Investigating and stimulating walking after stroke

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Onderzoeken en stimuleren van het lopen na een beroerte

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 14 juni 2018 des middags te 12.45 uur

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“Walking is the best possible exercise.
Habituate yourself to walk very far.”

Thomas Jefferson 1743-1826

Contents

1

General introduction

The cover of this thesis shows two elderly persons, one of whom may have had a stroke, taking a stroll on a sandy beach in the beautiful province of Zeeland, the Netherlands. Such a stroll on the beach could be a desired outcome when a person is recovering from a stroke. However, achieving and sustaining this level of functioning requires fulfilment of a few preconditions. First, sufficient walking capacity as well as aerobic capacity are likely to be needed to make such a stroll on the beach possible. Second, it appears that one of the two persons is providing some physical assistance to the other one, illustrating that there may be a need to support postural control. Finally, the two persons walk together, which may illustrate the need for social support to facilitate the stroll on the beach. During rehabilitation, a stroll on the beach may have been mimicked in a task-oriented circuit class training, e.g., by using uneven surfaces for walking exercises to enhance walking capacity. This thesis reports on the evidence that we found for the effectiveness of task-oriented circuit class training for walking capacity after stroke. This thesis further elucidates the association between aerobic capacity and walking capacity and the role of postural control in people who have suffered a stroke. Finally, this thesis reports on perceived facilitators (such as social support) and barriers (such as the sand in the physical environment of the beach) for walking outdoors, in order to become a physically active person after a stroke.

Stroke

According to 2010 data, a staggering number of 33 million people[1, 2] who had survived a stroke were living with its consequences worldwide. In the Netherlands, approximately 315,000 people are currently living with the consequences of a stroke[3]. This estimate only includes the number of people recorded as such in primary care practices[3], suggesting that the actual number may be even larger. This thesis uses the definition of stroke proposed by the WHO[4]: “rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin”. The definition has since been updated and refined[5] as a result of increased diagnostic options, such as magnetic resonance imaging. For the purpose of the present thesis, however, the general definition used by the WHO suffices.

The clinical symptoms of a stroke include sensory-motor impairments such as muscle weakness and deficits of postural control, as well as cognitive impairments such as impairments of memory, executive function, mental speed, language and visuo-spatial functioning. Similar to the recovery from cognitive impairments such as visuo-spatial neglect[6], motor recovery after stroke is a combination of, on the one hand, processes that drive spontaneous biological recovery in the first ten weeks post stroke[7] and, on the other hand, effects of motor learning[8, 9]. However, the interactions between these two drivers of recovery are still unclear[10]. In addition, the recovery patterns are very heterogeneous, resulting in different final outcomes at six and 12 months post stroke in individual patients[11].

Even though around 61%[12] to 80%[13] of patients are able to walk independently again after a first-ever stroke, motor impairment as a consequence of residual hemiparesis often causes a decrease in walking performance over time. As a consequence, many people who have suffered a stroke continue to experience restrictions in their mobility and physical activities, such as walking, after one year[14] and even thereafter[15].

Walking after stroke

In the International Classification of Functioning, Disability and Health (ICF), published by the World Health Organization (WHO 2001), walking is classified within the domain of activities[16]. Figure 1 depicts walking after stroke as part of the ICF core set for stroke[17]. The generic qualifier of walking describes walking short (<1 km) and long distances (>1 km), walking on different surfaces and walking around obstacles[16]. In the present thesis, we distinguish between the constructs of capacity qualifier and performance qualifier within the activity domain of the ICF. Walking capacity is defined as walking ability at the highest level of functioning in standardized circumstances[16]. Consequently, walking capacity is defined using the speed of traversing a standardized distance, e.g., Ten-Meter Timed Walk Test or the distance a person achieves within a standardized timeframe, e.g., Six-Minute Walk Test. Walking performance is defined by the walking behaviors that a person shows in their current environment[16].

One of the major requirements for successful walking is postural control of the moving body[19]. Postural control is associated with functional walking after a stroke[20] and can be defined as “the act of maintaining, achieving or restoring a state of balance during any posture or activity”[21]. The ICF defines postural control during walking as the body function of “involuntary movement reaction functions” (b755). Postural control during walking can also be defined within the ICF as the activity of “maintaining a body position” (d415) (Fig. 1).

Another requirement for walking is sufficient muscle strength in the lower extremities, reflected by muscle power functions (b7302) emphasized? in Figure 1. Muscle weakness, specifically on the hemiplegic side, is a notable symptom after a stroke[22]. Muscle strength in the hemiplegic lower extremity in general, and specifically dorsiflexor ankle strength, has been shown to be associated with walking capacity[23].

Walking capacity after stroke

A recent meta-analysis of 128 studies[24] revealed a mean (SD) six-minutes’ walking distance of 248 (107) m in people in the subacute to chronic stages after stroke. This is significantly less than the mean value for healthy populations, which varies between 510 and 638 m[25].

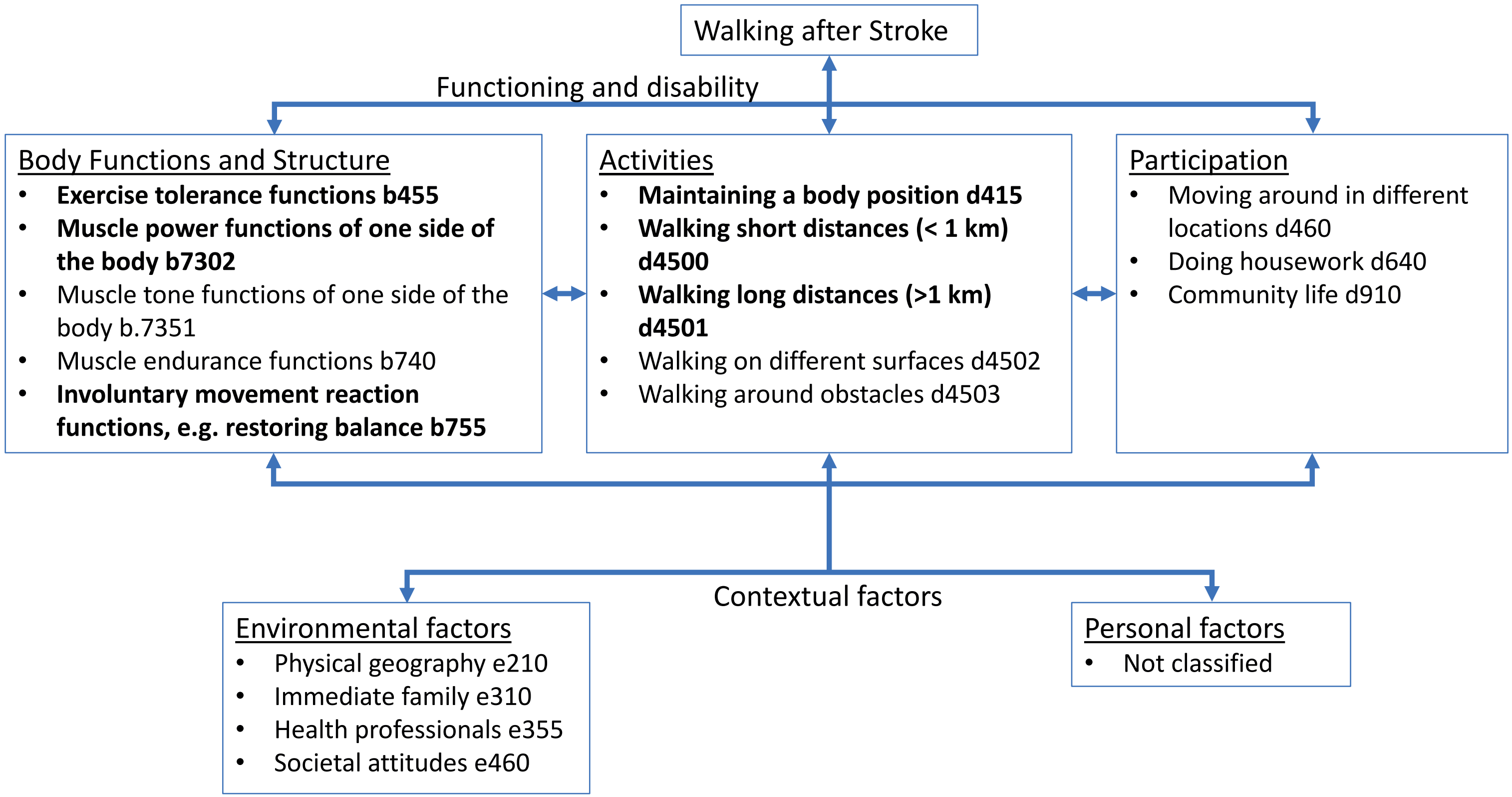

Figure 1. Walking (capacity and performance) after stroke classified using the ICF core set for stroke[17]. The bold items were the subjects of the trials and studies presented in this thesis.

Another meta-analysis[26], including 28 trials from subacute to chronic stages after stroke, showed mean walking speed values ranging from 0.11 to 1.63 m/s after the intervention. However, only one of the included trials[27] reported achieving walking speeds above 1.2 m/s, whereas the majority of the participants in the included studies did not achieve speeds beyond 0.8 m/s. These results suggest that walking speed after stroke is mostly below, or at the lower limit of values reported for healthy elderly people, which range from 1.2 m/s for those in their sixties to 0.9 m/s for those in their eighties[28].

In view of the considerable reduction of walking capacity after stroke, a major goal of physical therapy interventions during rehabilitation after stroke is to improve walking capacity. An emerging intervention strategy for this is that of task-oriented circuit class training (CCT)[29, 30].

Task–oriented circuit class training (CCT) to improve walking capacity after stroke

Physical therapy interventions to improve walking capacity after stroke are based on concepts of motor learning[30, 31, 32]. Although there is insufficient research into the best ways to apply the different concepts of motor learning to post-stroke rehabilitation, some evidence has emerged. There is strong evidence that if training is tailored to individual needs in a task-oriented manner, larger effects of therapies are achieved[33]. Second, performing large numbers of repetitions to stimulate motor learning leads to improved walking capacity[32]. Finally, a positive association has been reported between the benefits of gait rehabilitation and augmented therapy time[34, 35, 36]. Increasing therapy volume, i.e., augmenting therapy time and increasing the number of repetitions, as well as the integration of task orientation during training, can be accomplished by CCT.

In this thesis, we have adopted the description of CCT proposed by English et al. (2017)[30]: "The key components of CCT are that physical therapy is provided in groups (more than two participants per therapist) and there is a focus on repetitive practice of functional tasks and exercises that are continually progressed as the participant's function improves". CCT potentially allows for augmentation of therapy time, while reducing the strain on staff availability and costs.

Currently, task-oriented CCT is frequently used to address the reduced walking capacity of people after stroke and has been shown to have positive effects on walking capacity[29, 30]. However, there are some lacunae in the evidence on the use of task-oriented CCT programs. The first is that only two trials, one phase II[37] and one phase III trial[38], have been undertaken among people within the first three months post stroke[30]. As a consequence, the evidence for applying CCT programs within the first months post stroke is still weak. The importance of evaluating the effectiveness of CCT early after stroke lies in the opportunity of performing the study during the timeframe of enhanced levels of neuroplasticity early after stroke[10]. Animal studies in particular suggest that this time window of increased levels of neuroplasticity is restricted to the first weeks post stroke[39]. Although evidence for starting early is lacking in humans, one may hypothesize that the effects of early task-oriented CCT may interact favorably with underlying processes that drive stroke recovery. Furthermore, since task-oriented CCT is organized as a group training, it may be cost-effective and therefore put less strain on healthcare resources. From the perspective of costs and limited staff time resources for inpatient rehabilitation services[40], it is important to demonstrate the feasibility of task-oriented CCT early after stroke.

Second, task-oriented CCT specifically involves the repetitive practice of functional tasks and does not specifically focus on improving body functions such as aerobic capacity[30]. However, extremely low values of aerobic capacity (VO_{2peak}), ranging on average from eight to 22 mL/kg/min, have been reported in people after stroke[41]. The reported values of VO_{2peak} were lower as time since stroke onset was shorter. VO_{2peak} levels varied between 27% and 87% of normative values for age- and gender-matched healthy peers. At the same time, the energy cost of walking for people after stroke may be 1.5 to two times higher when walking at the same speed as their healthy peers[42, 43]. Thus, in view of their reduced aerobic capacity, many people after stroke may have to work to exhaustion or physiologically cross the anaerobic threshold to achieve basic activities of daily living or to walk at a speed required to safely walk in the community. Therefore, task-oriented CCT may need to address aerobic capacity more explicitly to improve walking capacity, by integrating aerobic exercise. Some evidence has been found for the beneficial effects of aerobic exercise on aerobic capacity and walking capacity in people after stroke[33, 44, 45]. Furthermore, using task-oriented CCT that integrates aerobic training is in line with the concept that the benefits of aerobic training in terms of walking capacity may be greater when it is applied in a functional approach[46]. It thus seemed appropriate to further investigate the role of aerobic capacity in walking capacity of people after stroke, to determine the importance of integrating aerobic training into task-oriented CCT to improve walking capacity.

Walking performance after stroke

Walking performance in the community is important to enable people to participate in community life, but also to reduce the health risks associated with an inactive lifestyle. It has been established, however, that the walking performance of people after stroke is limited. A prospective cohort study reported that over 20% of people in the chronic stage after stroke and living in the community after inpatient rehabilitation show reduced walking performance over time[47]. Eventually, less than 50% of these people after stroke were able to walk independently in their own community[12, 47]. A meta-analysis showed that 1105 people assessed between three months and 8.5 years after stroke took a mean of 4355 steps a day, well below the current recommendation for people with a disability, which is 6500-8500 steps a day[48]. Unfortunately, even though walking capacity seems a valid predictor of walking performance[49, 50], gains in walking capacity resulting from interventions such as task-oriented CCT do not necessarily translate into walking performance in the community[26, 51].

One cause of the failing transition to walking performance may be that walking capacity, in spite of improvements achieved by rehabilitation interventions, over time reduces to below the thresholds that are reported to be needed for community walking. The mean six-minutes' walking distances of 248 m after stroke[24] are below the thresholds of 300 m[52], 318 m[53] or 288 m[49] that have been reported to be needed for community ambulation. The reported mean walking speeds are rarely above 0.8 m/s[26] after stroke, and therefore partly below the speed of 0.44 -1.32 m/s that is necessary to cross a street within the time provided by a walk signal[54]. In general, it is suggested that a walking speed of >0.42 m/s allows for limited community walking, whereas a walking speed of >0.93 m/s is needed for unlimited community walking[49].

Task-oriented CCT could potentially provide ongoing exercise programs beyond rehabilitation to maintain or even improve walking capacity to the level that is needed to achieve the threshold for community walking and prevent decline.

Another cause of the limited translation of improved walking capacity into walking performance may be that behavioral change is needed. Hence, the barriers and facilitators for walking in the community that are perceived by people after a stroke needed to be identified to support the development of successful interventions to induce behavioral change. Barriers and facilitators such as self-efficacy, beliefs about physical activity, self-determination and social support, as well as ongoing professional support, have been identified for physical activity in general[55, 56, 57]. However, knowledge is scarce about perceived barriers and facilitators specifically for outdoor walking performance in the community with the aim of remaining or becoming physically active and reducing health risks. Moreover, to date, most studies aiming to identify barriers and facilitators for walking after stroke either focused on physical and environmental factors *or* on psychosocial factors[58]. Recently, however, an argument was made to integrate these factors in a more comprehensive approach[59], which could lead to the development of more effective interventions for behavioral change concerning walking performance in the community.

Aims and outline of the thesis

The aims of the present thesis are (1) to report on the effects of task-oriented circuit class training on walking capacity during inpatient rehabilitation after stroke, and (2) to report on the exploration of the factors explaining walking capacity as well as walking performance.

Chapters 2 and **3** of this thesis report on the effects of task-oriented CCT during early inpatient rehabilitation within the first three months after stroke. In **Chapter 2**, the effects of a task-oriented CCT on walking capacity are compared with those of individual usual care among an inpatient sample of people within three months after stroke, in a single-blinded randomized controlled trial (RCT). This trial was a collaborative effort of the Neurological Rehabilitation Center, Leipzig, Germany, the University Medical Centre Utrecht, De Hoogstraat Rehabilitation, and the University of Applied Sciences Utrecht, the Netherlands. **Chapter 3** then focuses on the effect of integrated aerobic exercise during task-oriented CCT. This chapter presents the findings of a pilot study assessing the feasibility and effects on walking capacity of task-oriented CCT training that integrated aerobic exercise compared to task-oriented CCT without aerobic exercise, for an inpatient sample of people within three months after stroke. The trial was a collaborative effort involving the University of Utrecht, the Netherlands, and the Odeborn Clinic for Neurological Rehabilitation, Bad Berleburg, Germany. Both trials presented in **Chapters 2** and **3** were performed in line with the Fitstroke program, which was originally funded by ZonMW (Dutch Organization for Health Research and Development; No 80-82310-98-08303[60].

The effectiveness of integrated aerobic exercise into task-oriented CCT training led to the question whether there is an association between aerobic capacity and walking capacity. The first effort to answer this question was made by performing a systematic review of the association between these two, which is reported on in **Chapter 4**. **Chapter 5** then reports on a further exploration of this association and the role of postural control in a cross-sectional analysis.

Improving walking performance would be the ultimate goal of rehabilitation. Barriers and facilitators for outdoor walking performance were explored in a qualitative study in a sample of community-dwelling people in the chronic stage after stroke. Results of this qualitative study are reported in **Chapter 6**.

The studies in **Chapters 4, 5** and **6** of this thesis were part of the Stimulating and Investigating Walking Activity in Stroke (SUSTAIN) program, which was funded by SIA RAAK Internationaal (Project number: 2010-2-024 INT). It consisted of a two-year prospective cohort study in a community-dwelling sample of people after stroke.

Finally, **Chapter 7** offers a general discussion of the main results reported in this thesis and presents theoretical considerations as well as implications for clinical practice and future research.

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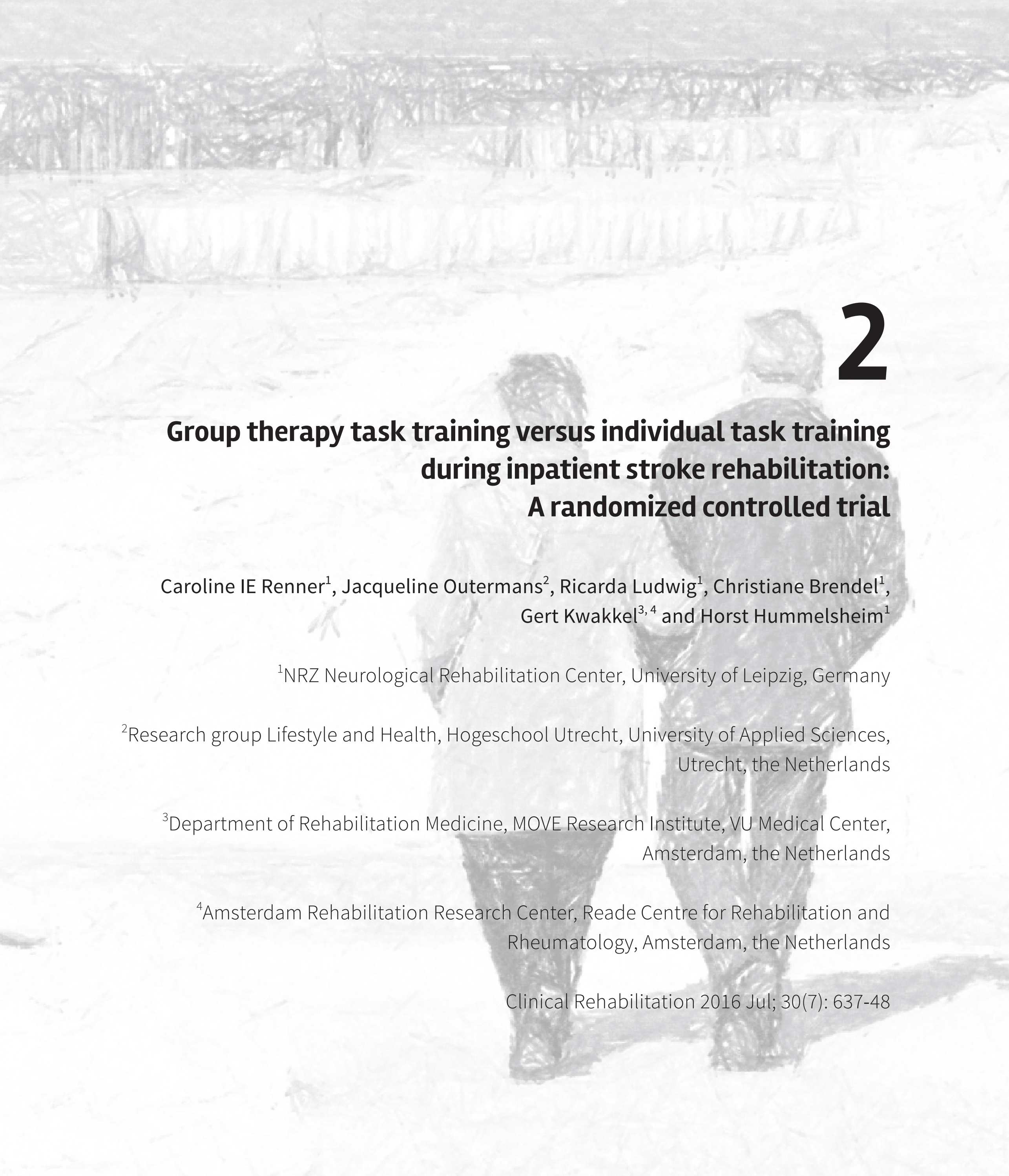

2

Group therapy task training versus individual task training during inpatient stroke rehabilitation: A randomized controlled trial

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Abstract

Objective: To compare the efficacy of intensive daily applied progressive group therapy task training with equally dosed individual progressive task training on self-reported mobility for patients with moderate to severe stroke during inpatient rehabilitation.

Design: Randomized controlled clinical trial.

Setting: Inpatient rehabilitation center.

Subjects: A total of 73 subacute patients with stroke who were not able to walk without physical assistance at randomization.

Interventions: Patients were allocated to group therapy task training (GT) or individual task training (IT). Both interventions were intended to improve walking competency and comprised 30 sessions of 90 minutes over six weeks.

Main measures: Primary outcome was the mobility domain of the Stroke Impact Scale (SIS-3.0). Secondary outcomes were the other domains of SIS-3.0, standing balance, gait speed, walking distance, stair climbing, fatigue, anxiety and depression.

Results: No adverse events were reported in either arm of the trial. There were no significant differences between groups for the SIS mobility domain at the end of the intervention ($z = -0.26$, $p = 0.79$). No significant differences between groups were found in gait speed improvements (GT: 0.38 ± 0.23; IT: 0.26 ± 0.35), any other gait related parameters, or in non-physical outcomes such as depression and fatigue.

Conclusion: Inpatient group therapy task training for patients with moderate to severe stroke is safe and equally effective as a dose-matched individual task training therapy. Group therapy task training may be delivered as an alternative to individual therapy or as valuable adjunct to increase time spent in gait-related activities.

Introduction

Research shows that augmentation of therapy time increases the positive effects of rehabilitation interventions after stroke[1]. Due to the increasing prevalence of stroke and overstretched health resources worldwide, innovative strategies are needed to render rehabilitation more cost-effective[2]. A promising way to increase therapy time without increasing staff time is by offering task-oriented circuit class training in which people practice tasks repetitively with ongoing progression in a supervised group setting[3].

A number of meta-analyses have shown that task-specific circuit class training in a group has been effective at improving walking competency, as it consists of high intensity walking practice with sufficient repetitions and tailoring (including ongoing progression) of exercises according to the participants' needs[3, 4–6]. However, most studies were conducted in patients who were able to walk ten meters independently with, or without, walking aids[7–9] or performed in an outpatient setting[9], leaving the effectiveness for more severely affected patients unclear.

In the multicenter CIRCIT trial[10], three different models of physical therapy service delivery for people receiving inpatient rehabilitation after stroke were compared: usual care therapy five days a week; standard care therapy seven days a week; and group circuit class therapy five days a week. Although participants in the seven days per week arm received an additional three hours and those in the circuit class arm an additional 22 hours of physical therapy over the course of the study, there were no significant between-group differences after four-weeks in walking distance. Nevertheless, we need to know the effectiveness of group therapy compared to dose-matched individual therapy for patients with moderate to severe hemiparesis.

The objective of the present inpatient trial was to investigate the effects and safety of daily intensive, structured, progressive, group therapy task training as an alternative to dose-matched individual task training during inpatient rehabilitation to improve walking. We hypothesized that group therapy task training is a safe treatment strategy superior when compared to equally dosed individual task training in terms of self-reported mobility for patients who were not able to walk independently.

Methods

We used a single center, single-blinded, randomized, controlled trial with repeated measurements to compare the effects of structured progressive group therapy task training with individually tailored progressive task training.

The methodology of the FIT-Stroke trial[11] was adapted to fit the more severely affected population during inpatient rehabilitation (i.e., the training was given daily, and the complexity and difficulty of exercises at the workstations were adapted to the patients' muscle strength, physical fitness, and mobility status). Two trained research assistants (CB, RL), who were blinded to treatment allocation, measured all outcomes at baseline, after six weeks, and after 24 weeks (follow-up after discharge home) in face-to-face meetings at the rehabilitation center. Each patient was assessed by the same assessor on each occasion. Randomization was performed by a person independent from the study using an "online" minimization procedure[12]. He directly accessed the online randomization program for allocation.

Participants

All inpatients with a primary diagnosis of a first-ever stroke were screened for eligibility for the study during their first week at the Neurological Rehabilitation Center, Leipzig-Bennewitz. For inclusion, eligible patients had to have had a verified stroke according to the WHO definition[13], and were able to: 1) sit and stand independently, and walk with assistance (i.e., Functional Ambulation Categories (FAC) ≥ 2 and ≤ 5) with or without an aid or orthosis[14]; 2) give informed consent and be motivated to participate in a six-week intensive program of physical therapy; and 3) able to understand instructions (as evaluated by the Mini-Mental State Examination (>23 points)[15]. Patients were excluded if they lived more than 70 km from the rehabilitation center. The treating physical therapist identified the patients satisfying these criteria. These patients were then consecutively invited by a researcher to participate in the study and gave informed consent prior to commencing the study. Hemorrhagic or ischemic stroke was confirmed by non-contrast cranial CT scan. Ischemic stroke was classified according to the Oxfordshire Community Stroke Project criteria[16].

The ethics committee of the University of Leipzig approved the protocol. The study was in accord with the Helsinki Declaration of 1975 regarding the treatment of human participants in research. The trial is registered at the German Trial Register (DRKS 00005353).

Interventions

Group therapy task training

Patients assigned to the experimental group received a 90-minute, structured progressive task training program five times a week over a six-week period (30 sessions). Each training included eight out of ten available workstations, intended to improve tasks relating to walking competency, such as balance control, stair walking, turning, transfers and speed walking[11]. Graded progression was achieved by (1) increasing the difficulty of the task, (2) adding weights, or (3) increasing the number of repetitions. At each workstation, participants worked together in pairs: while one participant performed the task for three minutes, the other one observed him and counted the number of repetitions. After three minutes of practice or observation, they reversed roles. After six minutes at one workstation, each pair had one minute to go to the next workstation. Each participant's performance (i.e., number of repetitions) was recorded in a training log, which was used as a feedback motivational tool and as a training parameter during the next session. Motivational music was played in the background during the entire training session. The total group training program included four stages: warming up (ten minutes), task training (60 minutes), sports and games (15 minutes) and cooling down (five minutes). The physical therapist or sports therapists who conducted the program were trained in a one-day course before the study started. The staff recorded patients' attendance at the sessions and adverse events during the intervention. Serious adverse events were defined as any fall or other adverse event related to treatment that required the discontinuation of rehabilitation.

Individual task training

Patients allocated to the individual training received a 90-minute, progressive individually tailored task training five times a week over a six-week period (30 sessions) offered by one of the staff physical therapists. The training was tailored to the deficits of the patient and aimed to improve balance, physical condition and walking competency, preferably using a graded progression. Thus, therapy time and progression were equally dosed in both interventions. They differed by the individual tailoring of the training (individual task training) and the lower staff-patient ratio provided in the group therapy task training.

Both interventions lasted six weeks and were given during in-patient rehabilitation. The broad aim of both types of intervention was to improve the patients' mobility to allow safe discharge to their homes. Both groups received all other therapies including neuropsychology, speech, and occupational therapy for the upper paretic limb, as needed. The overall rehabilitation goals were made independently to the conduct of the study.

Outcomes

Primary outcome measure

The mobility domain of the Stroke Impact Scale (SIS) 3.0 is a self-reported, stroke specific, validated measure that includes 59 items and assesses eight domains related to activities and participation[17, 18]. The mobility domain of the scale includes nine questions about a patient's perceived competency to keep his or her balance, to transfer, to walk indoors and climb stairs, to get in and out of a car, and to move about in the community. Total scores range from zero to 100, higher scores indicating better mobility. The SIS was administered at baseline, at six weeks, and at 24 weeks after randomization. A difference of ten points on the 'mobility at home and in the community' domain of the stroke impact scale was regarded as clinically relevant[19].

Secondary outcome measures

Secondary outcomes included the other seven domains of the SIS 3.0, the Rivermead Mobility Index (RMI)[20], the Falls Efficacy Scale (FES-I) (international version)[21], the Hospital Anxiety and Depression Scale (HADS)[22], and the Fatigue Severity Scale (FSS)[23]. Other secondary outcomes were performance tests namely, the Motricity Index (MI-upper extremity and MI-lower extremity)[24], Functional Ambulation Categories (FAC)[25], Six-Minute Walk Test (6MWT)[26], Ten-Meter Timed Walk Test at comfortable speed (10MTWT)[27], Timed Balance Test (TBT)[28], Timed Up and Go (TUG)[29], Chair Rise Test (CRT) and modified Stairs Climb Test (m-SCT)[30], and Letter Cancellation Task (LCT)[31]. Extensive descriptions (including psychometric properties and references) of all secondary outcomes have been published[11].

The 6MWT and 10MTWT at comfortable speed are both widely used tests that detect with a high reliability changes in walking distance and walking velocity, respectively in stroke. However, the important determinant of achievement is whether a clinically relevant increase and/or clinically meaningful final attained walking distance or velocity has been achieved[32]. For the 6MWT, an increase beyond 54 m is considered the minimal detectable change[33], and the minimum distance necessary for independent community mobility starts at 300 m[34]. Similarly, for the 10MTWT an increase of comfortable walking speed of 0.16 m/s is regarded the minimal clinically important difference[35, 36], and the range for normal walking speed in the community including crossing streets is 1.2 - 1.4 m/s[32, 37].

All secondary outcomes (questionnaires and performance tests) were measured at baseline (T0), at six weeks (T1) and at 24 weeks (T2) after randomization. The physical therapist recorded adverse events, including falls and heart problems in the patients' diaries. Serious adverse events were defined as falls and incidents related to treatment leading to injury and requiring additional treatment. Serious adverse events required reporting to the medical ethics committee.

Data analysis

Differences in baseline values between group therapy task training and individual task training groups were tested with the Fisher's exact test or χ^2 test for nominal outcomes, the Mann-Whitney U test for ordinal scale outcomes, and the Student's t-test for independent groups, assuming equal variances for interval or ratio scale outcomes. To test equally dosing of therapy between group therapy task training and individual task training, we used the Student's t-test for independent groups.

Due to the large number of patients lost to follow up, two types of analyses were undertaken for the primary outcome measure: one including the data of all patients including those who dropped out using a linear mixed-models analysis, and one excluding those patients who dropped out. Subsequently, the change scores were calculated for the group therapy task training and individual task training groups from T0 to T1 for the intervention phase, and from T1 to T2 for the follow-up phase. Between group differences for ordinal scaled outcomes were calculated using the non-parametric Mann-Whitney U test, whereas the Student's t-tests for independent groups was used for testing differences between groups, assuming equal variances for interval or ratio scale outcomes.

We used the Fisher's exact test to determine the significance of the differences in proportion of patients who improved on walking speeds and walking distances beyond the smallest detectable differences. These responders were defined as participants whose change in distance showed a clinically relevant improvement of 54 m or more on the 6MWT, or a clinically relevant increase in comfortable walking speed of 0.16 m/s or more. In addition, we used Fisher's exact test to test for differences in the proportion of patients with as a clinically relevant increase of ten points in the SIS mobility domain[19], with a final attained walking distance above 300 m[21], and with a final attained walking speed above 1.20 m/s[32]. All hypotheses were tested two sided, with a critical value of <0.05. Statistical analyses were performed with SPSS for Windows, version 20.0.

Results

Between November 2008 and November 2011, 73 patients were randomly assigned to group therapy task training (n = 34) or individual task training (n = 39). Recruitment of patients for this trial is shown in Figure 1. These 73 patients represent 5% of the total population of stroke patients who were admitted (average 35 days post stroke) to the inpatient rehabilitation center in this period.

A total of 114 of admitted patients could not participate in the study because they did not fulfil the inclusion criteria and/ or fulfilled the exclusion criteria. Of the 92 patients who did fulfil the inclusion criteria, 19 patients did not participate because they feared the daily intensive training, wanted to be discharged in less than six weeks (n = 12), or were not interested in participating in a study (n = 7). Of the 73 included patients, five patients in the group therapy training and four in the individual training dropped out during the first weeks of intervention as they perceived the training session as too heavy or insisted on early discharge. These early drop outs were excluded from analysis in Table 1. Patients allocated in the group therapy task training attended an average of 29.21 ± 1.0 of the 30 sessions, whereas patients allocated to the individual task training attended an average of 29.19 ± 1.3 of the 30 individual training sessions. No adverse events were reported in the group therapy training or the individual training groups.

