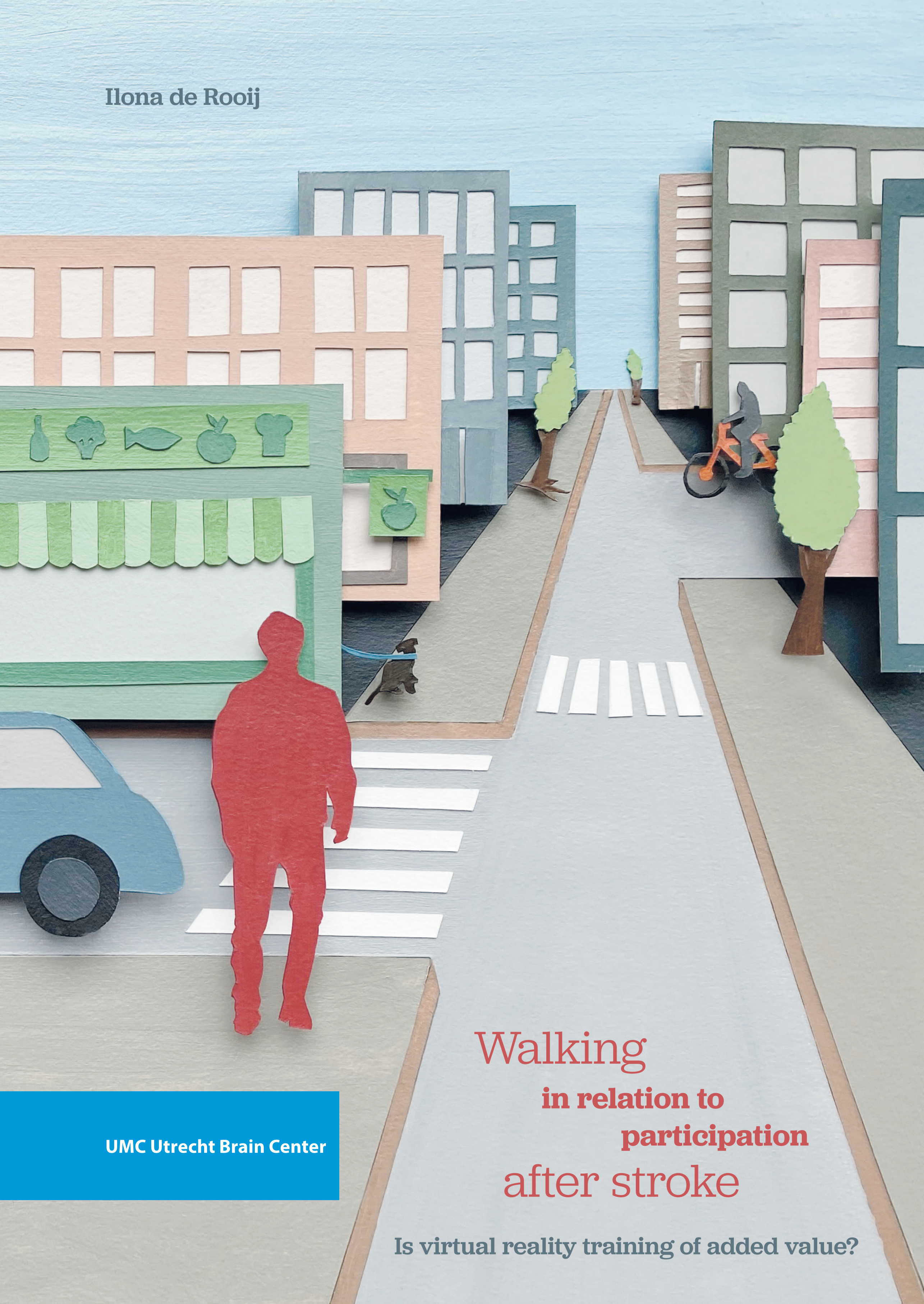

Ilona de Rooij

Walking in relation to participation after stroke

Is virtual reality training of added value?

UMC Utrecht Brain Center

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Walking in relation to participation after stroke

Is virtual reality training of added value?

Lopen in relatie tot participatie na een beroerte

Is training met virtual reality van toegevoegde waarde?

(met een samenvatting in het Nederlands)

Proefschrift

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door

Ilona Johanna Maria de Rooij

geboren op 30 mei 1993
te Liempde

Promotor:	Prof. dr. J.M.A. Visser-Meily
Copromotoren:	Dr. I.G.L. van de Port Dr. J.W.G. Meijer

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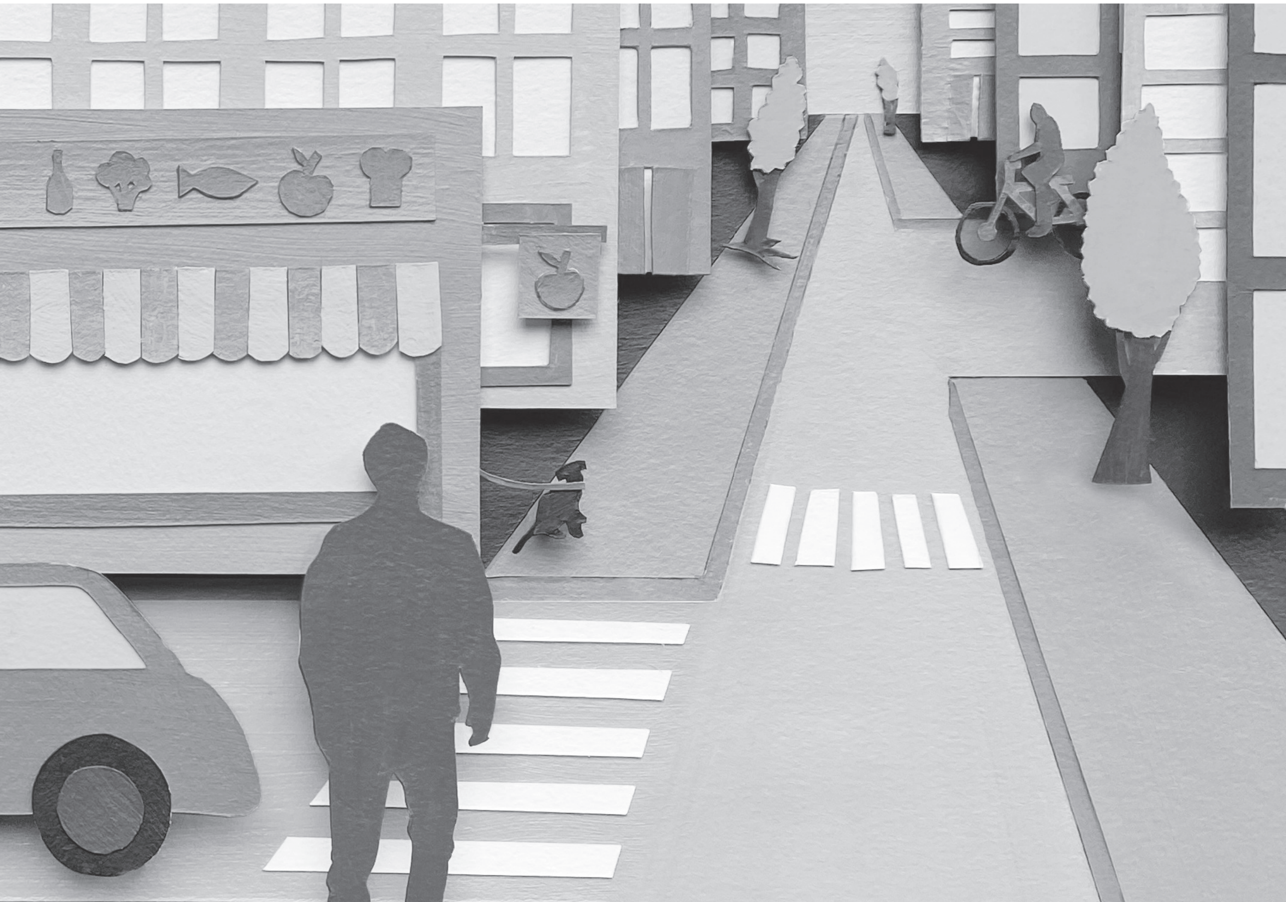
Chapter 1

General introduction



Almost 14 million people worldwide are affected by a first-time stroke each year.[1,2] As populations are ageing, the prevalence and burden of stroke are expected to further increase in the upcoming years.[3] A stroke is an interruption of the blood and oxygen supply to parts of the brain and the consequences of a stroke depend on the location of the interruption and size of the damaged brain tissue. Therefore, people after stroke can experience a wide range of impairments, including motor impairment, sensory impairment, visual impairment, and cognitive impairment.[4-6] Most of the impairments are long lasting and can have a substantial impact on peoples' daily life.[7,8]

Walking ability and participation after stroke

After a stroke, walking is often affected by motor impairments such as muscle weakness and loss of voluntary movements and coordination.[5,9] A substantial part of the people after stroke regain the physical capacity to walk without physical support from others, which is generally regarded as independent walking function.[10,11] Previous research, however, showed that improvements in walking function (e.g., step length and gait speed) do not necessarily translate to a better walking ability necessary to participate in the community.[12,13] Walking ability, generally defined as the competency to walk at the activity level of the International Classification of Functioning, Disability and Health (ICF),[14] seems to be an important physical factor to achieve an appropriate level of participation.[15,16] The importance of walking ability for participation is supported by a recent study that found that experienced participation restrictions are especially present during activities that involve walking.[17]

Participation

Participation is a comprehensive concept that is described by multiple definitions and measured by different instruments.[24-26] The most frequently used definition of participation is described in the International Classification of Functioning, Disability and Health (ICF), which states that participation is about "the person's involvement in a life situation".[14] Problems that people after stroke experience in daily life situations are defined as participation restrictions. Among the measures for participation, the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) is a self-reported instrument that adequately defines the overall concept of participation. The questionnaire assesses 3 aspects of participation: the pattern in frequency of participation (Frequency scale), experienced restrictions in participation (Restrictions scale), and people's satisfaction with their participation (Satisfaction scale).[27]

To perform these daily life activities, a complex level of walking is necessary that requires people to adjust their walking to tasks and demands from the environment.[18] For example, one has to perform dual tasks and has to encounter irregular terrain, changes in level, obstacles, and busy crowds.[19] This ability to adjust walking is often reduced in people after stroke,[18,20-22] leading to difficulties with what we call *gait-related participation*. Gait-related participation includes, for example, walking to go shopping or to perform household chores, work, and leisure activities.[23]

Improving walking ability

Various interventions have been shown to be effective for rehabilitation of walking, including treadmill training (with or without body weight support), circuit class training, outdoor ambulation practice, and robotic-assisted therapy.[28-30] However, effects of these interventions on participation level are not clear as relatively few intervention studies have participation as a primary outcome measure. This is surprising since improving participation is a main focus of stroke rehabilitation.[31-34] Two recent reviews found some preliminary evidence that exercise-based interventions, such as treadmill training, might be effective to improve participation after stroke.[35,36] In contrast, another review concluded that there is yet insufficient evidence that interventions aimed to improve walking in the community will induce improvements on the level of participation.[37] More research is necessary to investigate whether specific types of exercise-based interventions can improve participation. Studies recommended that the ability to adjust walking should be trained in safe environments that represent the community.[22,38] These environments should include possibilities to practice multiple stimuli and attention demanding tasks.[22] In order to improve participation in activities involving walking, one might suggest therefore that training may focus on walking with additional tasks and changing contexts and environments.

Virtual reality interventions

Virtual reality (VR) is a relatively new technology that may have added value to train complex levels of walking by using different environments and additional tasks. Previous studies found beneficial effects of VR training for improving balance and walking in people after stroke.[39-42] Most of the studied VR interventions combine treadmill-based systems with a screen or a head-mounted device to provide immersive virtual environments.[40] The use of VR is expected to have a couple of advantages over conventional training interventions. First, VR training has the opportunity to simulate real-life environments in a safe training environment. While walking, people have to react to unexpected situations and can be maximally challenged to train their walking ability.[43,44] Second, a therapist can easily make changes in the environment and can add dual tasks or unexpected constraints (e.g., obstacles and perturbations) to individualize the training based on the abilities of the patient. Third, VR may promote multiple principles of motor learning by providing a goal-oriented, high-intensity, and varied training with real-time feedback.[42,45] The interactive and immersive environments with game elements are expected to increase motivation of patients to train more intensively.[44,46,47]

The GRAIL

For this thesis, we provided VR gait training with the GRAIL (Gait Real-time Analysis Interactive Lab, Motek Medical, Amsterdam, the Netherlands). The GRAIL integrates an instrumented dual-belt treadmill with a motion-capture system and a 180° semi-cylindrical screen for the projection of synchronized virtual environments. The treadmill platform can move to simulate uphill or downhill walking and to generate sideways perturbations during walking. Reflective markers are placed on the body of the patient to be able to interact with the virtual environment. Various VR environments are available to train specific rehabilitation goals, for example to train reactive balance or dual tasks. During a training session, safety is ensured by a harness that does not provide weight support.

Although beneficial effects of various VR systems have been found, the literature is yet inconsistent about the effect of VR on walking ability after stroke and how VR training should be applied.[43] There is little evidence about the long-term effects of VR training because follow-up assessments are scarce. More important, previous studies did not aim to achieve improvements in participation and therefore lacked analyses on participation level.[43,48] Hence, it remains unknown whether improvements in walking after VR training translate to an improved participation in daily life.

Aims and outline of this thesis

As described in this introduction, walking ability might influence participation after stroke and if so, training walking ability might play an important role to improve post-stroke participation. Yet, literature about the relation between walking ability and participation in people after stroke is limited, particularly over time. VR interventions have potential to improve walking ability and participation by providing an advanced level of training in different context and environments. However, effects of VR training have still to be established, especially on participation level. Therefore, the main aims of this thesis are to 1) explore walking in relation to participation after stroke and 2) to investigate the effect of VR gait training on walking ability and participation in people after stroke. Hence, this thesis is divided in 2 main parts.

Part I Walking ability and participation after stroke

The first 2 chapters explore walking in relation to participation. They focus on understanding the concept of gait-related participation and the relation between walking ability and participation. **Chapter 2** describes a qualitative study that explored the perceived barriers and facilitators for gait-related participation from the perspective of people after stroke. Twenty-one people after stroke were interviewed about their experiences with gait-related participation. In **chapter 3**, the longitudinal relation between walking ability and participation is investigated. We aimed to describe to what extent an improvement in walking ability is associated with an improvement in participation over time.

Part II Virtual reality gait training

In the second part of this thesis, we study the potential effects of VR gait training on walking ability and participation after stroke. **Chapter 4** reviews the literature regarding the effect of VR training on balance and gait ability in patients with stroke and provides a systematic overview with meta-analysis. In **chapter 5**, a description of the protocol of the ViRTAS (Virtual

Reality Training After Stroke) study is given. The ViRTAS study is a randomized controlled trial that aims to investigate the effect of VR gait training in people within 6 months after stroke. This chapter describes the inclusion and exclusion criteria, the interventions, the timing of the assessments and the outcome measures used. The main outcome measure was participation as measured with the Utrecht Scale for Evaluation of Rehabilitation-Participation. **Chapter 6** presents the results of the ViRTAS study by describing the effect of VR gait training on participation. The VR gait training is compared with a non-VR gait training. This chapter includes both quantitative results of the between-group comparisons and a description of qualitative results from semi-structured interviews. In **chapter 7**, results of a pilot study about the feasibility of VR training in an inpatient population of people after stroke are reported.

General discussion

Finally, **chapter 8** provides a general discussion of the main results of this thesis, directions for future research, and implications for stroke rehabilitation.

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PART I

Walking ability and participation after stroke

Chapter 2

Perceived barriers and facilitators for gait-related participation in people after stroke: from a patients' perspective

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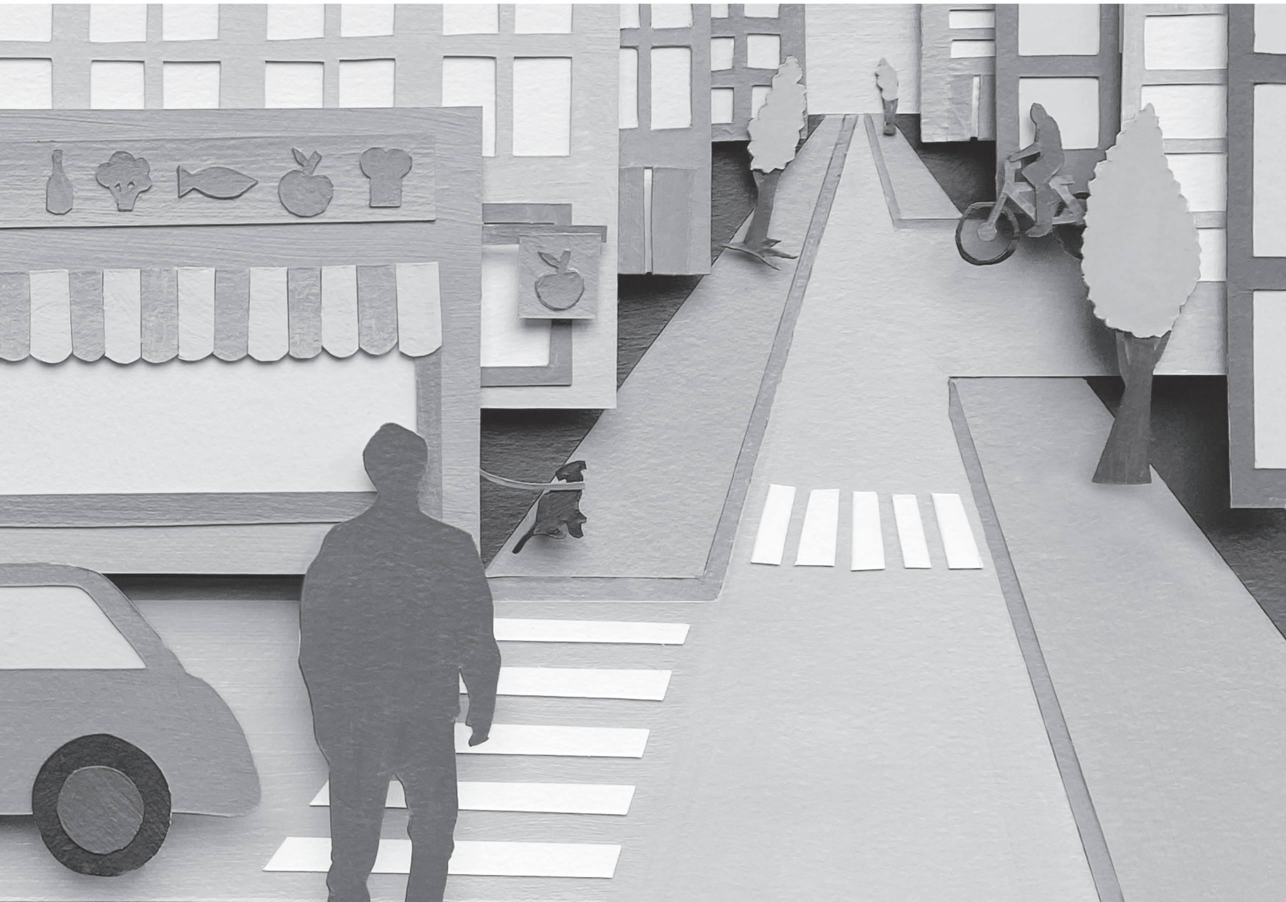

Abstract

Background: An important focus of post-stroke physical therapy is to improve walking and walking capacity. However, many people after stroke experience difficulties with gait-related participation, which includes more than walking capacity alone. Gait-related participation involves walking with a participation goal and requires to deal with changes in the environment during walking and perform dual tasks, for example.

Objective: To explore barriers and facilitators for gait-related participation from the perspective of people after stroke. This knowledge can contribute to the development of effective interventions to improve gait-related participation.

Methods: Semi-structured interviews were conducted to investigate how people after stroke experience gait-related participation. Audio-recorded interviews were transcribed, anonymized, and analyzed thematically. Barriers and facilitators were categorized according to the International Classification of Functioning, Disability and Health (ICF) framework.

Results: Twenty-one people after stroke participated. Median age was 65 years, median time since stroke 16 weeks. Barriers were reported in movement-related functions, cognitive functions, mobility, personal factors, and environmental factors. Facilitators were found on participation level and in personal and environmental factors, such as motivation and family support.

Conclusion: People after stroke who were physically able to walk independently still described multiple barriers to gait-related participation in all components of the ICF framework.

Introduction

In Europe approximately 1.1 million people suffer a stroke each year and the prevalence is expected to increase in the upcoming years because the population is aging.[1,2] After a stroke, many people experience decreased walking ability.[3,4]

Walking is necessary in order to perform many daily activities within the World Health Organization's International Classification of Functioning, Disability and Health (ICF) activity and participation domains: mobility, self-care, domestic life, major life areas, and community, social and civic life.[5,6] We defined walking with a goal on these ICF domains as gait-related participation. Gait-related participation includes walking to go shopping and walking to perform household chores, work, and leisure activities. It can involve indoor and outdoor walking, in private and public environments.

Gait-related participation comprises not only the walking activity in itself but requires people to consider the context and environmental changes during walking; like terrain irregularity, changes in level, obstacle avoidance, and crowds.[5] In addition, gait-related participation requires people to perform dual tasks while walking, for example paying attention to traffic when crossing a busy road with sufficient speed.[7] In order to be able to deal with these specific contexts or changes in the environment, both motor and cognitive function are essential. Motor function during walking comprises leg strength, balance, and coordination.[8,9] Cognitive function during walking comprises the allocation of attention and executive functioning.[10,11] People after stroke often have difficulty adapting their walking to environmental constraints because of their motor and cognitive impairments, however subtle they may be.[12] Impaired physical walking capacity (e.g., walking speed and distance), impaired cognition, and multiple personal and environmental factors can negatively affect gait-related participation.[13-17] Because of these impairments, many stroke survivors cannot retain their previous level of gait-related participation, which restricts them in real-life, everyday situations.[18]

Proper understanding of barriers and facilitators for gait-related participation is important in order to improve guidance during therapy and to further develop effective physical therapy interventions. Recently, barriers and facilitators have been studied for outdoor walking in people with chronic stroke.[19] This study focused on a person's outdoor walking activity with the goal to become physically active. The current study focused on gait-related participation which includes a broader range than only outdoor walking, namely all walking with a goal on ICF participation level.

What makes this study unique is the use of a qualitative design considering all components of the ICF framework to give a comprehensive overview of factors influencing gait-related participation.[17] Qualitative studies can give a detailed overview of the patients' perspective and are increasingly accepted in rehabilitation research.[20,21] The importance of exploring patients' perspectives is also seen in the rising interest in patient-reported outcome measures in research and clinical care.[22] Therefore, the present study uses a qualitative design and aims to explore barriers and facilitators for gait-related participation from the perspective of people after stroke. We include factors from all components of the ICF framework that may affect gait-related participation, covering ICF body function or structure level, activity level, participation level, personal factors, and environmental factors.

Methods

Design

We used semi-structured interviews to investigate how people experience gait-related participation after their stroke. The COnsolidated criteria for REporting Qualitative research guidelines were followed for reporting this study.

Participants

Participants in the semi-structured interviews were recruited from the Virtual Reality Training After Stroke (ViRTAS) study. This study was a randomized controlled trial designed to examine how virtual reality gait training affects participation in community living people between 2 weeks and 6 months after stroke.[23] Participants in the ViRTAS study experienced constraints with walking in daily life and were minimally able to walk without physical assistance for balance and coordination (Functional Ambulation Category ≥ 3). They received virtual gait training or non-virtual gait training for 6 weeks.

From January 2018 to January 2019, participants were informed about the semi-structured interviews by the principal investigator during the post-intervention assessment of the ViRTAS study. A description of the content of the semi-structured interviews was included in the subject information and informed consent of the overall study. If participants were willing to participate in the semi-structured interviews, an appointment was made with the interviewer.

Demographic and injury-related information about the participants was taken from the data collected in the randomized controlled trial. The study has been approved by the Medical Ethics Review Committee of Slotervaart Hospital and Reade, Amsterdam, The Netherlands (P1668, NL59737.048.16) and is registered in the Netherlands National Trial Register (NTR6215).

Data collection

Participants were interviewed in a face-to-face session at their homes or at the rehabilitation center in Breda, the Netherlands. The interviews were performed by 2 female researchers with experience in patient care (VB, LH) of which one is a physiotherapist and the other a human movement scientist. The interviewers were not known to the interviewee before the start of this study. The interviewer started the session with a brief introduction about her role and the aim of the study. Family members were allowed to stay in the same room as the interviewee. However, the interviewer requested that the family members only participated in the interview when they had the feeling that important information could be missed. The interviews lasted 14−50 minutes and were audio-recorded with the permission of the participants to increase the reliability of the data. In addition, field notes were taken if necessary. An interview guide with directional questions was used to guide the interviewer (Table 2.1). Gait-related participation included both walking in the community and walking in or around the participant's home. The questions were checked beforehand in a test-interview with a person after stroke who received outpatient rehabilitation. We did not perform repeat interviews with any of the participants.

Table 2.1. Interview guide with directional questions for the semi-structured interviews

Interview guide
• How do you experience your walking in daily life? • How satisfied are you with your gait-related activities? • Which gait-related activities are difficult for you to perform? • Why are these gait-related activities difficult for you to perform? • What hinders you or holds you back from walking or performing gait-related activities? • What makes it easier or stimulates you to walk or to perform gait-related activities?

