (SES; number of SD units [SDU]) with 95% CI. To measure statistical consistency, the  $I^2$  statistic was used. An  $I^2$  of >50% indicates substantial heterogeneity and was used as cut-off.<sup>14</sup> A fixed-effects model was applied in case of statistical homogeneity, a random-effects model was applied in case of statistical heterogeneity. Subgroup analyses were performed for treatment contrast (<1000 versus  $\geq$ 1000 minutes), timing poststroke (start of therapy <1 versus  $\geq$ 1 month, <3 versus  $\geq$ 3 months),<sup>15</sup> and type of control intervention (i.e. the same intervention, a different intervention, or an additional intervention). In addition, a sensitivity analysis was performed to explore if the methodological quality (high versus moderate) influenced the SES for additional time spent in exercise therapy. Based on the SES, the mean effect was calculated. For rejecting the null hypothesis, the probability value was set at <0.05 (2-tailed). According to Cohen, effect sizes were classified into small (<0.2), medium (0.2–0.8), and large (>0.8).<sup>16</sup>

## RESULTS

### Study identification

Supplemental Figure I (<http://stroke.ahajournals.org>) shows the results of the literature search. In total, 14 studies out of 4966 unique hits were identified.

Supplemental Table I (<http://stroke.ahajournals.org>) represents 14 randomized controlled trials involving 725 patients with stroke.<sup>17–30</sup> In 3 of these studies,<sup>20,26,29</sup> 2 experimental groups were compared with 1 control group. These experimental groups were analyzed separately (i.e. 17 comparisons). Mean time of randomization since stroke onset ranged from <24 hours<sup>21</sup> to 5.45 months.<sup>30</sup> Three studies<sup>20,22,27</sup> compared the same intervention of different duration for the experimental group and the control group, whereas 2 studies<sup>21,29</sup> compared 2 types of intervention of different durations. In 12 studies, the experimental group received the control treatment and augmented exercise therapy of a different type of intervention.<sup>17–20,23–26,28–30</sup> In these studies, the additional therapy consisted of, for example, overground walking,<sup>28</sup> backward walking,<sup>30</sup> standing

practice,<sup>17,23</sup> treadmill training,<sup>24</sup> or functional strength training.<sup>20</sup> The intervention period ranged from 2<sup>21,26</sup> to 20 weeks<sup>25</sup> with a frequency of 3<sup>18,19,23,24,30</sup> to 5 sessions<sup>17,21,22,25,28,29</sup> per week. The total intended additional therapy time ranged from 270<sup>30</sup> to 3000 minutes<sup>25</sup> (Supplemental Table I; <http://stroke.ahajournals.org>). The experimental group spent approximately 37 minutes per working day in augmented exercise therapy during a mean of 5.7 weeks. In 4 studies reporting both the intended and applied therapy time, the mean applied time ranged from 58% to 100% of the intended time.<sup>20,22,23,25</sup>

### **Quality appraisal**

Supplemental Table II (<http://stroke.ahajournals.org>) shows the PEDro scores of the studies, which ranged from 5<sup>26,28,29</sup> to 8<sup>20,22</sup> points. In 2 studies, assessors were not blinded to treatment allocation<sup>28,30</sup> and 5 studies performed an intention-to-treat analysis.<sup>17</sup> Interrater reliability on item level between the 2 assessors ranged from moderate (item 7, Cohen's K 0.58; 95% CI, 0.3–1.0) to full agreement (items 1, 2, 6, and 11).

### **Analysis**

Pooling of results was possible for walking ability, comfortable and maximum walking speed, and basic and extended ADL. In 3 studies, means and SDs were obtained by contacting authors.<sup>18,28,29</sup>

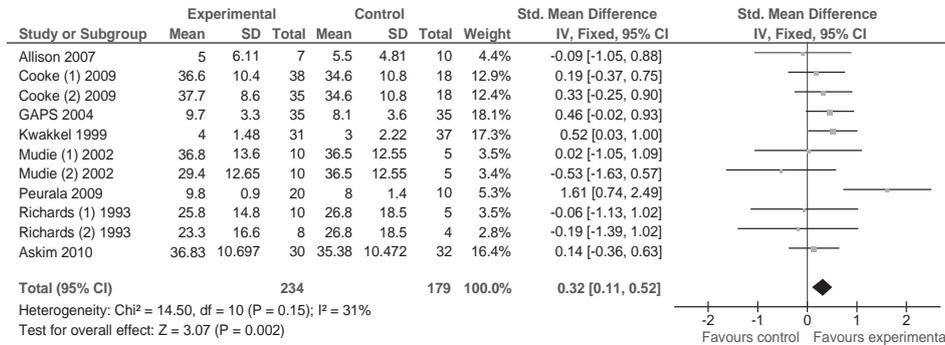
### ***Gait and gait-related outcomes***