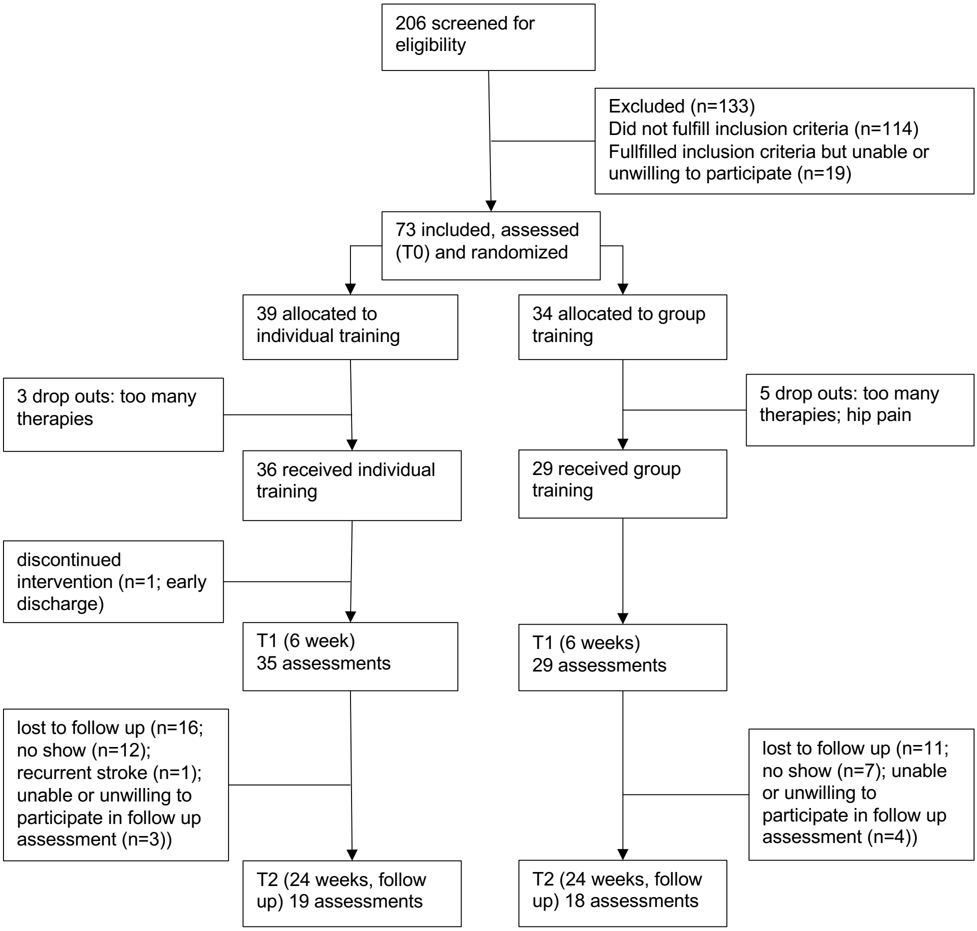

Figure 1. Flow of patients with stroke through study of group therapy task training compared with individual task training during inpatient rehabilitation.

Table 2 shows the baseline characteristics of patients for the primary and secondary outcomes. At study onset the treatment groups were homogenous for patients' characteristics including the primary outcome metric. However, the performance measures such as the MI-lower extremity, 6MWT, TUG, and m-SCT showed significantly better records in favor of the patients assigned to the group therapy task training (supplementary material addendum of Table 2).

Outcomes

Table 1 shows the effects (mean and standard deviation) of time within intervention groups (six and 24 weeks) and the effects (change in scores) between groups for the intervention phase (baseline to six weeks) for the primary and secondary outcomes.

Table 1. Outcomes at 6 and 24 weeks for people with stroke randomized to group therapy task training or individual task training. Values for after treatment (6 weeks) and follow-up (24 weeks) are means (SD).

	Circuit class training		Individual training		Change scores		
					Circuit class training	Individual training	
	6 weeks (n = 29)	Follow -up (n = 18)	6 weeks (n = 35)	Follow-up (n = 18)	Baseline to 6 weeks	Baseline to 6 weeks	p-value
Primary outcome SIS 3.0 (0-100)							
Mobility	92.05 (11.33)	92.92 (7.39)	92.14 (7.67)	91.71 (9.09)	13.57 (13.97)	14.29 (17.93)	0.79
Secondary outcomes, other domains of SIS 3.0 (0-100)							
Strength	72.11 (22.97)	72.93 (21.32)	66.45 (17.42)	63.16 (18.97)	10.71 (13.59)	16.55 (19.03)	0.23
Memory and thinking	90.86 (15.56)	90.28(9.82)	90.73 (11.29)	90.48 (9.21)	3.91 (18.47)	3.30 (8.51)	0.59
Mood and emotions	60.53 (9.51)	63.27 (6.29)	63.33 (5.46)	62.28 (7.71)	-2.68 (10.38)	1.51 (9.68)	0.26
Communication with others	91.71 (17.60)	93.86 (9.93)	94.19 (14.96)	92.3 (11.31)	0.89 (19.08)	2.31 (7.81)	0.69
ADLs during typical day	88.04 (14.12)	84.96 (17.37)	85.72 (12.00)	85.64 (14.68)	8.41 (11.52)	12.49 (13.91)	0.21
Ability to use most affected hand	69.82 (32.81)	75.56 (27.06)	66.71 (31.74)	64.47 (34.64)	17.14 (27.33)	23.86 (28.54)	0.51
Social participation in ADLs	75.01 (18.55)	80.03 (20.76)	64.49 (25.53)	72.54 (20.38)	23.14 (25.99)	11.35 (26.22)	0.13
Stroke recovery	69.29 (21.38)	68.88 (20.54)	72.03 (18.43)	69.17 (18.65)	11.15 (21.90)	13.77 (20.81)	0.71
FSS (1-7)	2.89 (1.85)	2.39 (1.69)	2.70 (1.89)	3.09 (1.99)	0.30 (1.77)	0.03 (2.38)	0.28
FES (16-64)	20.14 (6.20)	21.17 (7.12)	21.60 (5.59)	20.17 (3.78)	-4.11 (9.31)	-3.71 (8.84)	0.51
HADS:							
Depression (0-21)	3.33 (3.06)	3.47 (2.72)	3.85 (4.06)	3.50 (4.00)	-0.75 (1.98)	-1.03 (3.51)	0.92
Anxiety (0-21)	4.71 (4.10)	3.29 (3.14)	4.18 (3.49)	4.28 (4.48)	0.25 (2.61)	-1.58 (2.96)	0.03
RMI (0-15)	13.75 (0.93)	13.72 (0.96)	13.29 (1.15)	13.78 (0.73)	3.00 (2.29)	3.49 (2.70)	0.49
TBT (0-5)	4.61 (0.69)	4.50 (0.79)	4.29 (0.93)	4.50 (0.86)	0.96 (1.20)	1.12 (1.27)	0.51
MI-Upper extremity (0-100)	83.89 (20.57)	87.56 (19.16)	79.26 (18.77)	81.17 (24.58)	9.04 (11.33)	11.74 (12.71)	0.41
MI-Lower extremity (0-100)	89.39 (11.82)	93.39 (10.09)	84.60 (14.37)	88.06 (13.53)	8.36 (12.74)	13.86 (13.50)	0.09

Table 1. Outcomes at 6 and 24 weeks for people with stroke randomized to group therapy task training or individual task training. Values for after treatment (6 weeks) and follow-up (24 weeks) are means (SD). (continued)

					Change scores		
	Circuit class training		Individual training		Circuit class training	Individual training	
	6 weeks (n = 29)	Follow -up (n = 18)	6 weeks (n = 35)	Follow-up (n = 18)	Baseline to 6 weeks	Baseline to 6 weeks	p-value
LCT Percentage correct (0-100)	96.19 (8.13)	98.72 (1.63)	97.78 (3.64)	99.61 (1.12)	2.98 (13.72)	0.43 (4.15)	0.38
FAC (0-5)	4.89 (0.32)	5.00 (0.00)	4.69 (0.76)	5.00 (0.00)	1.04 (1.14)	1.29 (1.34)	0.54
10MTWT (m/s)	1.24 (0.31)	1.62 (1.62)	0.94 (0.32)	1.25 (1.73)	0.38 (0.23)	0.26 (0.35)	0.13
6MWT (m)	409.7 (102.2)	413.4 (88.9)	328.5 (114.5)	349.6 (119.3)	112.52 (67.85)	98.66 (95.13)	0.50
TUG (s)	9.3 (4.4)	8.8 (3.7)	12.1 (6.6)	11.9 (12.1)	-4.64 (6.03)	8.00 (10.26)	0.29
CRT (s)	10.4 (3.0)	11.1 (2.7)	12.2 (4.4)	11.1 (4.3)	-3.63 (4.17)	-4.87 (6.33)	0.38
m-SCT (s)	12.3 (4.3)	12.6 (4.9)	15.5 (6.8)	15.9 (12.9)	-6.07 (5.99)	-13.88 (19.24)	0.03

Abbreviations: SIS: Stroke Impact Scale, ADL: Activities of Daily Life, FSS: Fatigue Severity Scale, FES: Falls Efficacy Scale, HADS: Hospital Depression and Anxiety Scale, RMI: Rivermead Mobility Index, TBT: Timed Balance Test, MI: Motricity Index, LCT: Letter Cancelation Test, FAC: Functional Ambulation Categories, 10MTWT: Ten-Meter Timed Walk Test, 6MWT: Six-Minute Walk Test, TUG: Timed Up and Go, CRT: Chair Rise Test, m-SCT: modified Stair Climb Test.

We found no significant differences between groups for self-reported mobility on the SIS (p = 0.73) performing a linear mixed-models analysis (with time and group as fixed effects, and with subjects as a random effect). Furthermore, there was no significant difference between interventions at the end of six weeks (z = -1.46, p = 0.14) and at follow up (z = -1.76, p = 0.08), when undertaking a full intention-to-treat analysis by using last outcome measures for the drop-outs. Seventeen out of 35 (49%) patients in the individual task training group, and 13 out of the 28 (46%) in group therapy task training group showed a clinically meaningful increase of ten points or more for mobility on the SIS (p = 0.87).

Table 2. Baseline characteristics of people with stroke allocated to group therapy task training or individual task training. Values are means (SD) unless stated otherwise.

	Group training (*n* = 34)	Individual training (*n* = 39)	p-value
Patients' characteristics			
No (%) of men	22 (65)	29 (74)	0.45
Age (years)	56 (10)	55 (10)	0.80
No (%) by type of stroke:			
Ischaemic	22 (65)	31(81)	0.19
Haemorrhagic	12 (35)	8 (19)	
No (%) by site of hemiparesis			
Right	15(44)	22 (56)	0.57
Left	19 (56)	17 (43)	
No (%) by Bamford classification:			
Total anterior cerebral infarct	0 (0)	0 (0)	0.26
Lacunar circulation infarct	0 (0)	2 (7)	
Partial anterior cerebral infarct	16 (73)	18 (58)	
Posterior circulation infarct	6 (27)	11 (35)	
Time from stroke onset to randomization (days)	39 (25)	32 (11)	0.08
BI (0–100)	67.5 (21.93)	72.70 (24.03)	0.23
Cumulative Illness Rating Scale (0–56)	8.81 (2.79)	8.86 (2.62)	0.88
Primary outcome			
SIS 3.0 mobility (0–100)	77.00 (21.54)	71.48 (19.68)	0.27
Secondary outcome			
RMI (0–15)	10.69 (2.9286)	9.92 (2.71)	0.27
MI:			
Upper extremity (0–100)	73.82 (24.02)	67.21 (23.04)	0.17
Lower extremity (0–100)	76.36 (13.62)	65.90 (16.63)	**0.01**
FAC (0–5)	3.04 (1.17)	3.00 (1.22)	0.92

Abbreviations: BI: Barthel Index, SIS: Stroke Impact Scale, RMI: Rivermead Mobility Index, MI: Motricity Index, FAC: Functional Ambulation Categories.

The linear mixed-models analysis (with time and group as fixed effects, and with subjects as a random effect) demonstrated a significant between-group effect favoring the group therapy task training for the 10MTWT test ($p < 0.0001$) and for the 6MWT ($p < 0.0001$) after correcting for multiple comparisons. There were no other significant differences between groups for the other secondary outcomes after correcting for multiple comparisons.

Twenty-four out of 35 (69%) patients in the individual task training group and 24 out of the 28 (86%) in the group therapy task training group showed clinically meaningful changes of at least 54 meters on the 6MWT ($p = 0.10$). Thirteen out of 27 (77%) patients in the individual task training group and 24 out of the 28 (86%) in the group therapy task training group showed clinically meaningful changes of at least 0.16 m/s on 10MTWT ($p = 0.52$). Twenty-one out of 35 (60%) patients in the individual task training group, and 23 out of the 28 (82%) in the group therapy task training group attained a final walking distance above 300 m at the end of intervention ($p = 0.096$).

For the final attained walking speed, we found a trend for the group therapy task training group to be more effective ($p = 0.004$) than the individual task training group, but this finding did not reach statistical significance after correction for multiple comparisons: 17 patients out of 28 (61%) versus eight out of 35 (23%) patients achieved a normal community walking speed of at least 1.20 m/s at the end of treatment.

Discussion

Ninety minutes daily applied structured progressive group therapy task training for 6 weeks in patients with moderate to severe disability post stroke, is as safe and as effective as an equally dosed individual task training during inpatient rehabilitation in the first three months after stroke. We found that group therapy task training was equivalent to individual task training as measured by self-reported mobility. Also, the proportion of patients who had a clinically meaningful increase of ten points for mobility on the stroke impact scale did not differ significantly between the two groups. These results are consistent with the findings of Van de Port and colleagues[9] also using the SIS as primary measurement of outcome in their trial. In that study, they compared the structured progressive circuit class training to individual physical therapy without any temporal or content specifications, while the two interventions in our study were dose-matched. The 90-minute group therapy task training in the study by Van de Port and collegues[9] was given twice a week over a 12-week period comprising a total of 24 sessions. In the present study the 90-minute group therapy task training was given daily on workdays over six weeks comprising a total of 30 sessions. In designing the trial for patients unable to walk in a subacute stage we assumed more sessions are needed to achieve mobility[1, 3]. Possibly the length and/or number of sessions in both groups may have contributed to the high drop-out rate, although we had no adverse events and none of the patients complained of pain with one exception.

Also, the secondary outcome measures showed improvements over time but without statistically significant differences between interventions. An exception was the improvement in comfortable walking speed and distance walked during the 6MWT. Both showed highly significant differences between groups when using a linear mixed-models analysis. Yet these results must be interpreted with caution. We chose the linear mixed-models method due to the high drop-out rate and considerable amount of missing data. We had observed differences between the two groups at baseline on secondary outcomes such as the 6MWT. Therefore, we also compared the two interventions using change scores by Student's t-tests. This analysis revealed an equivalent increase in walking speed and in the distance walked during the 6MWT in both groups. Fisher's exact tests also showed comparable proportions of patients who had a clinically meaningful improvement on the 6MWT of at least 54 m, and on the 10MTWT of at least 0.16 m/s in both treatment groups. Similarly, the gains in FAC, TBT, TUG, and CRT did not differ significantly between the two interventions. These findings are in accordance with the findings of English and colleagues[38]. They compared circuit class therapy with individual therapy in an inpatient setting and found equivalent improvements in walking distance and comfortable walking speed in both groups, although the individual therapy session was only 74 minutes per day, while the circuit class was 180 minutes per day. Another recent publication of an observational study by the same group reported that the time spent in walking practice was not different in circuit class and individual therapy in an inpatient setting[39]. This may also explain why we did not find significant differences between groups in primary and secondary outcome measures in our study, although we did not specifically collect any data on active therapy time or time spent in actual walking practice to test this assumption.

Van de Port and collegues[9] observed higher scores in gait speed and walking distance associated with the group therapy training versus individual therapy, but no difference in self-reported mobility. English and colleagues[10] observed that gains in walking speed and walking distance did not necessarily translate into improvement in patients' perception of gait performance, nor did they generalize into the ability to ambulate in the community[32]. The present study therefore examined whether group therapy was more effective in achieving a walking speed above 1.20 m/s crucial for community ambulation[32, 37], and in achieving a walking distance beyond 300 meters in 6MWT, the minimum distance necessary for independent community mobility[21]. There was no significant difference in the proportion of patients in the two groups achieving these standards reflecting their ability to ambulate in the community. Furthermore, community ambulation is the ability to integrate walking with other tasks in a complex environment. The presence of possible cognitive and behavioral deficits will further interact with the performance of gait and impair community ambulation[40]. Our trial, as well as the one by van de Port and collegues[9] however, showed no improvement from training either individual or in a group setting for the cognitive and behavioral domains of the stroke impact scale such as memory and thinking, mood and emotions, or communication with others. Along the same lines the patients' perception of fatigue or fear of falling did not differ significantly between the two interventions.

The present study had a number of limitations. First, we found significant baseline differences in favor of the group therapy task training group for a few of the secondary outcomes. We adjusted for these by comparing the changes rather than the absolute values between the groups. A second limitation is the high drop-out rate during the intervention and at follow up. It should be emphasized that only patients who felt confident enough to participate in group training and who were willing to engage in such a highly dosed training completed the study, which limits the generalizability of our trial. Comparably to our study English and colleagues[10] also observed a high drop-out rate, while van de Port and colleagues[9] did not observe such a high drop-out rate. Possibly patients treated in an outpatient rehabilitation are more capable and/or willing to invest in high intensity training sessions of about 90 minutes. Although the dose-response relationship between intensity of therapy and increased motor recovery after stroke is well known[1], not all patients are willing to comply for reasons of physical capacity, prior sedentary lifestyle, etc. Further research is needed to examine factors that improve a patient's compliance during inpatient rehabilitation. Along the same lines we were not able to recruit the required number of patients according to the sample size calculations in an acceptable time interval. Thus, possible differences between the two therapies may remain uncovered due to a small sample size. Third, an inclusion rate of 5% of all patients, comparable to the one reported by Kwakkel et al.[41] further limited its generalizability. These limitations of study design underscore the difficulties inherent to clinical research, especially finding a balance between the ideal study design, the practicalities of clinical research, and the applicability of the findings to a real-world clinical setting[38].

An important aspect of the group therapy task training is that it was offered in groups ranging from two to eight patients therefore lowering the ratios of staff to patients. Several meta-analyses[3, 5] suggest that a ratio of 1:3 (one staff member for three patients) is feasible in circuit class training. When circuit training is done in pairs, an even higher ratio can be achieved[9]. The ability to provide a significantly greater amount of therapy-time with a lower staff to patient ratio in the study by English and colleagues[38] suggested that the circuit class therapy may also be a more cost-effective method of therapy delivery for inpatient rehabilitation. In the present study the same therapy time was provided at a lower staff to patient ratio in the circuit training group than in the individual training group. The total amount of therapist time required to provide circuit class therapy for an average of four patients was 90 minutes a day, whereas the total amount of therapist time required to provide individual training for four patients was 360 minutes a day. This is a difference of 270 minutes of therapist time per day. The group therapy training comprised a structured progressive task training program with the complexity and difficulty of exercises adapted to the patients' muscle strength, physical fitness and mobility status that challenged the patient to his maximal ability. It could be used alone or in addition to the individual therapies in order to increase the amount of walking practice per day to prevent the reported disparity between functional recovery and daily use of the lower extremities[42], provided the patient is able and willing to invest in more therapy hours per day. Another benefit of group therapy task training may be the peer support experienced in a group setting especially when patients complete the exercises in pairs. In contrast practice within an individual therapy session, a therapist is available to the participant for the duration of the therapy session, allowing greater opportunity to practice tasks that require supervision or assistance to complete safely. Possibly, some patients unable to walk feel more confident practicing walking related activities with a therapist continuously at their side. Further research is warranted, examining patient satisfaction with both models of therapy delivery.

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Supplementary material

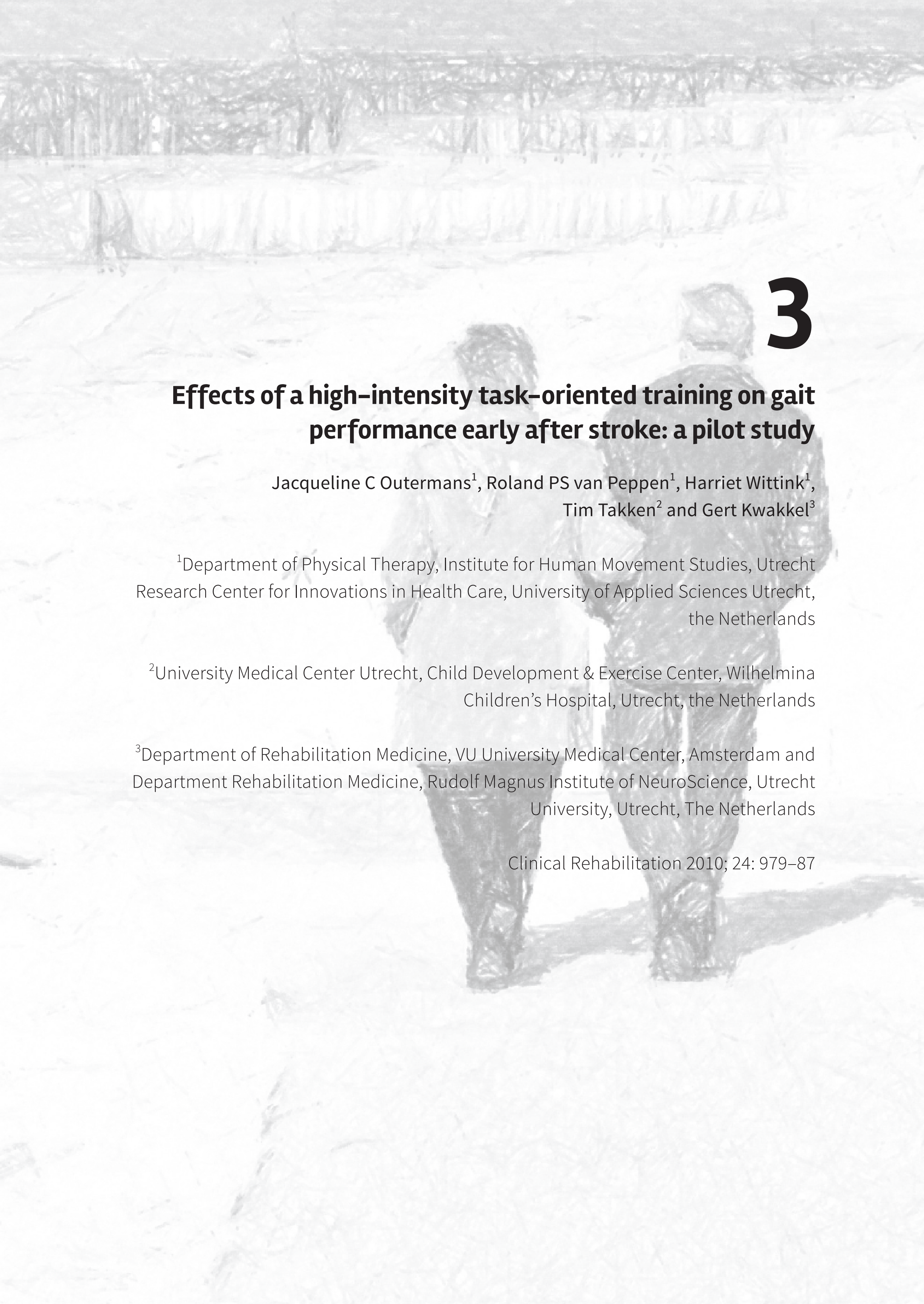
Table 2. Addendum Baseline characteristics of people with stroke allocated to circuit class training intervention or individual training. Values are means (SD) unless stated otherwise.

	Circuit class training (n = 34)	Individual training (n = 39)	p-value
Patients' characteristics			
No (%) of men	22 (65)	29 (74)	0.45
Age (years)	56 (10)	55 (10)	0.80
No (%) by type of stroke:			
Ischaemic	22(65)	31(81)	0.19
Haemorrhagic	12 (35)	8 (19)	
No (%) by site of hemiparesis			
Right	15(44)	22 (56)	0.57
Left	19 (56)	17 (43)	
No (%) by Bamford classification:			
Total anterior cerebral infarct	0 (0)	0(0)	0.26
Lacunar circulation infarct	0(0)	2 (7)	
Partial anterior cerebral infarct	16(73)	18 (58)	
Posterior circulation infarct	6 (27)	11 (35)	
Time from stroke onset to randomization (days)	39 (25)	32 (11)	0.08
Barthel Index (0-100)	67.5 (21.93)	72.70 (24.03)	0.23
Cumulative Illness Rating Scale (0-56)	8.81 (2.79)	8.86 (2.62)	0.88
Primary outcome			
SIS 3.0 mobility (0-100)	77.00 (21.54)	71.48 (19.68)	0.27
Secondary outcomes			
SIS 3.0:			
Strength (0-100)	60.18 (20.62)	51.33 (25.63)	0.09
Memory/thinking (0-100)	87.11 (17.79)	87.75 (13.25)	0.63
Emotion (0-100)	64.33 (9.53)	62.47 (10.06)	0.52
Communication (0-100)	89.84 (18.27)	91.54 (16.63)	0.71
ADL/IADL (0-100)	81.45 (16.33)	73.89 (16.64)	0.03
Hand function (0-100)	48.59 (42.96)	45.13 (38.77)	0.89
Participation (0-100)	52.64 (25.80)	53.93 (26.65)	0.75
Stroke recovery (0-100)	59.94 (24.18)	57.67 (20.68)	0.94
Fatigue severity scale (1-7)	2.76 (1.89)	2.72 (1.56)	0.80
FES (16-64)	24.12 (7.94)	25.41 (9.29)	0.42
HADS:			
Depression (0-21)	3.59 (3.10)	4.56 (4.47)	0.63
Anxiety (0-21)	4.19 (3.23)	5.17 (4.26)	0.39
RMI (0-15)	10.69 (2.9286)	9.92 (2.71)	0.27

Table 2. Addendum Baseline characteristics of people with stroke allocated to circuit class training intervention or individual training. Values are means (SD) unless stated otherwise. (continued)

	Circuit class training (n = 34)	Individual training (n = 39)	p-value
TB (0-5)	3.61 (1.29)	3.18 (1.25)	0.15
MI-Upper extremity (0-100)	73.82 (24.02)	67.21 (23.04)	0.17
MI-Lower extremity (0-100)	76.36 (13.62)	65.90 (16.63)	**0.01**
LCT Percentage correct (0-100)	93.38 (11.63)	95.34 (10.02)	0.46
Mini-Mental-State-Examination (0-30)	27.21 (3.3)	27.8 (1.9)	0.89
FAC (0-5)	3.04 (1.17)	3.00 (1.22)	0.92
10MTWT (m/s)	0.84 (0.27)	0.68 (0.44)	0.08
6MWT (m)	291.0 (98.5)	232.9 (128.0)	**0.04**
TUG (s)	13.7 (6.4)	19.3 (13.0)	**0.03**
CRT (s)	14.3 (5.4)	16.5 (7.1)	0.17
m-SCT (s)	19.2 (9.1)	29.8 (22.9)	**0.01**

Abbreviations: SIS: Stroke Impact Scale, (I)ADL: (Instrumental) Activities of Daily Life, FSS: Fatigue Severity Scale, FES: Falls Efficacy Scale, HADS: Hospital Depression and Anxiety Scale, RMI: Rivermead Mobility Index, TBT: Timed Balance Test, MI: Motricity Index, LCT: Letter Cancelation Test, FAC: Functional Ambulation Categories, 10MTWT: Ten-Meter Timed Walk Test, 6MWT: Six-Minute Walk Test, TUG: Timed Up and Go, CRT: Chair Rise Test, m-SCT: modified Stair Climb Test.



3

Effects of a high-intensity task-oriented training on gait performance early after stroke: a pilot study

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Abstract

Objective: To investigate the feasibility and the effects on gait of a high intensity task-oriented training, incorporating a high cardiovascular workload and large number of repetitions, in patients with subacute stroke, when compared to a low intensity physical therapy program.

Design and subjects: Randomized controlled clinical trial: Forty-four patients with stroke were recruited at two to eight weeks after stroke onset.

Measures: Maximal gait speed assessed with the Ten-Meter Timed Walk Test (10MTWT), walking capacity assessed with the Six-Minute Walk Test (6MWT). Control of standing balance assessed with the Berg Balance Scale (BBS) and the Functional Reach test (FR). Group differences were analyzed using a Mann–Whitney U-test.

Results: Between-group analysis showed a statistically significant difference in favor of the high intensity task-oriented training in performance on the 10MTWT ($z = 2.13$, $p = 0.03$) and the 6MWT ($z = 2.26$, $p = 0.02$). No between-group differences were found for the BBS ($z = -0.07$, $p = 0.45$) and the FR ($z = -0.21$, $p = 0.84$).

Conclusion: A high-intensity task-oriented training program designed to improve hemiplegic gait and physical fitness was feasible in the present study and the effectiveness exceeds a low-intensity physical therapy program in terms of gait speed and walking capacity in patients with subacute stroke. In a future study, it seems appropriate to additionally use measures to evaluate physical fitness and energy expenditure while walking.

Introduction

Disability due to hemiparesis limits independent functioning, including gait related activities in more than half of the stroke survivors[1]. With that, regaining and enhancing walking competency is a major target in stroke rehabilitation[2]. Traditionally, physical therapy concepts were focused on restoring reduced motor control of the affected limb as well as postural control. However, recently evidence was found on improved walking ability not being associated with improved motor control of the paretic lower limb[3, 4] but rather with the development of compensation movement strategies[5, 6] and improved coping with loss of function in enhancing the ability to maintain balance over the non-paretic lower limb[6, 7]. Repetitive training of tasks results in improvement in lower limb function, as a recent Cochrane review by French and colleagues[8] showed, supporting the idea that a high dose of repetitions are effective for improving gait-related activities.

Furthermore, muscle strength[9, 10] as well as cardiorespiratory capacity[11, 12] are decreased in stroke and are found to be significantly associated with insufficient walking capacity[11, 13]. Evidence was found on the beneficial effects of muscle strength training in terms of lower limb muscular strength[14], but no favorable effects were found of strength training in terms of mobility-related tasks, such as stair walking, turning, making transfers, walking quickly, and walking for specified distances, whereas some evidence was found for cardiorespiratory training on walking capacity in terms of distance[15–17]. In line with these findings, training should be oriented on those tasks that are meaningful for daily life[14, 15].

One general problem in demonstrating the specific effects of any given task across rehabilitation trials has been the low dose of training, which might limit the robustness of finding differential effects[18]. To overcome the problem of time dedicated to practice, Dean and colleagues developed circuit class training, in which patients are able to practice at their own functional level in groups[19]. A recent meta-analysis demonstrated significant homogeneous summary effect sizes in favor of task-oriented circuit class training for walking distance, gait speed and a timed up-and-go[20]. Unfortunately, only one study did investigate the effects of circuit class training in the first weeks post stroke[21], and one study investigated additional cardiorespiratory workload on gait training in subacute stroke[16]. Therefore, there are only few data available to guide clinical practice at present with regard to the effectiveness of task-oriented fitness training interventions after stroke[22].

The purpose of the present pilot study was to establish the feasibility of a high-intensity task-oriented training incorporating a high number of repetition and high cardiorespiratory workload when compared with a low-intensity physical therapy program both delivered in circuit class training in the 2nd–12th week after stroke onset, and to determine the effects on walking competency in terms of walking distance, gait speed and postural balance.

Methods

Participants

The study was performed in a neurorehabilitation clinic in Bad Berleburg, Germany. All participants were inpatients.

Eligibility criteria included: (1) clinical diagnosis of hemiplegia following first or recurrent stroke, (2) time since most recent stroke and time of recruitment between two and eight weeks, (3) the ability to walk ten meters without assistance; Functional Ambulation Categories (FAC)[23] ≥ 3. Subjects were excluded in case of (a) cardiovascular instability, (b) acute impairments of the lower extremities influencing walking ability and (c) sensory communicative disorders. Cardiovascular instability was defined as resting systolic blood pressure over 200 mmHg and resting diastolic blood pressure over 100 mm Hg[24].

Design

This pilot study was a randomized clinical trial. After baseline measurements participants were allocated to the high intensity task-oriented training or the low-intensity physical therapy. Allocation was performed by drawing randomly generated lots enclosed in opaque envelopes.

Baseline measurements were taken on the second day after admission in the rehabilitation clinic. Post-trial measurements were scheduled immediately after the trial, or before in case of early discharge (Fig 1). All clinical assessments were conducted by one assessor (JO), who was not blinded for allocation. To minimize bias, the assessor was not present at the group training at any time. Also, previous assessments were not available during post-test assessment and all instructions were standardized. All eligible patients who were willing to participate signed an informed consent in which the project was explained as well as the use of their assessment data for analysis.

Intervention

All participants engaged in usual individual physical therapy for half an hour each day. Information about intensity and content of the therapy beyond the trial were documented in a patient's record. Therapists were instructed not to depart from their usual care during the trial. This was monitored using the available documentation.