Data analysis

Data analysis and data collection were performed in parallel to ensure that new insights or missing themes that emerged from the analysis could be incorporated in the subsequent interviews. Data collection ended when saturation was achieved. In this study, saturation was defined as the point at which no new themes or insights emerged from the last 2 interviews.[24] Two researchers (IR, LH) analyzed the transcriptions of the interviews by performing a thematic analysis using the Framework Method.[25,26]

The Framework Method consists of 7 stages. In the first stage, the audio-recorded interviews were transcribed verbatim. Transcriptions were anonymized and then checked for errors by another research member. In the second stage, the researchers thoroughly read the transcriptions to become familiar with the interviews. If a passage in the transcription was unclear, the audio recordings were listened back to get a better understanding of that passage. The transcriptions were not returned to the participants for comments. In the third stage, the researchers started open coding of the barriers and facilitators using NVivo 12 (QRS International). The researchers analyzed the first 4 interviews independently by selecting interesting parts of text and describing the content of each text part with a code. In the fourth stage, the researchers compared and discussed the codes that they had applied in the first interviews to align their way of coding and to define a description for each code. Codes that were related were grouped and subdivided. Thereafter, the researchers decided which sets of codes were applied in analysis of the subsequent interviews. In the fifth stage, the subsequent interviews were labeled by applying the existing codes and still considering new codes. Also in this stage, the researchers compared their coding of interview parts and discussed discrepancies. If no consensus was reached, a third researcher (IP) made the final decision. In the sixth stage, the codes were summarized using a framework matrix. This matrix comprised one row per interview and one row per code. In the seventh stage, the researchers started with the interpretation of the data of the interviews by categorizing the codes according to the components of the ICF framework and searching for overarching themes. The categories and overarching themes were discussed with all authors. Also, 2 participants were asked to discuss the interpretation of the interviews with the researchers in this last stage.

Results

All potential participants that were invited for an interview agreed to participate. We excluded 1 participant because he refused to allow the interview to be recorded. Twenty-one participants (14 males and 7 females) were included. Table 2.2 shows the demographic and clinical characteristics of the participants. The median age was 65 (IQR 56, 71) years and median time since stroke was 16 (IQR 14, 22) weeks at the time of the interview.

All barriers and facilitators that emerged during the semi-structured interviews were categorized according to the 5 components of ICF framework: body function or structure level, activity level, participation level, personal factors, and environmental factors. We describe the barriers and facilitators for gait-related participation that were mentioned by the participants per component of the ICF framework.

Barriers and facilitators identified on ICF body function or structure level

The barriers that emerged on the function level of the ICF framework can be divided in 3 ICF domains: 1) neuromusculoskeletal and movement-related functions; 2) sensory functions and pain; and 3) mental functions. No facilitators were mentioned on ICF function level.

Table 2.2. Demographic and clinical characteristics of the participants (N = 21)

Characteristics	Values
Age (y)	65 (56–71)
Gender (male/female)	14/7
Time since stroke onset (wk)	16 (14–22)
Type of stroke (infarction/hemorrhage)	20/1
Side of stroke	
Left	6
Middle	3
Right	12
Previous stroke (yes/no)	4/17
Assistive devices for use outdoors	
None	12
Rollator	5
Cane and rollator	3
Mobility scooter	1
Ankle-foot orthosis (yes/no)	3/18
Functional Ambulation Category score	
3	0
4	6
5	15
Partner (yes/no)	18/3
Region of residence	
Rural or small town (< 10,000 inhabitants)	7
Small urban (10,000–99,999 inhabitants)	11
Large urban (≥ 100,000 inhabitants)	3

Values are n or median (IQR).

Barriers in the domain neuromusculoskeletal and movement-related functions were motor impairment, decreased muscle strength, decreased endurance, decreased coordination, fatigue, and stiffness. Multiple participants named motor impairment and decreased muscle strength because of difficulties with the paretic leg. A 74-year-old male participant said:

> *"Lifting my left leg (affected leg) high enough is the biggest limitation during walking."*

Difficulties with controlling a paretic leg became more apparent during a longer walk in which fatigue was more present toward the end of the walk. Fatigue was present throughout the day for many participants and consisted of both physical and mental fatigue.

Barriers in the domain sensory functions and pain included impaired visual function, dizziness, tingling or unusual sensations, and pain. Pain and unusual sensations were mainly experienced in the legs and feet. Impaired visual function after stroke limits participants to perform gait-related activities.

Barriers in the domain mental functions were motor dual tasks, allocation of attention, diminished stimulus processing, and delayed information processing. Multiple participants recognized that the impairment of their cognitive functioning was a barrier for their gait-related participation. This could be related to a decreased ability to allocate attention or to perform motor dual tasks, a higher sensitivity to stimuli such as crowds and busy traffic, or a delayed information processing. A 56-year-old female participant described delayed information processing as follows:

> *"When I stand on a curb to cross the road, sometimes a car will suddenly turn around the corner. Then I have to go back. In my head I already started taking that step forward, which makes it quite difficult to go back. Before my stroke I did not think about this at all, but now I have to give my brains an extra moment to think hey guys I have to go back."*

Difficulties with the allocation of attention are explained by a 26-year-old female participant:

> *"Nowadays, I do my groceries without my son (toddler) because doing the groceries and having him around does not go well together. The cognitive changes after my stroke are still there."*

Barriers and facilitators identified on ICF activity level

The barriers and facilitators that emerged on the activity level of the ICF framework covered the mobility domain. Barriers included decreased balance, decreased walking speed, and decreased walking distance. Many participants could not walk fast and/or far enough to perform activities that they were used to doing before their stroke, for example visiting friends or family. A 65-year-old female participant said:

> *"I cannot go to my friend who lives in another village. At this moment, her house is too far away to reach on foot or by bike. Also, the nearest bus stop is too far to walk."*

Decreased balance was explained by a 66-year-old male participant:

> *"In the supermarket it is difficult to bend my knees and pick up a product at the bottom of a shelf. I will easily lose my balance."*

Barriers and facilitators identified on ICF participation level

The barriers and facilitators that emerged on the participation level of the ICF framework can be divided in the domains: 1) domestic life; 2) mobility; 3) major life areas; and 4) community, social, and civic life. The only barrier that was mentioned on ICF participation level was outpatient rehabilitation. Because some participants followed outpatient rehabilitation for 2 or 3 days per week they felt they had not enough time to perform the gait-related activities that they would like to do in their home environment.

Regarding domestic life, participants mentioned as a facilitator that they feel responsible for the household. This responsibility stimulates them to perform household tasks, to go shopping, and to gather daily necessities. Also, taking care of a dog is an often mentioned facilitator to go for a walk.

Facilitators in the domains mobility and major life areas were the use of public transportation and having work that requires many activities that involve walking.

Regarding community, social and civic life, participants mentioned visiting friends or family, hobbies, social activities, and social contacts as facilitator to perform gait-related activities. Many participants like to walk to their friends or family or to social and leisure activities as playing petanque or watching a soccer match of a grandchild. Several participants explained that they liked to go for a walk for their social contacts. A 65-year-old female participant said:

> *"I like to go for a walk because of the social aspect. You usually, not always, but frequently come across the same people so you just have a chat with them."*

Barriers and facilitators identified for the personal factors component of the ICF

Because no classification in ICF domains consists for the personal factors component, we did not further categorize the barriers and facilitators for this component. Personal barriers that emerged from the interviews were: feelings of being watched, anxiety and insecurity, stress, decreased initiative or lack of a purpose to go for a walk, dislike walking, co-morbidities, and overestimation of own limits. Some participants felt anxious or insecure when walking in the community or taking the stairs which makes them walk more cautious and conscious. A 74-year-old male participant explained:

> *"I'm a little bit insecure when taking the stairs. If I don't lift my leg high enough, I hit the steps. So, I'm more conscious about how I place my foot."*

Other participants mentioned that after their stroke they had a decreased initiative to undertake activities or missed a purpose to go for a walk. Also, sometimes participants overestimated their own limits. This was described by a 65-year-old female participant:

> *"My grandchildren came and we went for a walk together. I have no idea why, but I suddenly felt exhausted. My grandchild asked: grandma should I hold your hand? And I said: Yes do that, your grandmother is suddenly very tired. Maybe I did too much this morning. I did not rest enough. And then misjudged how tired I was."*

Personal facilitators that emerged from the interviews were an active personality, motivation, fulfillment, loving nature, fresh air or tranquility, and good planning skills. Multiple participants mentioned their motivation to walk and to regain gait-related activities. They explained they performed gait-related activities with the goal to train their walking ability. A 63-year-old male participant described:

> *"I try to walk the route around the pond every day. I don't like walking, but I do this to be active and to improve my condition and balance. I see it like a kind of therapy."*

Also, being a nature lover stimulated people to go for a walk outside. A 56-year-old female participant explained:

> *"I live near the woods, that is at the end of the street. I like being outdoors and love to go for a walk in the woods. I enjoy the nature, the birds, and the squirrels."*

Having good planning skills helps participants to make the most out of their day or week. A 26-year-old female participant described:

> *"It all continues after my stroke. However, the difference is that I have found more balance and peace in it. This positively affects my leg and my walking. I notice that when I rest between activities, I get through the day much better."*

Barriers and facilitators identified for the environmental factors component of the ICF

The environmental barriers and facilitators that emerged from the interviews can be divided in the domains: 1) support and relationships; 2) products and technology; and 3) natural environment and human-made changes to environment. Barriers in the domain support and relationships included worries from family members and physical impairments of a partner. A 63-year-old male participant explained what worried his wife:

> *"My wife accompanies me when I go for a longer walk because she does not totally trust me to go alone. When I have to cross a road, my impaired sight hinders me."*

Facilitators were advice from caregivers, physical support from a partner, mental support from family and friends, and having a walking companion. A 70-year-old male participant explained:

> *"My wife loves to go for a walk and I accompany her for fun. And also for some exercise."*

Mental support from family or friends was mentioned multiple times. Family could support actively by stimulating to walk or to perform gait-related activities or more passively by letting their partner do as much as possible himself.

Assistive products were mentioned as facilitators and included the use of a walking aid (e.g., cane or rollator) and ankle-foot orthosis or external guidance from a shopping cart, baby carriage, or banister. The availability of a cane or rollator stimulates people to go for a walk, go shopping or visit friends or family.

Barriers in the natural environment were bad weather, absence of daylight, terrain irregularity, steps (e.g., curbs, doorsteps or stairs), traffic, busy environments, and external time constraints. A 71-year-old male participant explained his difficulties with terrain irregularity:

> *"Sidewalks are difficult because the pavements are very unequal in our village. I have to look at the ground all the time to see the irregularities in the pavements. It is a challenge to walk outside."*

Also, traffic and busy environments were often experienced as difficult. For example, walking in a shopping mall or at the airport is challenging for many participants because they have to concentrate on their walking and the crowd at the same time. An example of the barrier external time constraints is given by an 80-year-old male participant:

> *"A few days ago, the trains were late and the train that I had to take arrived at another platform than I was at. I quickly had to go to the other platform and then I stumbled two times when climbing the stairs. Luckily, I could rectify myself with my non-affected hand on the steps that were higher. This was a situation in which I was less attentive and lost the routine."*

Facilitators in the physical environment were availability of places to sit down and nice weather.

Discussion

This study explored the barriers and facilitators for gait-related participation from the perspective of people after stroke using semi-structured interviews. We found barriers and facilitators for gait-related participation in all components of the ICF framework, including body function or structure level, activity level, participation level, personal factors, and environmental factors. Despite the fact that the majority of the participants had the ability to walk independently without physical assistance (Functional Ambulation Category 5), many of them were not completely satisfied with their gait-related participation and still experienced restrictions in walking in daily life. This confirms that gait-related participation is influenced by more factors than physical walking capacity alone. Also, it indicates that these relatively good walkers still have a need for improvement and sometimes additional treatment, which has to focus on more than walking alone. The barriers and facilitators found in this study may help to guide this treatment.

Many barriers that were mentioned are related to physical impairments that are known to be present after stroke, including motor impairment, sensory impairment, and fatigue. In addition, barriers in mental functions appeared to be important for people after stroke to perform gait-related participation. The relationship between cognition and walking in daily life is more and more acknowledged.[7,11] Previous qualitative studies that searched for barriers and facilitators for travelling outdoors[27] and walking outdoors,[19] however, did not find the various barriers in mental functions. This may be explained by the fact that our study was more focused on walking with a participation goal requiring more cognitive abilities. In the present study impaired cognitive functioning was described as delayed information processing, diminished stimulus processing, or difficulties with the allocation of attention when performing dual tasks.

Studies focusing on dual-task walking showed that people after stroke have difficulty in combining walking with simultaneous cognitive or motor tasks.[7,28] Walking with simultaneous dual tasks requires high attentional demands, especially since walking may be less automatic after a stroke.[11] However, the cognitive ability to allocate attention can also be impaired in people after stroke.[29] As a result, the combination of walking and performing a dual task may lead to decreased performance in walking (e.g., slowing down or colliding with an obstacle), deterioration of the cognitive task, or both.[16] The decreased performance in walking may in turn lead to incidents such as falls[10,30] or could refrain people after stroke from gait-related participation. This makes it important to consider cognitive functioning necessary for gait-related participation.

Furthermore, anxiety and insecurity were found as personal barriers to gait-related participation. Often anxiety and insecurity were mentioned together with loss of balance and fear of falling. This suggests that the barriers anxiety and insecurity are in line with previous studies that identified balance self-efficacy as an important facilitator for walking in daily life.[15,31]

High motivation, advice of caregivers, and physical and mental support from family and friends were shown to positively influence gait-related participation. Majority of the participants emphasized that they felt that feeling motivated to recover was important to regain gait-related participation. Motivation to recover is thought to be influenced by rehabilitation professionals and family members.[32] Therefore, physiotherapists might consider exploring motivation of people after stroke in order to improve gait-related participation. The importance of family support in stimulating walking and participation has been confirmed in previous studies.[19,33,34]

Using all components of the ICF framework together, we provided a thorough overview of the barriers and facilitators that affect gait-related participation. Current physical therapy interventions have the tendency to focus predominantly on ICF function or structure level.[35] However, because people after stroke reported barriers and facilitators in all components of the ICF framework, physical therapy or adjuvant rehabilitation interventions should also focus on improving cognitive functioning and identifying personal and environmental barriers and facilitators to improve gait-related participation. To improve cognitive function necessary for gait-related participation, walking should be exercised more often in combination with high cognitive demands such as dual tasks and stimulus-rich environments. Stimulus-rich environments can be created with the use of virtual reality. Using virtual reality training, people can learn in a safe environment to react on unexpected disturbances, obstacles, distractions, and dual tasks during walking.[23] Also, training in lively community environments such as shopping areas, train stations, and busy intersections might help to improve cognitive functioning necessary for gait-related participation. Besides cognitive functioning, interventions should focus more on exploring personal and environmental factors. By identifying personal factors, a therapist could find out how to motivate people after stroke and their environment to regain gait-related participation. Insight in environmental factors such as support and relationships and the physical environment of people after stroke can help to design personalized interventions for gait-related participation. These findings are in line with the study of Nanninga et al.[36] which suggested that walking in home and community environments should be seen as a personal goal. Future research should further explore how barriers and facilitators for gait-related participation can be influenced in clinical practice.

The qualitative study design using semi-structured interviews allowed the participants to describe their view about gait-related participation in their own terms. The interviewer could elaborate on the participants' answers to collect the most detailed information. However, our study has some limitations. First, the participants were recruited from a subcohort of the ViRTAS study. The participants of the current study might have been selected on their willingness and determination to improve walking because they all voluntarily participated in the 6-week intervention of the ViRTAS study. This may limit the transferability of the results to people after stroke in general. Second, participants were invited for an interview at the end of a 6-week intervention. They might be influenced by healthcare professionals in how they view their walking and how they apply strategies for walking in daily life. However, conducting the interviews at the end of the intervention has the advantage that participants are home for a longer time period and can therefore better describe their barriers and facilitators. Third, participants could have some cognitive impairments which might have influenced their perception of gait-related participation and the depth of their answers. The interviewer asked questions in different ways to get the most detailed and in-depth answers from the participants.

In conclusion, barriers and facilitators were reported in all components of the ICF framework. Gait-related participation is an important outcome measure. People after stroke may further improve on this outcome when considering movement-related functions, cognitive functions, personal factors, and environmental factors together during and after rehabilitation.

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Chapter 3

To what extent is walking ability associated with participation in people after stroke?

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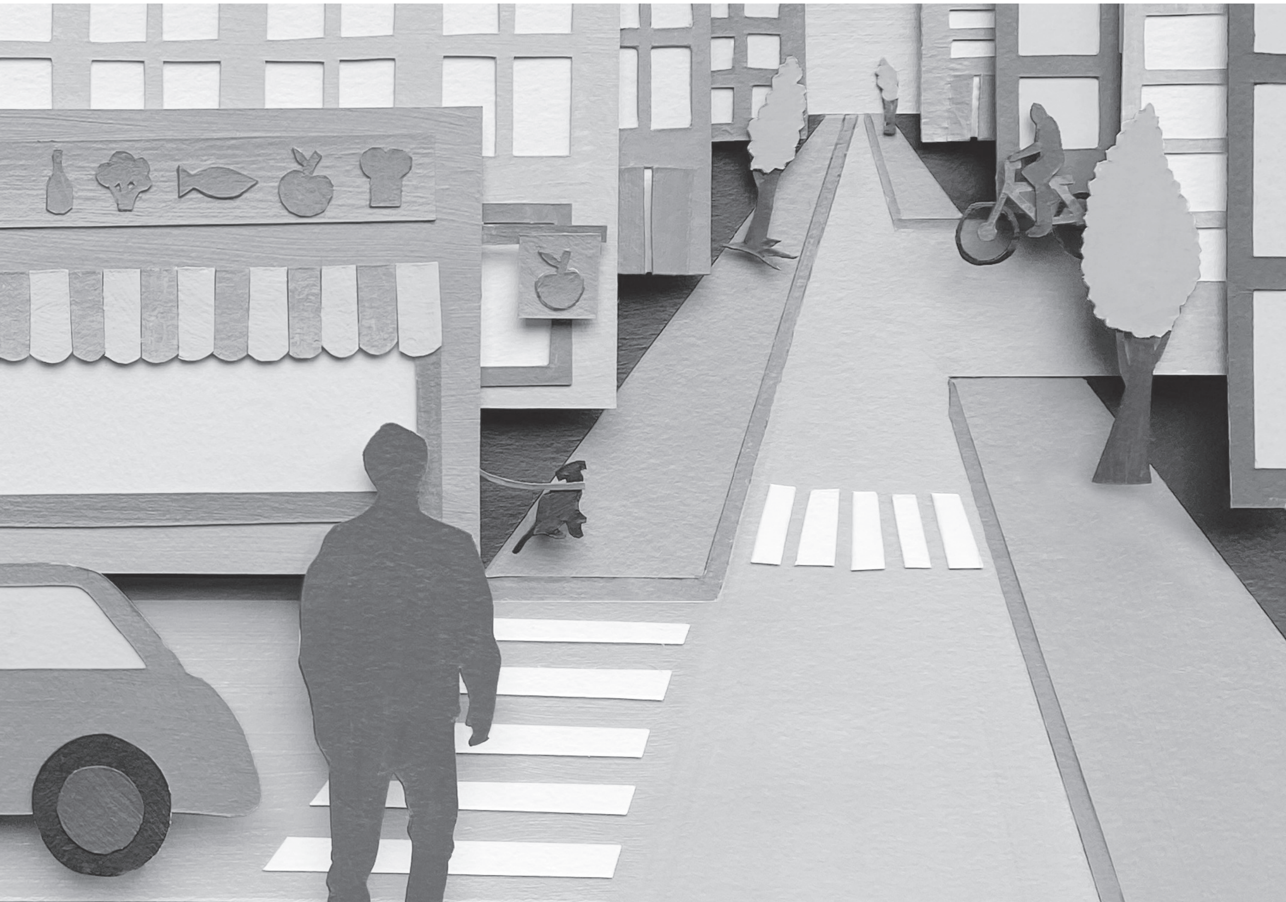

Abstract

Objectives: This study aims to 1) identify the relation between walking ability and participation after stroke and 2) explore whether change in walking ability is associated with change in participation over time in community-living people after stroke.

Materials and methods: Fifty-two people after stroke were assessed at baseline and after a 6-week gait training intervention. People were included between 2 weeks and 6 months after stroke. The Utrecht Scale for Evaluation of Rehabilitation-Participation was used to measure participation. Assessment of walking ability included the 6-minute walk test (6MWT) for walking endurance, Timed Up & Go (TUG) test for functional mobility, Mini Balance Evaluation Systems Test (Mini-BESTest) for dynamic balance, and total duration of walking activity per day to measure walking activity.

Results: At baseline, 6MWT, TUG, and Mini-BESTest were univariately associated with participation ($P < .001$). Backward multiple regression analysis showed that the Mini-BESTest independently explained 55.7% of the variance in participation at baseline. Over time, only change in the 6MWT was positively associated with change in participation ($R^2 = 0.087$, $P = .040$).

Conclusions: Cross-sectional associations showed that walking ability, and especially dynamic balance, contributes to participation after stroke. Dynamic balance, as underlying variable for walking, was an important independently related factor to participation after stroke which needs attention during rehabilitation. Longitudinally, improvement in walking endurance was significantly associated with improvement in participation, which indicates the relevance of training walking endurance to improve participation after stroke.

Introduction

Worldwide, nearly 14 million people suffer from a stroke each year.[1] As a result, people after stroke cope with a wide range of impairments affecting motor, sensory, and cognitive function.[2,3]

Due to these impairments on function level, people after stroke are often restricted in their ability to participate optimally in the community.[4-7] In the International Classification of Functioning, Disability and Health (ICF), participation is defined as "the person's involvement in a life situation".[8] Previous studies have shown that many community-living people after stroke experience restrictions in participation, even on the long term after stroke.[9-12] Participation restrictions limit people regarding work, household, and social and leisure activities.[13] As a result of these restrictions, participation is decreased compared with their life before the stroke, and a majority of the people are dissatisfied with their level of participation.[9] Therefore, improving participation is considered a primary goal in stroke rehabilitation.[14] Better understanding of factors that influence the improvement in participation can help to further direct the content of stroke rehabilitation.

Participation after stroke is shown to be associated with demographic and stroke-related factors (e.g., age, stroke severity) and various stroke-related impairments, including impaired cognitive functioning, emotional functioning, and mobility.[13,15,16] Regarding mobility, regaining sufficient walking ability is a requisite to promote participation in daily life and is a main focus in post-stroke physical therapy.[17] Improving walking ability seems to be even more important as participation restrictions are especially present during activities that involve walking.[13] Cross-sectional studies found that walking ability was generally moderately correlated with participation.[18-23] In addition, 4 prospective studies found walking ability to be a predictor for short and long-term participation after stroke.[24-27] However, few longitudinal studies are performed, which are important to identify causal relationships between walking ability and participation.[15] Also, little is known about how different aspects of walking ability (e.g., walking endurance, walking speed, and walking activity) are related to participation. Greater understanding of the extent to which walking ability variables and participation are associated over time can help to guide rehabilitation approaches. If improvement in participation appears to be strongly dependent on the improvement in walking ability, rehabilitation might focus even more on improving walking skills. Therefore, this study explored the cross-sectional and longitudinal relation between walking ability and participation in community-living people included between 2 weeks and 6 months after stroke. Walking ability was determined with 4 commonly used outcomes: walking endurance (6-minute walk test), functional mobility (Timed Up & Go test), dynamic balance (Mini Balance Evaluation Systems Test), and walking activity using accelerometer monitoring. The specific aims of this study were:

1. To identify the cross-sectional relation between walking ability and participation at baseline.
2. To explore whether change in walking ability variables is associated with change in participation over time.

We hypothesized that improvement in walking ability is positively associated with improved participation.

Methods

Design and procedure

The data for this study is collected as part of the ViRTAS study,[28] which is an assessor-blinded randomized controlled trial. The ViRTAS study examined the effect of virtual reality gait training on participation in community-living people between 2 weeks and 6 months after stroke. Participants followed a 6-week training intervention in addition to usual care and rehabilitation. The training intervention consisted of a virtual reality gait training (intervention group) or a non-virtual reality gait training (comparison group) that combined conventional treadmill training and functional gait exercises. Both interventions contained 12 training sessions of 30 minutes. People after stroke were recruited between April 2017 and July 2019.

Assessments for the ViRTAS study took place at baseline (T0), post intervention (T1, 6 weeks), and follow-up (T2, 3 months post intervention). The current study reports data from the assessments at baseline (T0) and post intervention (T1) because most change in walking ability is expected during the 6-week intervention. The ViRTAS study protocol has been approved by the Medical Ethics Review Committee of Slotervaart Hospital and Reade, Amsterdam, The Netherlands (P1668, NL59737.048.16) and the study is registered in the Netherlands National Trial Register (NTR6215).

Participants

Participants were enrolled in the ViRTAS study if they (1) were diagnosed with stroke according to the World Health Organization (WHO) definition;[29] (2) suffered from stroke 2 weeks until 6 months ago; (3) were able to walk without physical assistance for balance and coordination (i.e., patient may require verbal supervision or stand-by help from a person or may use a walking aid) (Functional Ambulation Category ≥ 3); (4) experienced self-perceived constraints with walking in daily life; (5) lived in the community and (6) were in the age from 18 to 80 years. Potential participants were excluded if they (1) had insufficient cognitive skills or understanding of the Dutch language to reliably answer simple questions; (2) suffered from severe visual impairments, severe forms of ataxia, or uncontrolled epileptic seizures; and (3) suffered from orthopedic disorders or other comorbidities that may limit current walking ability. Written informed consent was obtained from all participants.