#### **Walking ability**

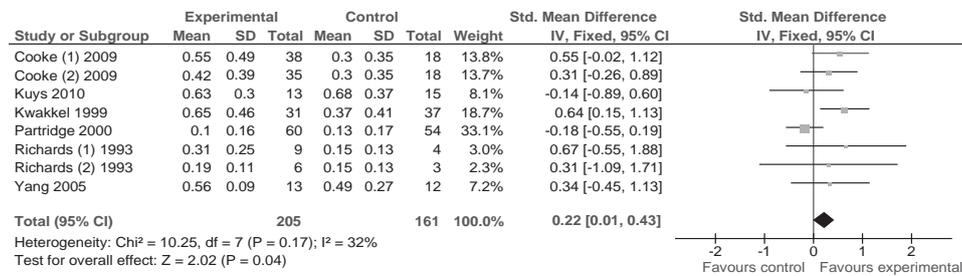
Eleven studies (N=413)<sup>17,18,20,22,25,26,28,29</sup> used the Rivermead Mobility Index,<sup>20,22,28</sup> Functional Ambulation Categories,<sup>25,28</sup> Rivermead Motor Assessment gross motor function,<sup>17,28</sup> Barthel Index ambulation,<sup>26,29</sup> or the Motor Assessment Scale<sup>18,28</sup> to measure walking ability. Peurala et al. used 3 outcomes, and only the Rivermead Mobility Index was analyzed because it was the most frequently used outcome in the other studies.<sup>28</sup> Pooling resulted in a significant medium homogeneous SES (SMD 0.32 SDU [fixed]; 95% CI, 0.11–0.52; p=0.002; I<sup>2</sup>=31%; Figure 6.1).

#### **Comfortable walking speed**

For the 8 studies (N=366) investigating comfortable walking speed, a small but significant homogeneous SES was found (SMD 0.22 SDU [fixed]; 95% CI, 0.01–0.43; p=0.040; I<sup>2</sup>=32%; Figure 6.2).<sup>20,24,25,27,29,30</sup>



**Figure 6.1** Summary effect size for walking ability



**Figure 6.2** Summary effect size for comfortable walking speed

**Maximum walking speed**

For the 3 studies (N=138) that investigated maximum walking speed, pooling resulted in a borderline significant, homogeneous SES (SMD 0.34 SDU [fixed]; 95% CI, 0.00–0.68; p=0.05; I<sup>2</sup>=0%; Figure 6.3).<sup>18,24,25</sup>

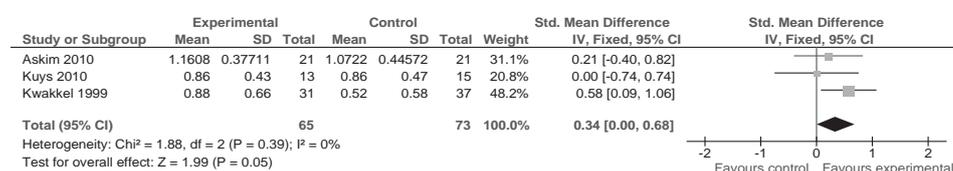
**Activities of daily living**

**Basic ADL**

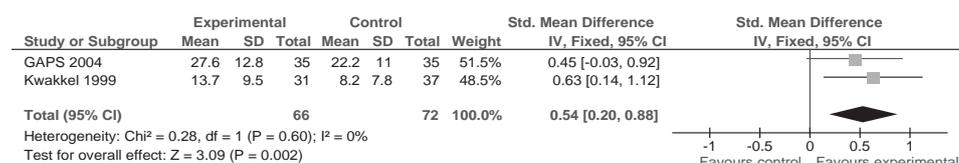
Six studies (N=288) used the Barthel Index to evaluate basic ADL.<sup>18,21,22,25,26</sup> A nonsignificant homogeneous SES was found (SMD 0.11 SDU [fixed]; 95% CI, -0.12–0.34; p=0.360; I<sup>2</sup>=23%).

**Extended ADL**

Two studies (N=138), each with a treatment contrast of >1000 minutes, which delivered the same type of intervention, assessed extended ADL.<sup>22,25</sup> Pooling resulted in a significant medium homogeneous SES (SMD 0.54 SDU [fixed]; 95% CI, 0.20–0.88; p=0.002; I<sup>2</sup>=0%; Figure 6.4).



**Figure 6.3** Summary effect size for maximum walking speed



**Figure 6.4** Summary effect size for extended activities of daily living

## Subgroup analyses

None of the subgroup analyses (i.e. for treatment contrast, timing poststroke, type of control intervention, and methodological quality) showed a significant effect modification.