The high-intensity task-oriented training program incorporated ten standardized workstations, focused on improving walking competency, similar to the study by Dean et al.[19] Participants in the high-intensity training group performed 45 minutes of circuit class training, held at the rehabilitation clinic three times a week for four weeks. All stations were practiced for 2.5 minutes, followed by a one-minute transfer to the next station. Afterwards, the participants joined in walking relays and races for ten minutes. The high-intensity training program focused on improving postural control and gait-related activities such as stair walking, turning, making transfers, walking quickly and walking for specified distances. In line with the recommendations of the American Heart Association[22], cardiorespiratory workload started at 40–50% of heart rate reserve. Progression was attained by increasing the workload to a maximum of 70–80% of heart rate reserve[25], and increasing the number of repetitions, both according to the observations and estimation of the therapists in charge and the patients perceived exertion. A 6–20 Borg Scale was used to rate subjects' perceived exertion[26].

The focus in the low-intensity physical therapy group was on improving motor control of the hemiparetic leg and balance. In contrast to the high-intensity training group there were no components of physical fitness training such as strengthening exercises or cardiorespiratory training, indicating that the training was set at a low-intensity profile aimed at learning gait-related activities. The participants in the low-intensity physical therapy group went through a 45-minute program of group exercises, three times a week for four weeks, thus matching therapy time to the high-intensity training group. The low-intensity physical therapy program was also based on a ten workstations circuit. All stations were practiced for 2.5 minutes, followed by a one-minute gap to transfer to the next station. Afterwards the participants joined in games, like passing through a ball, for ten minutes. Progression, according to the observations and estimation of the therapists in charge, was achieved by enhancing motor control challenge, not in enhancing the number of repetitions like the high-intensity training group.

Data collection

All participants underwent a pretest baseline assessment during which subject characteristics age, Body Mass Index (BMI), gender, hemiplegic side, blood pressure and resting heart rate were determined as well as walking capacity, maximal gait speed and control of standing balance. The outcome measures on walking distance and gait speed were selected in this trial according to the formal physical therapy guidelines of the Royal Dutch Society for Physical Therapy, the Clinical Practice Guideline for Physical Therapy management of patients with Stroke[23].

The Six-Minute Walk Test (6MWT) was selected as a measure of walking capacity, being a general challenge to walking ability[27]. This test incorporates walking speed, dynamic balance and submaximal endurance, which are important requirements of ambulation. The 6MWT is valid and reliable in a stroke population[27, 28]. It was performed according to the American Thoracic Society Guidelines[29] on a 50-meter course with ten-meter increments marked discretely on the wall. Subjects were instructed to walk the course back and forth. The total distance covered was determined by adding the laps and the surplus, measured with a tape measure to the last marker, on countdown. Afterwards perceived exertion was evaluated using the 6–20 Borg Scale[26]. To ensure safe exercise and to objectify perceived exertion, heart rate was recorded during the 6MWT using a Polar F1 heart rate monitor (Polar Oy, Kempele, Finland).

Maximal gait speed was assessed using the Ten-Meter Timed Walking Test (10MTWT). The subjects were instructed to walk as fast as possible. To avoid the effects of acceleration and deceleration, gait speed was measured for ten meters on a 15-m course. This test was performed three times and the mean was used for analysis. The 10MTWT showed high intra-rater reliability (intraclass correlation coefficient (ICC) = 0.95) and validity (r_s = 0.79) in patients with stroke[30]. During 6MWT and 10MTWT the assessor remained behind the participant to avoid influencing performance, but still ensuring safety.

Control of standing balance was assessed with the Berg Balance Scale (BBS)[31] and the Functional Reach test (FR)[32]. In stroke populations the BBS has shown good intra-rater reliability (ICC = 0.97) and internal consistency Cronbach's alpha 0.92-0.98, but tends to show a ceiling effect[33], therefore FR was also assessed. In a stroke population the FR showed high intra-rater reliability (ICC = 0.89) and validity (r_s = 0.71) [34]. The FR was measured beside a wall. Standing upright, the participant was asked to reach forward with the non-paretic arm as far as possible without touching the wall or taking a step.

Data analysis

Analyses in this study were performed using an intention-to-treat analysis to determine the effects of both interventions. Missing values were imputed using the assumption of a worst-case scenario in which the baseline value was carried forward.[35] Descriptive statistics were used for baseline characteristics, measures of central tendency and variability. Group comparisons at baseline and post intervention were analyzed using a Mann-Whitney U-test, considering the small group sizes. An alpha level set at 0.05 determined significance in two-sided hypothesis testing. All analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, IL, USA).

Results

Sixty-five potential participants were screened for the present pilot study; 44 subjects satisfied the selection criteria and were included in the trial. Figure 1 shows the trial profile of patient recruitment and drop-outs during the study. Twenty-three participants were allocated to the high-intensity task-oriented training group and 21 were allocated to the low-intensity physical therapy group. In the high-intensity training group one participant was excluded afterwards due to a wrong diagnosis with respect to 'stroke', leaving 22 participants for analysis.

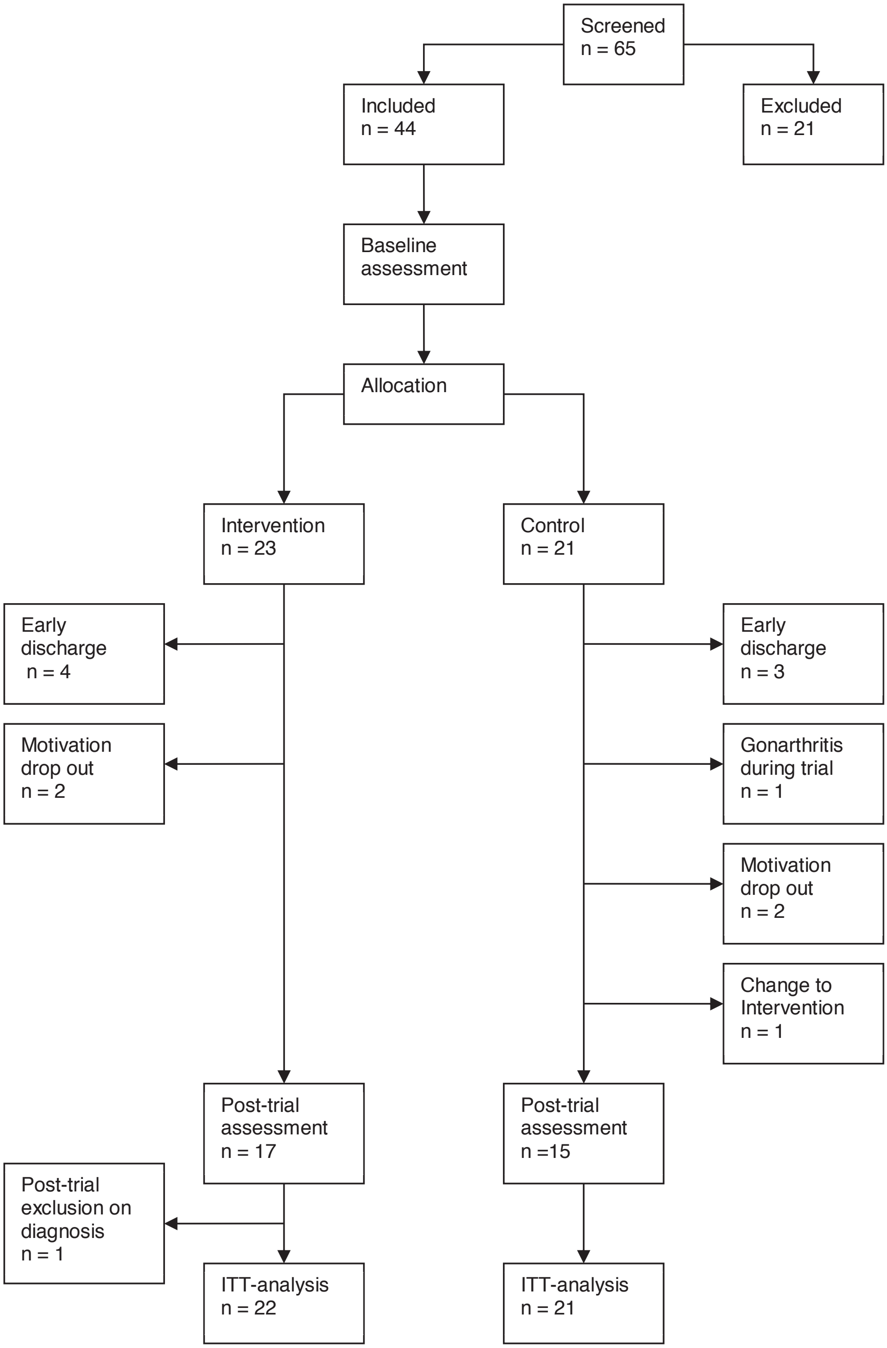

Figure 1. Patient flow and study design.

Due to an early discharge, four participants were lost before the post-trial assessment. One participant suffered from a recurrent stroke and was transferred to acute care, and two participants dropped out for motivational reasons. In the low-intensity physical therapy group 21 participants were analyzed. Three participants were lost before post-intervention assessment due to early discharge. During the program two participants dropped out for motivational reasons, a third participant did not receive treatment as allocated and a fourth dropped out because of acute gonarthritis. Two participants in the intervention and three in the control group participated for less than 20 days but could be assessed post trial. In neither group any adverse events occurred during the trial.

Baseline characteristics

Table 1 shows the patient characteristics of the both groups at baseline. No statistically significant differences between both groups were found with respect to patient characteristics such as age, body mass index, mean time since onset or mean participation duration. No statistically significant differences were found ($p > 0.05$) with respect to measurement of 6MWT, 10MTWT, BBS and FR

Table 1. Baseline results.

	HiTT Group n = 22 mean (SD)	LoPT Group n = 21 mean (SD)	z	Sig. (2-tailed)
Age (years)	56.8 (8,6)	56.3 (8,6)	- 0.09	0.92
BMI (kg/m$^{2)}$	26.9 (9.3)	27.8 (4.9)	- 0.47	0.64
Sex (male)	19	17		
Hemi-side	11 left-sided	11 left-sided		
Time since onset (days)	22.5 (8.2)	23.5 (7.8)	- 0.40	0.69
Intervention Duration (days)	25.2 (5.2)	21.4 (9.7)	-1.10	0.27
6MWT (m)	459.8 (145.8)	401.0 (131.5)	-1.53	0.13
10MTWT (m/s)	1.5 (0.5)	1.4 (0.5)	- 0.84	0.40
BBS	53.1 (3.3)	53.2 (2.3)	- 0.21	0.83
FR (cm)	24.6 (9.3)	25.6 (7.4)	- 0.24	0.81

Abbreviations: HiTT: High intensity Task-oriented Training, LoPT: Low intensity Physical Therapy, BMI: Body Mass Index, 6MWT: 6-Minute Walk Test, 10MTWT: 10-Meter Timed Walk Test, BBS: Berg Balance Scale, FR: Functional Reach Test.

Walking distance and maximal gait speed

The 6MWT showed an increment of 54.0 m (SD 65.1) to mean 518.7 m (SD 165.2) in the high-intensity training group compared with an increment of 21.4 m (SD 43.2) to a mean 422.4 m (SD 127.9) in the low-intensity physical therapy. Table 2 shows the mean scores for both groups post intervention. A subsequent between-group analysis found a significant difference in favor of the high-intensity training group (z = -2.26, p = 0.02) (Table 2). The improvement on the 10MTWT was 0.3 m/s (SD 0.3) to a mean 1.7 m/s (SD 0.5) for the HiTT group compared with a post-trial mean of 1.4 m/s (SD 0.4) for the low-intensity physical therapy group. This difference in improvement was statistically significant in favor of the HiTT group (z = -2.13; p = 0.03).

Table 2. Post intervention results.

	HiTT Group n = 22 mean (SD)	LoPT Group n = 21 mean (SD)	z	Sig. (2-tailed)
6MWT (m)	518.7 (165.2)	422.4 (127.9)	-2.26	0.02
Change score 6MWT	54.0 (65.2)	21.4 (43.2)		
10MTWT (m/s)	1.7 (0.5)	1.4 (0.4)	-2.13	0.03
Change score 10MTWT	0.3 (0.3)	0.0 (0.1)		
BBS	54.1 (3.0)	54.1 (1.7)	- 0.07	0.45
Change score BBS	1.0 (1.5)	0.9 (1.3)		
FR (cm)	27.0 (7.9)	27.4 (9.1)	- 0.21	0.84
Change score FR	1.9 (3.6)	2.3 (5.7)		

Abbreviations: HiTT: High intensity Task-oriented Training, LoPT: Low intensity Physical Therapy, 6MWT: 6-Minutes Walking Test, 10MTWT: 10-Meter Timed Walking Test, BBS: Berg Balance Scale, FR: Functional Reach Test.

Balance control

The scores on the BBS increased 1.0 points (SD 1.5) to a mean of 54.1 (SD 3.0) in the high-intensity training group. The low-intensity physical therapy group showed an increase of 0.9 points (SD 1.3) to a mean score of 54.1 (SD 1.7). An increase of 1.9 cm (SD 3.6) to a mean of 27.0 cm (SD 7.9) in the HiTT group was found compared with an increase of 2.3 cm (SD 5.7) to a mean of 27.4 (SD 9.1) in the low-intensity physical therapy group. Table 2 shows between-group analysis on both balance measures, revealing a nonsignificant difference between both groups on the BBS (z = -0.07, p = 0.45) and FR (z = -0.21, p = 0.84).

Discussion

The high-intensity task-oriented training program in this pilot study implementing a high number of repetitions and a high cardiorespiratory workload, designed to improve hemiparetic gait was feasible and exceeds the effectiveness of a low intensity physical therapy program in terms of walking capacity and walking speed. Since no adverse events occurred and dropout rate for motivational reasons was equally low in both groups, the high-intensity program seemed to be feasible as well as safe and acceptable in the sample of the present pilot study.

The high-intensity task-oriented training program in this study was based on the program developed by Dean et al.[19] Similar circuit class training programs have been used in several other trials[21, 36, 37], although the low-intensity physical therapy program in the present study was, contrary to the control interventions in above-mentioned studies, (1) matched for amount of spent time of practice and (2) also focused on improving locomotor function. In particular this latter fact suggests that the higher intensity of practice including a high cardiorespiratory workload is responsible for the favorable effects of the high-intensity training program.

No significant effects on balance control were found as measured with the BBS. The lack of evidence for improved balance control on the basis of the BBS despite a higher dose of practice is in line with a previous meta-analysis of six RCTs on circuit class training showing no significant effects on balance control[20]. The lack of evidence for improved balance control may be related to lack of responsiveness of the BBS to change when relatively high scores on baseline are shown[33]. Most patients recruited in this study showed relatively high scores on the BBS at baseline, which limits further significant change on this scale[38]. On the other hand, balance control may be less influenced by a higher dose of practice when compared with more effort-related outcomes such as gait speed and walking distance.

There are a number of limitations of the present pilot study. First, the present pilot study lacks adequate blinding procedures for the observer, suggesting that results may have been biased in favor of the high-intensity training group. Second, the study was aimed at exploring the feasibility, including safety, of the high-intensity training program only in an early stage after stroke onset. In several other studies subjects were more severely impaired and in a chronic stage[19, 36], therefore it requires further investigation to determine the feasibility of these programs in other subpopulations and at different phases after stroke. Third, the subjects recruited for this trial performed on a relatively high level of physical functioning at baseline. In most cases, gait performance measured with 10MTWT was within the 95% confidence limits of measurement error and comparable to scores observed in healthy populations[10, 39]. In contrast, the scores on the 6MWT remained at 80% to observations in a healthy population[40], suggesting that physical condition to walk long distances was more compromised than gait speed. On the other hand, still clinical significant improvement on both gait measures, considering a minimal clinical important difference of 54.1 meter on the 6MWT[27] and 0.3 m/s on the 10MTWT[2,30], proved to be attainable in the present patient sample despite the relatively high pre-test performance stressing the feasibility of the program in this population. However, the generalization of this exercise program to more severely affected patients remains unclear. Fourth, there was no follow-up in the present pilot study. With that, the long-term effects of the high-intensity program on ambulatory activity for walking competency in the community remain unclear. Furthermore, the underlying mechanisms that drive the observed changes in gait performance following a high-intensity task-oriented training program remain unclear. Above findings are in agreement with the observation that improvement of walking ability is weakly associated with observed changes in strength and synergism of the paretic leg itself[3, 4, 7] and suggest that improvements in gait could be associated with increased cardiorespiratory capacity and adaptations of the non-hemiplegic side rather than restoration of motor impairments on the hemiplegic side[7], enabling a decrease in energy expenditure. Finally, the findings in the present study suggest to be in line with observations in studies which used measures to evaluate cardiorespiratory capacity[17, 41]. However the measures in the present study were not feasible as to reveal underlying mechanisms in terms of cardiorespiratory capacity or energy expenditure. Therefore, future research should emphasize on clarifying whether increased walking competency is due to a more efficient energy-expenditure induced by improved motor control during walking (i.e., restitution of function) or rather an increased cardiorespiratory capacity (i.e., compensation), or both[5].

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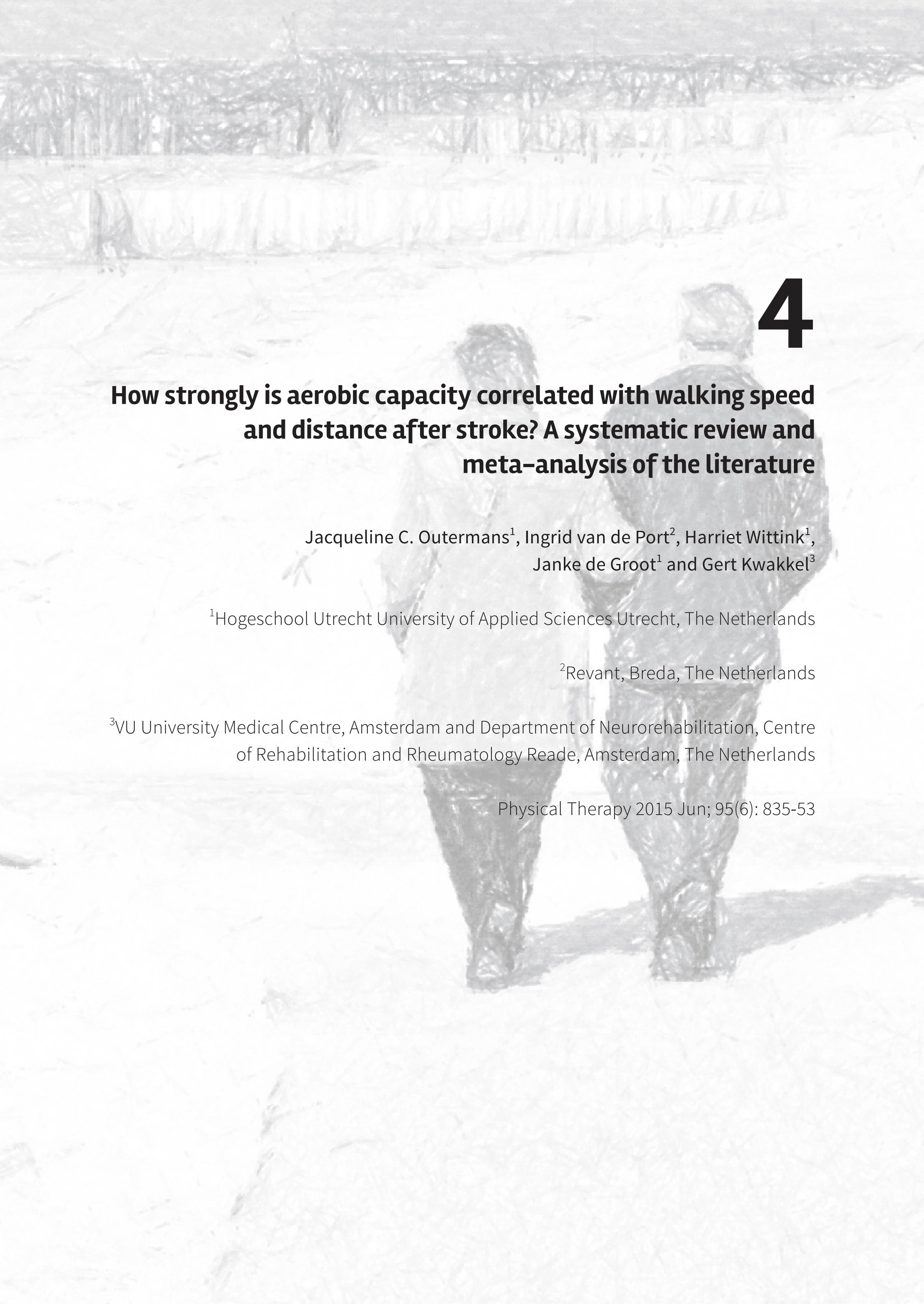

4

How strongly is aerobic capacity correlated with walking speed and distance after stroke? A systematic review and meta-analysis of the literature

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Abstract

Background: Restoration of walking capacity as reflected by walking speed and walking distance is a primary goal after stroke. Peak aerobic capacity (VO_{2peak}) is suggested to be correlated with walking capacity post stroke. Although the strength of this correlation is unclear, physical therapy programs often target walking capacity by means of aerobic training.

Purpose: The purpose of this systematic review was to summarize the available evidence on the correlation between VO_{2peak} and walking capacity.

Data sources: The databases MEDLINE, CINAHL, Embase, Cochrane and Sportdiscus were searched up to May 2014.

Study selection: Cross-sectional studies reporting correlation coefficients between VO_{2peak} and walking capacity in stroke were included, along with longitudinal studies reporting these correlation coefficients at baseline.

Data extraction: The methodological quality of the studies was assessed using a checklist of 27 items for observational research. Information on study design, stroke severity and recovery, assessments and outcome of VO_{2peak} and walking capacity as well as the reported correlation coefficients, were extracted.

Data Synthesis: Thirteen studies involving 454 participants were included. Meta-analyses showed combined correlations coefficients (r_m) of VO_{2peak} and walking speed and VO_{2peak} and walking distance of r_m = 0.42 (95%CI: 0.31 – 0.54) and r_m = 0.52 (95%CI; 0.42 – 0.62), respectively.

Limitations: The studies included in the present review had small sample sizes and low methodological quality. Clinical and methodological diversity challenged the comparability of the included studies, despite statistical homogeneity. Relevant data of three studies could not be retrieved.

Conclusions: The strength of the correlation of VO_{2peak} with walking speed was low and moderate for VO_{2peak} and walking distance, respectively, indicating that other factors, besides VO_{2peak}, determine walking capacity after stroke.

Introduction

Improving walking capacity is often a primary goal in rehabilitation after stroke[1, 2]. In stroke, walking capacity reflects the autonomy in walking enabling daily life mobility[3], which can be expressed in walking distance and walking speed[4]. Recent large-scale intervention studies have demonstrated post rehabilitation mean walking distance achieved in six minutes ranging from 168 m[5] to 416 m[6] in individuals after stroke. These mean walking distances are significantly less than the mean value for healthy populations, which varies between 510 m and 638 m[7]. A meta-analysis on the effects of rehabilitation on walking speed after stroke, including 28 trials[8], showed mean values of walking speed at baseline in individuals with stroke varying between 0.11 m/s and 1.20 m/s, as opposed to 1.20-1.46 m/s in healthy elderly adults[9].

It has been suggested that walking capacity in individuals after stroke is positively associated with motor functions such as lower limb strength[10-12], balance[13-15] and cognitive functions[16]. Similarly, aerobic capacity (VO_{2peak}) has been suggested to be an important indicator of walking capacity after stroke [15, 17-19]. To date, statistically significant positive correlation coefficients (r) have been found between VO_{2peak}, and walking distance[15, 17] and walking speed[18, 19] after stroke. However, the magnitude of reported correlation coefficients between VO_{2peak} and walking capacity varies considerably. Some studies reported low correlation coefficients of 0.29[18] and 0.37[20], whereas other studies showed high values 0.71[21] and 0.74[17]. Despite this broad range of reported correlation coefficients, many physical therapy programs in stroke target walking capacity by means of aerobic training. A number of recent reviews[22-24] suggest that these programs have positive effects, which appears to confirm the relation between VO_{2peak} and walking capacity. However, these reviews[22-24] were not aimed at establishing an overall conclusion about the correlation between VO_{2peak} and walking capacity. Moreover, only a few of the included studies reporting on the effects of aerobic training on walking capacity, have actually measured both VO_{2peak} and walking capacity[24]. As a consequence, the true strength of the correlation between VO_{2peak} and walking capacity remains unclear.

A clearer perspective on the strength of the correlation between VO_{2peak} and walking capacity after stroke may add to the rationale behind the incorporation of aerobic exercise into rehabilitation programs. Therefore, the aim of the present systematic review is to summarize the available evidence on the magnitude of the reported correlation coefficients between VO_{2peak} and walking capacity (i.e., walking distance and walking speed) in individuals after stroke.

Methods

The present study was a systematic review of the available literature. The PRISMA-statement was followed for reporting items of this systematic review[25].

Data Sources and Searches

In the initial computerized search, the databases MEDLINE, CINAHL, Embase, Cochrane and Sportdiscus were searched for relevant publications. Included publications were screened by hand to identify any additional publications for inclusion. The search was completed on May 30, 2014.

The search terms “stroke”, “aerobic capacity” and “walking capacity” were used to develop a PubMed search string to search MEDLINE, which was afterwards adapted to the search machines of the other databases. All known synonyms and related terms of the search terms were collected, and, where available, Mesh-headings, CINAHL-headings and EMtree-headings were used in the search strategy. An information specialist (JM) was consulted to compile the search strings. Appendix 1. provides an expansion of all search terms entered in PubMed searching MEDLINE. The search strings used for the other databases are available on request from the corresponding author.

One researcher (JO) performed the data search in cooperation with the information specialist (JM). All retrieved citations were imported in RefWorks 2.0 (RefWorks, Bethesda, Maryland) after which the duplicates were removed.

Study selection

The following selection criteria were used to identify the relevant publications. First, the study design concerned cross-sectional or longitudinal studies, randomized controlled trials (RCT) and reliability studies reporting relevant correlation coefficients between VO_{2peak} and walking capacity (i.e., walking distance or walking speed). Second, the population included in the studies concerned stroke-patients, as defined by the World Health Organization (WHO)[26], over 18 years. Third, the investigated variables were walking capacity and VO_{2peak}.

Walking capacity was defined as “the degree of autonomy in walking, with or without the aid of appropriate assistive devices (such as canes or walkers), safely and sufficiently to carry out mobility-related activities of daily living”[3] expressed in walking distance or walking speed measured in standardized circumstances[4]. Peak aerobic capacity was defined as the highest oxygen uptake an individual attains during physical work using large muscles in lower extremities (i.e., during walking or cycling) while breathing air at sea level measured during standardized circumstances[27].

The studies had to report physically performed assessment of walking capacity, such as a Six-Minute Walk Test (6MWT) for walking distance (m) or a Ten-Meter Timed Walk Test (10MTWT) for walking speed (m/s), and VO_{2peak}, using treadmill or bicycle ergometer protocols and breath-by-breath gas analysis equipment. Last, the publications were written in English, Dutch, German or French.

All retrieved publications were screened with respect to the inclusion criteria first on title and abstract and subsequently on full text. Two researchers (JO and IvdP) independently performed the screening and selection of articles. Throughout the selection process all disagreement regarding inclusion was discussed until consensus with respect to the inclusion criteria was reached. If disagreement persisted a third author (HW) was consulted.

Data Extraction and Quality assessment

The following information was extracted: study ID (author and year); study design; source population and recruitment; number of participants; age; time since onset; stroke type, localization, and severity; assessment protocols; and mean values of VO_{2peak}, walking speed and/or walking distance and the correlation coefficients between walking capacity and VO_{2peak}. Corresponding authors of included studies were contacted in case of inconclusive or incomplete data.

Two researchers (JO and IvdP) independently performed the quality assessment. The quality of the studies was assessed with a checklist to evaluate prognostic studies[28], which is in line with the Strengthening Observational Studies in Epidemiology (STROBE) guidelines[29]. The 27-item checklist addresses six major risks of bias: study participation, study attrition, predictor measurement, outcome measurement, statistical analysis and clinical performance and validity. In case the included studies involved cross-sectional studies, the items “Inception cohort” (D5), “Information about treatment” (D6), “Number of loss to follow up” (A1), “Reasons for loss to follow up” (A2), “Comparison completers and non-completers” (A4) and “Appropriate end point of observations” (O4) were considered as “not applicable”. Each item was graded “positive”, “negative”, ”unknown/partial” or “not applicable”. A positive grade was given in case of sufficient information, indicating low risk of bias, assigning one point. A negative grade was given in case there was no information, indicating a high risk of bias, assigning zero points to the item. An unknown/partial grade was given in case of insufficient information, leaving the risk of bias is unknown, assigning a ‘?’. A not applicable (NA) grade was given when the item was not applicable for the evaluated study. Summing all items that were graded positive and dividing this by the total number of applicable items calculated the total score. A study was considered to have a low risk of bias when it scored ≥ 75% of its maximum score, otherwise they were considered to have a high risk of bias[28].

With respect to the interrater reliability of the quality assessment of the studies the percentage agreement on the items and Cohen’s kappa (κ) were calculated. Cohen’s kappa was considered poor (≤0.0), slight (0.0 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), or almost perfect (0.81 to 1.0)[30]. Calculations were performed with SPSS 20 (IBM Corp, Armonk, New York).

Data Synthesis and Analysis

To explore possible publication bias, a funnel plot was made by plotting the correlation coefficients (r) against the number of participants (n) in the study. Next the symmetry of the plot was assessed visually, where the studies should be symmetrically distributed on both sides of the combined correlation coefficient line to indicate the absence of publication bias[31]. The visual assessment was performed separately for the studies correlating VO_{2peak} and walking speed and VO_{2peak} and walking distance, respectively. A heterogeneity analysis was performed to determine statistical heterogeneity as a cause for asymmetry in the funnel plots[31], using the Higgins I^2-test[32]. As proposed by Higgins[32], a value higher than 50% was considered an indicator of substantial heterogeneity. The I^2 value was calculated from the Q statistic as proposed by Hunter-Schmidt[33, 34] from the samples sizes and effect sizes.

Two meta-analyses were performed pooling the studies with respect to walking speed and walking distance. The combined correlation coefficient (r_m) between walking capacity and VO_{2peak} was obtained by using all the reported correlation coefficients (i.e., Pearson correlation coefficient (r_p) as well as Spearman rank correlation (r_s)) using the random effects method as described by Hunter-Schmidt[33, 34]. In case of a longitudinal design, only reported baseline data were used for the present review. The combined correlation coefficient was considered low from r_m = 0.26 to 0.49, moderate from r_m = 0.50 to 0.69, high from r_m = 0.70 to 0.89 and very high from r_m = 0.90 to 1.00[35]. Generalizability of the calculated value was estimated by a credibility interval using the variance in population correlations[34]. The statistical significance of the difference between the combined correlation coefficient of VO_{2peak} with walking speed and walking distance, respectively, was calculated using a Students T-test ($P \leq 0.05$). The statistical analyses were performed using Microsoft Office Excel 2013 (Microsoft Corp, Redmond, Washington), incorporating the calculations as proposed by Hunter-Schmidt[33, 34].

Results

Study selection

The searches of the databases delivered a total of 1,613 citations, as shown in the flowchart (Fig. 1). After subtraction of the duplicate records 1,125 studies remained to be screened on title and thereafter 152 for screening on abstract. Four studies were excluded for language reasons, 25 were excluded on design, and 73 on outcome measures and only an abstract was available for five studies. Forty-five citations remained for full text examination. One study was excluded for non-availability of relevant data[36]. Fifteen studies were excluded for not reporting correlations between VO_{2peak} and walking capacity and 16 for not using physical assessments of performance. Finally, 13 studies were included in this review, all reporting correlations between VO_{2peak} and walking capacity as shown in Table 1.

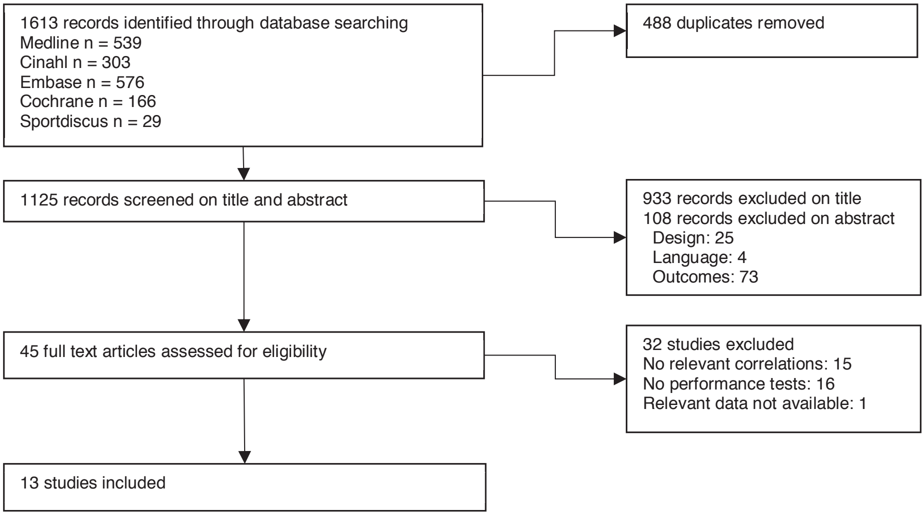


Figure 1. Flowchart of the publication selection.