Dependent variable

The Restrictions subscale of the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) was used to measure participation.[6] The Restrictions subscale of the USER-P consists of 11 items and evaluates the participation restrictions that a patient experiences in daily life activities. Questions can be answered with NA (not applicable), not possible (1), with assistance (2), with difficulty (3), and without difficulty (4). The not applicable score is recorded in case an item is not relevant or if the restriction is not attributed to the stroke. An example of a question is "Does your stroke currently limit you in sports or other physical exercise?". The total score of the USER-P Restrictions subscale is calculated by the sum of all items that are applicable, converted into a scale ranging from 0 to 100. A higher score corresponds with less experienced participation restrictions. The USER-P is a valid measure, with satisfactory reproducibility and high responsiveness.[30-32]

Independent variables

Demographic and stroke-related variables were assessed during the baseline assessment. Information about age, gender, type of stroke (ischemic or hemorrhagic), site of stroke (left hemisphere, right hemisphere, or brainstem), and time since stroke onset were taken from the data collected in the randomized controlled trial. Walking ability was measured by 3 performance tests for walking endurance, functional mobility, and dynamic balance and using daily life activity monitoring. Use of a walking aid or ankle-foot orthosis was permitted during the tests.

Walking endurance

The 6-minute walk test (6MWT) assesses walking endurance by measuring the maximal distance a participant is able to walk in 6 minutes. Participants were asked to walk at the fastest pace they felt they could maintain for 6 minutes.[33] The 6MWT was performed in a 40 m-long corridor with a marking every 5 meters. Each minute, the participant was told how much time has elapsed or was left. Participants were allowed to stand still or sit on a chair to rest during the test. The 6MWT is a valid and reliable test in people after stroke.[34]

Functional mobility

The Timed Up & Go (TUG) is a valid and reliable measure for functional mobility in people after stroke.[35-37] The test measures the time it takes to accomplish the following actions: rise from an armchair, walk 3 meters, turn around, walk back, and return to sitting.[38] The TUG is performed 3 times.

Dynamic balance

The Mini Balance Evaluation Systems Test (Mini-BESTest) is a reliable test to assess dynamic balance, including balance during walking.[39-41] The test consists of 14 items divided into 4 subdomains: anticipatory postural adjustments, reactive postural responses, sensory orientation, and dynamic gait. The items are scored with a scale ranging from 0 (unable to perform or requiring help) to 2 (normal performance). Higher scores indicate a better balance performance. The maximum total score is 28.[42]

Walking activity

Daily-life walking activity was measured by a tri-axial accelerometer (DynaPort MM, McRoberts BV, The Hague, The Netherlands) for 5 consecutive days. The accelerometer was placed at the middle of the lower back (above or underneath the clothes) using an elastic strap. Walking activity was preferable measured during 24 hours per day, but participants were allowed to take off the accelerometer during the night. A stroke-specific algorithm was used to analyze the walking activity data in Matlab (The MathWorks Inc., Natick, MA, USA).[43] In this study, walking activity was expressed as the total duration of walking activity per day (minutes). This variable was averaged over the days on which the participants wore the accelerometer for at least 8 hours. To be included in the analysis, participants had to wear the accelerometer for at least 3 days and had to walk at least 5 minutes per day.[44]

Data analysis

Analyses were performed in SPSS version 25 (IBM Corp., Armonk, New York). Change scores between baseline and post-intervention assessments were calculated for the USER-P and the walking ability variables. To determine if both intervention and comparison group from the ViRTAS study could be included in the analyses, we tested for differences in the change scores on the USER-P and walking ability variables between the groups. Normal distribution of the data was checked visually and was assessed based on skewness values > -2 and < 2. Participant characteristics and descriptive outcome measures were described using mean (standard deviation), median (25th, 75th percentile), or n (%).

The USER-P Restrictions items scores were dichotomized to give more insight into the presence of experienced participation restrictions. Scores not possible (1), with assistance (2), and with difficulty (3) were classified as "restrictions" and without difficulty (4) was defined as "no restrictions".[13] The proportion of people after stroke who are restricted is presented per item of the USER-P Restrictions subscale.

Linear regression analyses

The cross-sectional relation between walking ability and participation was assessed at baseline using univariate regression analyses. The USER-P Restrictions score was the dependent variable. Independent variables included the walking ability variables (TUG, 6MWT, Mini-BESTest, duration of walking activity per day) and demographic and stroke-related variables (age, gender, stroke type, site of stroke, time since stroke). Variables demonstrating P values < .20 were included in a linear multiple regression analysis using the backward method to determine which walking ability variables were significantly (P < .05) related to participation (aim 1).

The association between change in walking ability variables and change in participation was analyzed using univariate regression analyses. Change in USER-P Restrictions score was the dependent variable and change in the walking ability variables (TUG, 6MWT, Mini-BESTest, duration of walking activity per day) were the independent variables. Backward multiple regression was performed with variables demonstrating P values < .20 in the univariate analysis to identify a significant relationship (P < .05) between change in walking ability and change in participation (aim 2).

The assumptions for linear regression analyses, including independent and normally distributed errors, linearity, homoscedasticity, and multicollinearity, were checked and fulfilled. Multicollinearity of the independent variables was determined based on VIF < 10, Tolerance > 0.1, and correlations between the variables < 0.7. If the correlation coefficient was equal to or above 0.7, the independent variable with the lowest association with the dependent variable was excluded from the multiple regression analysis. Missing values in the regression analyses were excluded pairwise. Results were considered significant when P values are < .05.

Results

In total, 55 participants were included in the ViRTAS study. Three participants were excluded from the analysis of the current study because they did not attend the baseline or post-intervention assessment due to a recurrent stroke (n = 2) or unknown reason (n = 1). Fifty-two participants with complete data for the USER-P Restrictions subscale were included in this study. At baseline, 24 participants lacked Mini-BESTest scores, since this test was introduced after the start of the study.[45] In addition, 5 participants had no results for duration of walking activity per day because they refused to wear the accelerometer (n = 2), wore the accelerometer less than 3 days (n = 2), or walked less than 5 minutes per day (n = 1). At post intervention, results of 1 TUG, 3 6MWT, 1 additional Mini-BESTest and 5 additional measurements for duration of walking activity per day were missing. The change scores of the USER-P and walking ability variables did not significantly differ between the intervention and comparison group, allowing to include both groups in the analysis.

Table 3.1. Demographic and stroke-related characteristics of the participants (N = 52)

Characteristics	Values
Demographic variables	
Age (y)	61.58 (10.48)
Height (m)	1.74 (0.09)
Weight (kg)	78.19 (11.36)
Sex	
Men	36 (69.2)
Women	16 (30.8)
Partner	
Yes	43 (82.7)
No	9 (17.3)
Living situation	
Alone	9 (17.3)
With partner	42 (80.8)
With other family members	1 (1.9)
Stroke-related variables	
Time since stroke (d)	85.15 (37.63)
Type of stroke	
Ischemic	44 (84.6)
Hemorrhagic	8 (15.4)
Site of stroke	
Left hemisphere	27 (51.9)
Right hemisphere	20 (38.5)
Brainstem	5 (9.6)
Previous stroke	
Yes	6 (11.5)
No	46 (88.5)
Functional Ambulation Category score	
3	3 (5.8)
4	13 (25.0)
5	36 (69.2)
Intervention	
Virtual reality gait training	28 (53.8)
Non-virtual reality gait training	24 (46.2)

Values are displayed as mean (SD) or n (%).

Table 3.1 illustrates the demographic and stroke-related characteristics of the participants. The study included 36 male and 16 female participants with a mean age of 61.58 (10.48) years and time since stroke onset of 85.15 (37.63) days. Mean USER-P Restrictions score at baseline was 61.65 (17.29), with none of the participants receiving the maximum score (Table 3.2). At post intervention, 3 participants scored maximally. Change scores between baseline and post intervention showed a significant improvement in participation. Participation improved in 44 participants (84.6%), deteriorated in 3 participants (5.8%), and did not change in 5 (9.6%) participants. Furthermore, all walking ability variables improved significantly between baseline and post intervention (*P* < .05), except for duration of walking activity per day. The decline in duration of walking activity per day is strongly influenced by 3 participants who walked on average 57 to 69 minutes less per day during the post-intervention assessment. However, there was no justifiable reason to exclude these results in the analyses.

Table 3.2. Results of participation and walking ability variables at baseline and post intervention (N = 52)

Outcome measures	Baseline	Post intervention	Change score	*P*
USER-P (0–100)[a]				
Restrictions	61.65 (17.29)	73.49 (16.41)	11.84 (10.99)	< .001*
Frequency	27.03 (9.62)	32.75 (7.51)	5.71 (7.24)	< .001*
Satisfaction	57.08 (17.19)	69.16 (15.75)	12.08 (12.86)	< .001*
TUG (s), median (25th, 75th percentile)	10.94 (9.67, 14.05)	10.28 (8.10, 11.53)[b]	-1.36 (-2.72, -0.69)[b]	< .001*
6MWT (m)	358.73 (114.30)	417.29 (118.08)[c]	57.12 (46.30)[c]	< .001*
Mini-BEST (0–28)	18.64 (5.59)[d]	21.00 (5.81)[e]	2.30 (2.33)[e]	< .001*
Total duration of walking activity, per day (min)	45.52 (25.20)[f]	43.99 (22.51)[g]	-2.66 (20.38)[g]	.403
Accelerometer wearing time (h)	18.15 (3.16)[f]	18.79 (3.03)[g]	0.12 (2.86)[g]	.795

Values are reported as mean (SD) unless stated otherwise. 6MWT = 6-minute walk test; Mini-BESTest = Mini Balance Evaluation Systems Test; TUG = Timed Up & Go test; USER-P = Utrecht Scale for Evaluation of Rehabilitation-Participation. [a] Higher scores indicate better participation outcome. * Significant difference between baseline and post intervention (6 weeks) based on paired-samples *t*-test or Wilcoxon signed-rank test (*P* < .05). [b] n = 51. [c] n = 49. [d] n = 28. [e] n = 27. [f] n = 47. [g] n = 42.

Figure 3.1 illustrates the proportion of people after stroke who experience restrictions in participation items at baseline and post intervention. At baseline, many people experienced restrictions in items that involve walking, for example housekeeping (90.4%), mobility (88.5%), physical exercise (84.6%), going out (77.1%), and outdoor activities (86.5%). Furthermore, 97.1% of the people who had a job or received education at stroke onset were restricted in performing their work or receiving education. Between baseline and post intervention, the percentage of people who are restricted decreased with 19.5% for housekeeping, 19.8% for mobility, 23.7% for physical exercise, 19.7% for going out, and 21.6% for outdoor activities. The item regarding visits to family and friends showed the largest decrease in participation restrictions (28.9%).

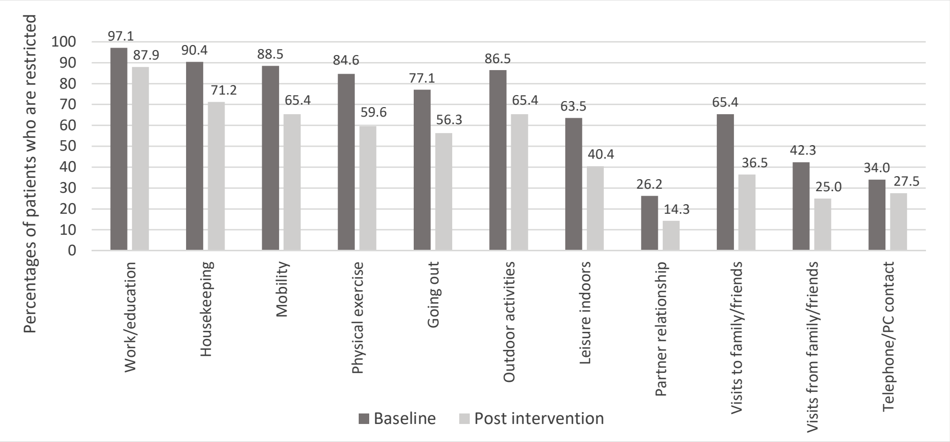

Figure 3.1. The presence of participation restrictions in items of USER-P.
Items include only those participants for which the items are applicable (baseline: work/education n = 35, going out n = 48, partner relationship n = 42 and telephone/PC contact n = 50; post intervention: work/education n = 33, going out n = 48, partner relationship n = 42 and telephone/PC contact n = 51).

Cross-sectional relation between walking ability and participation

Univariate regression analyses showed that time since stroke, TUG, 6MWT, and Mini-BESTest were significantly associated with the USER-P Restrictions subscale at baseline ($P < .20$, Table 3.3).

In the multiple regression analysis the 6MWT, the Mini-BESTest, and time since stroke were included. The TUG was not included because of multicollinearity with the 6MWT and Mini-BESTest. The analysis showed that only the Mini-BESTest was statistically significantly related to the USER-P Restrictions subscale ($P < .05$). A 1-point increase on the Mini-BESTest was associated with a 2.31 (95% CI = 1.48, 3.14) increase in USER-P Restrictions subscale. In this final model, the Mini-BESTest explained 55.7% of the variance in participation ($F(1,26) = 32.705$, $P < .001$).

Relation between change in walking ability and participation over time

Change in TUG, Mini-BESTest, or duration of walking activity per day was not associated with change in participation. A change of 1 meter on the 6MWT was statistically significantly associated with a change of 0.07 in USER-P Restrictions subscale between baseline and post intervention (Table 3.4). Change scores on the 6MWT could explain 8.7% of the variation in change scores in participation between baseline and post intervention (F(1,47) = 4.472, *P* = .040).

Table 3.3. Univariate regression analyses: cross-sectional relation between variables at baseline and USER-P Restrictions subscale (N = 52)

	B	95% CI	β	*P*	R^2
Age	-0.223	-0.687, 0.241	-0.135	.340	0.018
Gender (male = 0, female = 1)	-4.976	-15.416, 5.464	-0.134	.343	0.018
Type of stroke (ischemic = 0, hemorrhagic = 1)	0.738	-12.737, 14.214	0.016	.913	0.000
Site of stroke					0.013
Left vs. right	2.304	-8.084, 12.692	0.065	.658	
Left vs. brainstem	-4.464	-21.606, 12.679	-0.077	.603	
Time since stroke	-0.096	-0.224, 0.031	-0.209	.137*	0.044
TUG	-1.214	-1.854, -0.573	-0.474	< .001*	0.225
6MWT	0.080	0.043, 0.116	0.528	< .001*	0.279
Mini-BESTest[a]	2.307	1.478, 3.136	0.746	< .001*	0.557
Total duration of walking activity, per day[b]	0.064	-0.141, 0.269	0.094	.530	0.009

6MWT = 6-minute walk test; Mini-BESTest = Mini Balance Evaluation Systems Test; TUG = Timed Up & Go test. * *P* < .20. *P* values are used to determine inclusion in multiple regression analysis. [a] n = 28. [b] n = 47.

Table 3.4. Univariate regression analyses: association between change in walking ability and change in USER-P Restrictions subscale (N = 52)

	B	95% CI	β	*P*	R^2
TUG change (per second)[a]	-0.084	-1.161, 0.994	-0.022	.877	0.000
6MWT change (per meter)[b]	0.070	0.003, 0.137	0.295	.040*	0.087
Mini-BESTest change (per one point)[c]	-0.424	-2.356, 1.508	-0.090	.655	0.008
Total duration of walking activity per day change (per minute)[d]	-0.051	-0.223, 0.120	-0.095	.549	0.009

6MWT = 6-minute walk test; Mini-BESTest = Mini Balance Evaluation Systems Test; TUG = Timed Up & Go test. Change is calculated from baseline to post intervention. *P* values are used to determine inclusion in multiple regression analysis. * *P* < .20. [a] n = 51. [b] n = 49. [c] n = 27. [d] n = 42.

Discussion

This study showed that considerable restrictions in participation were experienced in people within 6 months after stroke, especially in activities involving walking such as housekeeping, mobility, and physical exercise. At baseline, univariate analyses revealed that walking endurance, functional mobility, and dynamic balance were significantly related to participation. However, only dynamic balance, as determined by the Mini-BESTest, was significantly related to participation in the multiple regression analysis, explaining a high proportion of variance in participation. Both participation and the variables for walking endurance, functional mobility, and dynamic balance improved significantly between baseline and post intervention (6 weeks, $P < .05$). Nevertheless, the change score of walking endurance was the only walking variable that was significantly associated with change in participation over time.

At baseline, greater walking endurance, better dynamic balance and functional mobility were univariately associated with a higher level of participation. Walking endurance, as determined by the 6MWT, could explain 28% of the variation in participation, which is comparable to 2 studies with people in the chronic stage after stroke. These studies found that the 6MWT explained respectively 30% and 28% of the variation in participation using the Participation domain of the Stroke Impact Scale.[19,20] Results for functional mobility were less consistent with a previous study in which the TUG explained 40% of the variance in participation.[20] However, in contrast to these previous studies, we assessed the relation between walking ability and participation in people within the first 6 months after stroke. In the multiple regression analysis, dynamic balance as measured with the Mini-BESTest independently accounted for 55.7% of the explained variance in participation at baseline. Despite the fact that the Mini-BESTest was examined in a lower number of participants, this proportion of explained variance shows that dynamic balance is an important factor related to participation after stroke. The Mini-BESTest consists of 4 domains of dynamic balance tasks, including reactive postural responses and dynamic gait. These domains comprise a range of balance skills that are requisites for walking in daily life. The dynamic gait domain, especially, involves higher level walking ability by assessing the performance of a cognitive dual task and the ability to change walking speed, step over an obstacle, and walk with a pivot turn.

Although dynamic balance was strongly related to participation at baseline and significantly improved over time, longitudinal analysis showed that the change score of the Mini-BESTest was not associated with change in participation. Change in distance walked during the 6MWT was the only walking variable that was significantly associated with a change in participation between baseline and post intervention (R^2 = 8.7%). These results might suggest that dynamic balance is a basic contributor to participation after stroke. When a sufficient level of dynamic balance is achieved, walking endurance may play a role to further improve participation. The positive association between change in walking endurance and participation suggests that training walking endurance may contribute to improvements in participation. Previous studies already showed that covering long distances can be a challenge for people after stroke, which emphasizes the need to improve walking endurance for daily life participation.[46,47]

While the current study focused on walking ability, other stroke-related impairments or personal and environmental factors may contribute to improvements in participation as well. Previous research showed that participation is a comprehensive and multidimensional concept that is associated with many factors.[14,48] To improve participation, therapists have to be able to understand the factors that influence participation and their relationships so they can focus interventions accordingly.[14] These factors will likely be dependent on the needs and interests of the person after stroke, which stresses the importance of patient-centered rehabilitation. A review of Ezekiel et al.[15] found that associations between biopsychosocial factors and participation varied at different time points post stroke. Although no conclusions could be drawn about which factors were associated at which time point, our findings suggest that walking ability is a basic contributor to participation in daily life, which is especially important in the early phase of rehabilitation. When walking ability improves later in rehabilitation, participation may become less restricted by physical impairments and more by various degrees of cognitive impairments or personal and environmental factors. In addition, more aids may be used over time to assist people with physical impairments, such as a mobility scooter, taxi services, or help from a family care giver, which can facilitate participation.[49] To individually tailor rehabilitation programs, future studies should further investigate which factors contribute to improvement in participation, thereby considering possible differences in time since stroke.

Some limitations of the present study should be mentioned. First, although the people after stroke included in this study experienced self-perceived constraints with walking, they were living in the community and had a relatively good walking ability. This limits the generalizability of the results to a general stroke population, as there are many people after stroke with more severe walking impairments. Second, analyses of the Mini-BESTest included scores from 28 of the 52 participants because this measure was added after the start of the ViRTAS study. However, none of the participants scored more than 3 standard deviations from the mean Mini-BESTest score at baseline or post intervention and assumptions for linear regression analysis were fulfilled. Finally, there were many individual differences in the magnitude and direction of the change scores of both walking ability and participation.

Improvements in walking ability variables were in some participants accompanied by deteriorations in participation and vice versa. This individual variability might have influenced the associations between change in walking ability and change in participation over time.

In conclusion, people after stroke experienced considerable restrictions in participation and improved their participation during the 6-week gait training intervention (i.e., less experienced restrictions). We found that walking ability variables were significantly related to participation. The results suggest that especially dynamic balance is an important basic contributor to participation which needs attention during rehabilitation. In addition, improvement in walking endurance between baseline and post intervention was significantly associated with further improvement in participation, thereby indicating a role for walking endurance to improve participation after stroke.

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PART II

Virtual reality gait training

Chapter 4

Effect of virtual reality training on balance and gait ability in patients with stroke: systematic review and meta-analysis

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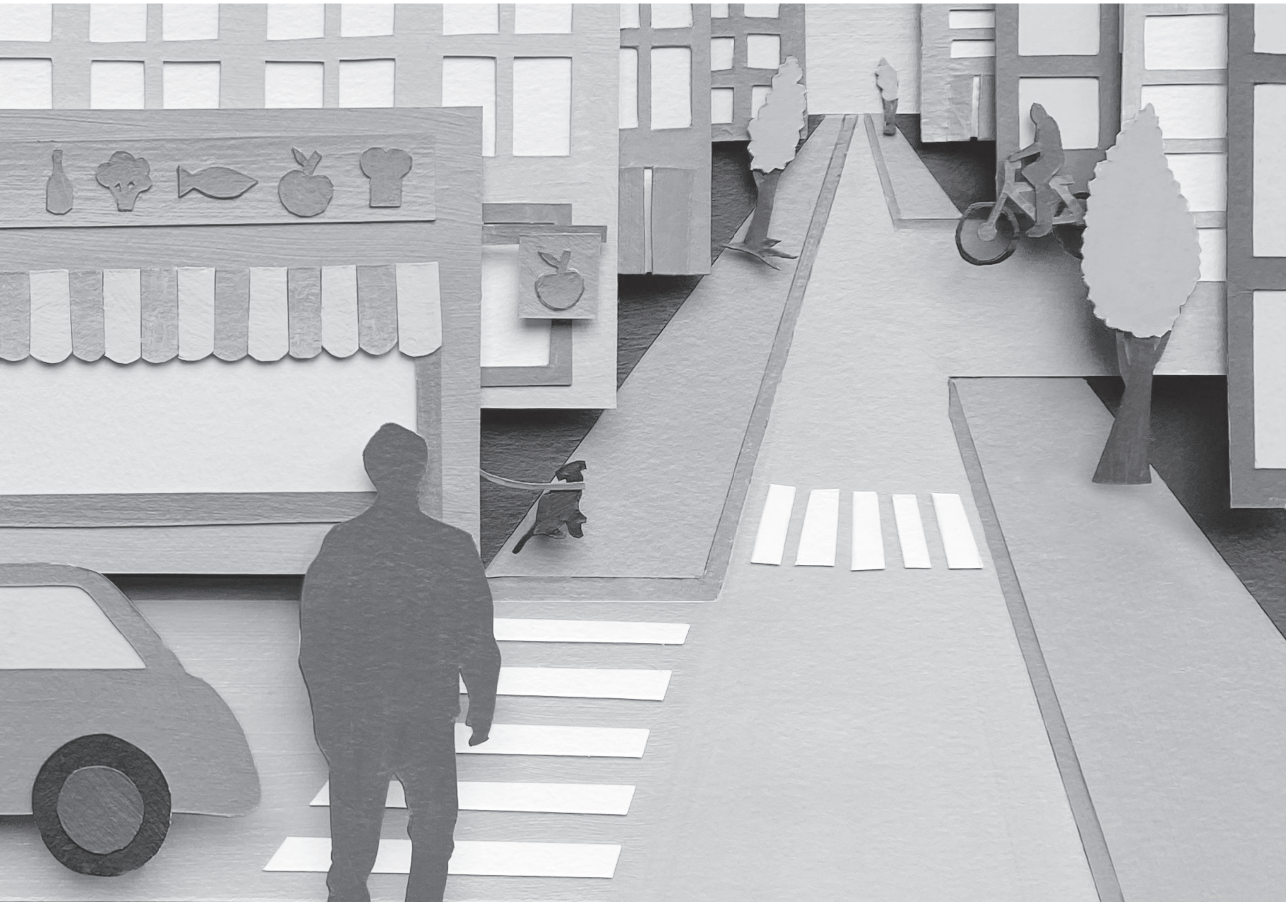


Abstract

Background: Virtual reality (VR) training is considered to be a promising novel therapy for balance and gait recovery in patients with stroke.

Purpose: The aim of this study was to conduct a systematic literature review with meta-analysis to investigate whether balance or gait training using VR is more effective than conventional balance or gait training in patients with stroke.

Data sources: A literature search was carried out in the databases PubMed, Embase, MEDLINE, and Cochrane Library up to December 1, 2015.

Study selection: Randomized controlled trials that compared the effect of balance or gait training with and without VR on balance and gait ability in patients with stroke were included.

Data extraction and synthesis: Twenty-one studies with a median PEDro score of 6.0 were included. The included studies demonstrated a significant greater effect of VR training on balance and gait recovery after stroke compared with conventional therapy as indicated with the most frequently used measures: gait speed, Berg Balance Scale, and Timed Up & Go test. Virtual reality was more effective to train gait and balance than conventional training when VR interventions were added to conventional therapy and when time dose was matched.

Limitations: The presence of publication bias and diversity in included studies were limitations of the study.