## DISCUSSION

To improve the comparability between studies in terms of timing and training modality, the present meta-analysis included 14 randomized controlled trials that investigated the effects of augmented exercise therapy dedicated to gait and gait-related activities started within the first 6 months poststroke. Based on the results from moderate and high-quality studies, it is shown that patients with stroke benefit from additional time spent in lower limb exercise therapy with regard to walking ability, walking speed, and extended ADL within the first 6 months after stroke. The small to medium SEs suggest an average improvement of approximately 10% for both walking ability and extended ADL. Comfortable walking speed increased with a mean of 0.10 m/s and the gain for maximum walking speed amounted 0.20 m/s.

In contrast to our previous cumulative meta-analysis that focused on augmented exercise training for outcome of ADL,<sup>1</sup> we were not able to show in a sensitivity analysis that a minimal treatment contrast in lower limb exercises of approximately 16 hours is sufficient to achieve significant effects on lower limb-related activities. However, a positive trend favoring higher treatment contrasts was found in terms of walking ability, walking speed, and ADL. This latter finding suggests that

additional dose-response trials with high contrasts in intensities between treatment arms are needed. Our 95% CI of the SES in terms of comfortable walking speed is in agreement with a recently published meta-analysis including studies on both upper and lower extremity therapy.<sup>31</sup> Nevertheless, a true comparison of our findings with those of other reviews is difficult because different research questions were addressed, resulting in various definitions of “intensity” as well as different inclusion criteria for studies concerning focus, type, and timing of exercise therapy poststroke.<sup>1,8,9,31</sup> This also underlines that investigating dose-response relationships in complex stroke rehabilitation interventions is challenging. Our review showed that only 6 randomized controlled trials investigated a dose-response relationship by changing the total amount of training time spent on identical lower limb exercise therapy.<sup>20-22,25,27,29</sup> Besides, because a standardized and universally accepted definition of “intensity” (or dose) is lacking,<sup>2</sup> operationalization in terms of workload input and output is difficult.<sup>32,33</sup> The intended and actually applied therapy time was reported in 4 publications and illustrates that the actual contrast in training time is approximately 75% of the pre-planned contrast,<sup>20,22,23,25</sup> which may be explained by factors such as fatigue in the early phase poststroke, patients’ schedules, or lack of staffing. Recording the actual therapy time was not common, and 7 of 14 studies did not provide any data about the applied therapy time. Thus, conclusions about the effect of augmented therapy time should be interpreted with caution. Future trials should consider, next to recording time and the number of repetitions, also using portable systems such as actigraphs, accelerometers, and/or portable oxygen analyzers to estimate the actual dose of exercise therapy in terms of workload input and output in complex stroke rehabilitation interventions.

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The present review has some limitations. First, although the search included the 4 major publication languages, some publications could have been missed. Second, despite the application of explicit inclusion criteria, studies with varying training modalities were retrieved. Third, the cut-off point of 16 hours used in the subgroup analysis is based on findings of a previous meta-analysis of 20 randomized controlled trials,<sup>1</sup> but, for example, the recommendation of the US Department of Health and Human Services for adults and older adults to perform moderate-intensity physical activity for at least 150 minutes a week to obtain substantial health benefits could also be used as a cut-off.<sup>34</sup> Fourth, although most studies were of high methodological quality, some did not perform blinding of observers and/or an intention-to-treat analysis, which could be sources of bias. Finally, due to the low number of studies and small sample sizes, the statistical power of the present meta-analysis was moderate.

Future high-quality randomized controlled trials investigating a dose-response relationship in complex stroke rehabilitation interventions should meet the following criteria: (1) discriminate

between intended and applied dose of exercise therapy by monitoring workload input and output by using contemporary methods to record therapy time and number of repetitions combined with more sophisticated methods; (2) all arms in the randomized controlled trial should receive the same training modality with different doses to isolate the effect of augmented training; (3) also include measures on the participation level<sup>10</sup> and the level of body function,<sup>35</sup> including movement kinematics, and not restrict their rehabilitation outcomes to the activities level alone. The latter would allow discernment whether effects of augmented exercise training are mainly driven by compensation strategies or also by “true neurological repair.”<sup>35</sup> To date, longitudinal studies suggest that the pattern of motor recovery is highly predictable in terms of impairments such as synergism, showing an almost invariant fixed proportional relationship between initial impairment early after stroke and final outcome at 6 months.<sup>35-37</sup>

In conclusion, dose-response trials in complex stroke rehabilitation focusing on lower limb exercise therapy are heterogeneous in terms of type of intervention. Unfortunately, appropriate designs to conduct dose-response relationships in complex rehabilitation interventions after stroke are still nonexistent in the literature. Nevertheless, the present meta-analysis suggests that increased time spent in exercise therapy results in small to moderate effects in terms of walking ability, walking speed, and extended ADL within the first 6 months after stroke.

### **Acknowledgments**

We thank Norine Foley, research associate at Lawson Health Research Institute, Canada, for her valuable comments on the article.

### **Sources of funding**

This study was funded by the Wetenschappelijk College Fysiotherapie (grant number 274729) of the Royal Dutch Society for Physical Therapy (KNGF), the Netherlands.

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