Visual assessment of the funnel plots showed slight asymmetry (Figs. 2 and 3). Heterogeneity analysis showed an overall homogeneous sample for the studies concerning walking speed (I^2 = 0%, Q = 3.80, df = 4, p = 0.63) as well as walking distance (I^2 = 0%, Q = 0.24 df = 9, p = 0.51).

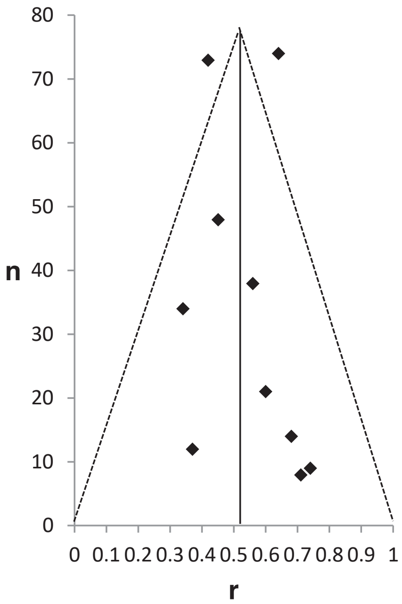


Figure 2. Funnelplot for the included studies concerning walking distance.

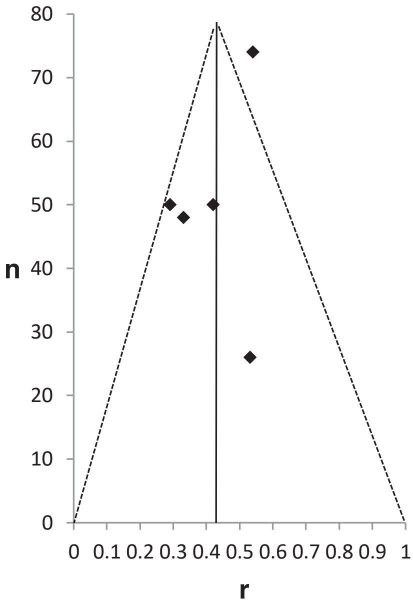


Figure 3. Funnelplot for the included studies concerning walking speed.

Table 1. Study Characteristics.

Citation	Design	n (male)	Age mean (SD)	Time since Onset & Stroke severity mean (SD)	Stroke type & Stroke localization
Baert et al. 2012[19]	Longitudinal cohort, repeated correlations, baseline correlation included	40 (26)	57.2 (11.4)	3 months **NIHSS 4.9 (4.2)**	31 Ischemic, 19 Left, 7 bilateral
Calmels et al. 2011[42]	Clinical trial, baseline assessment included	14 (12)	53.7 (8.6)	12.1(7.52) months. **BFM LE 19.2 (6)**	11 Ischemic, 7 Left
Carvalho et al. 2008[40]	Cross -sectional	34	60 (4.1)	62 (33) months **BFM LE 30 (13)**	23 Ischemic, 19 left
Courbon et al. 2006[37]	Cross -sectional	21 (18)	53.48 (7.65)	24.52 (27.98) months. **BFM LE 19.1 (6.3)**	17 Ischemic, 12 Left
Eng et al. 2004[20]	Reliability study, baseline assess-ment included	12 (11)	62.5 (8.6)	3.5 (2.0) years **AHASOC II (8), III (4). Chedoke McMaster Stroke Assessment LE 9.4(2.5) (1-14)**	8 ischemic, 7 Left

Measures & Protocols VO_{2peak} (mL/kg/min)		Measures & Protocols Walking Capacity		Correlations
Cycle protocol mean (SD)	Treadmill protocol mean (SD)	Speed (m/s) mean(SD)	Distance (m) mean(SD)	
VO_{2peak} :18.1(6.2) Symptom limited graded cycle ergometer test, start at 10 W, stepwise increment 10W/min, 50-60 RPM VO_{2peak}: Average value of sec 20-50 of the last completed increment		10MTWT: *1.52(0.28)* maximal speed		$r_p = 0.42$ $p > 0.01$
VO_{2peak} 18.5 (3.7) Symptom limited graded cycle ergometer test, start at 10 W, stepwise increment 10W/min, 60 RPM			6MWT: *231. 3 (150.9)* 70 m course	$r_p = 0.68$ $p < 0.05$
VO_{2peak} 10.7 (5.5) Symptom limited graded one legged cycle ergometer test. Peak level of oxygen consumption			6MWT: *365.2 (142.6)* 30 m course ATS protocol	$r_s = 0.34$ not significant
VO_{2peak} 17.98 (4.24) Symptom limited graded cycle ergometer test, start at 10 W, stepwise increment 10W/min, 60 RPM		20MTWT: 10 m and return *Time needed:* *42.88 sec. (30.52)*	6MWT: *267.8 (154.9)* 100 ft course	VO_{2peak}-20MTWT no significant correlation VO_{2peak}-6MWT $r_p = 0.60$ $p < 0.0032$
VO_{2peak} 17.2 (3.0) Symptom limited graded cycle ergometer test, start at 0 W, stepwise increment 20 W/min VO_{2peak}: 1) RER ≥ 1.15, 2) failure of HR to increase with further increases in exercise intensity, 3) a plateau in VO_2 or < 1.5 mL/kg/min increase in VO_2 following workload increases, or 4) volitional fatigue.			6MWT: *378.3 (123.1)* around a 42 m rectangular path	$r_p = 0.37$ $p > 0.05$

Table 1. Study Characteristics. (continued)

Citation	Design	n (male)	Age mean (SD)	Time since Onset & Stroke severity mean (SD)	Stroke type & Stroke localization
Michael et al. 2005[18]	Cross -sectional	50 (28)	65 (Range 45-84)	10.3 months (Range 6-166) **NIHSS 3.6**	50 ischemic
Ovando et al. 2011[21]	Feasibility study on assess-ment VO_{2peak}	8 (6)	53 (17)	18 (11) months **BFM LE 25 (4.5)**	5 Ischemic
Patterson et al. 2007[15]	Cross -sectional	74 (43)	64 (10)	48 (59) months **NIHSS 4.9 (4.2)**	
Pang et al. 2005[14]	Cross -sectional	73 (36)	65.3 (8.7)	5.5 (4.9) years **AHASOC II (34), III(17)**	24 Ischemic, 22 Left

Measures & Protocols VO_{2peak} (mL/kg/min)		Measures & Protocols Walking Capacity		Correlations
Cycle protocol mean (SD)	Treadmill protocol mean (SD)	Speed (m/s) mean(SD)	Distance (m) mean(SD)	
	VO_{2peak} 11.7 (2.8) Constant velocity, graded treadmill test VO2peak at volitional fatigue	10MTWT: *0.42 (0.20)* 10 m with ramp up ramp down		$r_p = 0.29$ $p > 0.05$
	VO_{2peak} 20.6 (5.7) Graded velocity, from 70%-140% of comfortable overground walking speed and graded inclination (max 10%) treadmilltest VO_{2peak}: highest VO2 achieved	10MTWT: *0.90 (0.30),* comfortable speed *1.26 (0.40),* fastest speed 14 m course, time to walk 10 meters recorded	6MWT: *400.9 (136)* 30 m course	No significant correlations VO_{2peak} and 10MTWT VO_{2peak}-6MWT: $r_s = 0.71$ $p = 0.04$
	VO_{2peak} 13.1 (4) Constant velocity, graded treadmill test	30 ft TWT (9.1MTWT): self-selected speed 0.*51 (0.26)*		VO_{2peak}-30footTWT: $r_p = 0.54$ $p < 0.001$ VO_{2peak}- 6MWT. $r_p = 0.64$ $p < 0.001$
Symptom limited graded cycle ergometer test, 29 less impaired subjects start 20 W, increments 20W/min, 34 more impaired subjects start at 10 W, increments 10W/min 60 RPM VO_{2max}: (1) RER ≥ 1.0, (2) plateau VO_2 (<150 mL/min) with increase in exercise intensity, or (3) volitional fatigue (*i.e.*, decline in cycling rate <30 RPM) *VO_{2max} 22.0 (4.8)*			6MWT: *370.2 (159.6)* 42 m rectangular course, normalized for leg length	$r_p = 0.40$ $p < 0.05$

Chapter 4

Table 1. Study Characteristics. (continued)

Citation	Design	n (male)	Age mean (SD)	Time since Onset & Stroke severity mean (SD)	Stroke type & Stroke localization
Ryan et al. 2001[38]	Cross sectional	26 (22)	66 (9)	3.2 (4.7) years	
Severinsen et al. 2011[39]	Cross sectional	48 (35)	68 (9)	18 (6) months **SSS 51(6).** **BFM 68(25)**	48 Ischemic
Tang et al. 2006[41]	Cross sectional	38 (14)	64.6 (14.4)	< 3 months **NIHSS 2.8.** **Chedoke McMaster Stroke Assess ment LE 5.1 (1-7)**	25 Ischemic, 1 unknown
Tseng et al. 2009[17]	Cross sectional	9 (2)	56.8 (11.8)	47.6 (51.2) months **BFM 79 (32)**	

Abbreviations: NIHSS: National Institutes of Health Stroke Scale, BFM: Brünstrom Fugl Meyer , LE: lower extremity, AHASOC: American Heart Association Stroke Outcome Classification, SSS: Scandinavian Stroke Scale, V: speed, d: distance, W: watts; VO_2: volume oxygen; 10MTWT: 10 meter timed walking test; 6MWT: 6 minute walk test; RPM: revolutions per minute; ATS: American Thoracic Association; RER: respiratory exchange ratio; HR: heart rate.

Study and subjects' characteristics

Table 1 shows that 10 of the 13 included studies were cross-sectional cohort studies [14, 15, 17, 18, 21, 37-41]. Three studies used other designs: two studies used a longitudinal design[19, 20] and one study concerned the baseline analysis of a CT[42]. Of these 3 studies the

Measures & Protocols VO_{2peak} (mL/kg/min)		Measures & Protocols Walking Capacity		Correlations
Cycle protocol mean (SD)	**Treadmill protocol mean (SD)**	**Speed (m/s) mean(SD)**	**Distance (m) mean(SD)**	
	VO_{2peak} 15.6 (4.4) *Constant* velocity, graded treadmill test: Inclination increments 2%/ 2 min VO_{2peak}: highest value in the last minute of exercise	30 ft TWT (9.1MTWT): self-selected speed 0.*63 (0.31)*		$r_p = 0.53$ $p < 0.01$
VO_{2peak} 16.3 (4.9) Maximal progressive cycle ergometer test, VO_{2peak}: maximal rate achieved during any 30 s period		10 MTWT: *0.84 (0.30)*	6MWT: *291.0 (171.0).* 100 ft course ATS protocol	VO_{2peak}-10MTWT $r_p = 0.33$ $p < 0.05$ VO_{2peak}-6MWT. $r_p = 0.45$ $P < 0.05$
VO_{2peak} 12.3 (3.1) Maximal progressive semi recumbent cycle ergometer test, start at 10 W, increments 5 W/ min, 50 RPM VO_{2peak}: maximal rate achieved during any 30 s period			6MWT: *d: 341.6 (107.9)* 30 m course ATS protocol	$r_p = 0.56$ $p < 0.001$
VO_{2peak} 12.91 (3.7) Maximal progressive cycle ergometer test, start at 0 W, increments 10 W/min, 50 RPM VO_{2peak} was determined by 1) reaching 90% of the predicted maximal heart rate [(220-age) x 0.9], and 2) RER ≥ 1.1			6MWT: *295.5 (171.4)* 100 ft course	$r_p = 0.74$ p= 0.03

correlation coefficients that were calculated from baseline assessments only were used in the analyses of the present review.

A total of 454 participants (184 females, 270 male), with a mean age ranging from 53[21] to 68 years[39] were included in the present review. In two of the studies the participants were less than three months post stroke[19, 41] (Table 1). Two studies did not report stroke type[15, 38]. The majority of the patients in the remaining studies (i.e., 258 of the 335), had an ischemic stroke. Six studies reported stroke localization[14, 19, 20, 39, 40, 42] showing 110 out of 236 participants sustained a left hemispheric stroke, 117 a right hemispheric stroke and nine a bilateral hemispheric stroke (Table 1). Stroke severity was reported in four studies[15, 18, 19, 41] using the National Institutes of Health Stroke Scale (NIHSS) with scores ranging from mean 2.8 to 4.9 points out of maximally 42 points. Two studies[14, 20] classified their sample according to the American Heart Association Stroke Outcome Classification. One study[14] classified 70%, and the other study[20] 100% of their sample in categories II and III. Two studies[20, 41] used the Chedoke-McMaster Stroke assessment of the lower extremities to determine stroke recovery. Eng et al.[20] reported a mean score of 9.4 (maximum score = 14 points) 3.5 years post stroke. Tang et al.[41] reported a mean score of 5.1 (maximum score = 7 points) 3 months post stroke. The Brunnstrom-Fugl Meyer (BFM) was used in four studies[21, 37, 40, 42] to assess motor recovery in the lower extremities. The scores ranged from mean 19.1 to 30 points at 12.1- 62 months post stroke. Two studies[17, 39] reported a mean total score on the BFM of 79[17] and 68[39] at 47.6[17] and 18[39] months post stroke, respectively.

Outcome assessments

Table 1 shows that in four studies VO_{2peak} was assessed on a treadmill[15, 18, 21, 38] and that a bicycle ergometer was used in the remaining nine studies. Mean VO_{2peak} ranged from 10.7[38] to 22[14] mLO_2/kg/min. One study[40] used a one-legged bicycle protocol. Eight studies[14, 15, 17, 19, 20, 38, 40, 41] used the Guidelines of the American College of Sports Medicine (ACSM)[43] and two studies[37, 42] followed the approach described by Åstrand and Rodahl[44] to determine VO_{2peak}. Two studies[19, 38] reported the determination of VO_{2peak} during the last minute of the test. Two studies[14, 20] reported VO_{2max} in all participants, and one study[17] reported this in three out of nine participants. Four studies[14, 19, 21, 38] reported respiratory exchange ratios (RER) with mean values of 0.96[21, 38], 1.01[19] and 1.12[14]. Three studies[14, 20, 21] reported peak heart rate (HR_{peak}) as a percentage of predicted maximal heart rate ($\%HR_{max}$) showing means of 77.8%[21], 98.1%[14] and 94.7%[20].

Walking speed was assessed in seven studies[15, 18, 19, 21, 37-39]. Two studies used a 30-ft (1ft = 0.3048 m) timed walk[15, 38], one study used a 20-m timed walk[37] and the other four studies used the 10MTWT. Two studies used maximal gait speed[19, 21] as opposed to self-selected gait speed in the other 5 studies. Mean walking speed varied from 0.42 m/s[18] to 1.52 m/s [19] (Table 1.). Walking distance was assessed with the 6MWT in ten studies[14, 15, 17, 20, 21, 37, 39-42]. Seven studies[15, 17, 21, 37, 39-41]used a straight course of 30 m. or 100 ft. One study[42] used a straight course of 70 m. and two studies[14,20] used rectangular courses of 42 m. All studies[14, 15, 17, 20, 21, 37, 39-42] reported the maximal walking distance in six minutes, which ranged from a mean 216.0[15] to 400.9[24] m. One study[14] reported the walking distance adjusted to leg length.

Study quality

Table 2 shows that all studies scored less than 53% (range = 38-53%) of the maximal methodological quality score and were classified as ‘high risk of bias. The items that were most often scored negative were "source population and recruitment" (item D1), "important key characteristics" (item D3), "measurement of VO_{2peak} valid and reliable" (item P2), all items on statistical analyses and all items on clinical performance.

Percentage agreement on the individual items between the two raters was 91%, with a Cohens kappa of 0.60. Percentage agreement on the qualification of risk of bias was 100%. Both raters scored all studies as having a high risk of bias.

Synthesis of the results

Correlations VO_{2peak} and walking speed

Seven studies calculated the correlation coefficient between walking speed assessed with a short timed walk and VO_{2peak} [15, 18, 19, 21, 37-39]. Two studies found a statistically nonsignificant correlation coefficient, but did not report the values[21, 37]. Figure 4 shows the five studies[15, 18, 19, 39, 40] reporting statistically significant correlations coefficients (r) ranging from 0.29[18] to 0.54[15].

Correlations VO_{2peak} and walking distance

Figure 4 shows the ten studies that calculated the correlation coefficient between walking distance assessed with the 6MWT and VO_{2peak}[14, 15, 17, 20, 21, 37, 39-42]. All studies demonstrated statistically significant correlation coefficients (r) varying between 0.42[14] and 0.74[17], except for Eng et al.[20] and Carvalho et al.[40], who reported non-significant correlation coefficients of 0.37 and 0.34, respectively.

Three studies[14, 15, 41] conducted a multivariate analysis. The study by Patterson et al.[15], found that VO_{2peak} explained most of the variance (48%) in walking distance on a 6MWT. The study also explored the difference in explained variance in two subgroups of slow (< 0.48 m/s) and faster (> 0.49 m/s) walkers and found that balance explained 42% of the variance in the slower walkers, whereas VO_{2peak} explained 26% of the variance in faster walkers. The other two studies[14, 41] did not find VO_{2peak} to be a significant determinant of walking distance on the 6MWT.

Meta–analyses

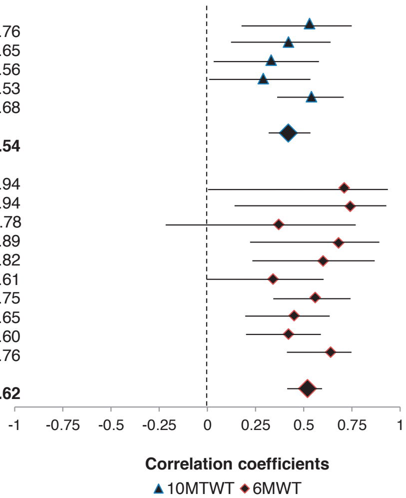
Figure 4 shows first the meta-analyses of the correlation coefficients between VO_{2peak} and walking speed. A combined correlation coefficient (r_m) of 0.42 (95% credibility interval [95% CI] = 0.31 - 0.54) was calculated. Figure 4 also shows the meta-analysis of the correlation coefficients between VO_{2peak} and walking distance. A combined correlation coefficient of 0.52 (95%CI = 0.42 - 0.62) was calculated. The difference between combined correlation coefficients of VO_{2peak} with walking speed and of VO_{2peak} with walking distance was not statistically significant ($p = 0.61$).

Table 2. Quality assessment of the included studies.

	Items	Baert et al. 2012[19]	Calmels et al. 2011[42]	Courbon et al. 2006[37]	Eng et al. 2004[20]	Michael et al. 2005[18]	Ovando et al. 2001[21]	Pang et al. 2005[14]	Patterson et al. 2007[15]	Ryan et al. 2001[38]	Severinsen et al. 2007[39]	Tang et al. 2006[41]	Tseng et al. 2009[17]	Carvalho et al. 2008[40]
D1	Source population and recruitment	?	?	?	?	?	?	n	?	n	y	?	n	?
D2	Inclusion and exclusion criteria	y	y	y	y	y	y	y	y	?	y	y	y	y
D3	Important baseline key characteristics of study sample	?	?	?	y	?	?	?	?	?	?	?	?	?
D4	Prospective design	n	y	n	n	n	n	n	n	n	n	n	n	n
D5	Inception cohort	y	n	n	na	n	na	n	n	na	n	na	na	n
D6	Information about treatment	na	?	na	na	na	na	na	na	na	na	na	na	na
A1	Number of loss to follow-up	na	y	na	na	na	na	na	na	na	na	na	na	na
A2	Reasons for loss to follow-up	na	y	na	na	na	na	na	na	na	na	na	na	na
A3	Methods dealing with missing data	n	n	y	y	n	y	y	n	y	y	n	y	n
A4	Comparison completers and non-completers	na	n	na	na	na	na	na	na	na	na	na	na	na
P1	Definition of independent variables/predictors	y	y	y	y	y	y	y	y	y	y	y	y	y
P2	Measurement reliable and valid	n	n	n	n	?	n	?	?	?	y	n	?	y
P3	Coding scheme and cut-off points	y	y	y	y	y	y	y	y	y	y	y	y	y
P4	Data presentation	y	y	y	y	y	y	y	y	y	y	y	y	y
O1	Outcomes defined	y	y	y	y	y	y	y	y	y	y	y	y	y
O2	Measurement reliable and valid	y	y	y	y	y	y	y	y	y	y	y	?	y
O3	Coding scheme and cut-off points	y	y	y	y	y	y	y	y	y	y	y	y	y
O4	Appropriate end-points of observation	y	y	na	na	na	na	na	na	na	na	na	na	n
O5	Data presentation	y	y	y	y	y	y	y	y	y	y	y	y	y
S1	Strategy for model building	n	n	n	n	?	n	?	?	n	n	?	n	n
S2	Sufficient sample size	n	n	n	n	n	n	n	n	n	n	n	n	n
S3	Presentation univariate analysis	n	n	n	n	n	n	n	n	n	n	n	n	n
S4	Presentation multivariate analysis	n	n	n	n	?	n	n	n	n	n	n	n	n
S5	Continuous predictors	n	n	n	n	y	n	y	y	n	n	y	n	n
C1	Clinical performance	n	n	n	n	y	n	n	y	n	n	n	n	n
C2	Internal validation	n	n	n	n	n	n	n	n	n	n	n	n	n
C3	External validation	n	n	n	n	n	n	n	n	n	n	n	n	n
	yes/applicable items	10/23	12/27	9/22	10/21	10/22	9/21	11/22	11/22	8/21	11/22	8/21	11/21	9/23
	% score	43%	44%	41%	48%	50%	43%	50%	50%	38%	50%	38%	53%	39%

Abbreviations: y = positive, n = negative, ? = unknown or partial, n.a. = not applicable. See appendix 2 for criteria to score the items.

Reference	n	r	95% CI
Ryan et al, 2001	26	0.53	0.18 - 0.76
Baert et al, 2012	40	0.42	0.12 - 0.65
Severinsen et al, 2011	48	0.33	0.05 - 0.56
Michael et al, 2005	50	0.29	0.01 - 0.53
Patterson et al, 2007	74	0.54	0.36 - 0.68
Weighted mean r_m 10MTWT	**238**	**0.42**	**0.31 - 0.54**
Ovando et al, 2011	8	0.71	0.01 - 0.94
Tseng et al, 2009	9	0.74	0.15 - 0.94
Eng et al, 2004	12	0.37	-0.26 - 0.78
Calmels et al, 2011	14	0.68	0.23 - 0.89
Courbon et al, 2006	21	0.60	0.23 - 0.82
Carvalho et al, 2008	34	0.34	0.00 - 0.61
Tang et al, 2006	38	0.56	0.29 - 0.75
Severinsen et al, 2011	48	0.45	0.19 - 0.65
Pang et al, 2005	63	0.42	0.19 - 0.60
Patterson et al, 2007	74	0.64	0.48 - 0.76
Weighted mean r_m 6MWT	**321**	**0.52**	**0.42 - 0.62**



Abbreviations: 10MTWT: 10 meters timed walking test, 6MWT: 6 minutes walk test

Figure 4. Forest plot depicting effect sizes (*r*) for the association of VO2peak with mean values of walking speed on 10 MWT and walking distance measured with the 6MWT, respectively for included individual studies. Error bars depict the 95% credibility interval.

Discussion

This systematic review provides an overview of the currently available evidence for the strength of the correlations between VO_{2peak} and walking capacity, expressed as walking speed or walking distance, after stroke. The results of this present study show a low positive combined correlation coefficient between VO_{2peak} and walking speed and a moderate combined positive correlation between VO_{2peak} and walking distance that are both statistically significant.

These findings suggest that other factors, such as age, balance, stroke severity or lower extremity muscle strength may influence the correlation between VO_{2peak} and walking capacity. In addition to the positive correlations between VO_{2peak} and walking capacity, four of the included studies[14, 15, 18, 40] reported significant positive correlation coefficients between balance and walking capacity (r = 0.38 - 0.85). Two studies [37, 40] reported significant positive correlation coefficients between stroke severity and walking capacity, (r = 0.59 - 0.72) and three studies[14, 15, 39] reported significant positive correlations between knee extensor muscle strength and walking capacity (r = 0.18 - 0.60). These reported correlation coefficients display a similar broad range and similar values as the ones between VO_{2peak} and walking capacity. Additionally, the highest correlation coefficients (r ≥ 0.60) were reported in the studies using younger (mean age ≤ 56 years) populations[17, 21, 37, 42] suggesting that age, as might be expected, may have influenced the correlation between VO_{2peak} and walking capacity. All of these factors: age, balance, stroke severity or lower extremity muscle strength, may have had an impact on the reported correlation coefficients and partly account for the broad range of correlation coefficients found in the present review.

Unfortunately, most studies included in this systematic review, were limited to bivariate analyses enabling an only restricted insight into factors influencing the correlation between VO_{2peak} and walking capacity. Only three of the included studies[14, 15, 41] applied multivariate analyses to identify the determinants of walking capacity, unfortunately displaying disparate results. The first of these studies[14] reported balance as the most important determinant for walking distance, explaining 66,5% of the variance of outcome. The second study[15] showed VO_{2peak} to be a significant predictor for 6MWT. This study[15] reported furthermore that the explained variance of the 6MWT by VO_{2peak} might differ in subpopulations, as balance was the strongest predictor in patients with slower walking speeds (< 0.48 m/s) whereas VO_{2peak} was the strongest predictor in faster (> 0.49 m/s) walker speeds. The last of these three studies[41] identified fast walking speed as the main determinant for the 6MWT, explaining 65,4% of the variance of outcome.

The high predictive validity of walking speed for outcome of walking distance[41] may also explain the absence of statistical significance with respect to the combined correlation coefficient of VO_{2peak} with walking speed when compared to that of VO_{2peak} with walking distance. This finding suggests that in individuals with stroke the contribution of VO_{2peak} is similar in walking speed, mostly assessed with short walks, and walking distance, mostly assessed with longer walks. This indicates that both outcomes have a common underlying construct in stroke patients, which is in line with several earlier studies[45, 46]. Physiologically, the expectation would be that there is a significantly stronger correlation of VO_{2peak} with walking distance than with walking speed, since a short walk would engage anaerobic metabolism, while a longer walk would engage aerobic metabolism[47]. However, this expectation was not confirmed in the present study.

The clinical and methodological variability of the included studies appear to be substantial. Time since stroke was diverse. Two studies[19, 41] presented a sample of stroke survivors less than three months post stroke, and two studies[14, 40] presented samples more than five years post stroke, reflecting clinical diversity. Overall, however, mild to moderate stroke severity as well as modest to good recovery were reported, suggesting a similar level of functioning between the samples.

Concerning the methodological variability, the assessment of walking capacity also displayed some diversity, specifically in the courses used in the 6MWT. According to the ATS guidelines[48] the effects of the length of the course may not affect the outcome as long as it measures between 50-164 ft. and presents a straight line. Three studies[14, 20, 42] deviated from this recommendation. Furthermore, one study[14] reported the results of the 6MWT adjusted for leg length, which may have affected the correlation. However, a *post hoc* sensitivity analysis without these studies[14, 20, 42] showed a nonsignificant increase of the combined correlation coefficient (r_m) of 0.57 (95%CI = 0.45 - 0.67). Likewise, the assessment of VO_{2peak} displayed diversity as four studies used a treadmill protocol[15, 18, 21, 38], whereas all other studies used a bicycle protocol.

It might be expected that the studies using a treadmill protocol to assess VO_{2peak} would report a stronger correlation with walking capacity as both assessments concerned walking protocols. However, this stronger correlation was not found in the present review. Furthermore, all except for two studies[14, 20] reported $VO_{2peak,}$ which reflects the highest amount of oxygen consumption attained during an exercise test but does not necessarily define the highest value attainable by the subject[49]. Although the majority of included studies reported the use of guidelines[43, 44], there was little information on the exact criteria used to determine $VO_{2peak.}$ Moreover, only five studies[14, 19-21, 38] reported RER or $\%HR_{max}$, which gives insight into the participants' effort during the assessments. The lack of information on both the exact criteria to determine VO_{2peak} and the participants' effort during the assessments, as well as the use of different protocols, presents a challenge to the comparability of the studies' reported values of VO_{2peak}. The differences in protocol and possibly participant's effort, in part, may explain the broad range of reported correlation coefficients.

In addition, the findings of the present study may be related to the lack of large-scale cohort studies affecting the precision of claimed correlation coefficients between walking speed and distance with VO_{2peak}. Half of the included studies had small sample sizes (30 or fewer participants), which challenges statistical power and representativeness of the sample and could lead to an overestimation of the combined correlation coefficient, as the highest correlation coefficients were found in the smallest studies[17, 20, 21, 42].

Despite the displayed clinical and methodological diversity, the included studies presented a homogeneous sample, according to statistical testing, indicating that the studies were comparable. This suggests that the combined correlation coefficients are a true representation of the correlations between VO_{2peak} and walking capacity in patients after stroke.

The methodological quality of all included studies was assessed as low which, although allowing for the pooling of the results of the included studies, challenges the strength of the evidence. Leaving out the studies that scored lowest in methodological quality of the meta-analyses only minimally altered the combined correlation coefficients between VO_{2peak} and walking speed (r_m = 0.41; 95%CI = 0.31 - 0.50) and of VO_{2peak} with walking distance (r_m = 0.54; 95%CI = 0.46 - 0.61)). This did not change the interpretation of the strength of the found correlations and the absence of a statistical significant difference between both combined correlation coefficients remained.

Limitations of the study

First, the assessment of methodological quality was based on recent recommendations for prognostic research as well as criteria used in previous scoring lists for assessment of prognostic stroke research, as specific quality assessments for cross-sectional studies are lacking. The assessment of methodological quality was performed strictly, which may have underestimated the quality of the studies. For example, "source population and recruitment" (item D1) and "important key characteristics" (item D3) were only graded positive in case the information matched exactly all criteria for the item. The overall negative grading of "measurement of VO_{2peak} valid and reliable" (item P2) was related to the lack of information on the effort of the participants during the assessments. However, the quality assessment provided a good insight of the strategies used to prevent bias and confounding. Second, relevant data of three studies could not be retrieved indicating data availability bias. Two studies[21,37], which were included for reporting a correlation coefficient between VO_{2peak} and walking distance, concluded that there was a nonsignificant correlation between VO_{2peak} and walking speed. Unfortunately, they did not report the correlation coefficient. A third study[36] reported correlation coefficients between both walking speed and distance and age adjusted VO_{2peak}. However, these three studies had small sample sizes varying from 8[21] to 21[37] suggesting that these correlation coefficients may only have had a minor impact on the found combined correlation coefficient. Third, despite a sensitive search, publication bias may still be present because of poor indexation of the literature reporting observational studies and because only published studies were considered. Visual inspection of the funnel plots showed slight asymmetry suggesting the presence of publication bias. Asymmetry could also be explained by heterogeneity in study methods[31]. However as statistical testing showed homogeneity of the included sample, the asymmetry of the funnel plots is likely to be explained by the presence of publication bias. Finally, none of the described methods to calculate combined correlation coefficients are completely suitable for a small number of studies and the Hunter-Schmidt method tends to underestimate the combined correlation coefficient[33, 34] a little (i.e., less than 0.01134). However, Field and Gillet[34] point out that in a Monte Carlo simulation the bias was negligible and produced accurate estimates of the population effect size. This finding indicates that the calculated combined correlation coefficient in the present study is probably accurate.

Future directions

Future observational research should follow the STROBE statements[29] to increase methodological quality and aim at conducting larger studies enabling multivariate analyses to reveal to which extent VO_{2peak} can explain walking capacity. Balance and stroke severity should be taken into the equation as well as age. Physiological reserve, defined as oxygen consumption during walking relative to VO_{2peak}[50], may also be considered as it was shown that reduced balance[51] and motor control[52, 53] increase oxygen requirements of walking in stroke. Although oxygen consumption during walking in stroke is minimized by means of reduction of walking speed[54] it can still remain at a high percentage of VO_{2peak}, as the latter is reduced in stroke[50] and decreases with age[47]. Therefore, the physiological reserve, as it depends on oxygen consumption during walking as well as VO_{2peak}, may therefore be more strongly related to walking capacity than VO_{2peak} itself. Consequently, in future research exercise physiological variables like oxygen uptake, RER or HR during the walking tests and during maximal exercise testing should be assessed and reported. Reporting those variables gives insight into the effort during maximal exercise testing, allowing calculation of the physiological reserve and increase comparability between studies.

Implications of the study

Although the results of the present study are to be considered carefully, a positive low to moderate correlation between walking capacity and VO_{2peak} is suggested. In physical therapy interventions aimed at improving walking capacity after stroke, therefore, it appears legitimate to address aerobic capacity. However, as other factors (e.g., age, balance, stroke severity and lower extremity muscle strength) are likely to affect the relationship between aerobic and walking capacity, a multifactorial approach appears to be the most efficient.