Conclusions: The results suggest that VR training is more effective than balance or gait training without VR for improving balance or gait ability in patients with stroke. Future studies are recommended to investigate the effect of VR on participation level with an adequate follow-up period. Overall, a positive and promising effect of VR training on balance and gait ability is expected.

Introduction

Many patients with stroke experience sensory, motor, cognitive, and visual impairments, which all have an impact on their ability to perform daily life activities.[1,2] Approximately 80% of patients with stroke are affected by motor impairment, which represents loss and limitation in muscle strength and coordination. Motor impairment in the legs greatly affects balance and walking ability.[3] In a study by Pollock et al.,[4] approximately 88% of all patients with stroke who were discharged from hospital reported insufficient walking ability. In addition, 26% to 33% of the home-dwelling patients with stroke were still unable to walk unsupervised in the community,[5-7] presumably mainly because of difficulties with negotiating stairs, inclines, or unlevel surfaces.[6,7] Therefore, gait recovery has been recognized as an important goal in stroke rehabilitation.[8-10]

Impaired gait is highly associated with balance dysfunction.[4,11] In addition, improvement in balance has been shown to be the most important determinant for regaining gait as measured with the Functional Ambulation Categories.[12] During balance and gait recovery, patients with stroke have to relearn voluntary control over the affected muscles. In conventional therapy, this relearning is done through physical therapy and occupational therapy, which focus on high-intensity, repetitive, and task-specific practice.[3,13] High-intensity, repetitive, task-orientated, and task-specific practice has proven to be important for effective therapy in all stages after stroke.[14] However, the conventional rehabilitation techniques are often labor- and resource-intensive, tedious, and result most of the time in modest and delayed effects in patients with stroke.[13] In addition, the frequency and intensity of the conventional therapies as performed in clinical practice have been found to be insufficient to achieve maximum recovery.[14,15]

In recent years, the use of virtual reality (VR) has been introduced in the field of stroke rehabilitation.[16] Virtual reality is an advanced computer-human interface with a variety of safe 3-dimensional environments in which patients with stroke can perform real-time tasks and anticipate and react to objects or events.[13,17,18] It has been shown that VR can improve upper extremity motor function in adults with chronic hemiparesis as a result from a stroke.[18] It also is thought that VR contributes to positive changes in neural organization and walking ability.[19]

Multiple recent systematic reviews about the effect of VR training supported the use of VR in lower extremity stroke rehabilitation to improve balance and gait ability.[9,20-23] Two of these reviews[9,21] lacked a meta-analysis, and the majority of the studies did not perform subanalyses of the results (e.g., by making a division between studies in which VR was time dose matched to conventional therapy and studies in which VR training was additional to conventional therapy). The most recent review about the effect of VR training on balance and gait ability showed significant benefits of VR training on gait speed, Berg Balance Scale (BBS) scores, and Timed Up & Go test (TUG) scores when VR was time dose matched to conventional therapy.[22] In contrast to the studies supporting VR training, 2 recently published reviews using a commercial VR system concluded that there was insufficient evidence to ensure the effectiveness of VR training on balance ability.[24,25] However, in the past year, new randomized controlled trials (RCTs) comparing the effect of VR training with conventional therapy have been published. Because of the inconclusive results in the previous reviews about the effect of VR training, the important question remains whether VR interventions are more effective than balance or gait training without VR in patients with stroke.[9] Therefore, the questions that are addressed in the present review are: (1) Are VR interventions to train gait or balance more effective than conventional gait or balance training on balance and gait ability in patients with stroke when time dose is matched? and (2) Are VR interventions in addition to conventional therapy more effective than conventional therapy alone in improving balance and gait ability in patients with stroke?

Method

Data sources and searches

A literature search was carried out using the databases PubMed (since 1950), Embase (since 1974), MEDLINE (since 1946), and Cochrane Library (since 1993) from inception until December 1, 2015. Search terms included key words related to VR (e.g., "game," and "gaming"), stroke ("cerebrovascular accident/disease," "brain attack"), balance ("posture," "postural control," "mobility"), or gait ("ambulation," "walking," "lower extremity," "endurance"). These terms were used as key words in the title and abstract in all databases. In PubMed, terms related to virtual reality also were searched in the full text. The search strategy used in PubMed is provided in Appendix 4.1. The titles and abstracts were displayed and screened by 2 reviewers to identify relevant studies.

Study selection

Only RCTs that compared the effect of gait or balance training without VR with the effect of gait or balance training with VR in patients with stroke were included. The VR intervention replaced the conventional therapy or was in addition to the conventional therapy. For inclusion, RCTs had to be peer-reviewed articles and written in the Dutch, German, or English language. Studies that compared VR interventions with no intervention or form of therapy were excluded. Gait ability could be measured using parameters of spatiotemporal gait ability, functional gait ability, or both, and balance ability could be measured using static and dynamic balance parameters. Furthermore, VR had to consist of a screen or a head-mounted device. The patients with stroke had to perform gait or balance exercises on the ground, a balance board, or a treadmill while looking at the VR scenes. This approach means that studies using robots or standing frames were excluded.

Data extraction and quality assessment

The following data were extracted from the included articles: sex, age, time since stroke, content of intervention, time dose of training, and significant main findings in measures of balance and gait ability between groups. Data extraction was performed by 2 independent researchers (IR, IP). They assessed the methodological quality of the RCTs using the PEDro scale.[26] This scale consists of 11 items that can contribute 1 point to the total score if they are satisfied, except for item 1 (eligibility criteria), which is scored "yes" or "no". The PEDro scale is proven to have sufficient reliability to determine the quality of RCTs. Articles with a score of 6 or higher are considered as high quality, and those with scores of less than 6 are defined as lower quality.[27] In case of disagreement in the quality assessment of the 2 reviewers, consensus was reached by discussion or consulting a third person. Publication bias was analyzed using forest plots for the measures gait speed and TUG.

Data synthesis and analysis

The included studies were analyzed based on participant characteristics, outcome parameters, content of VR interventions, and main findings. A meta-analysis of studies with a PEDro score of 6 or higher was performed using Review Manager Software, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).[28] The pooled effect estimates were computed from the change scores between baseline and end of the intervention, their standard deviations, and the number of participants. Authors were contacted via email for unreported data. Missing standard deviations of the change values in the studies of Barcala et al.[29] and Rajaratnam et al.[30] were imputed from other published literature. Other standard deviations of change values that were still not available after mail contact were estimated using the difference in means and *P* value, *t* value, or *F* value as described in the Cochrane Handbook.[31]

In case of low heterogeneity, the fixed-effect model was used to pool study results for the outcomes BBS, TUG, and gait speed. When significant heterogeneity was observed ($I^2 > 50\%$), the random-effects model was applied. In addition, a sensitivity analysis was conducted when heterogeneity was present. Forest plots were generated to present the pooled effect, and the mean difference (MD) with 95% confidence interval (CI) was calculated for the

BBS and TUG outcomes. For the outcome gait speed, the standardized mean difference (SMD) was expressed because this outcome was obtained through multiple measurement scales. A distinction was made between studies in which the VR intervention replaced the conventional therapy (time dose matched) and studies in which the VR intervention was added to the conventional therapy.

Results

Identification of studies

In total, 398 relevant articles were found in PubMed, Embase, MEDLINE, and Cochrane Library. In addition, 3 articles[29,32,33] were identified through hand searching reference lists. When duplicates were removed, 203 articles remained. Based on title and abstract of these 203 articles, 174 articles were excluded (Figure 4.1). The main reasons for excluding these articles were study designs other than RCTs, interventions focusing on the upper extremity or robotic devices, and participants who experienced other forms of acquired brain injury. Furthermore, 8 articles were excluded based on the full-text article. Two of these studies did not involve randomization,[34,35] 1 study lacked a control group,[36] and 4 studies contained a control group that did not receive conventional therapy[37] or a control group that also watched at a VR screen[38,39] or played VR at home.[40] Another reason for exclusion was VR training that did not involve balance or gait training.[41] Eventually, 21 articles were included in the review.

Description of included studies

In the 21 included studies, the mean age of the participants varied between 45.9 and 65.9 years in the VR group and 46.3 and 65.7 in the control group. Time since stroke ranged between 12.7 days and 11.3 years in the VR group and between 13.2 days and 11.6 years in the control group. Eight studies[8,32,42-47] were treadmill based and provided a VR intervention in combination with walking. The other 13 studies focused on balance interventions by performing exercises on the ground[16,48-53] or a balance board.[29,30,33,54-56] The focus of the balance interventions was on the lower extremities. In the study by Song et al.,[50] however, the upper extremity was involved more directly because the participants had to accomplish tasks with their arms in order to direct their center of pressure outside the feet. In 17 studies[8,30,32,33,42-49,51-53,55,56] the time dose of therapy in the VR and control groups was equal. In 4 studies,[16,29,50,54] the participants in the VR group performed the VR intervention in addition to a conventional therapy program, which means that the time dose of therapy was higher in the VR group compared with the control group (Table 4.1). The additional training of the VR group in these studies varied between 60[29] and 120[16] minutes a week.

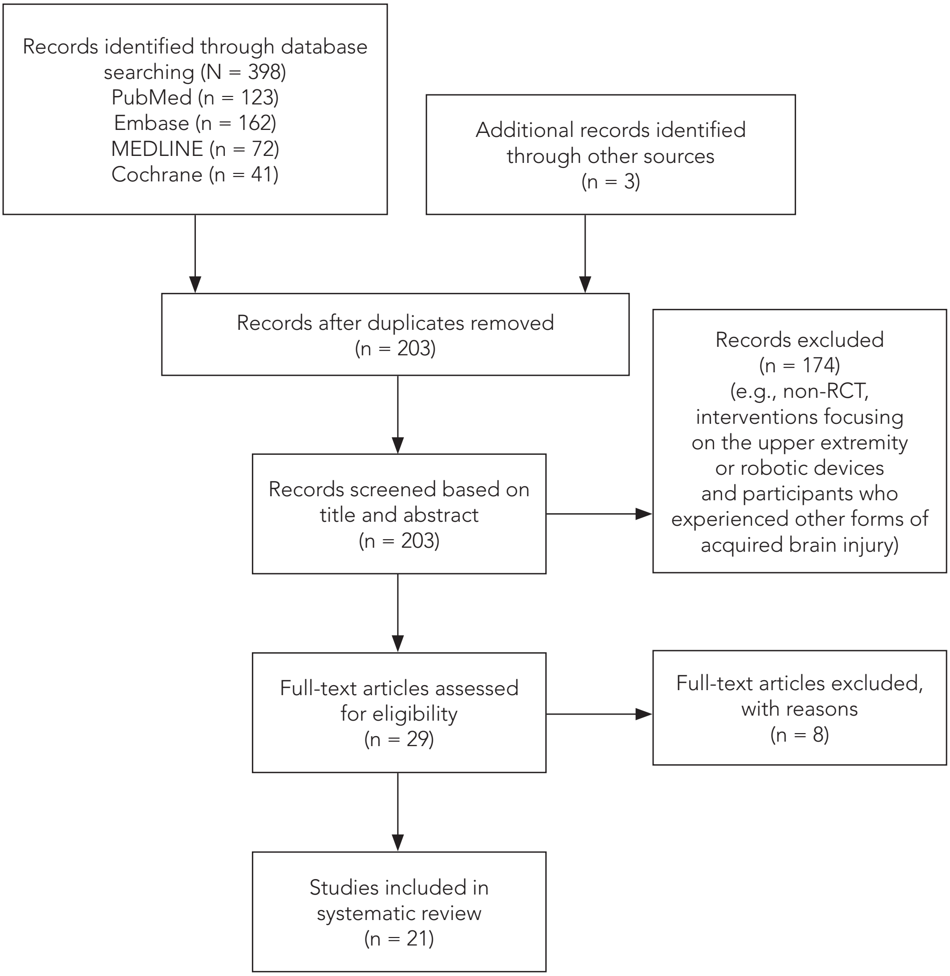


Figure 4.1. Flowchart of the study selection.
RCT = randomized controlled trial.

PEDro scores

The PEDro scores of included studies varied between 3 and 8, with a median of 6.0 and an interquartile range of 2.0 (Table 4.2). Thirteen studies had a score of 6 or higher and were considered of high quality. All trials randomly allocated the participants. Furthermore, the majority of trials reported eligibility criteria (95.4%), had similar groups at baseline (85.7%), performed between-group analyses (95.4%) and assessor blinding (61.9%), collected data of more than 85.0% of the participants (76.2%), and used both point measures and measures of variability (90.5%). In total, 23 (10.0%) of the 231 items from the PEDro scale were initially scored different by the 2 reviewers. After discussion, there was agreement for all items.

Table 4.1. Characteristics of the selected studies and analysis of outcome measures and of gait ability and balance and main findings[a]

Study	N (Male)	Mean age (SD) (y)	Time since stroke (SD)	VR intervention	Control intervention
Givon et al.,[52] 2016	47 (28)	VR group: 56.7 (9.3) Control group: 62.0 (9.3)	VR group: 3.0 (1.8) y Control group: 2.6 (1.8) y	VR group training	Conventional group therapy
Kim et al.,[47] 2015	17 (9)	VR group: 56.2 (7.56) Control group: 48.7 (9.3)	VR group: 7.5 (4.4) mo Control group: 16.6 (8.8) mo	Conventional therapy plus VR-based treadmill training	Conventional therapy
Lee et al.,[55] 2015	24 (16)	VR group: 45.9 (12.3) Control group: 49.2 (12.9)	nr	Conventional therapy plus VR training	Conventional therapy plus task-orientated training
Lee et al.,[56] 2015	20 (11)	VR group: 57.2 (9.2) Control group: 52.7 (11.7)	nr	VR training with cognitive tasks	PNF exercise program
Lloréns et al.,[49] 2015	20 (9)	VR group: 58.3 (11.6) Control group: 55.0 (11.6)	VR group: 407.5 (232.4) d Control group: 587 (222.1) d	Conventional therapy plus VR therapy	Conventional therapy
Song et al.,[53] 2015	40 (22)	VR group: 51.4 (40.6) Control group: 50.1 (7.8)	VR group: 14.8 (6.1) mo Control group: 14.3 (3.4) mo	VR training	Ergometer bicycle training
Cho et al.,[43] 2014	30 (15)	VR group: 65.9 (5.7) Control group: 63.5 (5.5)	VR group: 414.5 (150.4) d Control group: 460.3 (186.8) d	Conventional therapy plus VR-based treadmill training	Conventional therapy plus traditional non-VR treadmill training
Hung et al.,[33] 2014	28 (18)	VR group: 55.4 (10.0) Control group: 53.4 (10.0)	VR group: 21.0 (11.3) mo Control group: 15.9 (8.0) mo	Conventional therapy plus VR training	Conventional therapy plus weight-shift training

Table 4.1. *Continued*

Study	N (Male)	Mean age (SD) (y)	Time since stroke (SD)	VR intervention	Control intervention
Morone et al.,[51] 2014	50 (nr)	VR group: 58.4 (9.6) Control group: 62.0 (10.3)	VR group: 61.0 (36.5) d Control group: 41.7 (36.9) d	Conventional therapy plus VR therapy	Conventional therapy plus extra balance therapy
Song et al.,[50] 2014	20 (11)	VR group: 65.6 (13.5) Control group: 61.2 (13.8)	VR group: 12.7 (3.2) d Control group: 13.2 (3.4) d	Conventional therapy plus VR training	Conventional therapy
Barcala et al.,[29] 2013	20 (9)	VR group: 65.2 (12.5) Control group: 63.5 (14.5)	VR group: 12.3 (7.1) mo Control group: 15.2 (6.6) mo	Conventional therapy plus VR training	Conventional therapy
Cho et al.,[42] 2013	14 (7)	VR group: 64.6 (4.4) Control group: 65.1 (4.7)	VR group: 288.3 (69.2) d Control group: 312.4 (83.7) d	Conventional therapy plus VR-based treadmill training	Conventional therapy plus traditional non-VR treadmill training
Park et al.,[48] 2013	16 (11)	VR group: 48.8 (8.8) Control group: 46.3 (6.8)	VR group: 11.3 (4.5) y Control group: 11.6 (4.4) y	Conventional therapy plus reality-based training	Conventional therapy
Rajaratnam et al.,[30] 2013	19 (7)	VR group: 58.7 (8.6) Control group: 65.3 (9.6)	VR group: 14.7 (7.5) d Control group: 15.2 (6.3) d	Conventional therapy plus VR balance training	Conventional therapy
Cho et al.,[54] 2012	22 (14)	VR group: 65.3 (8.4) Control group: 63.1 (6.9)	VR group: 12.5 (2.6) mo Control group: 12.6 (2.5) mo	Conventional therapy plus VR balance training	Conventional therapy
Jung et al.,[44] 2012	21 (13)	VR group: 60.5 (8.6) Control group: 63.6 (5.1)	VR group: 12.6 (3.3) mo Control group: 15.4 (4.7) mo	VR treadmill training	Non-VR treadmill training

Table 4.1 continues on next page

Table 4.1. *Continued*

Study	N (Male)	Mean age (SD) (y)	Time since stroke (SD)	VR intervention	Control intervention
Kang et al.,[32] 2012	30 (15)	VR group: 55.9 (6.4) Control group 1: 56.3 (7.6) Control group 2: 56.1 (7.8)	VR group: 14.1 (4.4) mo Control group 1: 13.5 (4.0) mo Control group 2: 15.1 (7.4) mo	Conventional therapy plus VR treadmill training	Conventional therapy plus non-VR treadmill training (control group 1) or stretching exercises (control group 2)
Yang et al.,[46] 2011	14 (nr)	VR group: 56.3 (10.2) Control group: 65.7 (5.9)	VR group: 17.0 (8.6) mo Control group: 16.3 (10.4) mo	VR treadmill training	Non-VR treadmill training
Kim et al.,[16] 2009	24 (14)	VR group: 52.4 (10.1) Control group: 51.75 (7.1)	VR group: 25.9 (10.0) mo Control group: 24.3 (8.9) mo	Conventional therapy plus VR therapy	Conventional therapy
Yang et al.,[8] 2008	20 (10)	VR group: 55.5 (12.2) Control group: 60.9 (9.3)	VR group: 5.9 (4.2) y Control group: 6.1 (10.3) y	VR treadmill training	Non-VR treadmill training
Jaffe et al.,[45] 2004	20 (12)	VR group: 58.2 (11.2) Control group: 63.2 (8.3)	VR group: 3.9 (2.3) y Control group: 3.6 (2.6) y	Virtual object training	Stepping over real foam objects on a 10-m walkway

Table 4.1. *Continued*

Study	Time dose of VR group compared with control group	Outcome measures of gait ability	Significant between-groups findings	Outcome measures of balance	Significant between-groups findings
Givon et al.,[52] 2016	Equal	Functional: 10MWT	ns		
Kim et al.,[47] 2015	Equal			Static balance: PSPL (AP, ML, and total), APSS	PSPL (AP, ML, and total), APSS ($P < .05$)
Lee et al.,[55] 2015	Equal			Static balance: COP path length, COP velocity Dynamic balance: FRT	FRT ($P < .0001$)
Lee et al.,[56] 2015	Equal			Dynamic balance: BBS, TUG	BBS, TUG ($P <. 05$)
Lloréns et al.,[49] 2015	Equal	Functional: 10MWT	10MWT ($P < .05$)	Dynamic balance: BBS, Tinetti POMA, Brunel Balance Assessment	BBS ($P < .05$)
Song et al.,[53] 2015	Equal	Functional: 10MWT	10MWT ($P < .05$)	Static balance: weight-bearing ratio affected side, forward and backward LOS Dynamic balance: TUG	weight-bearing ratio affected side, forward and backward LOS, TUG ($P < .05$)
Cho et al.,[43] 2014	Equal	Spatiotemporal: gait speed, cadence, step length, stride length, double-limb support period, single-limb support period	Gait speed, cadence, single- and double-limb support period, step and stride length ($P < .029$)	Static balance: AP-PSV, ML-PSV, PSVM Dynamic balance: BBS, TUG	BBS, TUG ($P = .001$)

Table 4.1 continues on next page

Table 4.1. *Continued*

Study	Time dose of VR group compared with control group	Outcome measures of gait ability	Significant between-groups findings	Outcome measures of balance	Significant between-groups findings
Hung et al.,[33] 2014	Equal			Static balance: SI, weight-bearing asymmetry on affected leg Dynamic Balance: TUG, FRT	SI ($P < .05$)
Morone et al.,[51] 2014	Equal	Functional: 10MWT, FAC	10MWT ($P = .021$)	Dynamic balance: BBS	BBS ($P = .004$)
Song et al.,[50] 2014	Higher			Static balance: FI scores, SI, WDI Dynamic balance: BBS	SI and WDI while standing with eyes open and when standing on a pillow with eyes open ($P < .017$)
Barcala et al.,[29] 2013	Higher			Dynamic balance: BBS, TUG Static balance: COP oscillations	ns
Cho et al.,[42] 2013	Equal	Spatiotemporal: gait speed, cadence, paretic side step length, stride length, and single-limb support period	Gait speed, cadence ($P = .01$)	Dynamic balance: BBS, TUG	BBS, TUG ($P = .01$)
Park et al.,[48] 2013	Equal	Spatiotemporal: gait speed, cadence, step length, stride length Functional: 10MWT	Stride length ($P < .03$)		

Table 4.1. *Continued*

Study	Time dose of VR group compared with control group	Outcome measures of gait ability	Significant between-groups findings	Outcome measures of balance	Significant between-groups findings
Rajaratnam et al.,[30] 2013	Equal			Static balance: CoP sway Dynamic balance: BBS, TUG, FRT	FRT (P = .01)
Cho et al.,[54] 2012	Higher			Static balance: AP-PSV and ML-PSV (with eyes open or closed) Dynamic balance: BBS, TUG	BBS, TUG (P < .05)
Jung et al.,[44] 2012	Equal			Dynamic balance: TUG, ABC scale	TUG, ABC (P < .05)
Kang et al.,[32] 2012	Equal	Functional: 6MWT, 10MWT	6MWT, 10MWT (P < .05)	Dynamic balance: TUG, FRT	VR group vs control group 1: TUG (P < .05) VR group vs control group 2: TUG, FRT (P < .05)
Yang et al.,[46] 2011	Equal			Static balance: COPML, COPAP, COPE, COPA, symmetry index (quiet stance and sit-to-stand transfer), COPE/P (sit-to-stand transfer) stance time/P, step no./P, contact A/P (level walking)	COPML (P = .038)

Table 4.1 continues on next page

Table 4.1. *Continued*

Study	Time dose of VR group compared with control group	Outcome measures of gait ability	Significant between-groups findings	Outcome measures of balance	Significant between-groups findings
Kim et al.,[16] 2009	Higher	Spatiotemporal: cadence, step time, stance time, swing time, single/double support time, step/stride length Functional: 10MWT, MMAS	Cadence, step length, step time ($P < .014$)	Static balance: mean balance, sway area, sway path, maximal velocity Dynamic balance: BBS, AP angle, ML angle	BBS, AP angle, and ML angle ($P < .01$)
Yang et al.,[8] 2008	Equal	Functional: 10MWT, community walking time, WAQ	Pretest-posttest: 10MWT, community walking time ($P < .05$) Follow-up: WAQ ($P = .03$)	Dynamic balance: ABC scale	ns
Jaffe et al.,[45] 2004	Equal	Spatiotemporal: gait speed, cadence, step and stride length Functional: obstacle test, distance on 6MWT	Gait speed, stride length (ss), obstacle clearance, step length of nonparetic leg (ss) and paretic leg (fs) ($P < .05$)	-	-

[a] nr = not reported; ns = nonsignificant; 6MWT = 6-minute walk test; 10MWT = 10-meter walk test; ABC = Activities-specific Balance Confidence; AP = anterior-posterior; AP-PSV = anterior-posterior postural sway velocity; AP and ML angle = angle between a vertical line from the spatial center of the supporting feet and a second line connecting from the same point to the individual's center of gravity; APSS = average postural sway speed; BBS = Berg Balance Scale; contact A/P = contact area of the paretic limb; COP = center of pressure; COPA = center of pressure sway area; COPAP = center of pressure displacement in anterior-posterior direction; COPE = center-of-pressure total path excursion; COPE/P = center-of-pressure path excursion under the paretic limb; COPML = center-of-pressure displacement in medial-lateral direction; FI = falling index; fast = as fast as possible pace; FAC = Functional Ambulation Categories; FRT = Functional Reach Test; ML = medial-lateral; ML-PSV = medial-lateral postural sway velocity; MMAS = Modified Motor Assessment Scale; POMA = Performance-Oriented Mobility Assessment; PSPL = postural sway path length; PSVM = postural sway velocity moment; SI = stability index; ss = self-selected pace; stance time/P = stance time of the paretic limb; LOS = limit of stability; step no./ = step number of the paretic limb; TUG = Timed Up & Go test; WAQ = Walking Ability Questionnaire; WDI = weight distribution index.