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Appendixes

1. Search string Pubmed

STROKE : (“Gait Disorders, Neurologic”[Mesh] OR hemipar*[tiab] OR hemipleg*[tiab] OR “Hemiplegia”[Mesh]) OR ((intracerebral[tiab] OR intracran*[tiab] OR cerebell*[tiab] OR cerebr*[tiab] OR brain*[tiab]) AND (“Paresis”[tiab] OR “Paresis”[Mesh])) OR ((bleed*[tiab] OR “Hematoma”[Mesh] OR hematom*[tiab] OR haematom*[tiab] OR hemorrhage*[tiab] OR haemorrhage*[tiab]) AND (subarachnoid[tiab] OR intracerebral[tiab] OR intracran*[tiab] OR cerebell*[tiab] OR cerebr*[tiab] OR brain*[tiab])) OR ((occlus*[tiab] OR emboli*[tiab] OR thrombos*[tiab] OR infarct*[tiab] OR ischaemi*[tiab] OR ischemi*[tiab]) AND (intracerebral[tiab] OR intracran*[tiab] OR cerebell*[tiab] OR cerebr*[tiab] OR brain*[tiab])) OR (“Brain Ischemia”[Mesh] OR “brain ischemia”[tiab] OR “brain ischaemia”[tiab] OR SAH[tiab] OR apoplex*[tiab] OR cva[tiab] OR brain vasc*[tiab] OR cerebrovasc*[tiab] OR “post stroke”[tiab] OR poststroke[tiab] OR “cerebrovascular disorders”[mesh:noexp] OR “cerebrovascular disorder”[tiab] OR “cerebrovascular disorders”[tiab] OR “carotid artery diseases”[mesh] OR “carotid artery disease”[tiab] OR “carotid artery diseases”[tiab] OR “intracranial arterial diseases”[mesh] OR “intracranial arterial disease”[tiab] OR “intracranial arterial diseases”[tiab] OR “intracranial arteriovenous malformations”[mesh] OR “intracranial arteriovenous malformations”[tiab] OR “intracranial embolism and thrombosis”[mesh] OR “intracranial embolism and thrombosis”[tiab] OR “intracranial hemorrhages”[mesh] OR “intracranial hemorrhages”[tiab] OR “stroke”[mesh] OR “ischemic stroke”[tiab] OR “ischaemic stroke”[tiab] OR “brain infarction”[mesh] OR “brain infarction”[tiab] OR “brain infarctions”[tiab] OR “vasospasm, intracranial”[mesh] OR “intracranial vasospasm”[tiab] OR “cerebral angiospasm”[tiab] OR “vertebral artery dissection”[mesh] OR “vertebral artery dissection”[tiab]) OR ((“brain injuries”[mesh] OR “brain injury”[tiab] OR “brain injuries”[tiab]) AND (stroke[mesh] OR stroke[tiab] OR “cerebrovascular disorders”[mesh] OR “cerebrovascular disorder”[tiab] OR “cerebrovascular disorders”[tiab])) OR ((“cerebrovascular disease”[tiab] OR “cerebrovascular diseases”[tiab]) AND “basal ganglia”[tiab])

FITNESS: (“Physical Fitness”[Mesh]) OR (“physical fitness”[tiab]) OR (“Physical endurance”[Mesh]) OR (“physical endurance”[tiab]) OR (“Physical Exertion”[Mesh]) OR (“physical exertion”[tiab]) OR (“Exercise Test”[Mesh]) OR (“Exercise Test”[tiab]) OR (“maximum oxygen uptake”[tiab]) OR (“oxygen uptake”[tiab]) OR (“exercise capacity”[tiab]) OR (“vo2”[tiab]) OR (“exercise tolerance”[tiab]) OR (“aerobic capacity”[tiab]) OR (“Exercise tolerance Test”[tiab]) OR “oxygen consumption”[Mesh] OR “oxygen consumption”[tiab] OR “anaerobic threshold”[tiab]

WALKING: (“Walking”[Mesh]) OR (walk*[tiab]) AND ((capacit*[tiab] OR capabilit*[tiab] OR endurance[tiab] OR abilit*[tiab] OR competenc*[tiab] OR test[tiab])) OR (“Walking”[Mesh] OR Walk*[tiab] OR gait[tiab] OR ambulat*[tiab] OR mobil*[tiab] OR locomot*[tiab] OR stride[tiab]) OR ("six minute walk test"[tiab] OR "six minute walking test"[tiab] OR "6 minute walk test"[tiab] OR "6 minute walking test"[tiab] OR 6MWT[tiab]) OR ("two minute walk test"[tiab] OR "two minute walking test"[tiab] OR "2 minute walk test"[tiab] OR "2 minute walking test"[tiab] OR 2MWT[tiab]) OR ("twelve minute walk test"[tiab] OR "twelve minute walking test"[tiab] OR "12 minute walk test"[tiab] OR "12 minute walking test"[tiab] OR 12MWT[tiab]) OR (10MTWT[tiab] OR "10 meters timed walking test"[tiab] OR "ten meters timed walking test"[tiab])

The search strings for the other databases were adapted accordingly.

2. Quality assessment

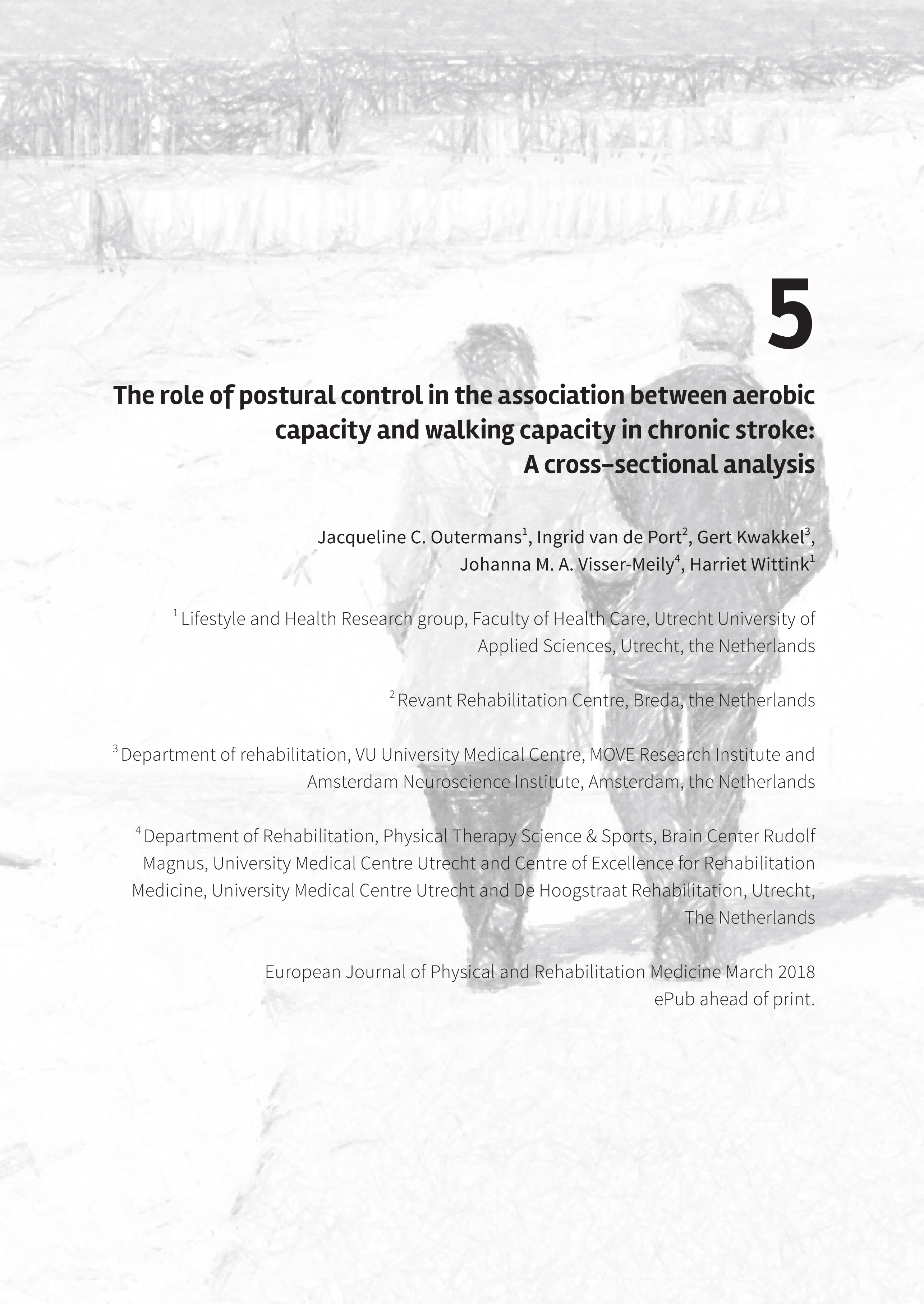
Outcome Strategies evaluation		Scale	Criteria
Study design			
D1	Source population and recruitment	Y/N/?	Positive when sampling frame (e.g., hospital based, community-based etc.) <u>and</u> recruitment procedure (place and time-period, methods used to identify sample) are reported
D2	Inclusion and exclusion criteria	Y/N/?	Positive if both inclusion and exclusion criteria are explicitly described
D3	Important baseline key characteristics of study sample	Y/N/?	Positive if the key characteristics: type, localization and number or history of stroke(s) (e.g., recurrent stroke), gender, age and stroke severity of the sample are described
D4	Prospective design	Y/N/?	Positive when a prospective design was used, or in case of a historical cohort in which prognostic factors are measured before the outcome is determined.
D5	Inception cohort	Y/N/?/NA	Positive if observation started at an uniform time point post stroke
D6	Information about treatment	Y/N/?/NA	Positive if information about the treatment during or immediately prior to the observation period is reported (e.g., medical care, usual rehabilitation care, experimental intervention, etc.)
Study attrition			
A1	Number of loss to follow-up	Y/N/?/NA	Positive if number of loss to follow-up during period of observation did not exceed 20%.
A2	Reasons for loss to follow-up	Y/N/?/NA	Positive if reasons are specified or in case of no loss to follow-up
A3	Methods dealing with missing data	Y/N/?	Positive if the methods of dealing with missing values is adequate (e.g., multiple imputation) or in case of no missing values
A4	Comparison completers and non-completers	Y/N/?/NA	Positive if article mentions that there are no significant differences between participants who completed the study and who did not, concerning key characteristics gender, age, type and severity and candidate predictors and outcome, or there was no loss to follow-up.

Predictor (Independent variables) measurement			
P1	Definition of independent variables/predictors	Y/N/?	Positive if all independent variables are defined (concerning both clinical and demographic features of the sample)
P2	Measurement reliable and valid	Y/N/?	Positive if _1 candidate predictors are measured in a valid and reliable way, or referral is made to other studies which have established reliability and validity.
P3	Coding scheme and cut-off points	Y/N/?	Positive if coding scheme for candidate predictors were defined, including cut-off points and rationale for cut-off points was given; or if there was no dichotomization or classification.
P4	Data presentation	Y/N/?	Positive if frequencies or percentages or mean (SD/CI), or median (IQR) are reported of all candidate predictors.
Outcome (Dependent variable) measurement			
O1	Outcomes defined	Y/N/?	Positive when a clear definition of the outcome(s) of interest is presented
O2	Measurement reliable and valid	Y/N/?	Positive when outcome is measured in a valid and reliable way, or there is referred to other studies, which have established reliability and validity.
O3	Coding scheme and cut-off points	Y/N/?	Positive if coding scheme of the outcome was defined, including cut-off points and rationale for cut-off points was given; or if there was no dichotomization.
O4	Appropriate end-points of observation	Y/N/?/ NA	Positive if observation was obtained at a fixed moment after stroke onset, negative when observation was obtained at discharge.
O5	Data presentation	Y/N/?	Positive if frequencies or percentages or mean (SD/CI) or median (IQR) are reported of the outcome measure.
Statistical analysis			
S1	Strategy for model building	Y/N/?	Positive if the method of the selection process for multivariable analysis is presented (e.g., forward, backward selection, including p-value).
S2	Sufficient sample size	Y/N/?	Positive if in logistic regression analysis number of patients with a positive or negative outcome (event) per variable is adequate, i.e., is equal to or exceeds 10 events per variable in the multivariable model (EPV), or in case of linear regression analysis, N is ≥100.
S3	Presentation univariable analysis	Y/N/?	Positive if univariable crude estimates and confidence intervals (β /SE, OR/CI, RR, HR) are reported. Negative when only p-values or correlation coefficients are given, or if no tests are performed at all.
S4	Presentation multivariable analysis	Y/N/?	Positive if for the multivariable models point estimates with confidence intervals (β/SE, OR/CI, RR, HR,) are reported.
S5	Continuous predictors	Y/N/?	Positive if continuous predictors are not dichotomized in the multivariable model.
Clinical performance			

C1	Clinical performance	Y/N/?	Positive if article provides information concerning ≥ one of the following performance measures: discrimination (e.g. ROC), calibration (e.g., HL statistic), explained variance, clinical usefulness (e.g., sensitivity, specificity, PPV, NPV)
C2	Internal validation	Y/N/?	Positive if appropriate techniques are used to assess internal validity (e.g., crossvalidation, bootstrapping), negative if split-sample method was used.
C3	External validation	Y/N//?	Positive if the prediction model was validated in a second independent group of stroke patients.

Y(positive) = 1 point, N(negative) = 0 points, ?(unknown, partial)

Chapter 4



5

The role of postural control in the association between aerobic capacity and walking capacity in chronic stroke: A cross-sectional analysis

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Abstract

Background: Reports on the association between aerobic capacity and walking capacity in people after stroke show disparate results.

Aim: To determine (1) if the predictive validity of peak oxygen uptake (VO_{2peak}) for walking capacity post stroke is different from that of maximal oxygen uptake (VO_{2max}) and (2) if postural control, hemiplegic lower extremity muscle strength, age and gender distort the association between aerobic capacity and walking capacity.

Design: Cross-sectional study

Setting: General community in Utrecht, the Netherlands.

Population: Community-dwelling people more than three months after stroke.

Methods: Measurement of aerobic capacity were performed with cardiopulmonary exercise testing (CPET) and differentiated between the achievement of VO_{2peak} or VO_{2max}. Measurement of walking capacity with the Six Minute Walk Test (6MWT), postural control with the Performance Oriented Mobility Assessment (POMA) and hemiplegic lower extremity muscle strength with the Motricity Index (MI-LE).

Results: Fifty-one out of 62 eligible participants, aged 64.7 (±12.5) years were included. Analysis of covariance (ANCOVA) showed a nonsignificant difference between the predictive validities of VO_{2max} (n = 22, β = 0.56; 95%CI 0.12 - 0.97) and VO_{2peak} (n = 29, β = 0.72; 95%CI 0.38 - 0.92). Multiple regression analysis of the pooled sample showed a significant decrease in the β value of VO_{2peak} (21.6%) for the 6MWT when adding the POMA as a covariate in the association model. VO_{2peak} remained significantly related to 6MWT after correcting for the POMA (β = 0.56 (95%CI 0.39 - 0.75))

Conclusions: The results suggest similar predictive validity of aerobic capacity for walking capacity in participants achieving VO_{2max} compared to those only achieving VO_{2peak}. Postural control confounds the association between aerobic capacity and walking capacity. Aerobic capacity remains a valid predictor of walking capacity.

Clinical Rehabilitation Impact: Aerobic capacity is an important factor associated with walking capacity after stroke. However, to understand this relationship, postural control needs to be measured. Both aerobic capacity and postural control may need to be addressed during interventions aiming to improve walking capacity after stroke.

Introduction

Worldwide, stroke is a prime cause of chronic walking disorders and reduced walking capacity. A recent review[1] showed that people who have suffered a stroke walk an average distance of 284 (± 107) m in a Six-Minute Walk Test (6MWT), which is commonly used to assess walking capacity. This mean distance is independent of the time since stroke onset and is approximately 50% of the average distance reported for gender- and age-matched healthy people[2].

Concurrently, low aerobic capacity has been recognized as a major problem after stroke[3]. Aerobic capacity is defined by maximal oxygen uptake (VO_{2max}), which indicates the limits of the cardiorespiratory system's response to exercise[4]. Peak oxygen uptake (VO_{2peak}) indicates the highest level of oxygen consumption attained during cardiopulmonary exercise testing (CPET) but does not necessarily reflect the highest value attainable by the subject[4]. Stroke research mostly reports on VO_{2peak}, because stroke-specific impairments such as reduced hemiplegic lower extremity muscle strength and poor postural control can compromise CPET performance[5, 6] and prohibit the achievement of VO_{2max}. VO_{2peak} has been reported to range from eight to 22 mLO_2/kg/min after stroke, which is 26–87% of that of age-matched healthy individuals[7].

On the assumption that aerobic capacity is predictive of walking capacity, aerobic exercise is widely used to improve walking capacity post stroke[8]. However, a recent meta-analysis[9] reported a wide variety of correlation coefficients between aerobic capacity and walking capacity, ranging from 0.37 to 0.74. For example, one of the two largest trials (n = 63)[10] reported a correlation coefficient of 0.40, whereas the other large trial (n = 74)[11] found a correlation coefficient of 0.64. The first trial[10] reported that all participants achieved VO_{2max} during CPET, whereas the second trial[11] reported only VO_{2peak} values, leaving it unclear how many participants achieved VO_{2max}. Therefore, we hypothesized that the predictive validity of VO_{2peak} for the 6MWT score would differ between people after stroke who achieve VO_{2max} during CPET and those who only achieve VO_{2peak}.

On the other hand, the association between VO_{2peak} and 6MWT may be distorted by hemiplegic lower extremity muscle strength and/or postural control, as they are both associated with 6MWT after stroke[10, 11] and could also influence the achieved level of VO_{2peak}[12, 13]. Likewise, age and gender could distort the association, as they are associated with both VO_{2peak}[14, 15] and 6MWT[16], although a recent meta-regression[1] suggested that the distance in a 6MWT after stroke may be independent of age and gender. However, the authors attributed this finding to the use of summary level data, rather than individual data, in their meta-regression.

Chapter 5

The first aim of the present study was to determine if the predictive validity of VO_{2peak} for walking capacity after stroke differs significantly from that of VO_{2max}. The second aim was to investigate to what extent postural control, hemiplegic lower extremity muscle strength, age or gender distort the association between aerobic capacity and walking capacity after stroke.

Methods

Design

This cross-sectional study was conducted at the exercise physiology laboratory at the Faculty of Healthcare of the HU University of Applied Sciences (HUAS), Utrecht, the Netherlands. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE)-guidelines[17] were used for the present report. The Medical Ethics Review Committee of the University Medical Centre Utrecht (ID041), chaired by Dr. P.D. Siersema, approved the research protocol (ID11/204) in December 2011. The present study was conducted in accordance with the declaration of Helsinki[18]. All participants provided written consent.

Participants

Community-dwelling individuals who had suffered a stroke were consecutively included from April 2012 to September 2014. To avoid selection bias, the participants were recruited from various settings, i.e., rehabilitation and daycare centers, physical therapy practices, community nurses in the region of the city of Utrecht, the Netherlands, and from the local group of the Dutch stroke patients' organization. A promotion flyer was used to inform potential participants. Inclusion criteria were (1) a stroke diagnosed according to the definition of the World Health Organization[19], (2) time since stroke onset longer than three months, (3) age over 18 years and (4) ability to walk on level surfaces under supervision, without physical assistance from another person[20], i.e., Functional Ambulation Category (FAC) ≥ 3. Exclusion criteria were (1) cognitive impairment, i.e., Mini Mental State Examination[21] (MMSE) < 24 points, (2) inability to communicate, i.e., Utrecht Communication State[22] (UCO) < 4 points, (3) unidentified cardiovascular risk using the Health/Fitness Preparticipation Screening Questionnaire[23] and (4) inability to walk on a treadmill.

Data collection

Procedures

Three physical therapists, experienced in stroke rehabilitation and exercise testing, conducted the assessments. Inter-assessor agreement was optimized during three two-hour sessions. The data were collected during two sessions, separated by one week. The first session served (1) to inform and determine the eligibility of the participants, (2) to familiarize the participants with the gas exchange equipment, the 6MWT and the treadmill and (3) to collect data on demographic and clinical characteristics. Age, gender, weight, height, hemiplegic side, time since stroke and the use of beta-blockers were assessed. Weight and height were assessed with a flat scale, type 791, and a measuring rod, type 222 (SECA, Hamburg, Germany) respectively. The second session started by measuring postural control and hemiplegic lower extremity muscle strength, followed by a 6MWT and a progressive maximal CPET. Participants were instructed not to eat, smoke, drink alcohol or coffee or engage in strenuous activities in the two hours preceding the CPET.

Aerobic capacity

The criterion measure of aerobic capacity is VO_{2max} (mL/kg/min), defined as the maximal rate at which the human body can transport and utilize oxygen during exercise[15, 24]. VO_{2peak} (mL/kg/min) is the highest value of oxygen uptake achieved by a person during CPET[4, 15]. The primary criterion to determine if the assessed value of VO_{2peak} met the criteria for VO_{2max} was the achievement of an oxygen uptake (VO_2) plateau. The VO_2 plateau was defined as a <150-mL/min change in VO_2 during the last 60 seconds (s) of testing[25] despite a rise in minute ventilation (VE)[26]. In case of an ambiguous VO_2 plateau, a secondary criterion, viz. respiratory exchange ratio (RER) was used. RER represents the ratio between exhaled CO_2 and inhaled O_2 during the last 30 s of testing. The criterion of RER ≥ 1.0 was used for participants over 65 years of age, RER ≥ 1.05 for participants aged 50-64 and RER ≥ 1.1 for participants younger than 49 years[26]. The participants who met the primary and/or secondary criterion were classified as having achieved VO_{2max} (yes), as opposed to participants who only achieved VO_{2peak} (no).

VO_{2peak} was determined by conducting a CPET on an EN-Mill treadmill (Enraf Nonius, Rotterdam, Netherlands) using a two-minute incremental workload protocol, developed for a stroke sample[27]. The participants were instructed to continue until exhaustion and use the handrail of the treadmill only as lightly as possible for balance support. The test was stopped at the participants' request for termination or when safety risks were observed[25]. Termination reasons were documented. Gas exchange data for cardiorespiratory responses were collected with a portable gas analysis system (Cortex Metamax B3, Cortex Biophysik GmbH, Leipzig, Germany). Each test was preceded by calibration according to the manufacturers' guidelines. The Cortex Metamax B3 is a reliable system to assess gas exchange[28]. During the test the following data were collected: VE (mL/min), heart rate (HR) (beats/min), VO_2 (mL/min), carbon dioxide production (VCO_2) (mL/min), and RER.

The CPET was only started if blood pressure (BP) values were below 180 mm Hg systolic and 100 mm Hg diastolic. BP was assessed with an M10-IT device (OMRON Europe, Hoofddorp, Netherlands). Preceding and throughout the CPET, an electrocardiogram (ECG) was obtained with a mobile 12-channel system (Custocor Custo Med, Ottobrunn, Germany).

The ECG signal was screened for ventricular arrhythmia and/or exercise-induced ischemia, i.e., ST-segment depression > 0.10 mV (1mm) for 80 ms[23].

Walking capacity

Walking capacity, defined as the distance covered by a person during a set time in standardized circumstances[29], was assessed with the 6MWT. The 6MWT is a valid and reliable test for the stroke population[30]. We performed the 6MWT according to the standardized instructions of the American Thoracic Society Guidelines[31] on a twenty-meter straight course. The total distance covered was determined by counting the laps and adding the surplus.

Postural control and hemiplegic lower extremity muscle strength

Postural control was defined as "the ability to maintain, achieve or restore a state of balance during any posture or activity"[32] and assessed with the Performance Oriented Mobility Assessment (POMA)[33]. The POMA has been validated in a stroke population[34]. POMA-A consists of 9 items observing postural control during stance, with a maximal score of 16 points. POMA-B consists of 7 items observing postural control during gait, with a maximal score of 12 points. A maximal total score of 28 points indicates optimal postural control[33]. A video observation of the first 20 meters of the 6MWT was used to assess the POMA-B.

We used the Motricity Index (MI) to assess hemiplegic lower extremity muscle strength (MI-LE). The MI is reliable and valid after stroke[35, 36]. It assesses muscle strength and a person's ability for voluntary knee extension, hip flexion and ankle dorsiflexion. The scores for each movement vary from 0 to 33 points for each dimension, indicating no activity (0) to maximal strength (33). At maximal scores, 1 point is added to a total score of 100 points.

Data analysis

Descriptive statistics were used to analyze demographic and clinical characteristics of the sample. Q-Q plots, kurtosis and skewness were assessed to determine the symmetry of distribution of all continuous variables. For normal distribution, values between -1 and 1 were set for kurtosis and skewness**.**

Bivariate linear regression was used to determine the predictive validity of VO_{2peak} for 6MWT in the group that achieved VO_{2max} during CPET and in the group, that did not. The slopes and intercepts of the two regression lines were tested for statistical differences using analysis of covariance (ANCOVA)[37]. The two groups were pooled for further analyses in case no significant differences in the associations between VO_{2peak} and 6MWT were determined.

Multiple linear regression analysis was applied to identify confounding covariates of the association between VO_{2peak} and 6MWT in the pooled sample[37]. The 6MWT was set as the dependent variable and VO_{2peak} as the primary determinant, while controlling for each candidate confounder covariate separately. The sample size calculation, based on Cohen's effect size f^2 = 0.35, a power level of 0.80 and P = 0.05, showed that for 5 predictors a minimum sample of 43 participants was needed[37]. The assumptions for multiple linear regression were tested. First, linear relationship was tested by visual inspection of the scatterplots of 6MWT and the independent variables, where applicable. Second, homoscedasticity was assessed by visual inspection of the scatterplots of the residuals and predicted values of the 6MWT. Third, tolerance was set at > 0.1 and VIF<10 to detect multicollinearity between the independent variables. Fourth, Q-Q plots were visually inspected for normal distribution of the residuals of the regression. Lastly, the presence of outliers of VO_{2peak} and the 6MWT was checked using the outlier labeling rule[38]. The threshold for confounding was set at a change of >10% of the standardized regression coefficient (β) of VO_{2peak} after adding the potential confounding covariate to the multiple linear regression analysis[39].

Correlation coefficients were calculated for the candidate confounders with VO_{2peak} and 6MWT so as to achieve a better understanding of the results of the multiple regression analyses. The correlation coefficient was considered low from r = 0.26 to 0.49, moderate from r = 0.50 to 0.69, high from r = 0.70 to 0.89 and very high from r = 0.90 to 1.00[37].

Only the complete cases were analyzed in the regression analyses, provided the participants with missing data were representative of the whole sample. All analyses were performed using SPSS version 22.0 (IBM/SPSS Inc., Chicago, Ill) and Microsoft Excel 2013. All hypotheses were tested 2-tailed with an alpha < 0.05.

Results

Figure 1 shows that one of the 62 eligible persons did not attend the first appointment and three cancelled due to lack of time. Three of the 58 included participants did not participate in the second session; one for personal reasons, one was scheduled for surgery and one had started a rehabilitation program and was therefore no longer available. Two of the remaining 55 participants reported extreme exhaustion, preventing CPET and two sessions were hampered by technical problems with the gas-analysis equipment. Complete data of 51 participants were included for analyses. The seven incomplete cases were not significantly different from the complete cases, as shown in Table 1.

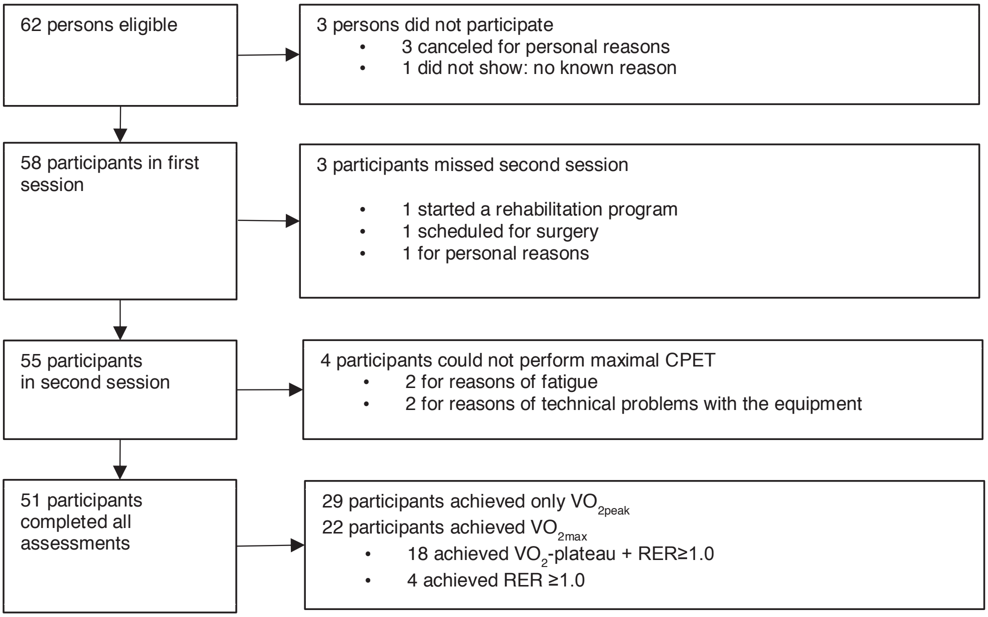

Figure 1. Flowchart of the subjects' participation.

Table 1. Differences between participants and incomplete cases.

	Participants n = 51 mean (SD)	Incomplete cases n = 7 mean (SD)	Difference Sig. (2-tailed)
Age (y)	64.7 (12.5)	62.7 (13.7)	0.691[$]
TsO (months)	58.2 (60.5)	45.5 (37.0)	0.771[$]
Gender, male (%)	29 (57%)	2 (28%)	0.159[^]
Hemiplegia left-sided (%)	27 (52%)	3 (50%)	0.891[^]
6MWT (m)	381 (127.1)	398.9 (136.6)	0.655[$]
MI-LE (0-100)	78.7 (18.3)	81.4 (6.7)	0.911[$]
POMA (0-28)	23.5 (3.9)	24.7 (3.9)	0.542[$]
Beta-blockers (%)	6 (12%)	0 (0%)	0.561[^]

Abbreviations. SD: standard deviation, TsO: Time since Onset, 6MWT: 6 Minute Walk Test, MI-LE: Motricity Index Lower Extremity, POMA: Performance Oriented Mobility Assessment. Differences between groups calculated with [$]Mann Whitney U-test or [^]Pearson Chi square test.

Table 2 shows the demographic and clinical characteristics of the participants. All variables, except for MI-LE, were normally distributed. Mean distance on the 6MWT was 380 m (SD = 126.3) and mean VO_{2peak} was 21.7 mL/kg/min (SD = 6.3) in the pooled sample. Means values of 6MWT ($p = 0.0001$), VO_{2peak} ($p = 0.0001$), and POMA ($p = 0.038$) were significantly higher for the participants who achieved VO_{2max}.

Table 2. Participants and clinical characteristics.

	Total sample n = 51 mean (SD)	CPET: Criteria VO_{2max} achieved n = 22 mean (SD)	CPET: Criteria VO_{2max} not achieved n = 29 mean (SD)	Difference Sig. (2-tailed)
Age (y)	64.7 (12.5)	61.3 (13.8)	67.8 (10.6)	0.066#
TsO (months)	58.2 (60.5)	62.8 (75.9)	55.0 (50.3)	0.662#
Gender, male (%)	29 (57%)	13 (59%)	16 (55%)	0.842^
Hemiplegia left-sided (%)	27 (52%)	12 (54%)	15 (52%)	0.842^
BMI	27.5 (5.2)	27.4 (5.1)	27.8 (4,5)	0.570#
6MWT (m)	381.0 (127.1)	444.4 (111.9)	331.2 (115.6)	0.001#
VO_{2peak} (mL/kg/min)	21.7 (6.3)	24.5 (6.2)	19.4 (5.6)	0.004#
MI-LE (0-100)	78.7 (18.3)	83.3 (9.8)	74.6 (23.0)	0.470$
POMA (0-28)	23.5 (3.9)	24.7 (3.6)	22.4 (4.0)	0.038#
RER	0.97 (.10)	1.06 (.08)	0.90 (.06)	0.0001#
HR_{max} (b/min)	130 (21.3)	144 (16.3)	118.7 (17.9)	0.0001#
Beta-blockers (%)	6 (12%)	3 (14%)	3 (10%)	0.773^
RPE (6-20)	15.9 (1.7)	15.8 (1.9)	16.0 (1.5)	0.757#

Abbreviations. SD: standard deviation, CPET: cardiopulmonary exercise testing, TsO: Time since Onset, BMI: Body Mass Index, 6MWT: 6 Minute Walk Test, $VO_{2peak:}$ peak oxygen uptake, MI-LE: Motricity Index Lower Extremity, POMA: Performance Oriented Mobility Assessment, RER: Respiratory Exchange Ratio, HRmax: maximal heart rate, RPE: Rate of Perceived Exertion. Differences between groups calculated with #Students' t-test, $Mann Whitney U-test, ^Pearson Chi square test.

Bivariate regression analysis

The β for VO_{2peak} was 0.56 (95%CI 0.12 - 0.97; $p < 0.01$) for those who met the criteria for VO_{2max}. In participants who were unable to meet these criteria, the calculated β was 0.72 (95%CI 0.38 - 0.92; $p < 0.01$), as depicted in Figure 4.

The ANCOVA revealed that both interaction effects ($p = 0.28$) and the main effect ($p = 0.07$) were not significant (Fig. 2). Therefore, the two groups were pooled for further analyses. In the pooled sample the β of VO_{2peak} was 0.71 (95%CI 0.39 - 0.84) ($p < 0.01$) for 6MWT.

Multiple linear regression analysis and correlations

All assumptions for multiple linear regression analyses were met. Table 3 shows the results of the multiple regression analysis. Entering POMA lowered ß for VO_{2peak} by 21.6 %, while MI-LE lowered the ß for VO_{2peak} by 8.6%. Neither age nor gender changed the ß for VO_{2peak}. VO_{2peak} remained significantly related to 6MWT after the POMA had been entered as a co-variate (β = 0.56 (95%CI 0.39 - 0.75))

Chapter 5

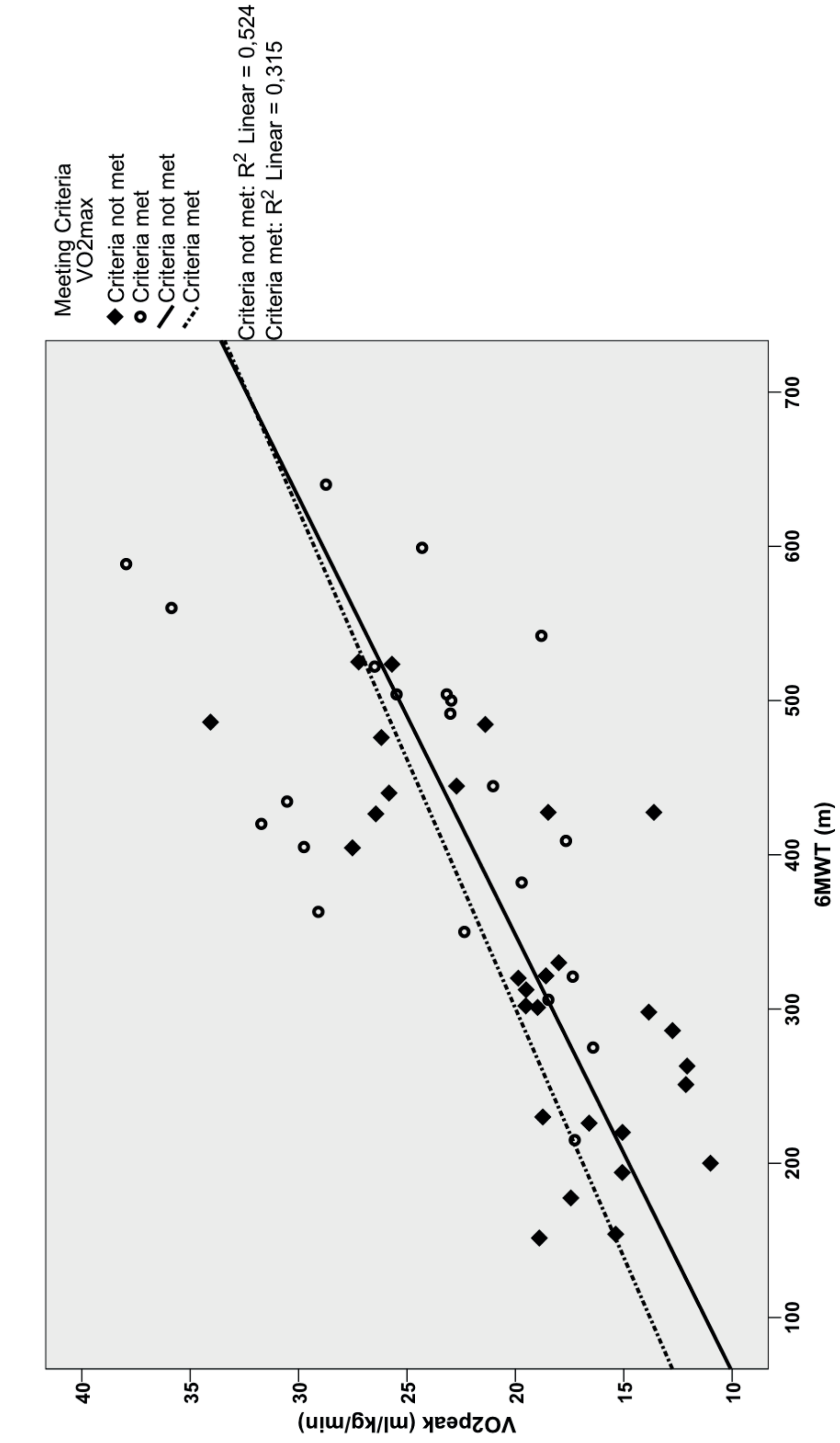

Figure 2. Regression lines of VO_{2peak} with 6MWT differentiated between participants who met the criteria for VO_{2max} and those who could not.

Table 3. Multiple linear regression analysis of the pooled sample with 6MWT as dependent variable and VO_{2peak} as primary determinant.

	Confounder		VO_{2peak}		Relative change in β of VO_{2peak} (%)
Main determinant	B (SE)	Beta (ß)	B (SE)	Beta (ß)	
VO_{2peak}(ml.kg^{-1}.min^{-1})			14.19 (1.99) **	0.71**	
Candidate confounders					
POMA	14.10 (2.78)	0.44**	11.11 (1.73)	0.56**	**21.6**
MI-LE	2.72 (0.56)	0.40**	12.96 (1.67)	0.65**	**8.6**
Age	0.01 (1.12)	0.00**	14.12 (2.19)	0.71**	**0**
Gender	5.80 (26.25)	0.02**	14.29 (2.07)	0.72**	**0**

Abbreviations: B: unstandardized regression coefficient, Beta: standardized regression coefficient, SE: standard error, **P < 0.01, 6MWT: 6 Minute Walk Test, VO_{2peak}: peak aerobic capacity, POMA: Performance Oriented Mobility Assessment, MI-LE: Motricity Index Lower Extremity

Table 4 shows the correlations of the candidate confounders with VO_{2peak} and 6MWT in the pooled sample as well as in both sub-groups. Significant correlation coefficients were found for POMA with the 6MWT in the pooled sample (r = 0.66) and in the VO_{2peak} group (r = 0.74) and for POMA with VO_{2peak} in the pooled sample (r = 0.35) and in the VO_{2peak} group (r = 0.47). MI-LE showed a significant correlation coefficient with 6MWT in the pooled sample (r = 0.47) as well as the VO_{2peak} group (r = 0.62). Age showed significant correlation coefficients only in the pooled sample with VO_{2peak} (r = 0.38) and 6MWT (r = 0.31). Gender showed a significant correlation coefficient with 6MWT in the VO_{2max} group (r = 0.47).

Table 4. Correlations of candidate confounders with VO_{2peak} and 6MWT.

	Pooled sample		Criteria for VO_{2max} achieved		Criteria for VO_{2max} not achieved	
	VO_{2peak}	6MWT	VO_{2max}	6MWT	VO_{2peak}	6MWT
POMA	0.35* #	0.66** #	-0.13 ^	0.34 ^	0.47* ^	0.74** ^
MI-LE	0.13 ^	0.47** ^	-0.07 #	0.28 #	0.12 #	0.62** ^
Age	-0.38** #	-0.31* #	-0.38 #	-0.22 #	0.26 #	-0.14 ^
Gender	-0.18 $	-0.17 $	-0.41 $	-0.47* $	-0.08 $	0.10 $

Abbreviations: 6MWT: 6 Minute Walk Test, VO_{2peak}: peak aerobic capacity, POMA: Performance Oriented Mobility Assessment, MI-LE: Motricity Index Lower Extremity. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). #Pearsons correlation coefficient, ^Spearmans rank correlation coefficient, $Bipoint serial correlation coefficient.

Discussion

We found no statistically significant difference between the predictive validities of VO_{2peak} and VO_{2max} for the 6MWT. This suggests that the predictive validity of VO_{2peak} for the 6MWT in the present sample does not depend on meeting the criteria for VO_{2max}. Consequently, the diversity of the correlations coefficients reported by earlier similar studies[9, 10, 11] is not explained by these results. However, the small sample sizes may have contributed to the non-significant result. Moreover, the two studies[10, 40] in a recent meta-analysis[9] that reported that all their participants had achieved VO_{2max} found the weakest correlations between VO_{2max} and 6MWT of all ten studies. This would support the notion that the association between VO_{2max} and 6MWT may in fact be weaker than between VO_{2peak} and 6MWT.

Concerning our second objective, the results showed that only postural control distorts the association between VO_{2peak} and 6MWT. We found a moderate association between postural control and 6MWT, in line with associations reported from a similarly mildly affected sample with respect to postural control[10] as well as from a more severely affected sample[11] compared to ours. We also found a weak, but significant association between postural control and VO_{2peak}. Unfortunately, reports on the association between postural control and aerobic capacity are scarce. Only one study[13], in a more severely impaired sample in terms of postural control, reported a similarly low and statistically significant correlation coefficient of 0.37. Nevertheless, postural control is likely to influence the assessment of VO_{2peak}. The choice of a treadmill protocol to perform CPET, for example, may have influenced the assessment of aerobic capacity specifically in the more impaired VO_{2peak} group. In fact, postural control was significantly better in de VO_{2max} group, suggesting its contribution to achieving VO_{2max}. Therefore, the confounding effect of postural control may explain the divergence in the associations between VO_{2peak} and 6MWT reported to date[9]. For example, a study[10] that used a bicycle ergometer protocol, possibly demanding less postural control, in a mildly impaired sample similar to ours in terms of postural control, reported a weak correlation. Another study[11] used a treadmill protocol to assess VO_{2peak} in a moderately impaired sample in terms of postural control. They reported a moderate correlation between VO_{2peak} and 6MWT. However, aerobic capacity remained a significant predictor of walking capacity in the present sample after correction for postural control.

Contrary to our expectations, age or gender did not distort the association between aerobic capacity and walking capacity. For age, but not for gender, we did find statistically significant weak correlations with both VO_{2peak} and 6MWT in the pooled sample. These results suggest that age and gender are unimportant factors in this mildly impaired and relatively young sample of community walkers after stroke. The strength of the hemiparetic lower extremity was significantly associated with the 6MWT scores, which is in line with several other studies[10, 11]. Unexpectedly however, it did not affect the association between VO_{2peak} and 6MWT, as we found a non-significant and weak association with VO_{2peak}. This is probably due to the small sample size, while an alternative explanation could be that it is lean muscle mass that is associated with VO_{2peak} rather than muscle strength[3, 41].

Limitations of the study.

First, the sample sizes in the two sub-groups were too small to perform separate multiple regression analyses, which would have allowed us to identify differences in confounding factors between the two sub-groups. However, the correlations of postural control and lower extremity muscle strength with aerobic capacity and walking capacity were considerably lower and not statistically significant in the VO_{2max} group. This suggests that the confounding effect may only be evident in the VO_{2peak} group, i.e., in people with a lower level of functioning after stroke. Second, the commonly used threshold of 10% for change of the regression coefficient is an arbitrary choice. However, as the change in the β value of VO_{2peak} entering POMA was well over 10%, it seems plausible that postural control does indeed confound the association between VO_{2peak} and 6MWT. Third, the relatively small sample limits generalizability. Moreover, in view of their mild impairments, the participants may not be representative of the general stroke population and may possibly only be considered a representative sample of independent community-dwelling people in the chronic stage after stroke. Lastly, although the results of the present cross-sectional study confirm that VO_{2peak} is associated with 6MWT, they do not imply that change in VO_{2peak} is associated with change in the 6MWT. In fact, a significant correlation between the effect size of VO_{2peak} and that of walking capacity, as a result from aerobic training, has not yet been established[8]. One study reported that improvement of VO_{2peak} was significantly associated with improved walking capacity during the first three months after stroke[42]. Unfortunately, the reported gains were below the known smallest detectable changes in both 6MWT[30] and VO_{2peak}[41], which leaves the clinical relevance unclear.

Conclusions

Prospective cohort studies are needed to explore the longitudinal association between changes in VO_{2peak} and 6MWT. Research may need to consider the confounding potential of postural control to achieve more precise results with respect to the association between VO_{2peak} and 6MWT.

Overall, clinicians can consider aerobic capacity a valid predictor of walking capacity in mildly impaired people after stroke, in spite of the confounding role of postural control. Clinicians should, however, be aware of the distorting effect of postural control on the association between VO_{2peak} and 6MWT. For example, the assessments of VO_{2peak} during CPET may be less influenced by postural control when utilizing bicycle protocols, in line with the recommendations in a recent review[6].

In spite of the fact that the cross-sectional nature of our study prohibits the establishment of causal relations, the results still underline that aerobic capacity may need to be addressed during rehabilitation interventions to improve walking capacity after stroke.

However, just as postural control may influence the assessment of VO_{2peak}, it may also influence the achievement of sufficient exercise intensity to actually improve aerobic capacity. Therefore, it seems advisable to simultaneously address postural control during rehabilitation.

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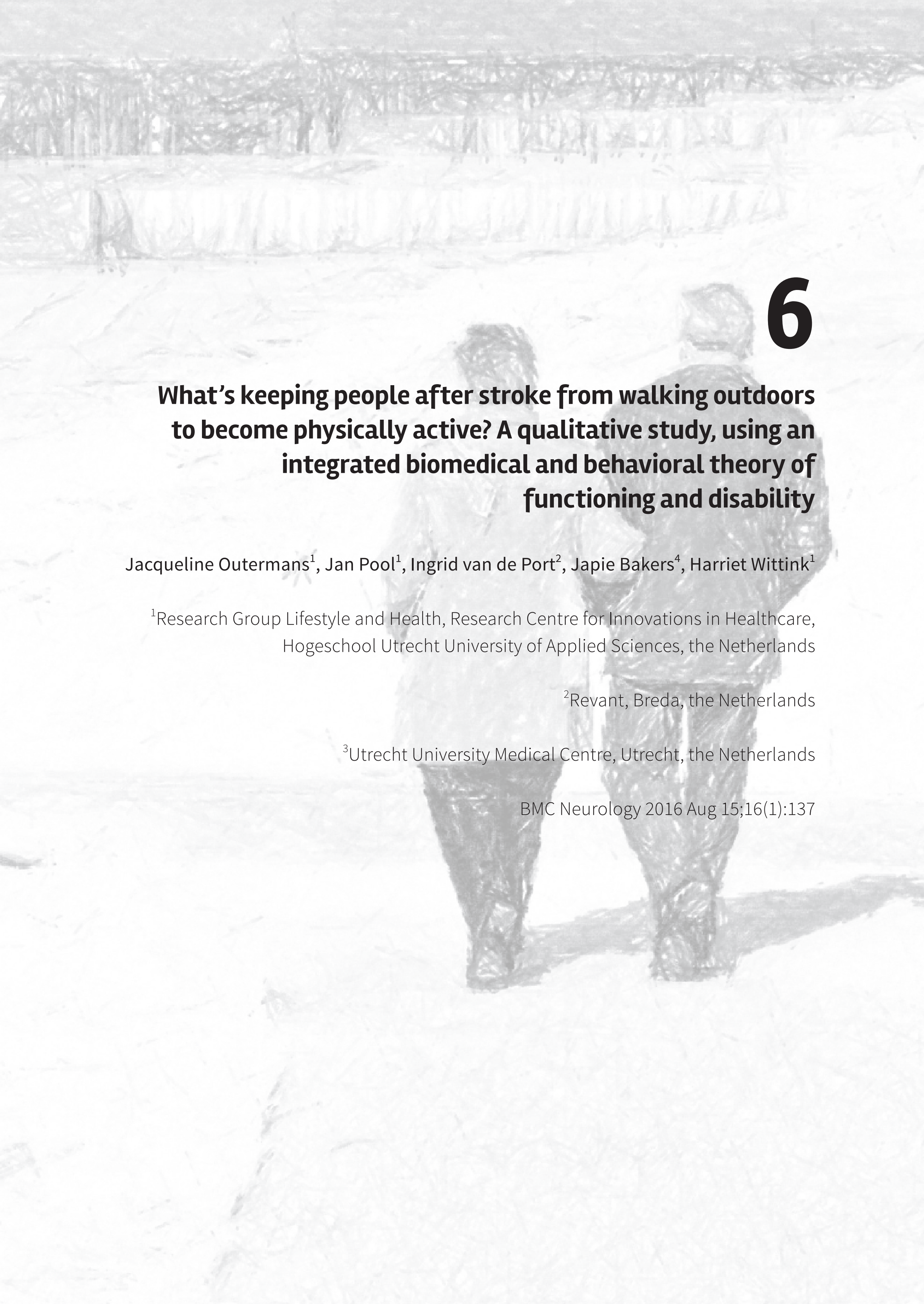

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What's keeping people after stroke from walking outdoors to become physically active? A qualitative study, using an integrated biomedical and behavioral theory of functioning and disability

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Abstract

Background: In general people after stroke do not meet the recommendations for physical activity to conduct a healthy lifestyle. Programs to stimulate walking activity to increase physical activity are based on the available insights into barriers and facilitators to physical activity after stroke. However, these programs are not entirely successful. The purpose of this study was to comprehensively explore perceived barriers and facilitators to outdoor walking using a model of integrated biomedical and behavioral theory, the Physical Activity for people with a Disability model (PAD).

Methods: Included were community dwelling respondents after stroke, classified ≥ 3 at the Functional Ambulation Categories (FAC), purposively sampled regarding the use of healthcare. The data was collected triangulating in a multi-methods approach, i.e., semi-structured, structured and focus-group interviews. A primarily deductive thematic content analysis using the PAD-model in a framework-analysis' approach was conducted after verbatim transcription.

Results: 36 respondents (FAC 3-5) participated in 16 semi-structured interviews, eight structured interviews and two focus-group interviews. The data from the interviews covered all domains of the PAD model. Intention, ability and opportunity determined outdoor walking activity. Personal factors determined the intention to walk outdoors, e.g., negative social influence, resulting from restrictive caregivers in the social environment, low self-efficacy influenced by physical environment, and also negative attitude towards physical activity. Walking ability was influenced by loss of balance and reduced walking distance and by impairments of motor control, cognition and aerobic capacity as well as fatigue. Opportunities arising from household responsibilities and lively social constructs facilitated outdoor walking.

Conclusion: To stimulate outdoor walking activity, it seems important to influence the intention by addressing social influence, self-efficacy and attitude towards physical activity in the development of efficient interventions. At the same time, improvement of walking ability and creation of opportunity should be considered.

Introduction

In the Netherlands approximately 220 thousand stroke survivors, as part of a population of 17 million inhabitants, suffer from more or less severe functional impairments[1]. Although 39–85% of the stroke survivors attain an independent level of walking[2, 3], it has been shown that 26% of home dwelling stroke patients show no or limited walking activity three years after inpatient rehabilitation due to stroke[4, 5]. A meta-analysis[6] showed that among 1105 people, between three months to 8,5 years after stroke, a mean of 4355 steps a day were taken, which is well below the current recommendation for people with a disability of 6500-8500 steps a day[7]. This inactive lifestyle may perpetuate existing impairments and deconditioning. Deconditioning, resulting in low levels of physical fitness, specifically aerobic capacity, has been recognized as a major problem in stroke[8]. It is associated with health risks such as metabolic syndrome, cardiovascular disease or recurrent stroke[8, 9] as well as with reduced walking capacity[10]. Evidence for benefits of increased physical activity on health in stroke is getting stronger[11] although it is not yet clear if it also reduces recurrent stroke risk. Furthermore, moderate to vigorous walking interventions on a treadmill were shown effective in improving aerobic capacity after stroke[12].

Therefore, it seems paramount to establish effective programs to stimulate outdoor walking to become physically active. Being physically active has been defined as "meeting established guidelines for physical activity, that are activities of at least moderate intensity"[13]. To accomplish that, knowledge about perceived barriers and facilitators specifically to outdoor walking aimed at staying or becoming physically active and reduce health risks is needed. However, many of the patient perceptions of barriers and facilitators that have been reported seem to be focused on community ambulation[14], travelling outdoors[15, 16] or physical activity in general[17]. Barriers and facilitators such as self-efficacy, beliefs about physical activity, self-determination and social support as well as ongoing professional support have been identified[14-17]. However, as the purpose of community ambulation and travelling outdoors may lay within the domain of participation International Classification of Functioning, Disability and Health (ICF)[18], the purpose of being physically active lies primarily within the ICF domain of activities with the specific goal of reduction of health risks or conducting a healthy lifestyle. Therefore, barriers and facilitators to being physically active may differ from those to community ambulation or traveling outdoors. Other studies[19, 20] explored patient perceptions influencing participation in structured exercise programs, being a subset of physical activity[21] after stroke. These studies showed that people after stroke have a preference for group exercise in a structured and dependent manner[19] and found that perceived impairments, lack of motivation and availability of facilities to exercise were barriers to exercise[20]. Exercise facilitators were social support from professionals and peers and planned activities to fill daily schedules. However, similar to community ambulation and outdoor traveling, the purpose of exercise, i.e., improvement of physical fitness[21], primarily lying within the ICF domain of body function and structures, is different from the purpose of becoming physically active. Again, barriers and facilitators may therefore differ.

Moreover, programs designed in the last decade to improve physical activity and community ambulation after stroke have not been successful[22, 23]. Interventions such as supervised exercise[24], lifestyle counseling[25], repeated instructions[26] or supervised outdoor walking[27-29] did not increase the level of physical activity after stroke. One explanation could be that many studies on barriers and facilitators, that form the foundation of programs to improve physical activity to date, either only used or developed behavioral theory[22] *or* only used the ICF. No comprehensive approach integrating these models has been undertaken to date. Johnston and Dixon[30] suggest that models integrating the ICF with behavioral models are more effective in explaining functional behavior than the ICF or behavioral theory separately. Van der Ploeg and colleagues[31] proposed the Physical Activity for people with a Disability model (PAD-model), which integrates the Attitude, Social influence and self-Efficacy (ASE) model[32], which is based on the Theory of Planned Behavior (TPB)[33, 34], with the ICF model. We hypothesized that the PAD-model would provide a comprehensive overview of behavioral and physical barriers and facilitators for outdoor walking to increase physical activity. To our knowledge there is no study that explored the usefulness of this model in a stroke population.

The first aim of this study was to establish the barriers and facilitators from the perspective of Dutch home dwelling individuals after stroke in the chronic stage to outdoor walking to be physically active. The second aim was to determine the usefulness of the PAD model to generate a comprehensive overview of barriers and facilitators.

Methods

Design

This study employed qualitative methodology to ensure that the experiences and views of the participants would be identified so that perceived barriers and facilitators to walking outdoors and their meaning among a group of community dwelling stroke survivors could be better understood.

The first researcher (JO) was a physical therapist with 25 years of experience in neurological rehabilitation. The second researcher (SL), who participated in the analysis, was a fourth-year student of the bachelor program in physical therapy, who had minor experience in neurological rehabilitation. The third researcher (JB) was a physical therapist with five years of experience in neurological rehabilitation. Two more researchers (JP and HW) with ample experience in conducting research completed the research team. All researchers were familiar with the PAD-model and as clinicians experienced in using the ICF in clinical reasoning.

Respondent recruitment

To recruit respondents for the individual interviews, an existing network of physical therapy practices and daycare departments of nursing homes was used. To increase representativeness, purposive sampling was used with respect to healthcare utilization as this was expected to influence walking activity. Respondents should either 1) utilize daycare facilities two or more days per week, or 2) visit their physical therapy private practice once or twice a week or 3) not use physical therapy regularly.

Inclusion criteria were; community dwelling people in the wider urban region of the city of Utrecht, the Netherlands, with 1) a diagnosed stroke, as defined by the World Health Organization (WHO)[35] and 2) ability to walk independently with supervision if needed, categorized as functional ambulation categories (FAC) ≥ 3[36]. Exclusion criterion was the inability to understand spoken or written language as a result from receptive aphasia defined as a score of ≤ 3 points using the Utrecht Communication Assessment (UCA)[37].

Potential respondents for the individual interviews were made aware of the study by their attending physical therapists or district nurse and registered if they were interested to participate. An information letter and informed consent form were subsequently sent to be signed by the potential respondent. Thereafter the researcher scheduled an appointment with the respondent at their homes.

Two focus-group interview sessions were organized during the monthly support meeting of the local group of the Dutch stroke patients' organization using convenience sampling. Inclusion criteria were the same as used for the individual interviews. Prior to the focus-group interview the entire group was informed and thereafter the group members who wanted to participate signed informed consent forms.

Data collection

A topic list to guide through the interviews was developed using the PAD-model[31] as a sensitizing concept (Table 1). After the first four individual semi-structured interviews, a structured interview form was created to use with the respondents who suffered from expressive aphasia (UCA > 3). The topic list was identical to the one that was used in the semi-structured interviews. Each question had a choice of answers generated from the results of the first four semi-structured interviews as shown in Table 1. This enabled the respondents suffering from expressive aphasia to participate and they were encouraged to elaborate on their answer of choice to the best of their abilities.

Table 1. Topic list semi-structured and structured individual interviews (phase 1) and focus-group interview (phase 2).

	Topics for all interviews	*Choice of answers only for structured interview*				
Topic 1: Walking for health	What's your opinion on your health situation?	Bad health	Not so healthy	Fair	Good	Don't know
	What's your opinion on your walking activity?	Little	Fair	Good	Very good	Don't care
	Is walking of influence on your health?	No	Not really	A little positively	Positively	Negatively
	Is your health situation of influence on your walking activities?	No	Not really	A little	Yes	Don't know
Topic 2: Exercise and physical activity	Did you participate in any sports or physical activity prior to your stroke?	No	Not really	A little	Yes	
	Is physical activity important to you?	Not at all	A little	Important	Very important	
	Are you currently participating in physical activity programs or exercise programs?	No	At the physical therapist'	At the sports club, the gym	By myself	
	When not, would you like to?	Yes, very much	Yes	Not really	No	
	What's keeping you?	Afraid, dangerous	Physically not possible	Not in the mood	Has no purpose	Have done enough
	What's driving you?	Keeping mobile and healthy	Just want to exercise	Partner/ healthcare professional says to	Meeting other people	Want to get out

Table 1. Topic list semi-structured and structured individual interviews (phase 1) and focus-group interview (phase 2). (continued)

	Topics for all interviews	*Choice of answers only for structured interview*				
Topic 3: Walking outside	Do you walk outdoors each day?	Every day	2-3 times a week	Once a week	Almost never	More than once a day.
	What are your reasons for walking outdoors?	Exercise	Just for fun, getting some fresh air	Meeting with friends	Running errands	
	What's keeping you from walking outdoors?	Uneven surfaces, crowds and obstacles	When there is no purpose to go outdoors	Have other means of transportation	Problems with orientation, motor control, balance or endurance.	Not allowed to go by myself, not safe
	How do you cope with problems when walking outdoors?	Avoid them	Encounter them	Ask assistance	Don't know	
	What stimulates you to walk outdoors?	Walking with peers	Nice weather	Necessity to go	Stimulating caregiver	Stimulating healthcare professional

The data was collected triangulating in a multi-methods approach, i.e., semi-structured, structured and focus-group interviews to increase the validity and rigor of the methods of the study. During the first phase of the study, the individual semi-structured interviews as well as the structured interviews were continued until there appeared to be saturation of data. Thereafter, in the second phase, two focus group sessions were performed. The focus-group interviews were used to confirm the saturation of the earlier collected data and as a means to validate these data. The respondents who participated in the individual interviews were different from the respondents whom participated in the focus group sessions. To increase the reliability of the collected data all semi-structured interviews and focus-group interviews were audio recorded. The structured interviews were not audio recorded to create a safe enough environment for respondents that suffered from expressive aphasia, allowing them to speak freely according to their ability. During all interviews field notes were taken.

To increase ecological validity, the individual interviews were conducted at the respondents' homes. Family members, when present, were allowed to stay in the interviewing room. They were requested not to participate in the interview, unless they felt that important information would be missed. The same researcher who performed the interviews (JO) moderated the focus-group interview sessions. Each individual interview as well as the focus-group interviews lasted approximately 40 minutes.

Data analysis and synthesis

Recordings were transcribed verbatim by research assistants and to verify their accuracy, one researcher (JO) independently checked the transcriptions.

A primarily deductive thematic content analysis, driven by the PAD model as directing concept, was performed using the five-stage 'Framework' approach[38, 39]. Stages of analysis included: (1) familiarization, (2) thematic framework development, (3) indexing, (4) charting, and (5) mapping and interpretation. The analysis was performed in Excel (Microsoft Office 2013).

The first stage involved repeated listening to and reading of the transcripts and collected field notes in order to become familiar with the data. During this stage, notes were taken on the recurrent themes and issues that emerged from the PAD model, keeping an open mind, however, to other emerging themes. In the second stage, the PAD model served as a theoretical framework to provide a priori determined key issues and concepts. Accordingly, a thematic framework was developed in which we explicated normative beliefs, control beliefs and behavioral beliefs originating from the TPB[33, 34], underlying social influence, self-efficacy and attitude respectively in the ASE-model[32], to be able to sort the data. The third stage was used to systematically apply the developed thematic framework to the data. All information from the transcripts that was relevant to each index heading was copied into the framework to build a descriptive overview for all headings. The fourth stage involved producing a summary of the respondents' views or experiences under each heading. During the final stage, the charts were reviewed systematically in order to detect patterns or associations within the data.

Two researchers (JO and SL) analyzed the individual interviews and two researchers (JO and JB) analyzed the data from the focus-group interviews. To increase the reliability and rigor of the analysis a consensus meeting was scheduled after each stage of the analysis. Furthermore, peer-debriefing sessions were conducted between three researchers (JO, JP and HW) in the fifth stage of analysis.

Results

A total of 36 home dwelling respondents, participated in the study. Table 2 shows that 15 respondents participated in the individual semi-structured interviews, eight respondents in the individual structured interviews and a total of 13 respondents in the two focus-group interviews. Seventeen respondents received daycare at a facility at least two times a week, 11 respondents received physical therapy treatment once or twice a week and eight respondents did not receive physical therapy regularly.

Table 2. Characteristics of the respondents.

	Phase 1		**Phase 2**	
	Semi-structured interview n = 15	**Structured interview** n = 8	**Focus Group A** n = 7	**Focus Group B** n = 6
Age (y)				
Mean (SD)	71.3 (13.3)	72.5 (8.8)	69.3 (9.2)	69.2 (10.3)
Range	(46-89)	(60-83)	(52-81)	(57-82)
Gender				
Male (%)	8 (53%)	7 (88%)	2 (29%)	4 (67%)
Marital status				
Married (%)	9 (60%)	3 (38%)	4 (57%)	4 (60%)
Utilization of healthcare (%)	4 PT (27%) 2 No regular PT (13%) 9 Daycare (60%)	3 PT (38%) 5 Daycare (62%)	2 PT (29%) 4 No regular PT (57%) 1 Daycare (14%)	2 PT (33%) 2 No regular PT (33%) 2 Daycare (33%)
FAC (%)	5 FAC3 (33%) 1 FAC4 (7%) 9 FAC 5 (60%)	3 FAC3 (38%) 3 FAC4 (38%) 2 FAC5 (24%)	 2 FAC4 (29%) 5 FAC5 (71%)	 2 FAC4 (33%) 4 FAC5 (67%)
Assistive devices (%)	1 cane (7%) 7 rollator (46%)	2 cane (25%) 3 rollator (38%)	2 cane (29%)	2 cane (33%)

Abbreviations: y: years, SD: standard deviation, FAC: Functional Ambulation Categories, PT: physical therapy.

Chapter 6

Eight respondents were able to walk independently but needed supervision. They were categorized into FAC 3. Eight respondents reached FAC 4, being able to negotiate all surfaces when even. Twenty (56%) respondents were able to walk on any, including uneven, surfaces, FAC 5. Seventeen (53%) respondents used assistive devices for walking. Ten respondents used a rollator and seven used a cane.

The data covered all domains of the PAD model[31] that was used. This is shown in Figure 1. Using the PAD-model three main categories were identified: 1). the intention to walk outdoors, 2). the ability to walk outdoors and 3). the opportunity to walk outdoors. The intention to walk outdoors results from the attitude and self-efficacy towards outdoor walking as well as social influence. Social and physical environment furthermore influence the intention to walk outdoors, where social environment seems to have a direct link to social influence and physical environment to self-efficacy as shown in Figure 1. The ability to walk outdoors consists of the ability to walk far enough and to maintain a standing posture. These abilities are influenced by body functions. The opportunity to walk outdoors is linked to occupational and leisure activities at the level of participation in the ICF.