Table 4.2. PEDro scores of the included studies[a]

Study	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Participant blinded	Clinician blinded	Assessor blinded	Data for at least 1 outcome from > 85% of participants	No missing data or if missing, intention-to-treat analysis	Between-groups analysis	Point estimates and variability	Total score (/10)
Givon et al.,[52] 2016	Yes	1	0	1	0	0	1	1	1	0	1	6
Kim et al.,[47] 2015	No	1	0	0	0	0	0	0	0	1	1	3
Lee et al.,[55] 2015	Yes	1	0	1	0	0	0	1	0	1	1	5
Lee et al.,[56] 2015	Yes	1	0	1	0	0	0	0	0	1	1	4
Lloréns et al.,[49] 2015	Yes	1	1	1	0	0	1	1	1	1	1	8
Song et al.,[53] 2015	Yes	1	0	1	0	0	0	0	0	1	1	4
Cho et al.,[43] 2014	Yes	1	1	1	0	0	1	1	0	1	1	7
Hung et al.,[33] 2014	Yes	1	1	1	0	0	1	1	0	1	1	7
Morone et al.,[51] 2014	Yes	1	1	1	0	0	1	1	1	1	1	8
Song et al.,[50] 2014	Yes	1	0	1	0	0	0	0	0	1	1	4
Barcala et al.,[29] 2013	Yes	1	1	1	0	0	1	1	0	1	1	7
Cho et al.,[42] 2013	Yes	1	1	1	0	0	1	1	1	1	1	8
Park et al.,[48] 2013	Yes	1	0	1	0	0	0	1	1	1	1	6
Rajaratnam et al.,[30] 2013	Yes	1	0	1	0	0	1	1	1	1	0	6
Cho et al.,[54] 2012	Yes	1	0	1	0	0	0	1	0	1	1	5
Jung et al.,[44] 2012	Yes	1	0	1	0	0	1	1	0	1	1	6
Kang et al.,[32] 2012	Yes	1	1	1	0	0	1	1	1	1	1	8
Yang et al.,[46] 2011	Yes	1	0	0	0	0	1	1	0	1	1	5
Kim et al.,[16] 2009	Yes	1	0	1	1	0	1	1	1	1	1	8
Yang et al.,[8] 2008	Yes	1	1	1	0	0	1	0	1	1	1	7
Jaffe et al.,[45] 2004	Yes	1	0	0	0	0	0	1	0	1	0	3

[a] 1 = yes, 0 = no.

Content of the VR interventions of included studies

There was a wide variety in frequency, intervention setup, and the content of the VR intervention (Supplementary Tables S4.1 and S4.2). The frequency varied between 2 and 5 VR training sessions a week. Eight studies[8,32,42-47] focused on a gait intervention, and 13 studies[16,29,30,33,48-56] focused on balance interventions. To project the virtual environment, a head-mounted device was used in 4 studies,[32,44,45,48] and the VR was projected on a screen in the other 17 studies.[8,16,29,30,33,42,43,46,47,49-56]

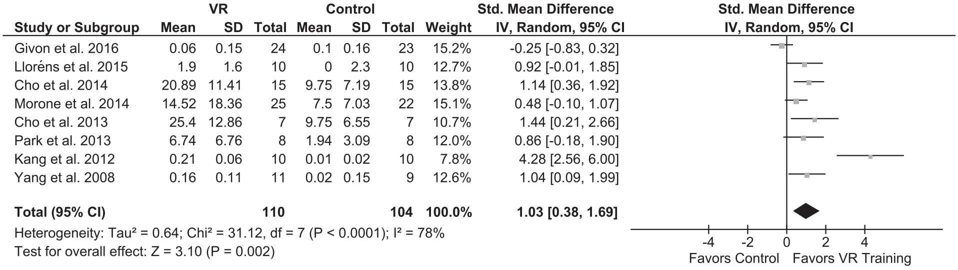
Outcome measures and main findings of included studies

All studies showed a significant difference between the VR and control groups in favor of the VR intervention in different measures of balance or gait ability, except for the studies by Barcala et al.[29] and Givon et al.[52] (Table 4.1). Four studies were not included in the meta-analysis: 3 studies[46,47,55] did not report gait speed, BBS scores, or TUG scores and reported only on static balance parameters, and data of 1 study[50] were not available for a pooled analysis.

Gait ability

Of the studies measuring gait ability, 2 studies[42,43] reported on spatiotemporal parameters, 3 studies[16,45,48] used both spatiotemporal and functional outcome measures, and 6 studies[8,32,49,51-53] focused only on functional gait ability. Gait speed was the most frequently used measure of gait ability, as all studies measuring gait ability included gait speed as an outcome measure. This outcome measure was obtained using pressure-sensitive equipment or the 10-meter walk test. Eight of the 11 studies (n = 211) showed significant greater increases in gait speed in the VR group (n = 108) compared with the control group (n = 103).[8,32,42,43,45,49,51,53] The effect of VR training on gait speed was further examined by pooling the data of 8 studies in which VR training was time dose matched to conventional therapy (Figure 4.2A). The pooled SMD showed that time dose-matched VR training improved gait

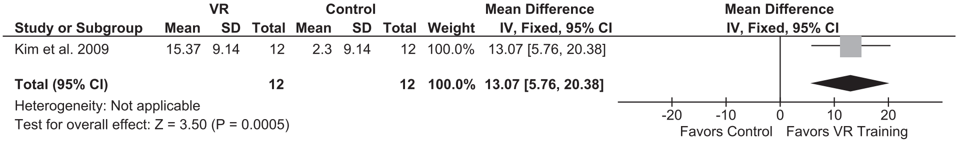
A. Time dose matched



Study or Subgroup	VR Mean	VR SD	VR Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Givon et al. 2016	0.06	0.15	24	0.1	0.16	23	15.2%	-0.25 [-0.83, 0.32]
Lloréns et al. 2015	1.9	1.6	10	0	2.3	10	12.7%	0.92 [-0.01, 1.85]
Cho et al. 2014	20.89	11.41	15	9.75	7.19	15	13.8%	1.14 [0.36, 1.92]
Morone et al. 2014	14.52	18.36	25	7.5	7.03	22	15.1%	0.48 [-0.10, 1.07]
Cho et al. 2013	25.4	12.86	7	9.75	6.55	7	10.7%	1.44 [0.21, 2.66]
Park et al. 2013	6.74	6.76	8	1.94	3.09	8	12.0%	0.86 [-0.18, 1.90]
Kang et al. 2012	0.21	0.06	10	0.01	0.02	10	7.8%	4.28 [2.56, 6.00]
Yang et al. 2008	0.16	0.11	11	0.02	0.15	9	12.6%	1.04 [0.09, 1.99]
Total (95% CI)			**110**			**104**	**100.0%**	**1.03 [0.38, 1.69]**

Heterogeneity: Tau² = 0.64; Chi² = 31.12, df = 7 (P < 0.0001); I² = 78%
Test for overall effect: Z = 3.10 (P = 0.002)

B. Additional



Study or Subgroup	VR Mean	VR SD	VR Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Kim et al. 2009	15.37	9.14	12	2.3	9.14	12	100.0%	13.07 [5.76, 20.38]
Total (95% CI)			**12**			**12**	**100.0%**	**13.07 [5.76, 20.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.50 (P = 0.0005)

Figure 4.2. Forest plot of the pooled results of the effect of VR training on gait speed in (A) time dose-matched studies (n = 214) and (B) studies in which VR was additional to conventional therapy (n = 24). VR = virtual reality; IV = inverse variance; CI = confidence interval.

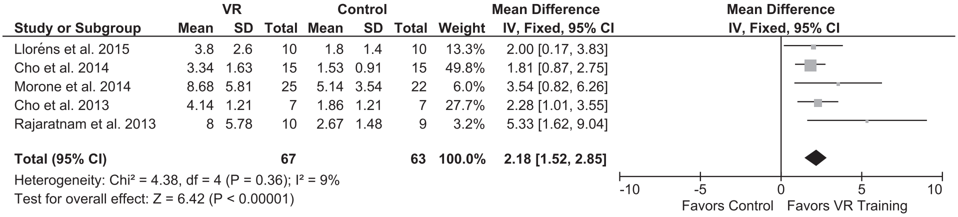
speed significantly more than conventional therapy (SMD = 1.03; 95% CI = 0.38, 1.69; *P* = .002). The I^2 statistic of 78% represents substantial heterogeneity. A sensitivity analysis showed that this heterogeneity was mainly due to the magnitude of the effect of the studies by Kang et al.[32] and Givon et al.[52] (Supplementary Figure S4.1). When these studies were excluded, the I^2 of the pooled effect became 0%, with an SMD of 0.86 (95% CI = 0.52, 1.20; *P* < .001).

In one study,[16] VR training was additional to conventional therapy. This study showed a significant improvement in gait speed in favor of the VR group (Figure 4.2B).

Balance

Regarding studies on balance, 7 studies[8,32,42,44,49,51,56] reported on dynamic balance, 2 studies[46,47] reported on static balance, and 9 studies[16,29,30,33,43,50,53-55] reported on both dynamic and static balance outcome measures. Significant differences in the effect on static balance between the VR group (n = 47) and control group (n = 44) were found in 4 of the 11 studies reporting on static balance.[46,47,50,53] The dynamic balance of patients with stroke seems to improve significantly more after a VR intervention compared with a conventional intervention. Significant differences were found for the BBS in favor of the VR group in 7 out of 10 studies reporting on this scale (n = 180).[16,42,43,49,51,54,56] The pooled MD for VR training time dose matched to conventional therapy showed that VR training significantly improved

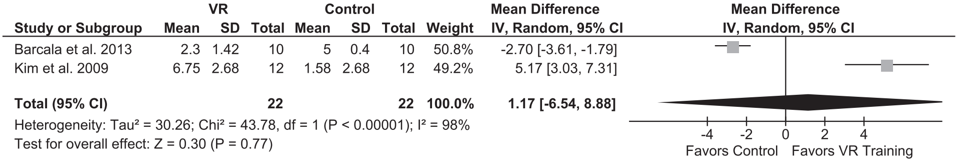
A. Time dose matched



Study or Subgroup	VR Mean	VR SD	VR Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Lloréns et al. 2015	3.8	2.6	10	1.8	1.4	10	13.3%	2.00 [0.17, 3.83]
Cho et al. 2014	3.34	1.63	15	1.53	0.91	15	49.8%	1.81 [0.87, 2.75]
Morone et al. 2014	8.68	5.81	25	5.14	3.54	22	6.0%	3.54 [0.82, 6.26]
Cho et al. 2013	4.14	1.21	7	1.86	1.21	7	27.7%	2.28 [1.01, 3.55]
Rajaratnam et al. 2013	8	5.78	10	2.67	1.48	9	3.2%	5.33 [1.62, 9.04]
Total (95% CI)			**67**			**63**	**100.0%**	**2.18 [1.52, 2.85]**

Heterogeneity: Chi² = 4.38, df = 4 (P = 0.36); I² = 9%
Test for overall effect: Z = 6.42 (P < 0.00001)

B. Additional



Study or Subgroup	VR Mean	VR SD	VR Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Barcala et al. 2013	2.3	1.42	10	5	0.4	10	50.8%	-2.70 [-3.61, -1.79]
Kim et al. 2009	6.75	2.68	12	1.58	2.68	12	49.2%	5.17 [3.03, 7.31]
Total (95% CI)			**22**			**22**	**100.0%**	**1.17 [-6.54, 8.88]**

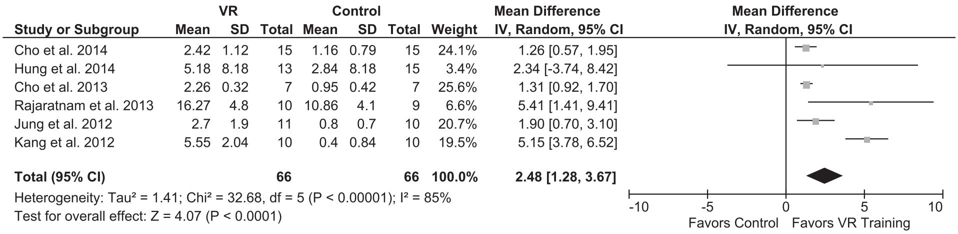
Heterogeneity: Tau² = 30.26; Chi² = 43.78, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.30 (P = 0.77)

Figure 4.3. Forest plot of the pooled results for effect of VR training on Berg Balance Scale in (A) time dose-matched studies (n = 130) and (B) studies in which VR was additional to conventional therapy (n = 44).
VR = virtual reality; IV = inverse variance; CI = confidence interval.

the BBS score with 2.18 (95% CI = 1.52, 2.85; *P* < .001) (Figure 4.3A). The I^2 statistic of 9% represents low heterogeneity. The heterogeneity between the 2 studies in which VR was added to the conventional therapy was high (I^2 = 98%). The pooled MD did not show a significant effect of VR training compared with conventional therapy (MD = 1.17; 95% CI = -6.54, 8.88; *P* = .77) (Figure 4.3B).

Time of the TUG improved significantly more in the VR group of 7 studies.[32,42-44,53,54,56] Only Barcala et al.,[29] Rajaratnam et al.,[30] and Hung et al.[33] did not find significant results for the TUG in favor of the VR group. The pooled results for the TUG showed a significant MD of 2.48 (95% CI = 1.28, 3.67; *P* < .001) in favor of the VR group. However, substantial heterogeneity was indicated with an I^2 statistic of 85% (Figure 4.4A). When excluding the studies by Rajaratnam et al.[30] and Kang et al.,[32] no heterogeneity (I^2 = 0%) was observed. The MD was 1.35 and remained significant in favor of the VR group (95% CI = 1.02, 1.67; *P* < .001) (Supplementary Figure S4.2). The pooled MD for VR training in addition to conventional therapy was reported in just one study.[29] This study showed a significant improvement in time of the TUG in favor of the VR group (Figure 4.4B).

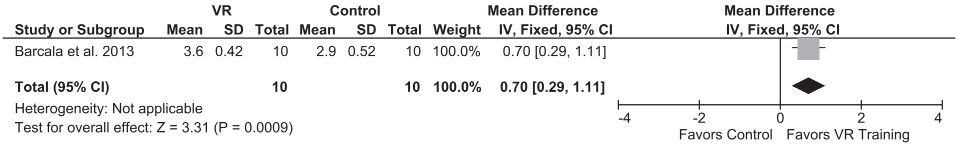
A. Time dose matched



Study or Subgroup	VR Mean	VR SD	VR Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cho et al. 2014	2.42	1.12	15	1.16	0.79	15	24.1%	1.26 [0.57, 1.95]
Hung et al. 2014	5.18	8.18	13	2.84	8.18	15	3.4%	2.34 [-3.74, 8.42]
Cho et al. 2013	2.26	0.32	7	0.95	0.42	7	25.6%	1.31 [0.92, 1.70]
Rajaratnam et al. 2013	16.27	4.8	10	10.86	4.1	9	6.6%	5.41 [1.41, 9.41]
Jung et al. 2012	2.7	1.9	11	0.8	0.7	10	20.7%	1.90 [0.70, 3.10]
Kang et al. 2012	5.55	2.04	10	0.4	0.84	10	19.5%	5.15 [3.78, 6.52]
Total (95% CI)			**66**			**66**	**100.0%**	**2.48 [1.28, 3.67]**

Heterogeneity: Tau² = 1.41; Chi² = 32.68, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 4.07 (P < 0.0001)

B. Additional



Study or Subgroup	VR Mean	VR SD	VR Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Barcala et al. 2013	3.6	0.42	10	2.9	0.52	10	100.0%	0.70 [0.29, 1.11]
Total (95% CI)			**10**			**10**	**100.0%**	**0.70 [0.29, 1.11]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.31 (P = 0.0009)

Figure 4.4. Forest plot of the pooled results for the effect of VR training on Timed Up & Go test in (A) time dose-matched studies (n = 132) and (B) studies in which VR was additional to conventional therapy (n = 20).
VR = virtual reality; IV = inverse variance; CI = confidence interval.

Discussion

This systematic review provided evidence for a stronger effect of VR training compared with conventional therapy, as suggested by the significantly greater improvements in balance and gait ability. Gait speed, BBS score, and time of TUG were the most frequently used measures to underpin the stronger effect of VR training. Pooled effect estimates showed significant improvements in these 3 outcome measures in favor of the VR group for both time dose-matched VR interventions and VR interventions in addition to conventional therapy. The positive findings of VR training are in line with previous reviews on the effect of VR on the lower extremity in patients with stroke.[9,20-23,57] The systematic reviews by Dos Santos et al.[24] and Cheok et al.[25] did not support these positive findings. This conflicting finding may be due to the fact that these reviews included only RCTs that used a Nintendo Wii (Nintendo, Kyoto, Japan) intervention as VR and, therefore, included only 5[24] or 6[25] studies. In addition, 2 of the included RCTs in both reviews concentrated on upper extremity motor function[58] or global motor function[59] and did not include dynamic balance measures (BBS, TUG) or static balance measures. The pooled effect for the BBS when VR was added to conventional therapy was the only measure that did not significantly improve more after VR training. The high heterogeneity between the 2 studies included in the analysis of the BBS may explain why there was no significant pooled effect of VR training in addition to conventional therapy. The meta-analysis included only studies of high quality, as indicated with a PEDro score of 6 or higher. However, when performing the same meta-analyses using all studies for which data were available, the conclusions were the same.

The added value of VR on balance and gait ability compared with most of the currently provided conventional therapies may be explained by multiple aspects. Virtual reality creates patient-specific motor training with a high level of repetitive and variable training. Repetitive training has been hypothesized to form the physiological basis of motor learning.[60] The majority of studies included in this review provided highly repetitive VR training. However, noticeable differences among the studies could be found in the intensity of training. In the studies by Jaffe et al.[45] and Park et al.,[48] the number of steps or corrections in balance that participants had to take were small, which is in contrast to the highly repetitive training in the other 19 studies. Because repetitive training has proven to be an important principle of motor learning,[60] these 2 studies may not have fully optimized the benefits of VR. This possibility is confirmed by the results for gait speed, which showed a nonsignificant or minor effect of VR in the studies by Park et al.[48] and Jaffe et al.,[45] respectively.

Besides repetitive training, variability in practice is important for motor learning because it will lead to improvement in the ability to adapt to novel situations.[13] Virtual reality also enables therapists to provide individualized training in which the intensity and difficulty of the training exercises can easily be adjusted to the characteristics and needs of the patient.[61] Controlled constraints can be applied to patients with stroke who are performing exercises, which is necessary for optimal learning.[9,17]

Besides, more feedback about the performance of participants can be given in VR training than would be possible in real-world practice. Feedback can be divided into intrinsic and extrinsic. Intrinsic feedback refers to somatic information, including tactile, proprioceptive, and kinesthetic information, and may be damaged in patients with stroke. Extrinsic or augmented feedback is provided through an external source.[62,63] This so-called augmented feedback can be provided in knowledge of results at the end of a training task or knowledge of performance concurrent with the performance of the training task.[64] It is well known that feedback improves the learning rate[64] and that patients with stroke benefit from practice with augmented feedback.[65] Visual feedback, specifically, has been shown to play a role in improving balance in patients with stroke.[66,67] All studies in this review included visual, auditory, or sensory augmented feedback, for instance, derived from real-world video recording or an avatar that copies the individual's movements. Therefore, this aspect of VR may play a crucial role in the positive effect of VR on improving balance and gait ability.

Lastly, VR is thought to improve motivation and enjoyment, to decrease the perception of exertion, and to increase the activity adherence in training.[68] The degree to which participants feel motivated and engaged during VR training can depend on the individual and the intervention. None of the included studies in the present review measured motivation. However, Lloréns et al.[40] already assessed motivation and showed that people with stroke considered a VR-based balance intervention as highly motivating. To study the role of motivation as one of the underlying mechanisms for the effect of VR training, future studies need to include motivation as an outcome measure.

The majority of the included studies provided high methodological quality. However, most studies did not perform concealed allocation and lacked an intention-to-treat analysis, which could have led to bias in the included trials. In addition, the majority of studies did not provide participant and clinician blinding, which was expected in this kind of intervention. However, the assessor who performed the measurements was blinded in the majority of the studies. Besides methodological quality, the transparency of the included studies may have had an influence on the results of this review. Not all included studies described the intervention and stroke population in detail and reported their results completely. We tried to retrieve most of the unreported data by contacting the authors through email. Regarding the stroke population, disease status or severity may influence the effect of VR interventions. Because half of the included studies did not report Brunnstrom stages or other measures of disease status, this stroke characteristic could not be included in this review.

Study limitations

The review identified some limitations that should be taken into account when interpreting the effect of VR training on balance and gait ability in patients recovering from stroke. First, the broad inclusion and diversity in the included studies bring some limitations with it. The included studies were diverse regarding the population of patients with stroke, especially regarding the wide variation in time since stroke. It was expected that the effect of VR training was higher in patients early after stroke because brain plasticity and structural reorganization is higher early after lesions[69] and endogenous recovery after stroke has been reported to reach a plateau in 6 months.[70] However, this expectation was not supported by our results because the 3 studies[30,50,51] with a mean time since stroke that did not exceed 2 months did not report another trend in the results compared with the other 18 studies with a mean time since stroke of more than 7 months. Because of a lack of a clear definition of VR, there is diversity in the VR interventions included in the review. In addition, there is diversity in control interventions, leading to a variation in contrast between intervention and control groups among the included studies.

It is important to point out that the reported control group mostly represents conventional therapy, which may not actually and truly control for the VR intervention. An appropriate control group should match the VR intervention in dose, intensity, structure, goal-oriented focus, progressive increase of tasks demands, and inclusion of an explicit balance or walking component.[71] For example, in the balance study by Morone et al.,[51] the control therapy consisted of both walking and balance exercises, whereas the VR training was specifically focused on balance. In the treadmill studies, the control therapy often consisted of treadmill training, but without VR. Using this design, the true additional value of VR could be studied. In this review, both VR in addition to conventional therapy and VR training time dose matched to conventional therapy showed a significantly greater effect on balance and gait ability compared with conventional therapy. The addition of VR appeared to have a smaller effect on improving balance and gait ability than time dose-matched VR training. However, the meta-analysis for additional VR training comprised only 3 studies.

Second, the generalizability of this review regarding age is questionable because only relatively young patients with stroke were included. It might be assumed that implementing VR in an older population is more challenging. In addition, the generalizability of the results of this review is limited to gait and balance outcomes and specifically gait speed, BBS scores, and TUG scores. We chose to include these uniform outcome measures to perform a valuable meta-analysis. However, in several of the included studies, other balance and gait outcomes were performed, and some of these performance-based outcome measures did not demonstrate significant differences between VR training and conventional therapy. In addition, there is a lack of outcome measures on participation level and follow-up analysis. The effectiveness of the VR intervention is measured using spatiotemporal or functional gait measures and dynamic or static balance measures. However, to our knowledge, how these outcome measures translate into daily life participation levels and quality of life has not been investigated. Other reviews[18,72] also concluded that there is a lack of RCTs that measure the effect of VR on participation level. The inclusion of outcome measures focusing on improvement of participation levels and quality of life would have strengthened the results on the effect of VR on balance and gait and the translation to real life, especially as a previous study[73] suggested that training in a virtual environment might improve quality of life and feeling of safety. Furthermore, most of the studies measured the effect of VR directly after the intervention; only 4 studies[8,33,48,52] also measured the effect of VR after 1 or 3 months of follow-up. However, it would be interesting to investigate the long-term effects of VR training to ascertain whether VR-induced improvement can be sustained over time and how the improvements translate into home or community environments.[16] To improve the strength of evidence on the effects of VR, future studies need to be large RCTs investigating the effect of VR from body function to participation level and have to be conducted with standardized training doses and adequate follow-up.

Lastly, we included 21 studies using broad inclusion criteria regarding the VR interventions, suggesting that we did not miss studies comparing VR training with gait or balance training without VR. However, visual inspection of funnel plots in which the SMDs for the TUG and gait speed were plotted against the standard error of the SMD shows asymmetry, which suggests the presence of publication bias. As most published studies show a positive effect, it might be suggested that studies with a negative outcome were missed.

In conclusion, this review suggests that VR training is more effective than conventional therapy without VR to improve balance and gait ability in patients with stroke, both when VR interventions are added to conventional therapy and when time dose is matched. Keeping in mind that different interventions and outcome measures were used, no definite conclusions can be drawn about the most effective sort of VR training intervention. Future studies are recommended to investigate the effect of VR on participation level with large sample sizes and an adequate follow-up period. Overall, a positive and promising effect of VR training on balance and gait ability is expected.

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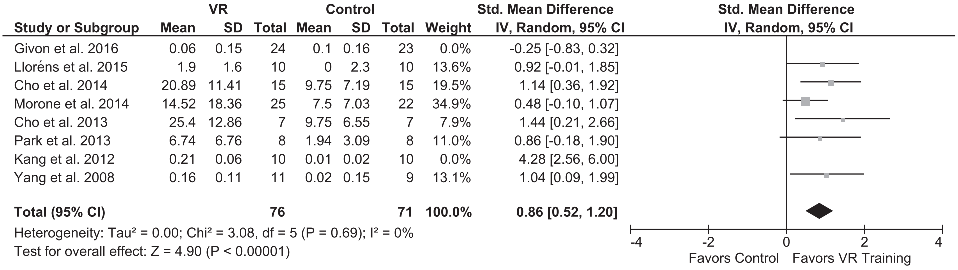
Appendix 4.1

Search String in PubMed

(((((((Virtual reality[Title/Abstract]) OR Gaming[Title/Abstract]) OR Game[Title/Abstract]) OR Virtual reality) OR Gaming) OR Game))) AND ((((Gait[Title/Abstract] OR Walking[Title/Abstract] OR Ambulation[Title/Abstract] OR Lower extremit*[Title/Abstract] OR Balance[Title/Abstract] OR Mobility[Title/Abstract] OR Posture[Title/Abstract] OR Postural control[Title/Abstract] OR Endurance[Title/Abstract]))) AND ((Stroke[Title/Abstract] OR Cerebrovascular accident[Title/Abstract] OR Cerebrovascular disease[Title/Abstract] OR Hemipare*[Title/Abstract] OR Brain attack[Title/Abstract])))

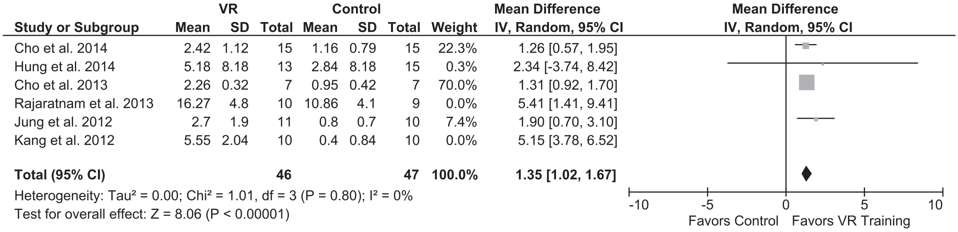
Supplementary data



Study or Subgroup	VR Mean	 SD	 Total	Control Mean	 SD	 Total	 Weight	Std. Mean Difference IV, Random, 95% CI
Givon et al. 2016	0.06	0.15	24	0.1	0.16	23	0.0%	-0.25 [-0.83, 0.32]
Lloréns et al. 2015	1.9	1.6	10	0	2.3	10	13.6%	0.92 [-0.01, 1.85]
Cho et al. 2014	20.89	11.41	15	9.75	7.19	15	19.5%	1.14 [0.36, 1.92]
Morone et al. 2014	14.52	18.36	25	7.5	7.03	22	34.9%	0.48 [-0.10, 1.07]
Cho et al. 2013	25.4	12.86	7	9.75	6.55	7	7.9%	1.44 [0.21, 2.66]
Park et al. 2013	6.74	6.76	8	1.94	3.09	8	11.0%	0.86 [-0.18, 1.90]
Kang et al. 2012	0.21	0.06	10	0.01	0.02	10	0.0%	4.28 [2.56, 6.00]
Yang et al. 2008	0.16	0.11	11	0.02	0.15	9	13.1%	1.04 [0.09, 1.99]
Total (95% CI)			**76**			**71**	**100.0%**	**0.86 [0.52, 1.20]**

Heterogeneity: Tau² = 0.00; Chi² = 3.08, df = 5 (P = 0.69); I² = 0%
Test for overall effect: Z = 4.90 (P < 0.00001)

Supplementary Figure S4.1. Sensitivity analysis of the pooled results for time dose-matched VR training on gait speed (n = 147).
VR = virtual reality; IV = inverse variance; CI = confidence interval.



Study or Subgroup	VR Mean	 SD	 Total	Control Mean	 SD	 Total	 Weight	Mean Difference IV, Random, 95% CI
Cho et al. 2014	2.42	1.12	15	1.16	0.79	15	22.3%	1.26 [0.57, 1.95]
Hung et al. 2014	5.18	8.18	13	2.84	8.18	15	0.3%	2.34 [-3.74, 8.42]
Cho et al. 2013	2.26	0.32	7	0.95	0.42	7	70.0%	1.31 [0.92, 1.70]
Rajaratnam et al. 2013	16.27	4.8	10	10.86	4.1	9	0.0%	5.41 [1.41, 9.41]
Jung et al. 2012	2.7	1.9	11	0.8	0.7	10	7.4%	1.90 [0.70, 3.10]
Kang et al. 2012	5.55	2.04	10	0.4	0.84	10	0.0%	5.15 [3.78, 6.52]
Total (95% CI)			**46**			**47**	**100.0%**	**1.35 [1.02, 1.67]**

Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 8.06 (P < 0.00001)

Supplementary Figure S4.2. Sensitivity analysis of the pooled results for time dose-matched VR training on the Timed Up & Go test (n = 93).
VR = virtual reality; IV = inverse variance; CI = confidence interval.

Supplementary Table S4.1. Analysis of intervention setup and VR content in gait intervention studies[a]

Study	Frequency	Intervention setup	VR content
Kim et al.,[47] 2015	12 sessions, 30 min/d, 3x/wk, for 4 wk	A virtual environment was displayed by a visual screen while the participant walked on a treadmill	Community ambulation including walking on sidewalks, level walking, slope walking, and walking over obstacles.
Cho et al.,[43] 2014	18 sessions, 30 min/d, 3x/wk, for 6 wk	Screenshots of 10-min real-world video recording with sound were displayed while the participant walked on a treadmill	Six different real-world videos: a sunny 400-m walking track, a rainy 400-m walking track, a 400-m walking track with obstacles, daytime walks in a community, nighttime walks in a community, and walking on trails.
Cho et al.,[42] 2013	18 sessions, 30 min/d, 3x/wk, for 6 wk	Screenshots of 10-min real-world video recording with sound were displayed while the participant walked on a treadmill	Six different real-world videos: a sunny 400-m walking track, a rainy 400-m walking track, a 400-m walking track with obstacles, daytime walks in a community, nighttime walks in a community, and walking on trails.
Jung et al.,[44] 2012	15 sessions, 30 min/d, 5x/wk, for 3 wk	Participants walked on a treadmill and wore an HMD on which they could watch the VR program	Simulation of a park stroll.
Kang et al.,[32] 2012	12 sessions, 30 min/d, 3x/wk, for 4 wk	Participants walked on a treadmill with optic flow and wore an HMD	Environment of walking on a street.
Yang et al.,[46] 2011	9 sessions, 20 min, 3x/wk, for 3 wk	A virtual environment was displayed by a visual screen with auditory output while the participant walked on a treadmill	Three scenes: straight-line treadmill walking, walking along a pathway with 8 right turns and 8 left turns and home activities, like turning the light on or off and opening a door.
Yang et al.,[8] 2009	9 sessions, 20 min/d, 3x/wk, for 3 wk	A virtual environment was displayed by a 3D visual screen with auditory output while the participant walked on a treadmill	A typical community in Taipei, including lane walking, street crossing, obstacles striding across, and park stroll. Different levels of complexity requiring faster gait speed, successful adaptation to changes in obstacle height and surface slopes, and increasing decision-making opportunities to avoid collisions are included.
Jaffe et al.,[45] 2004	6 sessions, 1 h/d, 3x/wk, for 2 wk	Participants walked on a treadmill and wore an HMD on which stationary images of virtual obstacles were displayed. The HMD showed also a lateral real-time image of the participant's legs and feet as a visual cue.	Stepping over virtual images of obstacles. Participants could observe the position of their feet, monitor their knee flexion, time their toe-off, and control their stepping height and length through the HMD.

[a] VR = virtual reality; HMD = head-mounted device; 3D = 3-dimensional.

Supplementary Table S4.2. Analysis of intervention setup and VR content in balance intervention studies[a]

Study	Frequency	Intervention setup	Virtual content
Givon et al.,[52] 2015	24 sessions, 60 min/d, 2x/wk, for 12 wk	Combination of Microsoft Xbox Kinect, Sony PlayStation 2 EyeToy, Sony PlayStation 3 MOVE, Nintendo Wii Fit, and SeeMe VR system	Alternately whole body, upper extremity, and lower extremity exercises, including weight shifting and trunk control.
Lee et al.,[55] 2015	18 sessions, 30 min/d, 3x/wk, for 6 wk	Nintendo Wii Fit with balance board and television	Seven exercises: sitting posture, knee bend and other leg knee extension, walking a tightrope, penguin teeter-totter, balance skiing, rolling marble board, and balance Wii.
Lee et al.,[56] 2015	18 sessions, 45 min/d, 3x/wk, for 6 wk	BioRescue platform and monitor	Three exercise games: city walking (left-right weight shift), hot air balloon (up-down weight shift), and bubble (total weight shift).
Lloréns et al.,[49] 2015	20 sessions, 30 min/d, 5x/wk, for 4 wk	VR environment displayed on a video system in which the participants' feet were represented by 2 shoes that mimicked their movement in real life	Tasks consisting of reaching items with one foot while maintaining the other foot within a circle.
Song et al.,[53] 2015	40 sessions, 30 min/d, 5x/wk, for 8 wk	Microsoft Xbox Kinect	Exercise games, including 10-pin bowling, skiing, golf, ground walking, walking over obstacles, and climbing stairs.
Hung et al.,[33] 2014	24 sessions, 30 min/day, 2x/week, for 12 weeks	Nintendo Wii Fit with balance board and television	Seven exercise games: table tilt, ski slalom, soccer heading, balance bubble, penguin slide, basic step, and warrior.
Morone et al.,[51] 2014	12 sessions, 20 min/d, 3x/wk, for 4 wk	Nintendo Wii Fit game system with balance board and television	Three exercise games: hula hoop, bubble blower, and sky slalom.
Song et al.,[50] 2014	9 sessions, 25 min/d, 3x/wk, for 3 wk	IREX VR system including gloves by which patients are recognized as markers for the tasks	Five tasks which required the patient to move in such a way that the COP was directed outside the feet.
Barcala et al.,[29] 2013	10 sessions, 30 min/d, 2x/wk, for 5 wk	Nintendo Wii Fit game system with balance board and television	Three exercise games: penguin slide, table tilt, and tightrope tension.

Supplementary Table S4.2 continues on next page

Supplementary Table S4.2. *Continued*

Study	Frequency	Intervention setup	Virtual content
Park et al.,[48] 2013	12 sessions, 30 min/d, 3x/wk, for 4 wk	VR program by which participants can alter their posture by watching their actual motion on an HMD	Exercises and visual feedback on the posture of the participant while executing the exercises included trunk stability and pelvic tilting in supine, sitting, and standing positions; lower extremity strengthening; and weight-bearing tasks under maintenance of trunk stability.
Rajaratnam et al.,[30] 2013	15 sessions, 20 min	Nintendo Wii Fit or Microsoft Kinect game console system with balance board and television	Nintendo Wii Fit: shifting weight during standing in response to the game Microsoft Kinect: changing center of mass while standing or sitting.
Cho et al.,[54] 2012	6 sessions, 30 min/d, 1x/wk for 6 wk	Nintendo Wii Fit game system with balance board and television	Six exercise games: balance bubble, ski slalom, ski jump, soccer heading, table tilting, and penguin slide.
Kim et al.,[16] 2009	16 sessions, 30 min/d, 4x/wk, for 4 wk	IREX VR system in which participants improve ambulation skills by manipulating objects in the virtual environment that is projected on a screen	Three exercise games: stepping up and down, sharkbait (capture stars while avoiding sharks and eels by means of weight shifting, stepping, squatting, and jumping), and snowboard game (jumping with the snowboard while avoiding obstacles).

[a] VR = virtual reality; HMD = head-mounted device; 3D = 3-dimensional; COP = center of pressure.

Chapter 5

Virtual reality gait training versus non-virtual reality gait training for improving participation in subacute stroke survivors: study protocol of the ViRTAS randomized controlled trial

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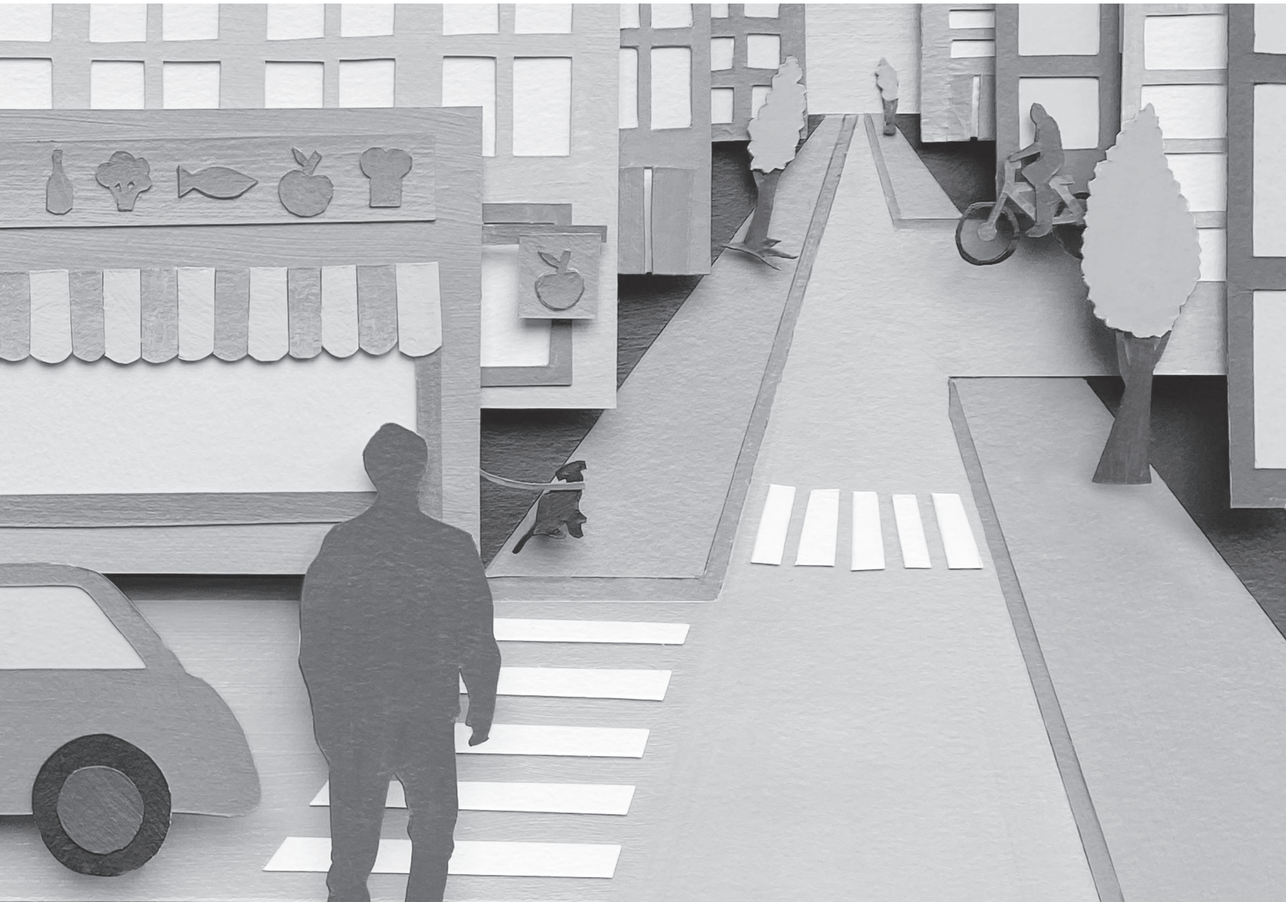
Ingrid G.L. van de Port
Johanna M.A. Visser-Meily
Jan-Willem G. Meijer

Trials. 2019;20:89



Abstract

Background: A stroke often results in gait impairments, activity limitations and restricted participation in daily life. Virtual reality (VR) has shown to be beneficial for improving gait ability after stroke. Previous studies regarding VR focused mainly on improvements in functional outcomes. As participation in daily life is an important goal for rehabilitation after stroke, it is of importance to investigate if VR gait training improves participation. The primary aim of this study is to examine the effect of VR gait training on participation in community-living people after stroke.

Methods/design: The ViRTAS study comprises a single-blinded, randomized controlled trial with 2 parallel groups. Fifty people between 2 weeks and 6 months after stroke, who experience constraints with walking in daily life, are randomly assigned to the virtual reality gait training (VRT) group or the non-virtual reality gait training (non-VRT) group. Both training interventions consist of 12 30-minute sessions in an outpatient rehabilitation clinic during 6 weeks. Assessments are performed at baseline, post intervention and 3 months post intervention. The primary outcome is participation measured with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P). Secondary outcomes are subjective physical functioning, functional mobility, walking ability, walking activity, fatigue, anxiety and depression, falls efficacy and quality of life.

Discussion: The results of the study provide insight into the effect of VR gait training on participation after stroke.

Trial registration: Netherlands National Trial Register, Identifier NTR6215. Registered on 3 February 2017.

Background

Stroke is the third most common cause of disability worldwide.[1] Globally, 17 million people suffer from a stroke each year.[2] A stroke may lead to a wide range of impairments affecting sensory, motor, cognitive and visual function. Impairment in motor function of the legs, specifically, leads to commonly seen gait deficits following stroke.[3,4] Approximately 50% of the people who regain ambulation after stroke experience difficulties with walking in the community, for example with terrain irregularity, changes in level, obstacle avoidance, walking far distances and performing secondary tasks, leading to limitations in walking in everyday life.[5-7] In addition, the ability to perform additional cognitive or motor tasks (i.e., dual tasks) during walking is often diminished after stroke.[8,9] This ability is necessary to adapt to environmental changes while walking (e.g., stepping over an obstacle or crossing a street). Because of the experienced walking impairments, people after stroke are limited in performing daily life activities[10] and not able to participate optimally in the community.[7] Many people after stroke experience participation restrictions in daily life,[7,11,12] which makes maximizing participation an important aspect of rehabilitation.[13]

Recent research has increasingly focused on the use of virtual reality (VR) in stroke rehabilitation, including to enhance walking.[14-16] Rehabilitation interventions in virtual environments can manipulate practice conditions to engage motivation, motor control, cognitive processes and sensory feedback-based learning mechanisms.[17] Principles of motor learning can be well applied in VR training by providing goal-oriented, repetitive and varied practice that is adjusted to the abilities of the patient.[18] Also, real-time feedback provided by using motion capture-based VR can stimulate motor learning after brain injury.[19,20] The adjustable practice conditions enable therapists to add dual tasks and unexpected situations so that patients can learn to adapt to environmental changes while walking. VR interventions to train gait frequently comprise treadmill training systems in combination with a screen or a head-mounted device to create an immersive environment.[16]

Although multiple studies have promising results showing that gait training using VR can improve balance and walking ability after stroke,[15,16,21,22] longer-term follow-up and outcomes on the level of activity and participation are lacking.[14,15] Currently, it is not known whether functional improvements in walking after a VR intervention are translated to real life by increasing activity and participation level. Because participation is one of the main priorities in rehabilitation care, it is of importance to investigate if VR gait training improves participation.

The primary aim of the ViRTAS (Virtual Reality Training After Stroke) study is to examine the effect of VR gait training on participation in community-living people between 2 weeks and 6 months after stroke. VR gait training is compared with a non-VR gait training consisting of conventional treadmill training and functional gait exercises. Both treadmill training and task-oriented gait exercises are commonly used rehabilitation interventions that have been demonstrated to be effective in people after stroke.[23-25] We hypothesize that VR gait training is a better training type for improving participation in subacute stroke survivors compared to non-VR gait training. In addition, we measure the effect on secondary outcome measures including subjective physical functioning, functional mobility, walking ability, walking activity, fatigue, anxiety and depression, falls efficacy and quality of life.

Methods/design

Study design

The study is a single-blinded, randomized controlled trial with 2 parallel groups that investigates the effects of VR gait training on participation, subjective physical functioning and walking activity in people after stroke. Participants are allocated to the virtual reality gait training (VRT) group or non-virtual reality gait training (non-VRT) group. The protocol is described according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Checklist for clinical trials.[26]

Setting

The training sessions and assessments for the study are conducted in outpatient rehabilitation clinic, Revant Rehabilitation Centres, Breda, The Netherlands.

Participants

Potential participants are included if they meet the following inclusion criteria: (1) diagnosed with stroke according to the World Health Organization (WHO) definition,[27] (2) a time since stroke between 2 weeks and 6 months, (3) ability to walk without physical assistance for balance and coordination (i.e., patient may require verbal supervision or stand-by help from a person or may use a walking aid) (Functional Ambulation Category ≥ 3), (4) experiencing self-perceived constraints with walking in daily life, (5) living in the community and (6) age 18 to 80 years. Potential participants are excluded if they (1) have insufficient cognitive skills or understanding of the Dutch language to reliably answer simple questions (based on the impression of the researcher), (2) suffer from severe visual impairments, severe forms of ataxia or uncontrolled epileptic seizures or (3) currently suffer from orthopedic disorders or other co-morbidities that may limit walking ability. The last 2 criteria are verified with the participant and when needed checked in medical records.

Recruitment and consent

Participants are primarily recruited from the rehabilitation center by their physician or physiotherapist who provide patients a brief description of the study. If patients are interested, the clinician obtains permission to pass contact details of the patient to the research team. The researcher then contacts the patient by telephone to give them more information about participation in the study and to verify whether all inclusion criteria are met (eligibility screening). After this contact with the researcher, potential participants can decide whether to participate. If patients are willing to participate, written informed consent is obtained and patient details are passed to an independent person for randomization. Besides recruitment from the rehabilitation center, participants are recruited via flyers at the neurology department of the local hospital, physiotherapy practices and general practices in the area. People after stroke are then invited to contact the research team by telephone call, email or post. All participants provide written informed consent, and anonymity is assured. The protocol of the ViRTAS study has been approved by the Medical Ethics Review Committee of Slotervaart Hospital and Reade, Amsterdam, The Netherlands (P1668, NL59737.048.16) and the study is registered in the Netherlands National Trial Register (NTR6215).

Procedure

Participants in both the VRT and non-VRT group follow a training intervention of 2 30-minute sessions per week for 6 weeks (12 sessions). Assessments are taken at baseline (T0), post intervention (T1, 6 weeks) and follow-up (T2, 3 months post intervention; Figures 5.1 and 5.2). To promote participant retention, we plan training sessions in consultation with the participants and inform participants timely about the entire training schedule and the assessments. All outcomes are assessed in face-to-face meetings by the researcher (IdR). Data is collected on data collection forms, coded and entered into an electronic database by double data entry. The paper forms are stored in a locked cabinet and maintained for a period of 15 years. The researcher is responsible for the data management during the study. Adverse events (e.g., falls, pain and dizziness) that occur during the study period, whether or not related to the study intervention, are registered and in case of a serious adverse event the intervention will be discontinued for the participant. A serious adverse event is defined as an event that is fatal or life-threatening, requires hospital admission or extension of the admission, or causes invalidity or work disability. Participants in both groups continue to receive usual care and rehabilitation as provided by the rehabilitation center or other services in the area. The duration of gait-related therapies that participants visit parallel to the study intervention, are documented. Also, for each participant the adherence to the training sessions of the ViRTAS study is monitored by registering presence and any reasons for absence. In case the training intervention is discontinued for any reason, a participant is still requested to participate in the post intervention and follow-up assessments.

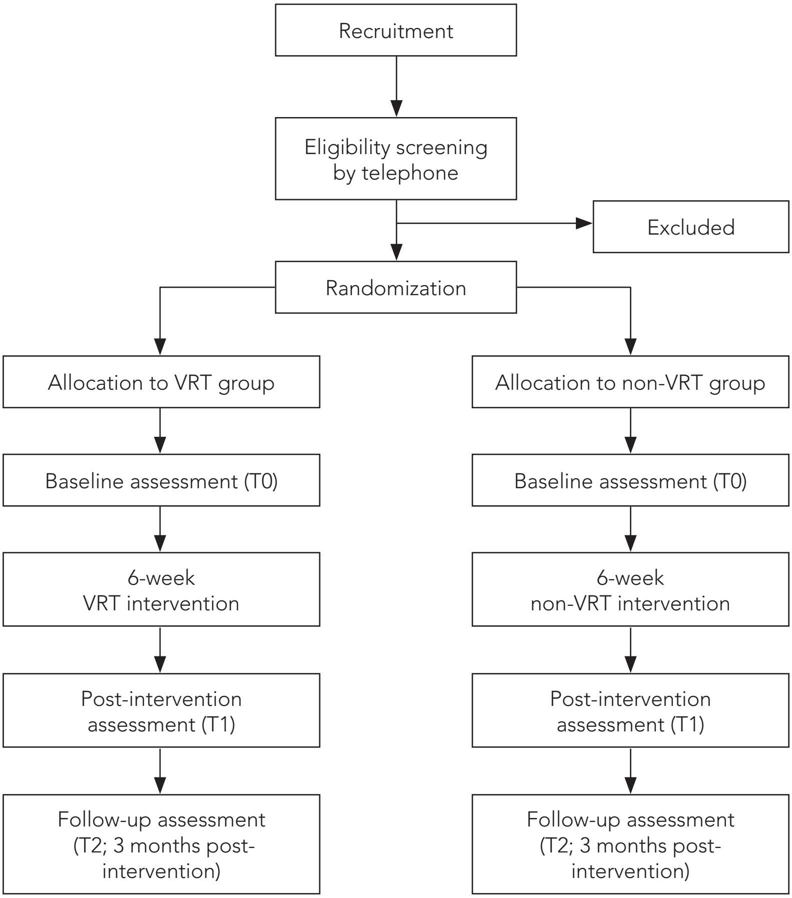


Figure 5.1. Flowchart of the study procedure.

Randomization and blinding

Participants are randomly assigned to the VRT group or the non-VRT group by an independent person who is not involved in the recruitment, intervention or assessments. The randomization is performed using sealed, opaque envelopes which contain a card stipulating to which group the participant is allocated. Twenty-five cards for both the VRT group and non-VRT group are placed in envelopes to ensure equal group sizes. The independent person picks a random envelope from the total set of envelopes and informs the participant and therapists about the treatment allocation. When randomization is done, the envelope is removed from the total set. The researcher who performs all assessments

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Follow-up
TIMEPOINT	$-t_1$	0	t_1 (baseline)	Intervention (6 weeks)	t_2 (post-intervention)	t_3 (3 months post-intervention)
ENROLMENT:						
Eligibility screening	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
VRT group				◆——◆		
Non-VRT group				◆——◆		
ASSESSMENTS:						
Demographic and clinical variables (listed in Table 5.1)			X			
Outcome variables (listed in Table 5.2)			X		X	X

Figure 5.2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments.

(IdR) is blinded to treatment allocation. Due to the nature of the intervention participants and physiotherapists providing the training intervention cannot be blinded to treatment allocation. Participants are explicitly asked not to disclose group allocation to the researcher. The assigned intervention is only revealed for the researcher when this is necessary to manage serious adverse events.