Facilitators and barriers for the intention to walk outdoors identified from the PAD model
Behavioral beliefs underlying the attitude towards walking, such as having walked enough over the life span as well as brisk walking being unhealthy for elderly were identified as barriers. As a 75-year-old respondent commented: *"I constantly come home more tired than when I left, that can't be right, can it? From exercise? I do not think so; it was too much. I felt my heart beat too quickly, that can't be good for me at my age? I did not like it very much."* Behavioral beliefs such as determination to walk and having affinity with physical activity as a healthy lifestyle were perceived as facilitators for walking outdoors. Illustrated by a respondents' view: *"I do not always particularly feel like it, but I think I should walk at least a little every day, I just have that feeling I should stay limber...because I know exercise is good for me"*

Normative beliefs underlying social influence such as "walking outdoors has to be for a purpose", for instance, to go the grocery store could be a barrier to walk outdoors to increase physical activity. Expressed by a female respondent as*: "There is nothing I dislike more than walking for no purpose."* Being ashamed of the decreased ability to walk or being accompanied by a much better walker was perceived a barrier to outdoor walking, formulated by a respondent as*: "No, in the beginning they walked with me, but I prefer to go alone. I feel like I am in the way. I am fine walking by myself."*

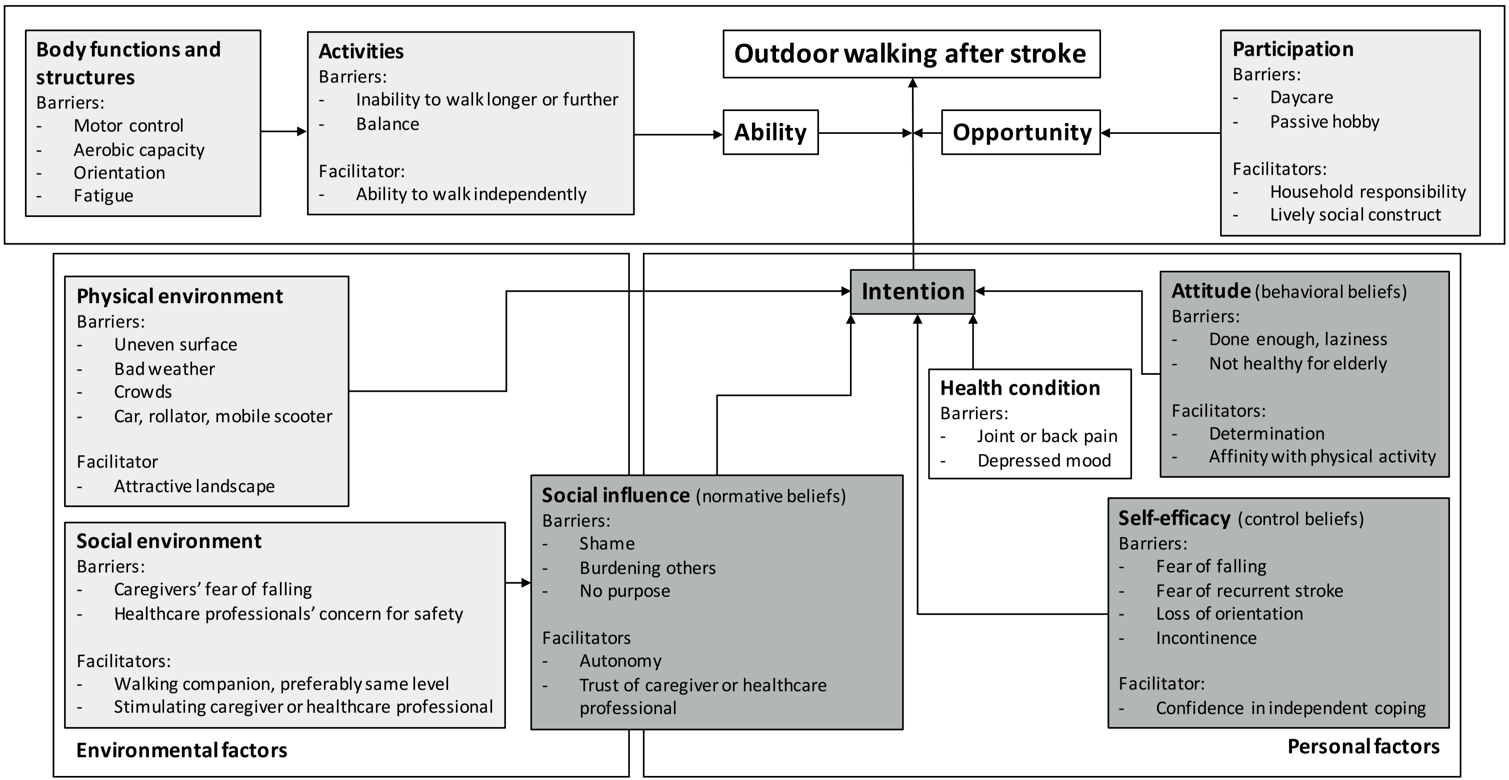

Figure 1. The PAD-model adapted to outdoor walking after stroke. The paler grey rectangles depict the ICF; the darker grey rectangles show the ASE-model.

Barriers to outdoor walking that were identified in the social environment were the caregivers' fear of falls and the healthcare professionals' primary concern for safety. Facilitators at this level were having a walking companion or a stimulating caregiver or healthcare professional. Facilitators had a positive impact on social influence in turn leading to a positive intention to walk outdoors. As a respondent said*: "But first I must have my confidence back and my wife also, because she saw me fall twice and had to help me. So you do not want to wait for it to happen a third time."* Or another respondents' comment*: "Yes, yes, because at the daycare center I walk without a cane and I did well. Last Tuesday there was a new physical therapist asking where I had left my cane. He was pretty anxious, more so than me, because I'm walking without the cane all the time."*

Control beliefs underlying self-efficacy such as low falls efficacy, were identified as a barrier to outdoor walking. One respondent said*: "No I am not afraid or anything, but walking is just more complicated. Perhaps you think all it takes is a little push from someone or other and I am down. I'd like to avoid that, of course."* Similarly, the view of another respondent*: "If you tell me to go to the market with my rollator I'd tell you to go yourself. You know, they all are constantly running you off your feet."* Furthermore, fear of recurrent stroke and loss of orientation as well as incontinence were identified as barriers. The belief to be able to cope independently or that an accompanying person would be able to cope in case of adverse events such as a fall seemed to facilitate outdoor walking. As a 50-year old respondent said: *"No, I am limber enough not to fall like a log."*

Joint pain, such as back pain, was indicated as a barrier to outdoor walking, illustrated by this comment*: "Well yes, when I walk my back starts hurting me and then I think I am not going to walk anymore, I can't walk anymore."* This barrier, accompanied with depressed mood, had a negative influence on both self-efficacy and attitude towards outdoor walking and thereby on the intention to walk outdoors.

Barriers in the physical environment were uneven surfaces outdoors and bad weather. A single living respondent commented on that: *"Yes, obviously the weather is very important. I am not fond of walking in storms and rain, but nothing much else prevents me from walking. If I want or need to walk, I go!"* Furthermore, crowds and conveniences such as the availability of a car, mobility scooter were barriers as well as the presence of a freezer, which reduced the necessity to go out for groceries. One respondent, who used a rollator said: *"…let's be honest, I have a mobility scooter that I love. Why would I walk with my rollator? You can only use that for exercise around the house perhaps, but nothing much else."* An attractive landscape and the availability of assistive devices such as canes or rollators were identified as a facilitator for outdoor walking. Illustrated by the following remark: *"And because of that I kept falling to the right, but without harm. I could get up myself with the* *help of my rollator."* Barriers in the physical environment negatively influenced self-efficacy in turn reducing the intention to walk outdoors.

Facilitators and barriers for the ability to walk outdoors identified from the PAD model
The barriers for walking outdoors at the level of body functions and structures were impaired cognitive function, e.g., memory, as well as reduced motor control and postural or balance reactions as a result of the hemiplegia, strength and aerobic capacity. One respondent, who used daycare: "*I say I have a leg that doesn't work. It causes one to shuffle. Can't lift it anymore."* Aerobic capacity was indicated as a barrier as another respondent in daycare said: *"I'll sit down on my rollator for a little while, because it is quite a distance and walking far is very difficult for me, I totally get out of breath."* Furthermore, fatigue was mentioned by one respondent*: "Isn't it strange, when I do nothing I am still tired."*

A barrier that was identified on the level of activities was the inability to walk longer distances, illustrated by an independently walking respondent: *"I'm partially paralyzed, so it is always difficult. But even with a cane I can walk only for 5 to 7 minutes."* Also inability to uphold balance was identified. Facilitators at this level were the ability to walk independently.

Facilitators and barriers for the opportunity to walk outdoors identified from the PAD model
Facilitators at the level of participation enhanced the positive intention for outdoor walking such as responsibilities in household tasks demanding walking, like shopping for groceries as a married respondent mentioned*: "When we are out of bread, I'm the one who walks to the market to get new supplies"* On the other hand, daycare offers little opportunity for walking outdoors like a respondent said:*" On the days that I am in the daycare facility, there's nothing much to do except for one half hour of physical therapy. We sit most of the time playing games and talking, drinking coffee or in the afternoon a small snifter".*

Discussion

The first aim of the study was to give insight into perceived barriers and facilitators in all domains of the PAD-model describing outdoor walking activity to become physically active in individuals after stroke. Overall, outdoor walking activity seems to be a result of the intention to walk, walking ability and opportunity to walk.

The intention to walk outdoors was determined by the perceived barriers and facilitators in social influence, self-efficacy and attitude with underlying environmental factors, i.e., social and physical environment. Social influence seemed impacted by social environment, which consequently influenced the intention to walk. For example, the respondents stated that they often felt inhibited by their caregivers, who felt it to be unsafe for them to walk outdoors. Additionally, they felt held back by their professional caregivers, as they seemed more concerned with safety than with improvement of physical activity, which was also reported in a hospital setting[40]. The cautiousness of caregivers and professionals has also been reported in studies on stimulating traveling outdoors early after stroke[15] and on physical activity in general in chronic stroke[41]. The intention to walk outdoors was positively influenced by opportunities that derived from participation such as hobbies, social activities and household responsibilities. For example, the respondents in the present study who were living alone or whose spouses did not take the household responsibility, all reported that the need to go out for groceries enhanced their walking activity. Conversely, the ones living with a partner that took all responsibilities felt no urgency to get out and about. These determinants are much like the reasons reported for resuming valued activities after stroke[42]. The barriers and facilitators, such as purposefulness and perceived burden on companions or caregivers that constructed social influence and lead up to intention, were in line with several other studies on physical activity[41], other valued activities[42] and travelling outdoors even early after stroke[15].

The ability to walk a reasonable distance and the ability to maintain balance were perceived as determinants for outdoor walking ability with underlying impairments of body functioning such as strength and aerobic capacity. Balance has previously been identified as an important barrier in line with studies that focused on barriers and facilitators for exercise[43] and resuming valued activities[42]. Physical and cognitive disability and fatigue were perceived as barriers to walking outdoors, which is similar to the findings for resuming valued activities[42]. Fatigue has also been identified in one study[44] that furthermore reported “shortness of breath” to be a barrier to physical activity. This is consistent with the findings in the present study where the respondents explicitly named fatigue, reduced aerobic capacity and the inability to walk long distances as barriers for outdoor walking. Interestingly, this perception of the relations between impaired body function, walking ability and outdoor walking seems consistent with quantitative research on the associations between community ambulation or physical activity in general and walking speed, physical fitness or balance[45,46].

Finally, the opportunities that arise from participation are indicated as factors that determine outdoor walking. These findings are in line with the outcome of a recent review where intention and actual control over the behavior, the latter comparable with walking ability in the present study, were indicated as important in predicting physical activity[30].

The second aim of this study was to determine the usefulness of the PAD model to generate a comprehensive overview of barriers and facilitators. As a result of the integration of the ASE-model at the level of personal factors in the ICF, the PAD-model enables a comprehensive overview of barriers and facilitators for walking outdoors after stroke, as the ICF itself has not specifically coded personal factors[18, 30, 47]. However, to enable a deeper understanding of the meaning of social influence, self-efficacy and attitude from the ASE model it was necessary to explicit the underlying beliefs, i.e., normative, control and behavioral beliefs originating from the TPB, that underlies the ASE model. This is in line with the finding of Johnston and Dixon[30] that, although the PAD model integrates psychological variables, i.e., the ASE model, it does not do so with a full behavioral model such as the TPB. Explicating the beliefs allowed us to achieve the comprehensive overview of barriers and facilitators for walking outdoors after stroke, that we aimed for.

Summarized, we were able to provide a comprehensive overview, addressing behavioral determinants along with physical and social determinants, that was lacking in the many earlier studies[48, 49]. We did not find significant differences from the facilitators and barriers that are already known to community ambulation aimed at improving participation or for exercise. Nor did we find significant differences between Dutch and the Anglo-Saxon populations in earlier studies. However, this underlines the validity of the barriers and facilitators that were identified by the respondents.

Strengths and limitations

The use of the PAD-model as a directing concept allowed for a multidimensional description of barriers and facilitators for walking outdoors after stroke, giving insight into personal factors, environmental factors and behavioral mechanisms as well as constraints caused by body functions, limitations of activities and participation. The inclusion of respondents suffering from expressive aphasia and the use of focus-group interviews in addition to the individual interviews ensured saturation of the data and offered an opportunity validate the earlier collected data, increasing the validity of the outcomes and rigor of the study. Finally, all respondents were living in the community and the interviews were conducted at their homes, increasing the ecological validity of the study.

There were some limitations to the present study. First, most of the respondents were recruited from an existing network of physical therapists. They were either participating in exercise interventions or daycare interventions, including physical therapy, or did so in their rehabilitation past, which may have influenced their views on facilitators and barriers to walking outdoors. However, as eight respondents did not receive physical therapy at the time of the interviews it may be assumed that non-biased perceptions were also reported. Second, purposive sampling or inclusion criteria were not applied to the cognitive state of potential respondents. The reported prevalence of cognitive impairment in stroke varies from 20-80%[50] indicating that in the sample of respondents in the present study cognitive impairment may have influenced the perceptions of facilitators and barriers to walking outdoors. However, as cognitive impairment is common after stroke it is plausible not to use it as an exclusion criterion. Third, convenience sampling regarding the focus-group interviews was challenging the diversity of the reported perceptions. Fortunately, the composition of the focus-groups proved similarly diverse to the group of respondents who participated in the individual interviews, allowing for the collection of rich data. Lastly, the researcher conducting the interviews had a vast experience in working with individuals after stroke. This could challenge unbiased analysis of the data. However, as the analysis was triangulated with four other researchers this effect should have been only small.

Conclusions

The PAD-model proved to be usable in displaying a comprehensive overview and insight in barriers and facilitators for outdoor walking in individuals after stroke and could support clinical reasoning and diagnostics in healthcare professionals. Specifically mapping environmental and personal factors as well as the domain of participation should receive adequate attention. It seems of particular importance to address social influence, e.g., care-givers' or professionals' influence, self-efficacy and attitude in the development of efficient interventions to influence the intention to walk outdoors. Furthermore, the improvement of walking ability and the creation of opportunities should be considered. As barriers and facilitators were reported in all domains of the PAD-model, the interventions that are provided by the healthcare professionals to stimulate outdoor walking should be tailored to fit specific needs, overcome barriers and make use of facilitators in each individual with stroke. This study shows that when developing research aimed at enhancing or further exploring underlying mechanisms for outdoor walking after stroke, the incorporation of behavioral, social, environmental as well as physical variables should be considered.

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7

General discussion

The first major objective of the present thesis was to assess if task-oriented circuit class training (CCT) influences walking capacity in people early after stroke. To achieve the first objective, two randomized clinical trials were conducted in two different cohorts in Germany to investigate the effects of task-oriented CCT applied in the early stages of rehabilitation. The second major objective was to explore the factors that could explain walking capacity and walking performance. To achieve this second objective, we started by studying the association between aerobic capacity and walking capacity after stroke, by systematically reviewing the results of available studies on this association. The association was studied further in a sample of community-dwelling people who had suffered a stroke in the Netherlands. Thereafter, we explored facilitators and barriers for walking performance, specifically walking outdoors, in a qualitative study.

This final chapter starts with a summary of the main findings presented in this thesis, which are displayed in Table 1, followed by a discussion of the main findings, with clinical implications and recommendations for future research.

Main findings

Chapters 2 and 3 show that task-oriented CCT is safe and feasible and effectively improves walking capacity in mildly as well as severely impaired people during inpatient rehabilitation early after stroke. **Chapter 2** reports on a study showing that task-oriented CCT was as effective as usual individual physical therapy, matched for therapy time, in severely impaired inpatients early after stroke in terms of improving walking capacity. **Chapter 3** shows that task-oriented CCT that integrates aerobic exercise was more effective in improving walking capacity in a sample of mildly impaired people early after stroke than a task-oriented CCT without integrated aerobic exercise.

To achieve a better understanding of the association between aerobic capacity and walking capacity, we conducted a systematic review of the literature reporting on observational studies. The meta-analyses in the systematic review in **Chapter 4** showed a weak association between aerobic capacity and walking capacity in terms of speed, and a moderate association between aerobic capacity and walking capacity in terms of distance. The question remained if other factors, such as postural control, strength, age or gender, are responsible for the limited strength of the associations found in our analysis. Furthermore, the systematic review showed that the criteria that were used to assess aerobic capacity were not clearly reported, which left it unclear whether maximal aerobic capacity or peak aerobic capacity was reported.

These questions were addressed in the study reported on in **Chapter 5**, which examined the association between aerobic capacity and walking capacity. No significant differences in correlation coefficients were found between maximal aerobic capacity and walking capacity on the one hand, and peak aerobic capacity and walking capacity on the other. The predictive validity of aerobic capacity for walking capacity after stroke was confirmed. Postural control was found to be an important confounder for the association between aerobic capacity and walking capacity after stroke in the sample as a whole.

Unfortunately, gains in walking capacity resulting from physical therapy interventions do not necessarily translate into gains in walking performance with the aim of participating in community life or reducing health risks in people after stroke. Therefore, the qualitative study presented in **Chapter 6** investigated the factors that may influence walking performance, specifically outdoor walking, by exploring the perceptions of community-dwelling people after stroke. The perceptions regarding barriers and facilitators for outdoor walking were classified into three categories: the intention to walk outdoors, the ability to walk and opportunities and tasks that demand walking performance. The intention to walk outdoors was determined by barriers and facilitators in the ICF domains of personal and environmental factors, namely social influence, self-efficacy and attitude. The ability to walk outdoors was determined by postural control, aerobic capacity and walking capacity. Opportunities and tasks demanding walking performance, such as household chores and lively social contacts outdoors, were also perceived as conditional to walking outdoors.

Theoretical and methodological considerations and implications for future research and clinical practice

1. Task-oriented CCT during inpatient rehabilitation early after stroke

1.1. Effectiveness

Chapters 2 and 3 underline the effectiveness of task-oriented circuit-class training as regards walking capacity in the early stages after stroke, as reported in the few earlier trials[1]. Since the optimal timing for interventions to induce recovery after stroke is not yet clear[2], there is a need for more research in the early subacute stage, using the window of enhanced endogenous plasticity. Such research should use the framework defining the stages of recovery after stroke suggested by Bernhardt et al.[2] (Fig. 1). In line with their recommendations, this implies that future rehabilitation trials need to report on the timeline of recovery, reporting the time since stroke onset and the timing of assessments, i.e., at fixed critical time points post stroke that are linked to current knowledge of biological and true recovery (Fig. 1), and the duration of the interventions.

Table 1. Summary of the main findings

Aim of the study	Outcome of the study
Chapter 2 The objective of this inpatient trial was to investigate the effects and safety of task-oriented CCT as an alternative to therapy-time-matched individual task training, during inpatient rehabilitation, starting a mean of 39 days after stroke onset, to improve walking in terms of self-reported mobility for patients who were not able to walk independently.	- CCT is safe for severely impaired people early after stroke during inpatient rehabilitation. - A therapy-time-matched CCT is as effective as individual therapy for severely impaired people during inpatient rehabilitation early after stroke.
Chapter 3 The purpose of this trial was to establish the feasibility of task-oriented CCT incorporating aerobic exercise and to determine the effects on walking capacity in terms of walking distance and gait speed, compared with a task-oriented CCT that did not incorporate aerobic exercise, starting a mean of 23 days after stroke onset during inpatient rehabilitation.	- Aerobic exercise during task-oriented CCT is feasible and significantly more effective in improving walking capacity in terms of gait speed and walking distance for mildly impaired people early after stroke than task-oriented CCT not incorporating aerobic exercise.
Chapter 4 The aim of the systematic review and meta-analysis was to summarize the available evidence on the magnitude of the reported correlation coefficients between aerobic capacity and walking capacity, i.e., walking distance and walking speed, in individuals after stroke.	- The summarized evidence showed a moderate association between aerobic capacity and walking capacity, i.e., speed and distance, after stroke.
Chapter 5 The first aim of the cross-sectional study was to determine if the predictive validity of VO_{2peak} for walking capacity after stroke differs significantly from that of VO_{2max}. The second aim was to investigate to what extent postural control, hemiplegic lower extremity muscle strength, age or gender distort the association between aerobic capacity and walking capacity after stroke.	- Aerobic capacity is a valid predictor of walking capacity, i.e., walking speed and walking distance, in a moderately impaired population of community-dwelling people more than three months after stroke. - Postural control confounds the association between aerobic capacity and walking capacity. However, aerobic capacity remains significantly associated with walking capacity even after correction for postural control.

Chapter 6
The purpose of the qualitative study was to identify barriers and facilitators for walking performance, specifically walking outdoors, from the perspective of community-dwelling individuals after stroke in the chronic stage, using the PAD model as a sensitizing concept.
	- Community-dwelling stroke survivors reported perceiving intention, ability and opportunity as determinants of walking performance
	  - Intention to walk is influenced by personal factors such as social influence, attitude and self-efficacy. Personal factors are influenced by social and physical environment.
	  - Ability to walk is determined by walking capacity and body functions, such as aerobic capacity and postural control.
	  - Opportunities for walking are influenced by social participation within the family, within the neighborhood and with friends.

Abbreviations: CCT: circuit class training, HRR: heart rate reserve, VO_{2peak}: peak aerobic capacity, VO_{2max}: maximal aerobic capacity, PAD: physical activity in disability.

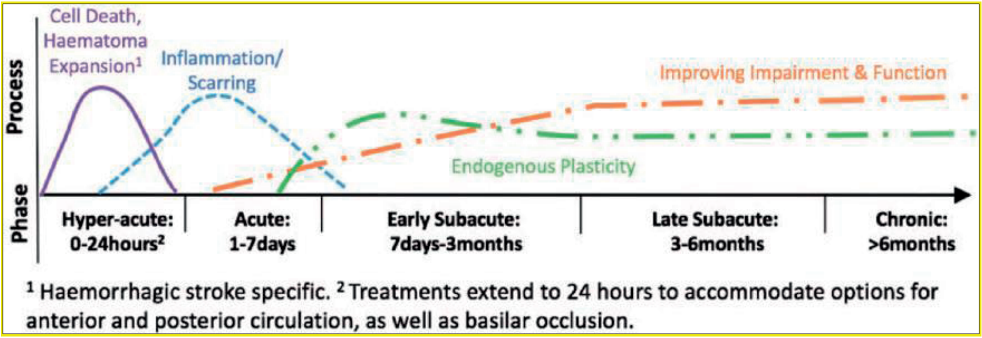

Figure 1. Framework defining the critical time points post stroke linking to current known biology from Bernhardt et al.[2]©

1.2. Safety and feasibility

In both of the trials described in **Chapters 2 and 3**, feasibility was demonstrated and no adverse events were recorded in terms of falls or cardiovascular events.

As falls are very common in people after stroke[3], the concerns of professionals and caregivers often focus on falls and the risk of falling. Therefore, the safety of the task-oriented CCT we studied, may contribute to its implementation in early subacute rehabilitation. The absence of adverse events that we found is in line with the very low risk difference between intervention and control groups in terms of falls that was reported in a recent meta-analysis of CCT compared to other interventions[1].

In terms of cardiovascular incidents, the trials described in **Chapters 2** and **3** showed no adverse events, in line with other trials to date that have investigated aerobic training early after stroke, and that also reported no adverse events related to the aerobic exercise[4-7]. Moreover, a recent meta-analysis found no evidence of an increased risk of cardiovascular adverse events in trials that involved aerobic exercise after stroke[7]. Nevertheless, integrating aerobic exercise in the program may not be without risks[8] in view of the association between cardiac events and the presence of cardiovascular disease (CVD)[9], and the prevalence of CVD of up to 75% in people after stroke[10]. Saunders et al.[7] suggested that they did not find an elevated risk because of rare or inadequate reporting of cardiovascular adverse events in trials involving aerobic exercise. On the other hand, the absence of reports of cardiovascular adverse events may also be related to the use of the proper safety precautions, such as using a pre-participation screening questionnaire and HR monitoring, that are recommended for aerobic exercise after stroke[8]. These precautions were also taken in our trial. Two meta-analyses[1, 7] included studies covering the entire process of rehabilitation. Combining this with the results of our trials, we suggest that, provided proper precautions are taken, task-oriented CCT is a safe and feasible intervention in terms of adverse events such as falls or cardiac events, which can be applied from inpatient rehabilitation early after stroke to outpatient rehabilitation in the later stages.

1.3. Therapy time and cost-effectiveness

Chapter 2 showed that during inpatient rehabilitation, task-oriented CCT is as effective as individual care in improving walking capacity, which is similar to the results of a later study[11]. The similar effectiveness of CCT and individual physical therapy suggests that task-oriented CCT may be more cost-effective, considering the staff-patient ratio. The potential cost savings could be invested in longer therapy time. More time dedicated to practice[13, 14] as well as task-specificity of practice[12, 14, 15] have been shown to result in better post-stroke outcomes regarding activities of daily living (ADL). However, to our knowledge there has been only one trial exploring the cost-effectiveness of task-oriented CCT during inpatient rehabilitation[16]. In the publication reporting the results of this trial[15], the cost-effectiveness was only reported in terms of duration of stay, for which no significant difference between the groups was found. Therefore, the cost-effectiveness of task-oriented CCT as opposed to conventional individual care needs to be further explored.

2. Integrating aerobic exercise into task-oriented CCT after stroke

2.1. Effectiveness of integrating aerobic exercise

The effect on walking capacity of integrating aerobic exercise into CCT is reported on in **Chapter 3.** The study presented in **Chapter 3** compared two task-oriented CCT programs. Both programs were matched for therapy time, but only one program integrated aerobic exercise. The intervention with the integrated aerobic exercise yielded better outcomes for walking capacity. These positive effects of integrating aerobic exercise in CCT on walking capacity suggest that aerobic exercise may enhance the outcomes of task-oriented CCT. Since aerobic exercises were incorporated into the functional exercises of the CCT, we followed the suggestion that aerobic training needs to be functional[17, 18] to yield the desired effects on walking capacity. In addition, it has been suggested that aerobic exercise may induce neuroplasticity[19, 20], similar to what was found in animal models after stroke, which may also partly explain the greater gains in walking capacity. However, even though in **Chapters 4** and **5** we have demonstrated a moderate association between aerobic capacity and walking capacity, the question whether gains in aerobic capacity are associated with improvements in walking capacity remains unanswered, as a result of the lack of longitudinal trials reporting on both outcomes[17]. Reporting on both aerobic and walking capacity was also a limitation of our trial described in **Chapter 3**, as we did not measure aerobic capacity due to lack of equipment and resources.

Saunders et al.[17] suggested that part of the effect of aerobic exercise on walking capacity could be attributed to a confounding effect of increased therapy time, which also has a positive effect on walking capacity[12]. However, as the therapy time in our trial (**Chapter 3**) was matched, our results suggest that the aerobic exercise during CCT may genuinely have made the difference.

2.2. *Intensity of aerobic exercise in task-oriented CCT for optimal effectiveness regarding walking capacity*

To integrate aerobic exercise into task-oriented CCT, we need to know what frequency, intensity, time and type, i.e., the FITT exercise principles[21] are best suited to yield optimal effect on walking capacity after stroke. Frequency is expressed as the number of exercise sessions per week, time is expressed as the duration of each session and the type of exercise would obviously be aerobic exercise. Intensity of exercise is expressed in terms of cardiovascular intensity. Unfortunately, data on the intensity of aerobic exercise achieved are not reported in most trials after stroke[7]. In our trial presented in **Chapter 3**, we used the age-predicted maximal heart rate (HR_{max}) for elderly people[22] to determine the dose of aerobic exercise. However, not only has it been shown that age-predicted HR_{max} may deviate considerably from actual HR_{max}, but age-predicted HR_{max} also does not take the use of beta-blockers into account. Therefore, this procedure may have caused differences in cardiovascular intensity during aerobic exercise among the participants, even though HR was monitored. To determine optimal intensity for aerobic exercise, it has been recommended to assess HR_{max} and aerobic capacity with a graded maximal cardio-pulmonary exercise test (CPET)[8], in accordance with current guidelines[23], rather than using age-predicted HR_{max}. In the study described in **Chapter 5** a CPET was conducted among 51 persons in the chronic stage after stroke. Only 40% of the participants were able to achieve a "true" VO_{2max}. This low percentage confirms the challenge posed by the assessment of maximal aerobic capacity after stroke[24, 25]. In **Chapter 5** we reported that postural control is a major confounder of the association between aerobic capacity and walking capacity, in that postural control influences both outcomes, as illustrated in Figure 2. To compensate for the influence of postural control during the assessment of aerobic capacity, it may be helpful to perform maximal CPET using a bicycle protocol[8, 25], instead of the treadmill protocol that was used in **Chapter 5**. However, even when bicycle protocols are used, the aerobic capacity thus assessed may be compromised by factors such as reduced lower limb function or cognitive function[26, 27]. Therefore, tests to determine the intensity for aerobic training that do not require maximal CPET need to be developed for the stroke population. As an alternative to maximal CPET, it may be valuable to perform submaximal exercise testing, as it has been suggested that the ventilatory threshold (VT) may be a more valid measure to determine the intensity of aerobic exercise after stroke than VO_{2max} [28]. The literature does not, however provide clear guidance on the optimal protocol to establish VT. A recent study on the use of the 6MWT to determine VT found that the utility of the 6MWT is limited, specifically in people with decreased postural control[29]. Therefore, we need more research and the development of protocols that are less dependent on subjects' balance control. Furthermore, training protocols integrating aerobic training into task-oriented circuit-classes need to be more transparent in terms of adherence to the FITT principles[30], to be able to determine the dose of therapy for optimal outcome. Intensity of training may have to be reported in terms of cardiovascular intensity as well as the number of repetitions. The number of repetitions and the time of therapy may give valuable information about the association between dose and effectiveness of the motor learning processes that are obviously part of the functionality of task-oriented CCT.

3. Task-oriented CCT and walking performance in community-dwelling people after stroke

3.1 Task-oriented CCT as an intervention to enhance walking performance

Task-oriented CCT is effective in improving walking capacity, as reported in **Chapters 2** and **3**. Task-oriented CCT may thus lead to the achievement and maintenance of the thresholds of walking capacity[31], which are necessary to achieve the walking ability needed for walking performance, specifically outdoor walking in the community. Increasing walking performance may be conducive to social participation and reduce health risks. However, gains in walking capacity are not always perceived as such, nor do they automatically lead to more physical activity like increased walking performance[32]. For example, the trial reported on in **Chapter 2** used the Stroke Impact Scale (SIS) to evaluate mobility and social participation, and did not find a significant effect, even though walking capacity showed clinical meaningful changes in 69% of the participants in the control group and in 86% of the task-oriented CCT-group. However, this may be related to the fact that the sample consisted of inpatients in the early stages of their rehabilitation process, who could not yet participate in community life. On the other hand, the systematic review by English et al.[1], which reported that 13 out of 17 included trials were conducted in community settings, only found a small effect of task-oriented CCT on SIS scores. SIS may not be a valid measure of walking performance, as the questions are more focused on the ability to walk or to participate, and not on the time spent or the number of steps in walking activities related to mobility and participation.

The results of our qualitative study in **Chapter 6** showed that physical factors determining walking ability, such as walking capacity, are important for walking performance (Fig.2). However, the results in **Chapter 6** also showed that walking ability interacts with the intention to walk and the opportunity for walking performance, as shown in Figure 2. **Chapter 6** also showed that intention was based on the personal behavioral factors of self-efficacy, social influence and attitude, interacting with environmental factors in the social and physical environment (Fig. 2).

The interaction between ability, intention and opportunity illustrates the comprehensive interaction of physical, social, environmental and behavioral factors. Interventions that have been designed in the last decade to stimulate walking performance after stroke have not been very successful[33, 34]. These interventions were intended to address either physical and environmental factors *or* behavioral factors[33]. It might be suggested therefore that a more comprehensive approach, using trials in which these factors are combined, would be more effective. Therefore, task-oriented CCT, effective though it is in terms of walking capacity, may need to be supplemented with a behavioral intervention, an environmental intervention and even a social intervention in a comprehensive approach in order to be effective in terms of walking performance, as depicted in Figure 2.

Firstly, to address self-efficacy, social influence and attitude, some of the components of task-oriented CCT may just need more explicit use to serve as behavioral interventions (Fig. 2). For example, the two interventions compared in **Chapter 2** were time-matched, so the main contrast was the task-oriented CCT group dynamics as opposed to individual physical therapy. Aspects of group dynamics such as peer support **(Chapter 6)** may be motivating factors[35], and the same may be true for monitoring (including self-monitoring) and feedback[35], which were also part of the task-oriented CCT. It remains to be investigated whether group dynamics, i.e., peer support, as well as monitoring (including self-monitoring) and feedback during task-oriented CCT can be used to stimulate walking performance.

Secondly, the caregivers' and healthcare professionals' concerns about safety, which were reported as a barrier for walking outdoors, and confirmed in a recent review[36], need to be considered. These concerns about safety that exist in the social environment and that could lead to a lack of social support, may need to be addressed simultaneously with a task-oriented CCT intervention, by means of an environmental intervention (Fig. 2), such as education. Recent research into behavioral change after stroke[33] suggests that positive social support may stimulate physical activity, including walking performance. Future research should be aimed at developing behavioral change interventions, using techniques such as those described in Michie's behavioral change taxonomy[35], to enhance physical activity, including walking performance, after stroke. These interventions can potentially be integrated into task-oriented CCT and should involve caregivers in the social environment. Finally, creating opportunities that demand walking performance, such as a walking club may be necessary as a social intervention (Fig. 2).