Intervention group

Participants who are allocated to the VRT group receive 2 30-minute sessions of VRT on the Gait Real-time Analysis Interactive Lab (GRAIL, Motekforce Link, Amsterdam, The Netherlands) per week for 6 weeks (12 sessions). The GRAIL consists of a dual-belt treadmill with force platform, a motion-capture system (Vicon Motion Systems, Oxford, UK) and a 180° semi-cylindrical screen for the projection of environments with optic flow (Figure 5.3).[28] During the training sessions participants wear a safety harness that is attached to an overhead suspension system. This harness does not provide weight support. Specialized physiotherapists, who are certified for working with the GRAIL, choose, based on the therapeutic goals, which VR applications are used during the training sessions. Also, the physiotherapist regulates, based on the clinical expertise, the intensity of the exercises, decides the amount of progression and ensures that safety and quality of movement is maintained during the training. All applications can be individualized in terms of difficulty, for

Figure 5.3. Setup of the virtual reality gait training intervention on the Gait Real-time Analysis Interactive Lab (GRAIL).

example by adjusting duration, speed, the amount of simultaneous tasks and the amount of real-time visual, auditory and/or tactile feedback during the exercises. The therapist records the settings of the VR applications and the perfomance of the participant.

Comparison group

Participants assigned to the non-VRT group receive 2 30-minute sessions of non-VRT per week for 6 weeks (12 sessions). The non-VRT consists of 2 stages: (1) conventional treadmill training (10–15 minutes) and (2) functional gait exercises (15 minutes). During the conventional treadmill training the speed is increased progressively. Also, the inclination angle of the treadmill may be increased. Functional gait exercises include 6 different exercises: (1) tapping or stepping up and down a step, (2) walking and picking up various objects from the ground, (3) walking on non-level surface, (4) walking a slalom, (5) stepping in hoops (increasing step length), and (6) stepping over a stick that is fixed between 2 pylons. The exercises are based on the exercises used in the FIT Stroke trial.[29] Training is guided by educated physiotherapists who can individualize the non-VRT. The therapists choose, based on the abilities and needs of the participants, which exercises are conducted during the different training sessions. Graded progression is achieved by increasing the difficulty of the tasks and increasing the number of repetitions. The exercises conducted in each training session are recorded by the physiotherapist.

Outcome measures

During the baseline assessment several demographic, injury-related and therapy-related variables are identified. These variables are presented in Table 5.1.

An overview of the measurement instruments used to assess the primary and secondary outcome variables is given in Table 5.2.

Primary outcome

The effect of the intervention on participation is measured with the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P). Participation can be defined as a person's involvement in all life situations, whereby participation restrictions are problems one may experience in involvement in daily life situations.[27,30] The USER-P assesses objective and subjective participation in persons with physical disabilities and covers 3 aspects of participation: Frequency, Restrictions and Satisfaction.[31] The Restrictions subscale of the USER-P is regarded as the primary outcome measure. The Restrictions subscale consists of 11 items and assesses the experienced participation restrictions in daily life activities including vocational, leisure and social activities. For example, "Does your stroke currently limit you in performing outdoor mobility?" Scores consists of NA (not applicable), not possible (1), with assistance (2), with difficulty (3) and without difficulty (4). The total score is calculated by the sum of all items converted into a 0–100 scale. A higher total score indicates less experienced restrictions.[31] The USER-P has satisfactory reproducibility,[32] high responsiveness[33] and good construct, concurrent and discriminative validity.[31]

Table 5.1. Baseline demographic and clinical variables

Demographic variables
Age of patient at inclusion
Gender
Height
Weight
Partner
Living situation
Region of residence
Injury-related clinical variables
Time since stroke at inclusion
Type of stroke
Site of stroke
Use of walking aids
Use of orthoses
Medication
Co-morbidities
Functional Ambulation Category score
Therapy-related variables
Duration of gait-related therapies parallel to study intervention

Table 5.2. Outcome domains and measurement instruments

Outcome domain	Measurement instrument	Abbreviation	T0	T1	T2
Participation	Utrecht Scale for Evaluation of Rehabilitation-Participation	USER-P	X	X	X
Subjective physical functioning	Stroke Impact Scale-16	SIS-16	X	X	X
Fatigue	Fatigue Severity Scale	FSS	X	X	X
Anxiety and depression	Hospital Anxiety and Depression Scale	HADS	X	X	X
Falls efficacy	Falls Efficacy Scale International	FES-I	X	X	X
Quality of life	Stroke Specific Quality of Life Scale	SS-QOL	X	X	X
Walking ability	6-minute walk test	6MWT	X	X	X
Functional mobility	Timed Up & Go test	TUG	X	X	X
Walking activity	Accelerometer monitoring (5 days)		X	X	X

T0 = baseline; T1 = post intervention (6 weeks); T2 = follow-up (3 months post intervention).

Secondary outcomes

Frequency and Satisfaction scales of the USER-P

The Frequency subscale of the USER-P is divided in parts A and B. Part A measures the time that an individual has spent on paid work, unpaid work, volunteer work and housekeeping using scores from 0 (not at all) up to 5 (36 hours or more). Part B registers the frequency of leisure and social activities in the past 4 weeks with scores ranging from 0 (not at all) to 5 (19 times or more). Furthermore, the Satisfaction subscale measures how satisfied someone is with vocational activities, leisure activities and social relationships. Items are scored on a scale of 0 (very dissatisfied) to 4 (very satisfied). The sum scores for the Frequency and Satisfaction scales are converted into a 0–100 scale. Higher scores represent a higher frequency and satisfaction.[31]

Stroke Impact Scale-16 (SIS-16)

The SIS-16 is a stroke-specific instrument for measuring subjective physical functioning and consists of 16 from the 28 items of the physical domain of the original SIS version 3.0. The items are scored on a 5-point scale, from "not difficult at all" to "cannot do it at all." The SIS-16 is an appropriate instrument to monitor physical limitations over time in subacute patients after stroke. The SIS-16 demonstrates good instrument reliability and concurrent validity.[34]

Timed Up & Go (TUG)

The TUG measures functional mobility.[35] Participants are asked to rise from an armchair, walk 3 m, turn around, walk back and return to sitting.[36] The TUG has a high degree of reliability and validity when applied in people after stroke.[37,38] Participants are allowed to use walking aids and/or ankle-foot orthosis if necessary. The TUG is performed 3 times to determine a mean test time.

6-minute walk test (6MWT)

The 6MWT is a commonly used valid and reliable test to assess walking ability in people after stroke.[39] Participants are instructed to walk as far as possible at comfortable, but fast pace for 6 minutes. Distance walked in 6 minutes is assessed in a 40 m-long testing corridor with marking per 5 m. Each minute, participants are told how much time has elapsed or is left to complete the test. During the test participants are allowed to stand still or sit on a chair if they feel a need to rest.

Fatigue Severity Scale (FSS)

The FSS measures the level of fatigue and the impact of fatigue on daily functioning. This questionnaire consists of 9 items that are scored on a 7-point scale from 1 (completely disagree) to 7 (completely agree). The total score is calculated by the mean of the 9 items.[40] Fatigue prevalence can be defined using a FSS score ≥ 4.[41] The FSS has satisfactory internal reliability and validity.[42]

Hospital Anxiety and Depression Scale (HADS)

The HADS is used to assess anxiety and depression. This questionnaire consists of 14 items (7 anxiety, 7 depression) and all items are scored on a 4-point scale from 0 to 3.[43] In the literature, a cutoff score of > 7 for both subscales is defined for the identification of depressive symptoms and symptoms of anxiety.[44] The HADS is a reliable and valid instrument that is sensitive over time.[45]

Falls Efficacy Scale International (FES-I)

The FES-I consists of 16 items about the person's level of confidence in avoiding falling during essential, non-hazardous activities of daily living.[46] The score of this instrument can range from 16 to 64, with higher scores indicating greater fear of falling or lower fall-related self-efficacy. The FES-I has good psychometric properties in older people[47] and people after stroke.[48]

Stroke Specific Quality of Life Scale (SS-QOL)

The SS-QOL is used to measure quality of life. This questionnaire is designed for use in clinical stroke trials and consists of 49 items divided over 12 domains: energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity function, vision and work/productivity. Each item is scored on a 5-point Likert scale and a total score is calculated by a mean of the 12 domains.[49] The SS-QOL has good test-retest reliability, internal consistency and validity in people after stroke.[50,51]

Activity monitoring

Participants wear a tri-axial accelerometer (DynaPort MM, McRoberts BV, The Hague, The Netherlands) to measure daily-life walking activity. The accelerometer (55 g) is worn for 5 consecutive days at baseline (T0), post intervention (T1) and follow-up (T2; 3 months post intervention). Five consecutive days of monitoring are necessary to obtain reliable walking activity data.[52] The measurement period includes always 1 or 2 weekend day(s). The device is placed at the middle of the lower back using an elastic strap and can be worn above or underneath the clothes. Participants are preferably monitored during day and night but are allowed to take off the accelerometer during night time. During water-related activities such as swimming and showering, the accelerometer is removed to prevent water damage.

Intensity of training sessions

To monitor the intensity of the training sessions in both the VRT and non-VRT group the BORG-RPE scale (CR-10) and a pedometer (Digi-Walker SW-200, Yamax Corporation, Tokyo, Japan) were used. The BORG-RPE scale (CR-10) asks participants about the rate of perceived exertion and workload during the training sessions and can be scored from 0 (no exertion) to 10 (maximal exertion).[53,54] This score is noted at the start and the end of a training session. In addition, participants wear a pedometer on the waistband on the non-hemiplegic side during the training to measure the number of steps taken in the training sessions.

Sample size

The sample size calculations are based on the primary outcome measure, the USER-P Restrictions subscale. A difference of 18.2 points on the USER-P Restrictions subscale is regarded as clinically relevant.[32] The standard deviation of the population is estimated at 17.9 points and the test-retest reliability (ICC) is suggested to be 0.85.[32] Based on an alpha of 0.05 and a power of 80%, a minimum of 14 participants per group is necessary.[55] However, a relative high clinical relevant difference of 18.2 points (18%) is not expected in this study. Therefore, we re-estimated the sample size based on a difference of 15% (15 points) on the USER-P Restrictions subscale, resulting in a minimum of 21 participants per group.[55] Expecting a dropout rate of 20%, we assume that a minimum of 50 participants is needed to achieve a sufficient statistical power of 80%. The majority of the randomized studies regarding the effect of VR that are published up to now included less than 25 participants per group.

Data analysis

Gait activity data monitored with the accelerometer is analyzed using a validated stroke-specific algorithm for gait detection and gait quantification in Matlab (The MathWorks Inc., Natick, MA, USA).[56] This algorithm has shown to have good criterion validity and test-retest reliability in people after stroke. The algorithm detects gait activity with a minimum length of 8 seconds or a multiple of 8 seconds.

The effectiveness of the intervention on the primary outcome measure, USER-P Restrictions subscale, is assessed using random coefficient analysis. We include time of assessment, group assignment (intervention and comparison group) and the interaction between time of assessment and group assignment in the multi-level regression model. Because random coefficient analysis can handle missing data, the analysis is performed with all available data, including data from participants with incomplete datasets.[57] Intention-to-treat analysis will be applied. Also, for the secondary outcome measures (USER-P Frequency subscale, USER-P Satisfaction subscale, SIS-16, TUG, 6MWT, FSS, HADS, FES-I, SS-QOL and gait activity) a comparable random coefficient analysis is performed to assess the effectiveness of the intervention. Demographic, injury-related and therapy-related variables of the 2 groups are examined using the independent *t* test or non-parametric equivalent, the Mann-Whitney *U* test. A X^2 test is used to examine categorical variables. Furthermore, to compare the intensity of the training sessions in the VRT and non-VRT groups, the mean number of steps measured with the pedometer and the mean BORG-RPE score are analyzed with an independent *t* test or the non-parametric equivalent. Results are considered significant when *P* values are < .05.

Discussion

The ViRTAS study examines the effect of VR gait training on participation in community-living people between 2 weeks and 6 months after stroke. Also, the effect of VR gait training on secondary outcome measures including subjective physical functioning, functional mobility, walking ability, walking activity, fatigue, anxiety and depression, falls efficacy and quality of life is discussed.

VR can be defined as a computer-based technology that simulates a real environment and provides the user with opportunities to interact with objects and events.[20,58] In this study the VR consists of high-end 3-dimensional environments with motion capture. VR is thought to enhance neuroplasticity and motor learning after stroke through facilitating brain reorganization and activating brain areas involved in motor planning, learning and execution.[59] Multiple studies have shown significant improvements in functional outcome measures as a result of VR gait training in people after stroke.[15,16] We believe that VR gait training for subacute stroke survivors is a valuable addition to conventional physiotherapy (e.g., treadmill training or functional gait exercises) by providing an intensive, variable and enjoyable therapy which can be easily adjusted to the abilities of the patient. Multiple principles of motor learning can effectively be applied during a VR gait training session.[18,60] Using VR gives the opportunity to perform multiple repetitions of different movements within meaningful tasks by varying the gait exercises and the settings of the exercises within a training session. Variability in training is thought to be important for retention and transfer of learned skills.[61] While walking in a virtual environment unexpected constraints (e.g., disturbances and obstacle avoidance) or dual tasks can be provided to stimulate patients to use problem-solving abilities. This is useful as it is known that problem-solving is an important principle to enhance the cognitive learning of new skills.[17] Using VR, environments can be manipulated more than during conventional physiotherapy. In addition, the use of enriched VR environments with game scores and a high virtual presence can improve motivation, enjoyment and engagement of patients probably more than during conventional physiotherapy interventions.[62,63] Another advantage of VR compared to conventional therapy could be that the task difficulty can easily be monitored with multiple options present to adjust the training to the abilities of the individual. Lastly, intrinsic and extrinsic feedback (knowledge of performance and knowledge of results) provided during a VR gait training session can promote motor learning after stroke.[19] In this study, we investigate whether these above-mentioned potentially beneficial characteristics of VR can lead to improvement in participation in people after stroke. We match both training interventions on frequency, duration and number of training sessions.

A foreseen difficulty of the study is that participants continue to receive usual care and rehabilitation which might interfere with the effect of the studied interventions. From an ethical perspective, it is not an option to withheld care or rehabilitation from subacute stroke survivors. As participants are within 6 months after stroke, they may receive other therapies focusing on gait. However, due to the randomization it is expected that there is no noticeable difference between the VRT and non-VRT group in the potential interference of usual care and rehabilitation. Still, the frequency and duration of the gait-related therapies are registered.

To the authors' knowledge this is the first study to investigate the effect of a VR gait training intervention on the level of participation in people after stroke. VR gait training might be a great potential for rehabilitation after stroke.

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Chapter 6

Effect of virtual reality gait training on participation in survivors of subacute stroke: a randomized controlled trial

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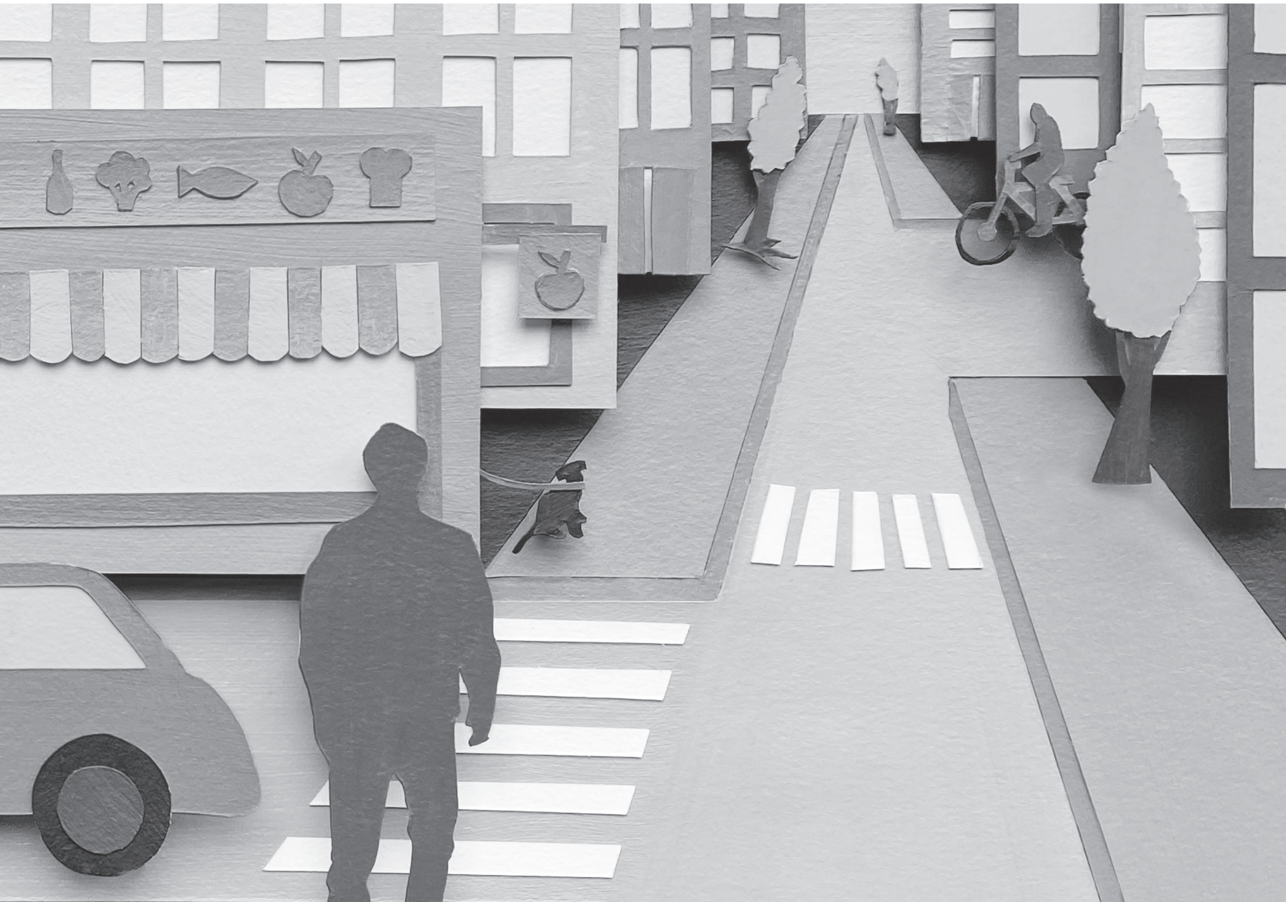

Objective: After stroke, people experience difficulties with walking that lead to restrictions in participation in daily life. The purpose of this study was to examine the effect of virtual reality gait training (VRT) compared to non-virtual reality gait training (non-VRT) on participation in community-living people after stroke.

Methods: In this assessor-blinded, randomized controlled trial with 2 parallel groups, people were included between 2 weeks and 6 months after stroke and randomly assigned to the VRT group or non-VRT group. Participants assigned to the VRT group received training on the Gait Real-time Analysis Interactive Lab (GRAIL), and participants assigned to the non-VRT group received treadmill training and functional gait exercises without virtual reality. Both training interventions consisted of 12 30-minute sessions during 6 weeks. Primary outcome was participation measured with the Restrictions subscale of the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) 3 months postintervention. Secondary outcomes included subjective physical functioning, functional mobility, walking ability, dynamic balance, walking activity, fatigue, anxiety and depression, falls efficacy, and quality of life.

Results: Twenty-eight participants were randomly assigned to the VRT group and 27 to the non-VRT group, of whom 25 and 22 attended 75% or more of the training sessions, respectively. No significant differences between the groups were found over time for the USER-P Restrictions subscale (1.23; 95% CI = -0.76 to 3.23) or secondary outcome measures. Patients' experiences with VRT were positive, and no serious adverse events were related to the interventions.

Conclusions: The effect of VRT was not statistically different from non-VRT in improving participation in community-living people after stroke.

Impact: Although outcomes were not statistically different, treadmill-based VRT was a safe and well-tolerated intervention that was positively rated by people after stroke. VR training might, therefore, be a valuable addition to stroke rehabilitation.

Lay summary: VRT is feasible and was positively experienced by people after stroke. However, VRT was not more effective than non-VRT for improving walking ability and participation after stroke.

Introduction

Although a substantial number of people after stroke regain the physical capacity to walk without support from others, many still experience difficulties with walking in the community and performing daily life activities.[1,2] Previous studies estimated that only approximately 18% to 64% of people after stroke achieve the ability to independently walk in the community without difficulty.[3-6]

An adequate walking ability is necessary to perform daily life activities and to fully participate in the community (e.g., work, household, and social activities).[2,7] Walking in community environments requires people to adjust their walking to task goals and environmental demands.[8] This ability is often reduced in people after stroke, and as a result, they experience difficulties with walking far distances; climbing steps, stairs, or inclines; managing terrain irregularity and changes in level; obstacle avoidance; and performing dual tasks during walking.[1,9] These difficulties with walking restrict people in performing daily life activities and can limit their participation in the community. Participation is described as "the person's involvement in life situations," and problems that one may experience in these life situations are called participation restrictions.[10] Since walking difficulties can limit participation, improving walking ability is one of the primary goals in stroke rehabilitation.[11] To achieve an adequate walking ability, it is important to train in different contexts and environments and to include participation as an outcome of rehabilitation.[12]

Virtual reality (VR) is increasingly studied in stroke rehabilitation, including to improve balance and walking function.[13] Dedicated VR systems with motion capture technology can provide realistic environments in which people can have real-time interaction with objects and events.[14] A major advantage of VR training is the ability to optimally challenge people in a safe training environment.[15] While walking in a treadmill-based virtual environment, people have to adapt their walking to unexpected situations (e.g., obstacles and perturbations) and can be challenged to perform dual tasks and use their problem-solving abilities. The training can be easily adjusted to the abilities of the patient and the provision of real-time feedback is thought to contribute to motor recovery and to enhance motivation.[13,16] Furthermore, principles of motor learning are expected to be applied easily by providing motivating, goal-oriented, varied, and high-intensity training.[13,15]

Reviews showed favorable effects of various VR systems on balance and walking function in people after stroke.[17-21] However, previous studies included little evidence about follow-up assessments and lacked outcomes on activities of daily living and participation.[13,15,17] It is therefore unknown whether effects on functional level are translated to real-life daily activity and improvement on participation level.

The primary aim of the present study was to examine the effect of VR gait training (VRT) on participation in community-living people included between 2 weeks and 6 months after stroke. In addition, the effect of VRT on secondary outcomes, including subjective physical functioning, balance and walking ability, and walking activity, was investigated. The second aim was to explore the experiences of people after stroke with VRT, since this training intervention was new for them. Also, we investigated their perception on how this training influenced their walking ability and participation. We hypothesized that treadmill-based VRT is a safe training intervention that is superior to a non-VRT consisting of conventional treadmill training and functional gait exercises.

Methods

Study design and participants

We conducted an assessor-blinded, randomized controlled trial with 2 parallel groups to investigate the effect of VRT on participation in people after stroke. Participants were equally allocated to the VRT group or non-VRT group. The full study protocol of this study, called ViRTAS (Virtual Reality Training After Stroke), has been published previously.[22] No changes were made to the study design or eligibility criteria after study commencement.

Participants were primarily recruited by their physician or physical therapist at the rehabilitation center. In addition, participants were recruited at the neurology department of the local hospital and physical therapy and general practices in the area. For inclusion, potential participants had to meet the following criteria: (1) diagnosed with stroke according to the World Health Organization definition,[23] (2) time since stroke between 2 weeks and 6 months, (3) ability to walk without physical assistance for balance and coordination (Functional Ambulation Category ≥ 3),[24] (4) experiencing self-perceived constraints with walking in daily life, (5) living in the community, and (6) age 18 to 80 years. Exclusion criteria were insufficient cognitive skills or understanding of the Dutch language to reliably answer simple questions; severe visual impairments, severe forms of ataxia, or uncontrolled epileptic seizures; and orthopedic disorders or other comorbidities that limited current walking ability. All participants provided written informed consent.

Procedures

Participants were randomly assigned to the VRT or non-VRT group by an independent expert not involved in the recruitment, intervention, or assessments. Randomization was performed using sealed, opaque envelopes that contained a card stipulating to which group the participant was allocated.

Both groups received a training intervention that consisted of 2 30-minute sessions per week for 6 weeks (12 sessions). Assessments were performed at baseline (T0), postintervention (T1, 6 weeks), and follow-up (T2, 3 months postintervention) by a researcher blinded to group allocation (IdR). The participants and intervention therapists could not be blinded to group allocation because of the nature of the intervention. Training sessions and assessments were conducted in the rehabilitation center, Revant Rehabilitation Centres, Breda, the Netherlands. All adverse events were registered and serious adverse events were reported to the medical ethics review committee.

Interventions

Experienced physical therapists conducted the VRT and non-VRT intervention and adapted each training session to the abilities and needs of the participants. Based on clinical expertise, the physical therapists regulated the intensity of the training, decided the amount of progression, and ensured safety and quality of movement during the training. During the 6 weeks of training difficulty was increased. The intensity of each training session was monitored by scoring the rate of perceived exertion with Borg's Category-Ratio Scale of Perceived Exertion (range, 0–10) and measuring number of steps taken with a pedometer (Digi-Walker SW-200; Yamax Corp, Tokyo, Japan).