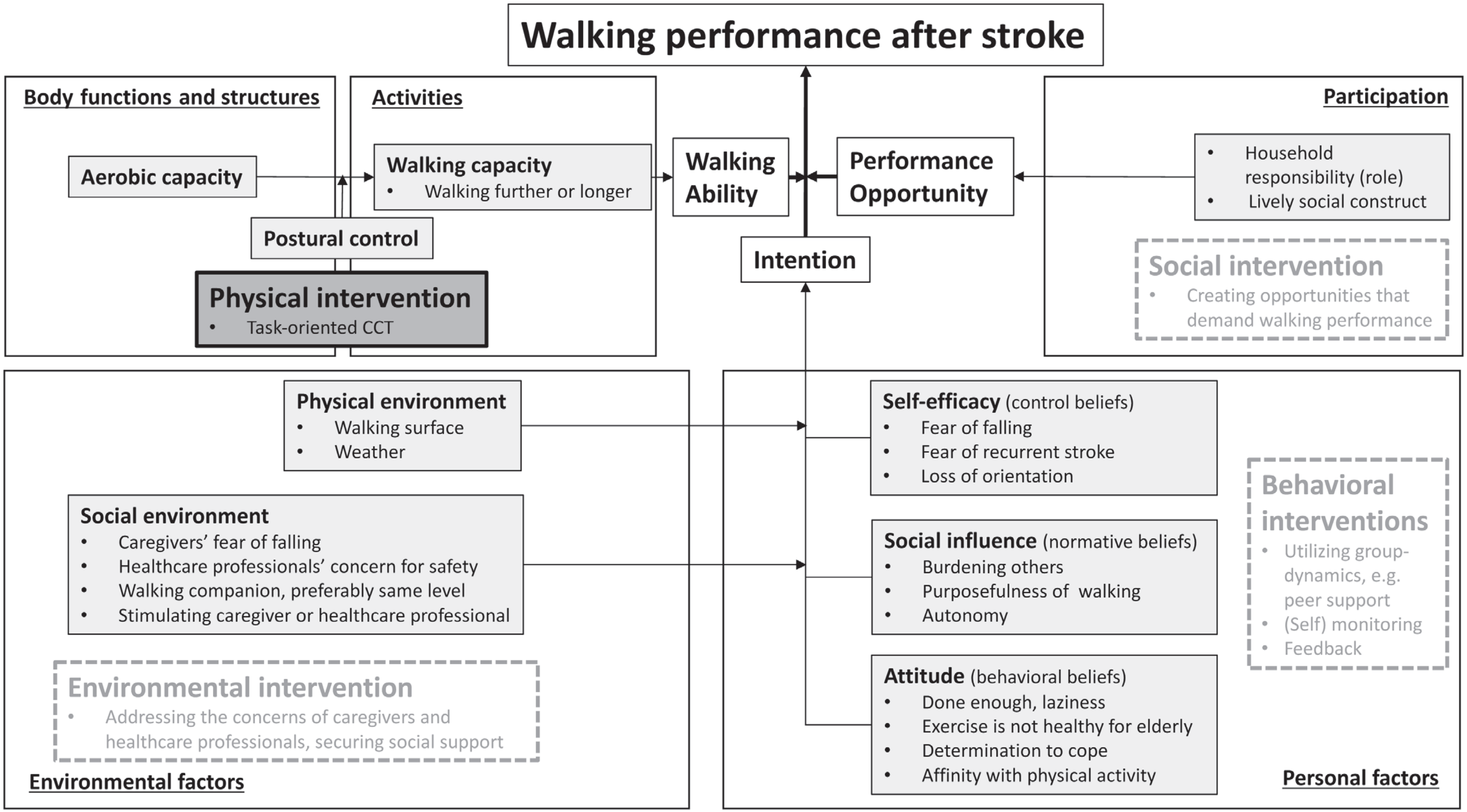

Figure 2. The ICF framework adapted to depict the interaction between ability, opportunity and intention for walking performance after stroke, incorporating the results of the studies reported in this thesis. The pale shaded rectangles depict the proposed interventions to enhance task-oriented CCT.

Chapter 7

3.2 Evaluating a comprehensive task-oriented CCT aimed at improving walking performance

In this thesis, the outcome of the task-oriented CCT mainly focused on walking capacity. However, when evaluating future trials on the effectiveness of a comprehensive task-oriented CCT, walking performance should not be the only outcome measure. Such trials should also assess the effects on important goals of the enhancement of walking performance, like improving cardiovascular health by lowering elevated cholesterol levels or high blood pressure, as well as improvement of community participation.

To date, the only positive effect that has been reported to result from comprehensive life-style interventions incorporating exercise and behavioral interventions is that on blood pressure[38]. However, the trials included in that review did not always combine aerobic training and behavioral interventions and did not always include an established theoretical framework of behavioral change, which once more emphasizes the need for comprehensive and transparent intervention protocols.

A final aspect of the evaluation of a comprehensive task-oriented CCT emerged from the results reported in **Chapter 6**, where cognitive functioning, such as orientation, and depressed mood were also indicated by the respondents as factors that may influence walking performance. There are some indications that aerobic exercise may positively influence cognition[39] and depression[40] after stroke. However, a recent meta-analysis[7] was unable to draw conclusions regarding the effect of aerobic training on cognitive functioning and mood, which may possibly be related to the fact that cognition and mood were mostly secondary outcomes in the few trials that were available. Therefore, future trials on the effects of a comprehensive task-oriented CCT may also need evaluate the effects on cognition and mood as a primary outcome.

Conclusions

The findings in the present thesis contribute to the evidence for and understanding of task-oriented CCT training during inpatient rehabilitation early after stroke. The studies on the association between aerobic capacity and walking capacity underline the importance of integrating aerobic exercise into task-oriented CCT. This may increase the effects of task-oriented CCT on walking capacity. However, addressing factors such as social influence, self-efficacy and attitude seems of prime importance in attempts to induce behavioral change towards a more physically active lifestyle, which is needed to preserve the gains in walking capacity that are achieved during rehabilitation. Moreover, caregivers' and professionals' concerns about safety need to be addressed, and opportunities that demand walking may need to be created. Task-oriented CCT should be a comprehensive intervention, integrating aerobic training and probably behavioral, environmental as well as social interventions, from the early subacute to the chronic stages after stroke. It should be continued throughout the rehabilitation process and also thereafter when its aim is to achieve or maintain a physically active lifestyle after stroke.

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Summary

Worldwide, stroke is one of the leading causes of disability. Many people who survive a stroke, experience physical consequences such as reduced walking ability, which may reduce walking capacity and walking performance. Research has shown that walking capacity, for instance the distance that a person is able to walk in six minutes in standardized circumstances after a stroke, is reduced to a mean of 50% of that of healthy peers. Similarly, walking performance, expressed as the amount of walking activity in the community, and measured as the number of steps a day that are taken, is reduced to a mean of 50% of the number of steps that are recommended for people after disability to stay healthy.

Task-oriented Circuit Class Training (CCT) is a physical therapy intervention aimed at improving walking after stroke. Positive effects of task-oriented CCT on walking capacity in the chronic stages (i.e., more than three months after the stroke) have been reported and are similar to the positive effects of individual physical therapy interventions. The effectiveness and feasibility of task-oriented CCT in the subacute stages (i.e., up to three months after the stroke), for example during inpatient rehabilitation, has remained unclear. Information about the effectiveness of interventions during this stage of rehabilitation may be of particular importance, as the period up to three months after stroke is regarded as a critical time window of enhanced neuroplasticity. Interventions during this period may enhance biological recovery and improve functional outcome.

Task-oriented CCT uses repetitive functional task practice and does not directly address the resolution of impairments such as decreased aerobic capacity. However, aerobic capacity is seriously reduced after stroke. Therefore, information about the feasibility and effectiveness of integrating aerobic exercise into task-oriented CCT early after stroke is important to determine if this can enhance the outcome regarding walking capacity. To support clinical reasoning and to validate the use of aerobic exercise to influence walking capacity, the association between aerobic capacity and walking capacity after stroke needs to be further elucidated.

Despite the positive effects of task-oriented CCT on walking capacity, these positive effects do not appear to translate into walking performance. Therefore, we need to know what keeps people who have suffered a stroke from walking in the community, in order to be able to retain or stimulate walking performance.

In the randomized controlled trial in **Chapter 2** the aim was to compare the effects of task-oriented CCT with equally dosed individual task training, in terms of self-reported mobility for patients with moderate to severe stroke during inpatient rehabilitation early after stroke. In this trial, 73 subacute inpatients after stroke, residing in a rehabilitation center and unable to walk without physical assistance, were randomized into a task-oriented CCT group and a usual physical therapy group. Both interventions were intended to improve walking and comprised 30 sessions of 90 minutes each over six weeks. Primary outcome was the mobility domain of the Stroke Impact Scale (SIS-3.0). Secondary outcomes were the other domains of SIS-3.0, as well as postural control, walking speed, walking distance, stair climbing, fatigue, anxiety and depression. The results of this trial showed no adverse events and no significant differences between groups regarding the SIS mobility domain at the end of the intervention. Furthermore, no significant differences between groups were found as regards walking-related parameters or non-physical outcomes such as depression and fatigue. These results showed that early inpatient task-oriented CCT for patients with moderate to severe impairments after stroke is safe and equally effective as a dose-matched individual task training therapy. Task-oriented CCT may thus be provided as an alternative to individual physical therapy.

The feasibility and effectiveness of aerobic exercise integrated into task-oriented CCT in the subacute stage after stroke was investigated in the trial described in **Chapter 3.** Forty-four inpatients with mild to moderate impairments after stroke were recruited in a rehabilitation center, two to eight weeks after stroke onset. They were randomized into two task-oriented CCT groups, one of which engaged in task-oriented CCT with integrated aerobic exercise. Walking capacity was the primary outcome, and was expressed as maximal gait speed, assessed by the Ten-Meter Timed Walk test (10MTWT), and walking distance, assessed by the Six-Minute Walk Test (6MWT). Secondary outcome was postural control. No adverse events occurred during the trial. The results of the analysis showed a statistically significant difference in favor of the task-oriented CCT with integrated aerobic exercise, in terms of the achievements on the 10MTWT and the 6MWT. No significant difference was found for postural control. These results showed that task-oriented CCT incorporating aerobic exercise, designed to improve walking capacity, was feasible and effective in this sample of mildly to moderately impaired inpatients in the subacute stage after stroke

As a consequence of the finding that the integration of aerobic exercise into task-oriented CCT appeared to increase its effectiveness in improving walking capacity compared to task-oriented CCT alone, the association between aerobic capacity and walking capacity was further investigated in **Chapter 4**. A systematic review was performed of the available evidence on the correlation between aerobic capacity and walking capacity. Walking capacity was operationalized as walking speed and walking distance. Thirteen cross-sectional studies reporting correlation coefficients between aerobic capacity and walking capacity in stroke were included, along with longitudinal studies reporting these correlation coefficients at baseline. The included studies involved 454 participants. Meta-analyses showed a low combined correlation coefficient (r_m) for aerobic capacity and walking speed, and a moderate r_m for aerobic capacity and walking distance. However, the studies included in the systematic review had small sample sizes and low methodological quality. Furthermore, clinical and methodological diversity challenged the comparability of the included studies, despite statistical homogeneity. Importantly, it remained unclear whether it was maximal aerobic capacity (VO_{2max}) which was achieved in the included studies, or peak aerobic capacity (VO_{2peak}). VO_{2peak} is the highest value of oxygen uptake found during a maximal cardiopulmonary exercise test (CPET), and does not necessarily reflect the maximal aerobic capacity, as this may be influenced by other factors like motor impairments or psychological factors. In conclusion, the results of the systematic review supported the notion that the association between aerobic capacity and walking capacity justifies the integration of aerobic exercise into task-oriented CCT. The wide range of correlation coefficients, that were reported in the included studies also suggested that other factors, besides aerobic capacity, determine walking capacity after stroke.

Following the remaining ambiguity on the association between aerobic capacity and walking capacity resulting from **Chapter 4**, the study in **Chapter 5** cross-sectionally scrutinized the association between aerobic capacity and walking capacity, in an effort to elucidate this association. The first aim of this study was to determine if the association between walking capacity and peak aerobic capacity (VO_{2peak}) post stroke is different from the association between walking capacity and maximal aerobic capacity (VO_{2max}). The second aim was to determine if postural control, hemiplegic lower extremity muscle strength, age and gender distort the association between aerobic capacity and walking capacity. Fifty-one community-dwelling people, more than three months after their stroke, were included in the study. Aerobic capacity was measured during CPET, differentiating between meeting (VO_{2max}) or not meeting (VO_{2peak}) the criteria for maximal aerobic capacity. Walking capacity was measured with the 6MWT and postural control was assessed with the Performance Oriented Mobility Assessment (POMA). Finally, hemiplegic lower extremity muscle strength was assessed with the Motricity Index (MI-LE). Twenty-two of the participants were able to achieve VO_{2max}. Analysis of variance showed no significant difference between the associations of VO_{2max} and VO_{2peak} with walking capacity. Multivariate analysis showed that postural control confounded the strong association between aerobic capacity and walking capacity after stroke. In conclusion, the findings showed that aerobic capacity is an important factor associated with walking capacity after stroke. Postural control, however, needs to be taken into account to understand this relationship. Both aerobic capacity and postural control may need to be addressed during interventions aiming to improve walking capacity after stroke.

Task-oriented CCT is effective in improving walking capacity, and its effectiveness may even be enhanced by incorporating aerobic exercise. However, the resulting gains in walking capacity do not seem to translate into walking performance, e.g., outdoor walking. People who have suffered a stroke generally fail to meet the recommendations for physical activity to conduct a healthy lifestyle. Programs that have been developed to stimulate walking performance are not entirely successful. This may be attributed to the fact that most studies and programs address merely one aspect of the comprehensive problem. For instance, task-oriented CCT aims at the physical problem, whereas behavioral, environmental or social problems may also need to be addressed. In the qualitative study presented in **Chapter 6** we therefore aimed to comprehensively explore perceived barriers and facilitators for outdoor walking, using a model of integrated biomedical and behavioral theory, the Physical Activity in people with a Disability model (PAD). Included were 36 moderately impaired community-dwelling respondents who had suffered a stroke, who were able to walk independently, and were classified ≥3 on the Functional Ambulation Categories (FAC) scale. They had been purposively sampled regarding the use of healthcare. The data was collected in a multi-methods approach including semi-structured, structured and focus-group interviews for triangulation. A primarily deductive thematic content analysis using the PAD model in a framework analysis approach was conducted after verbatim transcription. The results showed that outdoor walking was determined by intention, ability and opportunity. The intention to walk outdoors was determined by personal factors such as social influence, for instance from restrictive attitudes of caregivers in the social environment, as well as by self-efficacy, influenced by the physical environment, and by the attitude towards physical activity. Walking ability was influenced by loss of balance and reduced walking distance, and by impairments of motor control, cognition and aerobic capacity, as well as fatigue. Outdoor walking was facilitated by opportunities demanding walking performance arising from household tasks and lively social contacts. In conclusion, when encouraging outdoor walking, it seems important to influence the person's intention by addressing social influence, self-efficacy and attitude towards physical activity in the development of efficient interventions. At the same time, the improvement of walking ability and the creation of opportunities should also be considered.

In **Chapter 7**, the general discussion, the main findings reported in this thesis were summarized, and theoretical considerations are discussed. Clinical implications of the findings are discussed and suggestions were made for future research. The research reported on in this thesis found that task-oriented CCT in the subacute stages after a stroke is as effective as individual physical therapy interventions when it comes to improving walking capacity. It also found that addressing aerobic capacity during task-oriented CCT may enhance the effects on walking capacity. Finally, we suggest that task-oriented CCT as a physical intervention may need to be supplemented with behavioral, environmental and social interventions to be effective in terms of walking performance in people after stroke.

Samenvatting

Wereldwijd is een beroerte een van de belangrijkste oorzaken van functionele beperkingen. Veel mensen, die een beroerte overleven, ervaren lichamelijke gevolgen zoals een verminderde loopvaardigheid, die tot een verminderd loopvermogen en verminderde loopprestatie kan leiden. Onderzoek laat zien dat het loopvermogen, bijvoorbeeld de afstand die iemand kan lopen binnen zes minuten onder gestandaardiseerde omstandigheden, na een beroerte gemiddeld 50% verminderd is ten opzichte van vergelijkbare gezonde mensen. Hetzelfde geldt voor loopprestatie, uitgedrukt in de hoeveelheid van loopactiviteit in de leefomgeving en gemeten als het aantal stappen per dag die iemand zet, wat gemiddeld 50% lager ligt bij mensen na een beroerte dan de aanbevolen hoeveelheid stappen per dag voor mensen met een lichamelijke beperking.

Taak-georiënteerde circuit groepstraining (CCT) is een fysiotherapeutische interventie, die erop gericht is om het lopen na een beroerte te verbeteren. Er zijn positieve effecten beschreven van taak-georiënteerde CCT op het loopvermogen van mensen na een beroerte in de chronische fase (d.w.z. meer dan drie maanden na de beroerte), die vergelijkbaar zijn met de effecten van individuele fysiotherapie. De effectiviteit en uitvoerbaarheid van taak-georiënteerde CCT bij mensen na een beroerte in de subacute fase (d.w.z. minder dan drie maanden na een beroerte) is nog niet duidelijk. Informatie over de effectiviteit en uitvoerbaarheid van therapie interventies gedurende deze fase van revalidatie kan van bijzonder belang zijn, omdat de tijd tot drie maanden na een beroerte gezien wordt als een bepalend tijdsvenster van verhoogde neuroplasticiteit. Interventies gedurende deze periode kunnen mogelijk het biologische herstel bevorderen en de functionele uitkomst optimaliseren.

Taak-georiënteerde CCT is gebaseerd op het principe van herhaald oefenen van taken en niet direct op het verbeteren van lichamelijke beperkingen, zoals verminderd uithoudingsvermogen. Echter, het uithoudingsvermogen bij mensen na een beroerte is ernstig verminderd. Het is daarom van belang te onderzoeken of het integreren van het trainen van uithoudingsvermogen in taak-georiënteerde CCT binnen drie maanden na een beroerte effectief en uitvoerbaar is, om te bepalen of dit de uitkomst op loopvermogen kan verbeteren. Om het klinisch redeneren te ondersteunen en om het gebruik van training van uithoudingsvermogen te rechtvaardigen om loopvermogen te verbeteren, moet de samenhang tussen uithoudingsvermogen en loopvermogen na een beroerte nader belicht worden.

Ondanks de positieve effecten van taak-georiënteerde CCT op loopvermogen, lijken de positieve effecten niet over te gaan naar loopprestatie in de eigen leefomgeving. Daarom moeten we weten welke zaken mensen na een beroerte ervan af houden in de eigen leefomgeving te lopen om hun loopprestatie te behouden of te verbeteren.

Het doel in het gerandomiseerd gecontroleerde onderzoek in **Hoofdstuk 2** was om het effect van taak-georiënteerde CCT op zelf gerapporteerde mobiliteit van mensen met matig tot zware beperkingen gedurende de klinische revalidatie, te vergelijken met individuele taak training. Voor dit onderzoek werden 73 mensen in de subacute fase na een beroerte, verblijvend in een revalidatiekliniek en niet loopvaardig zonder hulp willekeurig ingedeeld in twee groepen, namelijk een taak-georiënteerde CCT en een normale individuele fysiotherapie groep. In beide groepen was de therapie op het verbeteren van het lopen gericht en omvatte 30 behandelingen van 90 minuten gedurende zes weken. De primaire uitkomstmaat was het mobiliteitsdomein van de Stroke Impact Scale (SIS-3.0). Secundaire uitkomsten waren de andere domeinen van de SIS-3.0, naast posturele controle, loopsnelheid, loopafstand, traplopen, vermoeidheid, onrust en depressie. De resultaten van dit onderzoek lieten geen ongewenste incidenten zien en geen verschillen tussen de twee groepen op het mobiliteitsdomein van de SIS-3.0 na afloop van de interventie. Er werden ook geen verschillen tussen de groepen gevonden ten aanzien van de verschillende loop-parameters en niet lichamelijke parameters, zoals vermoeidheid en depressie. Deze resultaten lieten zien dat vroege klinische taak-georiënteerde CCT bij mensen met matige tot zware beperkingen na een beroerte, veilig is en net zo effectief als een gelijk gedoseerde individuele fysiotherapeutische behandeling. Taak-georiënteerde CCT kan daarmee als alternatief voor individuele fysiotherapie gezien worden.

De toepasbaarheid en effectiviteit van training van uithoudingsvermogen geïntegreerd in taak-georiënteerde CCT in de subacute fase na een beroerte, werd onderzocht in het onderzoek dat beschreven is in **Hoofdstuk 3.** Er werden 44 klinische patiënten, twee tot acht weken na hun beroerte, met milde tot matige beperkingen geworven in een revalidatiekliniek. Ze werden willekeurig ingedeeld in twee taak-georiënteerde CCT groepen, waarvan er één groep de training van het uithoudingsvermogen geïntegreerd had. Loopvermogen was de primaire uitkomst, uitgedrukt in maximale loopsnelheid, gemeten met een Tien-Meter Looptest (10MTWT) en in loopafstand, gemeten met een Zes-Minuten Looptest (6MWT). Secundaire uitkomst was posturele controle. Gedurende het onderzoek was er geen spraken van ongewenste incidenten. De resultaten van de analysen lieten een statistisch significant verschil zien, ten gunste van de taak-georiënteerde CCT met training van het uithoudingsvermogen, op de behaalde prestaties op de 10MTWT en de 6MWT. Er werd geen significant verschil tussen de groepen op posturele controle gevonden. Deze resultaten laten zien dat een taak-georiënteerde CCT met integratie van training van uithoudingsvermogen, ontworpen om het loopvermogen te verbeteren, uitvoerbaar en effectief was in deze steekproef van mensen met milde tot matige beperkingen in de subacute fase na een beroerte.

Ten gevolge van het inzicht dat integratie van training van het uitvermogen in een taak-georiënteerde CCT het effect van taak-georiënteerde CCT op het loopvermogen leek te verhogen, werd de samenhang tussen uithoudingsvermogen en loopvermogen na een beroerte nader uitgezocht in **Hoofdstuk 4**. Er werd een systematisch literatuuronderzoek van het beschikbare bewijs over de correlatie tussen uithoudingsvermogen en loopvermogen na een beroerte uitgevoerd. Loopvermogen werd uitgedrukt in loopsnelheid en loopafstand. Er werden 13 onderzoeken, die correlatiecoëfficiënten tussen uithoudingsvermogen en loopvermogen na een beroerte rapporteerden, samen met longitudinale onderzoeken die deze correlatiecoëfficiënten op baseline rapporteerden, geïncludeerd. In totaal werden er 454 deelnemers onderzocht in de geïncludeerde studies. Meta-analysen lieten een lage gecombineerde correlatiecoëfficiënt (r_m) zien voor uithoudingsvermogen en loopsnelheid en een matige r_m voor uithoudingsvermogen met loopafstand. De geïncludeerde studies hadden echter kleine steekproeven en lage methodologische kwaliteit. Verder was de klinische en methodologische diversiteit tussen de studies een uitdaging voor de vergelijkbaarheid van de studies, ondanks de statistische homogeniteit. Een belangrijk aspect was de onduidelijkheid over het behaalde uithoudingsvermogen, namelijk maximaal uithoudingsvermogen of piek uithoudingsvermogen, dat gerapporteerd werd in de studies. Piek uithoudingsvermogen is de hoogste waarde van opgenomen zuurstof die gemeten wordt tijdens een maximale inspanningstest (CPET). Dit is niet noodzakelijk een afspiegeling van het maximale uithoudingsvermogen, omdat het piek uithoudingsvermogen mede bepaald kan worden door andere factoren zoals motorische beperkingen of psychologische factoren. Concluderend ondersteunen de resultaten van het systematische literatuuronderzoek het idee, dat de samenhang tussen uithoudingsvermogen en loopvermogen het integreren van training van het uithoudingsvermogen in een taak-georiënteerde CCT rechtvaardigt. De uiteenlopende correlatiecoëfficiënten, die in de studies gerapporteerd werden doen vermoeden, dat andere factoren, behalve uithoudingsvermogen het loopvermogen mede bepalen.

Ten gevolge van de resterende onduidelijkheid over de samenhang tussen uithoudingsvermogen en loopvermogen na een beroerte uit **Hoofdstuk 4**, werd in de studie in **Hoofdstuk 5** de samenhang tussen uithoudingsvermogen en loopvermogen nog eens cross-sectioneel onderzocht in een poging deze samenhang verder te belichten. Het eerste doel van de studie was te bepalen of er verschil was tussen de relatie van maximaal uithoudingsvermogen en loopvermogen, en de relatie van piek uithoudingsvermogen en loopvermogen. Het tweede doel van de studie was om te bepalen in hoeverre posturele controle, kracht in het hemiplegische been, leeftijd en geslacht de samenhang tussen uithoudingsvermogen en loopvermogen verstoren. Er werden 51 thuiswonende mensen, die langer dan drie maanden na hun beroerte waren in de studie geïncludeerd. Uithoudingsvermogen werd gemeten met een CPET, waarbij onderscheid gemaakt werd tussen het behalen van maximaal uithoudingsvermogen en piek uithoudingsvermogen. Loopvermogen werd gemeten met de 6MWT en posturele controle werd gemeten met de Performance Oriented Mobility Assessment (POMA). Tenslotte werd de kracht in het hemiplegische been gemeten met de

Motricity Index (MI-LE). Er waren 22 deelnemers, die maximaal uithoudingsvermogen haalden tijdens de CPET. Analyse van de variantie liet echter zien dat er geen significant verschil was tussen de relaties van maximaal of peak uithoudingsvermogen met loopvermogen. Multivariate analyses lieten zien dat posturele controle de belangrijkste verstoorder was van de sterke samenhang tussen uithoudingsvermogen en loopvermogen na een beroerte. Concluderend laten de resultaten zien, dat uithoudingsvermogen een belangrijke samenhangende factor met loopvermogen na een beroerte is. Echter moet er rekening gehouden worden met posturele controle om deze samenhang goed te begrijpen. Zowel uithoudingsvermogen als posturele controle moeten mogelijk behandeld worden tijdens interventies die op het verbeteren van loopvermogen na een beroerte gericht zijn.

Taak-georiënteerde CCT is effectief voor het verbeteren van loopvermogen en die effectiviteit wordt mogelijk nog verhoogd door de integratie van trainen van uithoudingsvermogen. Het lijkt er echter op, dat de winst in loopvermogen niet wordt omgezet in verhoogde loopprestaties in de eigen leefomgeving, zoals buiten lopen. Mensen na een beroerte bereiken over het algemeen niet de aanbevolen hoeveelheid lichaamsbeweging voor een gezonde leefstijl. De programma's die er tot nu toe zijn ontworpen om de loopprestaties te stimuleren zijn niet bijzonder succesvol. Dat kan mogelijk geweten worden aan het feit dat deze programma's zich merendeels richten op slechts één component van een veelomvattend probleem. Bijvoorbeeld, taak-georiënteerde CCT richt zich met name op de fysieke problemen, terwijl gedragsproblemen, problemen in de omgeving en sociale problemen mogelijk ook aandacht behoeven. De studie in **Hoofdstuk 6** was daarom gericht op het omvangrijk, d.w.z. alle componenten in ogenschouw nemend, exploreren van ervaren hindernissen en stimulering om buiten te lopen. Daarvoor werd het "Physical Activity in people with a Disability" (Fysieke Activiteit bij mensen met een Beperking) (PAD) gebruikt; een veelomvattend model dat gedragstheorieën integreert met biomedische aspecten. Er werden 36 thuiswonende mensen na een beroerte geïncludeerd met matige beperkingen, in staat om zelfstandig te lopen (Functional Ambulations Categories (FAC) ≥ 3). De respondenten werden gericht geworven m.b.t. hun gebruik van gezondheidzorg. De data werd verzameld op verschillende manieren; semigestructureerde, gestructureerde en focus-groep interviews om te trianguleren. Er werd een vooral deductieve thematische inhoudelijke analyse met gebruik van het PAD-model uitgevoerd volgens de "framework" benadering, nadat alle interviews uitgeschreven waren. De resultaten lieten zien, dat het buiten lopen door intentie, vaardigheid en gelegenheid bepaald werden. De intentie om buiten te lopen wordt bepaald door persoonlijke factoren zoals sociale invloed, bijvoorbeeld door terughoudende mantelzorgers, maar ook professionals in de sociale omgeving. Intentie wordt ook bepaald door zelfvertrouwen, wat bijvoorbeeld beïnvloed kan worden door de fysieke omgeving zoals een onregelmatige stoep, en door de houding van iemand t.a.v. lichaamsbeweging. Loopvaardigheid wordt beïnvloed door balans controle en verminderde loopafstand, maar ook door motorische controle, cognitie, uithoudingsvermogen en vermoeidheid. Buiten lopen werd bevorderd door de aanwezigheid van gelegenheid waarvoor lopen noodzakelijk is, zoals huishoudelijke taken of levendige sociale contacten. Om efficiënte interventies te ontwikkelen, die buiten lopen kunnen stimuleren lijkt het, concluderend, van belang om zowel de intentie om te lopen te beïnvloeden door rekening te houden met de sociale invloed, het zelfvertrouwen en de houding t.a.v. lichaamsbeweging. Tegelijkertijd zou de verbetering van loopvaardigheid en zelfs het creëren van gelegenheid om te lopen overwogen moeten worden.

In Hoofdstuk 7, de algemene discussie, werden de belangrijkste bevindingen van dit proefschrift samengevat en de theoretische overwegingen bediscussieerd. De aanbevelingen voor de klinische praktijk werden bediscussieerd en suggesties voor toekomstig onderzoek werden gedaan. De onderzoeken in dit proefschrift lieten zien dat taak-georiënteerde CCT in de subacute fase na een beroerte net zo effectief zijn als individuele fysiotherapie om loopvermogen te verbeteren. De onderzoeken suggereren daarnaast, dat trainen van uithoudingsvermogen de effecten van taak-georiënteerde CCT kan verhogen. Tenslotte suggereren we, dat taak-georiënteerde CCT als een vooral fysieke interventie aangevuld zou moeten worden met interventies gericht op gedragsverandering, interventies in de omgeving en mogelijk zelfs sociale interventies om effectief te kunnen zijn op loopprestaties van mensen na een beroerte.

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Kurt Tucholsky, 1890-1935

About the author

Curriculum vitae

Jacqueline Outermans, born on June 21, 1962 in Velp, the Netherlands now lives in Zeist, the Netherlands.

After the graduation from the Physical Therapy school at the University of Applied Sciences Zeeland in Vlissingen, the Netherlands in 1986, she worked in Germany as a physical therapist for 20 years. First from 1986 – 1991 at the Schloßbergklinik, Neurological Rehabilitation Clinic for MS and M. Parkinson in Bad Laasphe, Germany. Following from 1991 – 1995 she worked as director of the Physical Therapy dpt. at the Odebornklinik, Neurological Rehabilitation Clinic in Bad Berleburg, Germany. Finally, she owned private practice for Physical Therapy from 1995 – 2006 in Bad Berleburg. After attending a number of professional courses to keep up with the professional and scientific developments in physical therapy, the inevitable next step was to take up an education as a clinical health scientist at the Master program in Physical Therapy Sciences, Clinical Health Sciences, at the Utrecht University from 2003 – 2006 in Utrecht, the Netherlands.

After receiving her Master of Science degree in 2006 to the present date, she works as a lecturer in the Bachelor- and Master Programs of Physical Therapy at Hogeschool Utrecht University of Applied Sciences in Utrecht. From 2008 – 2010 she additionally worked as one of the Science program managers at the Master Programs Physical Therapy. Starting in 2008 she is currently the program manager and developer of the Minor Program Neurorehabilitation and Applied Research at the Hogeschool Utrecht University of Applied Sciences Utrecht. The Minor Program incorporates the implementation, execution and further development of task-oriented circuit class training for people after a stroke to encourage physical activity in a number of Physical Therapy settings in the region of Utrecht. From 2010 – 2016 she worked as an invited lecturer at the “Nederlands Paramedisch Instituut” (NPi) for the Courses in Neurorehabilitation in Stroke.

To date, starting in 2010 as a PhD-student, she is a member of the research group “Lifestyle and Health” of the Centre of Expertise “Sustainable and Healthy Living in the City” from the Hogeschool Utrecht University of Applied Sciences and Utrecht University in Utrecht. Finally, starting in 2017 she is now a Member of the Initiation Collective “NAH-Network Utrecht” in Utrecht, the Netherlands.

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- Mai 2015: “Associations between aerobic capacity and walking capacity after stroke; a cross-sectional analysis” Poster presentation at the Dutch Society of Neuro-Rehabilitation (DSNR) Annual meeting, Maastricht, the Netherlands,
- November 2015: “Cardiopulmonary effort, walking balance and upper limb strength distort the association between aerobic capacity and walking capacity after stroke” Poster presentation at the annual meeting of the “Kennisnetwerk CVA”, Zeist, the Netherlands,
- November 2015: “What’s keeping people after stroke from walking in the community to gain aerobic capacity?” Poster presentation at the annual meeting of the “Kennisnetwerk CVA”, Zeist, the Netherlands,
- February 2016: “Lopen na een CVA” Invited Lecture, Symposium 2016 of the RGW in Almelo, the Netherlands.
- March 2017: Invited Lecture Congress Therapie Leipzig: “Aerobe Kapazität und Gehfähigkeit nach Schlaganfall”

Research activities

- 2008 - 2012 FitStroke Leipzig; Circuit class training in subacute stroke, RCT,
- 2011 - 2016 SUSTAIN: Stimulating and investigating long term walking activity in stroke, Longitudinal cohort study,
- 2017 - present ActS: Active after Stroke, Feasibility study for behavioral change towards a physically active lifestyle after stroke.

Award

November 2015: “What’s keeping people after stroke from walking in the community to gain aerobic capacity?” Best Scientific Poster Award at the Annual Meeting of the “Kennisnetwerk CVA”, Zeist, the Netherlands