Intervention group

The VRT group trained on the Gait Real-time Analysis Interactive Lab (GRAIL; Motekforce Link, Amsterdam, the Netherlands). The GRAIL consists of an instrumented dual-belt treadmill combined with a motion-capture system (Vicon Motion Systems, Oxford, UK) and a 180° semi-cylindrical screen for the projection of synchronized 3-dimensional environments. To create a safe environment, participants wore a harness without providing weight support. Various rehabilitative applications (VR environments) with specific rehabilitation goals were available (e.g., to train reactive balance, maneuverability, or dual tasks). Difficulty level could be further modified within the applications by adjusting multiple training options: duration, treadmill speed, pitch and sway of the treadmill, belt acceleration or deceleration, amount of simultaneous tasks, frequency and position of environmental constrains (e.g., obstacles), and the amount and type of real-time feedback. VRT was conducted by specialized therapists who are trained to work with the GRAIL. The therapist chose, based on the therapeutic goals, which applications were used during a training session and could easily adapt the difficulty level to individual abilities of the participants.

Comparison group

The non-VRT intervention combined 2 commonly used interventions to improve walking ability: (1) conventional treadmill training (10–15 minutes) and (2) functional gait exercises (15 minutes). Duration, speed, and/or incline of the treadmill were increased and support from handrails was decreased to make the intervention progressive. The functional gait exercises included 6 directional exercises: (1) tapping or stepping up and down a step, (2) walking and picking up various objects from the ground, (3) walking on nonlevel surface, (4) walking a slalom, (5) stepping in hoops, and (6) stepping over a stick that is fixed between 2 pylons. The exercises were based on the exercises used in the FIT-Stroke trial.[25] The therapist chose which exercises were conducted during the different training sessions. Exercises were individualized by adapting amount of repetitions, distance, height, variation, and amount of dual tasks, for example.

Outcome measures

Primary outcome

The primary outcome measure was participation as measured with the Restrictions subscale of the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P) using all available data up to 3 months postintervention.[26] The Restrictions subscale of the USER-P assesses the experienced participation restrictions in daily life and consists of 11 items. The total score ranges from 0 to 100 with higher scores indicating less experienced restrictions.[27]

Secondary outcomes

Secondary outcome measures included the Frequency and Satisfaction subscales of the USER-P. Other outcomes were questionnaires regarding subjective physical functioning (Stroke Impact Scale-16), fatigue (Fatigue Severity Scale), anxiety and depression (Hospital Anxiety and Depression Scale), falls efficacy (Falls Efficacy Scale International), and quality of life (Stroke Specific Quality of Life Scale). Performance tests measured functional mobility (Timed Up & Go test), walking ability (6-minute walk test), and dynamic balance (Mini Balance Evaluation Systems Test [Mini-BESTest]). In addition, daily-life walking activity was measured with a triaxial accelerometer (hardware: DynaPort MM, McRoberts BV, the Hague, the Netherlands) during 5 consecutive days.

Detailed descriptions of all secondary outcomes are available in the original protocol.[22] The Mini-BESTest was added to the original protocol to assesses dynamic balance.[28] The test measures 4 underlying systems for balance control and consists of 14 items. The total score ranges from 0 to 28 points. A higher total score indicates better balance performance.[29]

Walking activity data from the accelerometer was analyzed with a stroke-specific algorithm for gait detection and quantification in Matlab (The MathWorks Inc., Natick, MA, USA).[30] Walking activity was expressed as total number of steps a day, total duration of walking activity per day (minutes), and step frequency (number of steps per minute of walking activity). The algorithm detected walking activity with a minimum length of 8 seconds or a multiple thereof. The total duration of walking activity was calculated as the sum of all 8-second walking bouts per day. Step frequency was calculated by dividing the total number of steps by the total duration of walking activity.[31] The walking activity values were averaged over the days on which participants wore the accelerometer for at least 8 hours. Participants had to wear the accelerometer for at least 3 days and had to walk, on average, at least 5 minutes per day to be included in the analysis.[31]

In addition, patients' experiences with VRT were explored using semi-structured interviews. The semi-structured interviews were conducted by 2 independent researchers at the end of the 6-week training period. In a face-to-face session, the interviewer asked participants about their experiences with VRT (including advantages or disadvantages) and their perception of how the VRT intervention influenced their walking ability and participation. Interviews were audio-recorded, transcribed verbatim, and analyzed thematically.[32] Themes and codes were analyzed and summarized in NVivo 12 (QRS International, Burlington, MA, USA).

Data analysis

The medical ethics review committee approved a sample size of 56 participants. This sample size was corrected when reviewers of the protocol article pointed out a miscalculation. In the revised calculation, a total of 50 (25 per group) people after stroke would be required to detect a mean difference of 15% (15 points, SD = 17.9) on the USER-P Restrictions subscale with 80% power and a 2-sided α of 5%, while accounting for an estimated dropout rate of 10% to 20%.[22] However, because randomization was already arranged, we aimed to recruit as close to 56 participants in the time available.

We visually checked normality for all continuous outcome measures. Right-skewed outcome variables involving time were log-transformed before the analyses. The analysis was performed based on a modified intention-to-treat principle including all participants who attended at least one follow-up measurement. The effectiveness of VRT on the primary outcome measure, USER-P Restrictions subscale, was analyzed using an analysis of covariance linear mixed-effects model. The fixed part of the model included an effect for baseline USER-P Restrictions, time in months, group assignment (VRT or non-VRT), and the interaction between time and group. The random part of the model contained a random intercept per individual. Treatment effectiveness was determined by evaluating the significance of the time by group interaction (i.e., is the effect over time different for participants allocated to VRT or non-VRT). For the secondary outcome variables, comparable linear mixed-effects models were used with correction for baseline scores of the respective outcome variables.

Furthermore, 2 sensitivity analyses were conducted for the primary outcome. In the first sensitivity analysis the interaction between baseline USER-P Restrictions and time was added as additional adjustment variable. In the second sensitivity analysis, we adjusted our primary model for time since stroke due to a potential imbalance between groups. In addition, we performed a per-protocol analysis for the primary outcome in which only data of participants who attended at least 75% of the training sessions were included. Analyses were performed in SPSS version 25 (IBM Corp, Armonk, NY, USA) and results were considered significant when *P* values were less than .05.

Role of the funding source

The funder played no role in the design, conduct, or reporting of the study.

Results

Between April 19, 2017 and July 26, 2019, a total of 55 participants were recruited as planned, of which 28 were randomly assigned to the VRT group (18 men, 10 women) and 27 to the non-VRT group (19 men, 8 women). Three participants in the non-VRT group were excluded from the modified intent-to-treat analysis because they did not complete any follow-up assessment. One did not attend any assessment and did not start the intervention (reason unknown because of nonresponse), and 2 other participants dropped out before the postintervention assessment because of recurrent stroke. Fifty-two participants were included in the modified intention-to-treat analysis (Figure 6.1). Of these 52 participants, 2 discontinued the VRT intervention because of unexpected abdominal surgery and low physical condition, and 1 the non-VRT intervention because of difficulties with transport.

Table 6.1 shows the baseline demographic and clinical characteristics of the participants. Baseline characteristics of the groups were similar, except for time since stroke which was higher in the VRT group (84 vs 66 days). Twenty-four participants in the VRT and 23 participants in the non-VRT group received additional outpatient rehabilitation (n = 39) or physical therapy and occupational therapy in primary care (n = 8) during the intervention period. Medication use and amount of comorbidities were comparable in both groups.

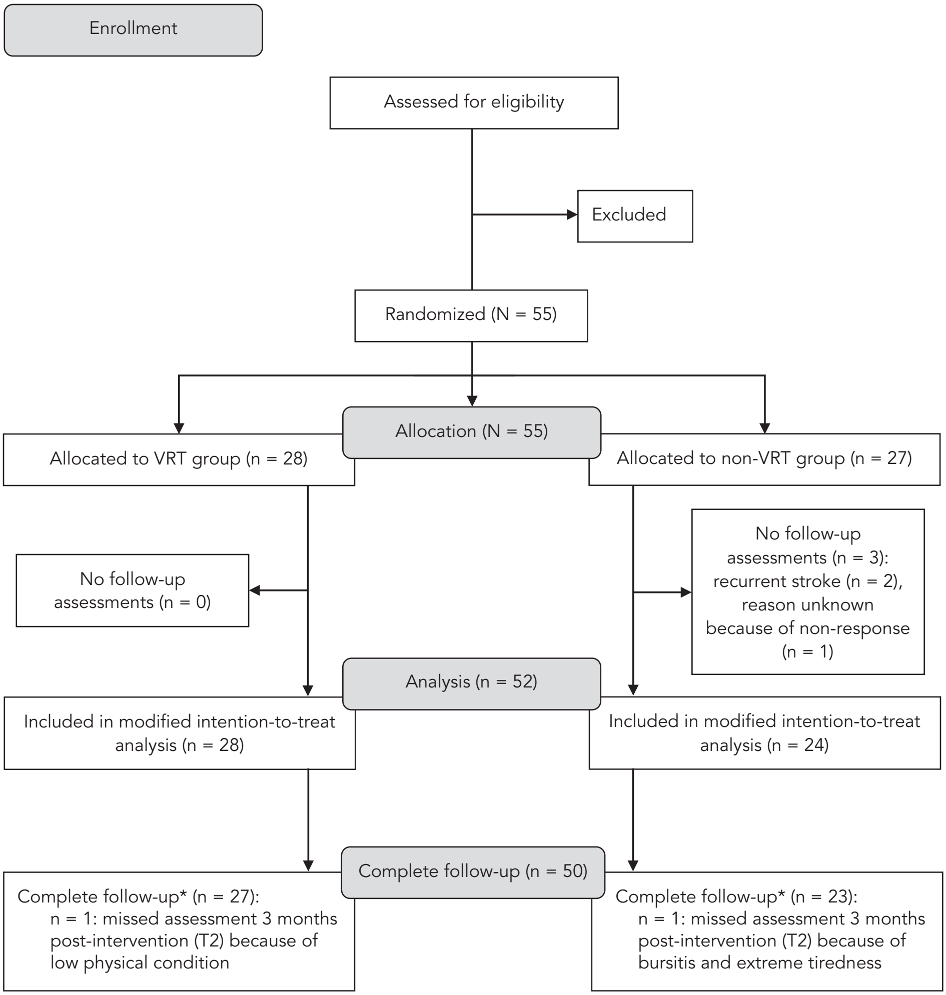

Figure 6.1. Flow diagram of participants.
* Complete follow-up included both the postintervention assessment (T1, 6 wk) and the follow-up assessment (T2, 3 mo postintervention).

Training characteristics and patients' experiences

In total, 89.3% of the participants in the VRT (n = 25) and 91.7% of the participants in the non-VRT group (n = 22) attended 75% or more of the training sessions. Intensity of the training sessions was comparable for both groups as shown with a mean number of steps of 1,305 (463) in the VRT (n = 25) and 1,271 (432) in the non-VRT group (n = 22, *P* = .80). The mean change in the Category-Ratio Scale of Perceived Exertion between start and end of a training session did also not significantly differ between the groups (VRT: 2.91

Table 6.1. Demographic and clinical characteristics of 52 participants in virtual reality gait training (VRT) and non-VRT groups at baseline[a]

Variable	VRT group (n = 28)	Non-VRT group (n = 24)	Overall group (N = 52)
Demographic			
Age at baseline, y[b]	65 (57–70)	61 (53–71)	63 (55–70)
Height, m[b]	1.75 (1.67–1.80)	1.76 (1.67–1.85)	1.75 (1.67–1.80)
Weight, kg[b]	77 (69–88)	75 (68–88)	76 (69–88)
Sex			
Men	18 (64.3)	18 (75.0)	36 (69.2)
Women	10 (35.7)	6 (25.0)	16 (30.8)
Partner			
Yes	23 (82.1)	20 (83.3)	43 (82.7)
No	5 (17.9)	4 (16.7)	9 (17.3)
Living situation			
Alone	5 (17.9)	4 (16.7)	9 (17.3)
With partner	23 (82.1)	19 (79.2)	42 (80.8)
With other family members	0 (0.0)	1 (4.2)	1 (1.9)
Region of residence[c]			
Rural or small town	10 (35.7)	4 (16.7)	14 (26.9)
Small urban	11 (39.3)	17 (70.8)	28 (53.8)
Large urban	7 (25.0)	3 (12.5)	10 (19.2)
Injury-related clinical			
Time since stroke at baseline, d[b]	84 (69–110)	66 (51–103)	76 (54–110)
Type of stroke			
Ischemic	24 (85.7)	20 (83.3)	44 (84.6)
Hemorrhagic	4 (14.3)	4 (16.7)	8 (15.4)
Site of stroke			
Left hemisphere	15 (53.6)	12 (50.0)	27 (51.9)
Right hemisphere	10 (35.7)	10 (41.7)	20 (38.5)
Brainstem	3 (10.7)	2 (8.3)	5 (9.6)
Previous stroke			
Yes	4 (14.3)	2 (8.3)	6 (11.5)
No	24 (85.7)	22 (91.7)	46 (88.5)
Functional Ambulation Category score			
3	3 (10.7)	0 (0.0)	3 (5.8)
4	4 (14.3)	9 (37.5)	13 (25.0)
5	21 (75.0)	15 (62.5)	36 (69.2)
Use of mobility aids outdoors, yes	14 (50.0)	11 (45.8)	25 (48.1)
Single-point cane or crutch	3 (10.7)	5 (20.8)	8 (15.4)
Rollator	8 (28.6)	7 (29.2)	15 (28.8)
4-point stick	2 (7.1)	0 (0.0)	2 (3.8)
Wheelchair	1 (3.6)	1 (4.2)	2 (3.8)
Mobility scooter	2 (7.1)	1 (4.2)	3 (5.8)

Table 6.1 continues on next page.

Table 6.1. *Continued*

Variable	VRT group (n = 28)	Non-VRT group (n = 24)	Overall group (N = 52)
Use of ankle-foot orthoses			
Yes	5 (17.9)	8 (33.3)	13 (25.0)
No	23 (82.1)	16 (66.7)	39 (75.0)
Therapy related			
Duration of gait-related therapies parallel to study intervention, h[b]			
Physical therapy	5.8 (4.0–7.6)	5.5 (4.5–6.0)	5.5 (4.3–6.0)
Occupational therapy	5.5 (2.5–6.0)	4.5 (2.0–5.5)	5.0 (2.4–6.0)
Medical fitness	10.0 (5.0–11.3)	10.0 (2.0–11.3)	10.0 (5.0–11.0)
Psychomotor therapy	3.5 (3.0–10.0)	8.0 (4.5–9.0)	7.0 (3.0–9.8)

[a] Values are reported as number (%) of participants unless stated otherwise. VRT = virtual reality gait training. [b] Reported as median (25th–75th percentiles). [c] Rural or small town = population of less than 10,000; small urban = population of 10,000 to 99,999; large urban = population greater than or equal to 100,000.

[1.15], non-VRT: 3.21 [1.39], *P* = .43). No serious adverse events were reported related to the study interventions. Adverse events reported during the VRT sessions included 3 near falls, dizziness (1 participant), fatigue (3 participants), and muscle stiffness or pain in the legs (4 participants). During the non-VRT sessions, adverse events were 3 near falls, headache, increased clonus in the foot, breathing difficulty (1 participant), dizziness (4 participants), fatigue (4 participants), and pain in the legs or back (3 participants). Some adverse events led to more rest breaks or premature stop of a training session but none of the events led to discontinuation of the intervention.

Results from 16 semi-structured interviews showed that participants experienced the VRT intervention as enjoyable, challenging, and intensive. The most frequently mentioned advantages included the safe training environment and the opportunities to train dual tasks, reaction time, obstacle avoidance, and reactive balance. In addition, participants appreciated the variation in exercises, the game elements, and the high intensity of the training. Experienced disadvantages were awareness of the safety harness, lack of real objects to step over, flash effects on the screen, and technical deficits of the VR system. The majority of the participants stated that VRT positively influenced their walking ability. Most mentioned effects that participants experienced were improved balance ability, improved ability to perform dual tasks, improved ability to take steps and to walk on irregular surfaces, improved reaction time, and a higher walking speed. In addition, some participants mentioned that walking was experienced with more ease and movement automaticity after the VRT intervention. Perceived effects on daily life participation were improved confidence during walking, improved ability to cope with busy environments and stimuli, improved walking endurance, and less difficulty with self-care and household chores. Despite the fact that participants also received other therapies, they felt that VRT definitely contributed to their experienced improvements.

Efficacy outcomes

Table 6.2 shows outcomes at baseline (T0), postintervention (T1), and follow-up (T2) for both groups. Baseline scores of the groups were similar for all outcome measures. Results for all participants together, irrespective of group allocation, showed significant improvements in participation and dynamic balance over time as quantified by the USER-P Restrictions subscale (monthly increase of 2.53 points; 95% CI = 1.52 to 3.54, $P < .001$), the USER-P Frequency subscale (1.05, 95% CI = 0.50 to 1.61, $P < .001$), and the Mini-BESTest score (0.62, 95% CI = 0.33 to 0.91, $P < .001$).

We found no statistically significant difference in USER-P Restrictions score between the VRT and non-VRT group over time. The VRT group increased by 3.11 points per month vs 1.88 points per month in the non-VRT group, resulting in a mean difference of 1.23 (95% CI = -0.76 to 3.23, $P = .22$). Although not significant, the USER-P Restrictions score improved 1.23 points more per month in the VRT group compared with the non-VRT group (Table 6.3). The 2 sensitivity analyses with the interaction between the baseline USER-P Restrictions variable and time and with time since stroke did not lead to substantially different results. Also, the per-protocol analysis, including participants who attended at least 75% of the training sessions (n = 47), yielded comparable results (mean difference = 1.47; 95% CI = -0.60 to 3.53, $P = .158$).

Secondary outcome measures did not reveal any statistically significant differences between the VRT and non-VRT group over time (Table 6.3).

Discussion

This study showed that VRT is a safe and well-received intervention. The positive patient experiences from the semi-structured interviews were not, however, supported by statistically significant between-group differences in quantitative outcome measures. The effect of VRT on participation was statistically not different from non-VRT in community-living people after stroke. Secondary outcome measures, including subjective physical functioning, balance and walking ability, walking activity, and falls efficacy, did also not show significant greater improvements in the VRT group compared to the non-VRT group.

Table 6.2. Outcomes at baseline, postintervention, and at follow-up assessment (N = 52)[a]

Outcome	VRT group Baseline (n = 28)	VRT group Postintervention (n = 28)	VRT group 3-mo follow-up (n = 27)	Non-VRT group Baseline (n = 24)	Non-VRT group Postintervention (n = 24)	Non-VRT group 3-mo follow-up (n = 23)
Primary						
USER-P Restrictions	59.70 (19.04)	71.58 (17.43)	80.76 (15.86)	63.92 (15.06)	75.72 (15.20)	81.62 (15.75)
Secondary						
USER-P Frequency	27.50 (8.19)	32.93 (7.74)	35.82 (7.71)	26.49 (11.22)	32.53 (7.40)	35.56 (9.04)
USER-P Satisfaction	56.76 (16.77)	69.18 (14.74)	72.47 (15.93)	57.47 (18.02)	69.14 (17.18)	72.92 (17.53)
6MWT, m	359.54 (124.26)	408.19 (125.34)[b]	419.22 (129.30)	357.79 (104.13)	428.45 (110.37)[c]	428.66 (103.37)[c]
TUG, s, geometric mean (95% CI)	12.41 (10.52 to 14.64)	10.76 (9.18 to 12.62)	10.37 (8.74 to 12.30)	11.85 (10.41 to 13.49)	9.94 (8.79 to 11.24)[d]	9.88 (8.89 to 10.99)
Mini-BESTest	17.56 (5.88)[e]	19.93 (6.84)[f]	21.67 (6.79)[f]	20.08 (5.07)[g]	22.33 (4.10)[g]	24.42 (2.02)[g]
FES-I	25.57 (9.57)	20.96 (4.75)	20.67 (5.68)	23.54 (5.12)	20.75 (5.56)	20.78 (6.16)
FSS	5.17 (1.41)	4.40 (1.62)	3.97 (1.65)	4.75 (1.56)	4.46 (1.17)	4.26 (1.66)
SIS-16	80.22 (12.31)	87.09 (9.46)	89.03 (11.13)	79.41 (9.71)	91.35 (7.52)	90.80 (7.86)
HADS anxiety	4.36 (3.70)	3.50 (3.18)	3.33 (3.46)	4.00 (2.80)	3.33 (2.68)	2.39 (2.50)
HADS depression	4.39 (3.35)	4.04 (3.49)	3.56 (3.51)	3.54 (2.28)	2.83 (2.16)	2.65 (2.50)
SS-QOL	3.87 (0.71)[h]	4.21 (0.56)[i]	4.36 (0.52)[j]	3.94 (0.56)	4.36 (0.50)	4.35 (0.55)
No. of steps/d	3643 (1859)[k]	3761 (1995)[c]	3870 (2417)[i]	4855 (2967)[c]	4588 (2745)[h]	4844 (2587)[l]
Walking duration, min/d	39.38 (19.46)[k]	39.70 (19.95)[c]	41.71 (25.59)[i]	52.50 (29.37)[c]	47.88 (24.34)[h]	51.12 (22.80)[l]
Step frequency, steps/min	92.52 (9.25)[k]	93.99 (10.52)[c]	92.78 (11.16)[i]	91.29 (10.80)[c]	94.38 (13.69)[h]	92.61 (13.92)[l]
Accelerometer wearing time, h	17.75 (3.60)[k]	17.94 (3.78)[c]	17.77 (3.89)[i]	18.61 (2.56)[c]	19.09 (3.21)[h]	18.83 (2.86)[l]

[a] Values are reported as mean (SD) unless stated otherwise. FES-I = Falls Efficacy Scale International, scored from 16 to 64; FSS = Fatigue Severity Scale, scored from 1 to 7; HADS = Hospital Anxiety and Depression Scale, scored from 0 to 21; Mini-BESTest = Mini Balance Evaluation Systems Test, scored from 0 to 28; 6MWT = 6-minute walk test; SIS-16 = Stroke Impact Scale-16, scored from 0 to 100; SS-QOL = Stroke Specific Quality of Life Scale, scored from 1 to 5; TUG = Timed Up & Go test; USER-P = Utrecht Scale for Evaluation of Rehabilitation-Participation, scored from 0 to 100; VRT = virtual reality gait training.
[b] n = 27. [c] n = 22. [d] n = 23. [e] n = 16. [f] n = 15. [g] n = 12. [h] n = 21. [i] n = 24. [j] n = 26. [k] n = 25. [l] n = 19.

Table 6.3. Monthly changes and *P* values per outcome (modified intention-to-treat analysis)[a]

Outcome	Monthly change in VRT group (95% CI) (n = 28)	Monthly change in non-VRT group (95% CI) (n = 24)	Mean slope difference (95% CI)	*P*
Primary				
USER-P Restrictions	3.11 (1.74 to 4.49)	1.88 (0.44 to 3.33)	1.23 (-0.76 to 3.23)	.221
Secondary				
USER-P Frequency	1.05 (0.28 to 1.82)	1.06 (0.25 to 1.86)	-0.01 (-1.12 to 1.11)	.992
USER-P Satisfaction	1.10 (-0.57 to 2.78)	1.14 (-0.62 to 2.90)	-0.04 (-2.46 to 2.39)	.976
6MWT, m	3.65 (0.28 to 7.01)[b]	0.00 (-3.60 to 3.61)[c]	3.64 (-1.29 to 8.57)	.144
TUG log transformed	-0.01 (-0.02 to 0.01)	-0.00 (-0.02 to 0.01)[d]	-0.01 (-0.03 to 0.01)	.453
Mini-BESTest	0.57 (0.19 to 0.96)[e]	0.68 (0.24 to 1.11)[f]	-0.10 (-0.69 to 0.48)	.721
FES-I	-0.06 (-0.61 to 0.49)	0.08 (-0.50 to 0.65)	-0.13 (-0.93 to 0.67)	.740
FSS	-0.13 (-0.30 to 0.04)	-0.06 (-.23 to 0.12)	-0.08 (-0.33 to 0.17)	.523
SIS-16	0.66 (-0.12 to 1.45)	-0.23 (-1.05 to 0.60)	0.89 (-0.25 to 2.03)	.123
HADS anxiety	-0.02 (-0.26 to 0.23)	-0.27 (-0.53 to -0.02)	0.26 (-0.10 to 0.61)	.148
HADS depression	-0.15 (-0.45 to 0.15)	-0.02 (-0.34 to 0.29)	-0.13 (-0.57 to 0.31)	.563
SS-QOL	0.04 (-0.01 to 0.09)[g]	-0.00 (-0.05 to 0.04)	0.04 (-0.03 to 0.11)	.204
No. of steps/d	133.84 (-137.22 to 404.90)[d]	122.26 (-157.12 to 401.64)[h]	11.58 (-377.60 to 400.76)	.952
Walking duration, min/d	1.69 (-0.90 to 4.27)[d]	1.26 (-1.41 to 3.93)[h]	0.43 (-3.28 to 4.14)	.816
Step frequency, steps/min	-0.42 (-1.94 to 1.11)[d]	-0.37 (-1.94 to 1.20)[h]	-0.05 (-2.24 to 2.14)	.964
Accelerometer wearing time, h	0.05 (-0.22 to 0.31)[d]	-0.16 (-0.44 to 0.11)[h]	0.21 (-0.17 to 0.60)	.265

[a] FES-I = Falls Efficacy Scale International, scored from 16 to 64; FSS = Fatigue Severity Scale, scored from 1 to 7; HADS = Hospital Anxiety and Depression Scale, scored from 0 to 21; Mini-BESTest = Mini Balance Evaluation Systems Test, scored from 0 to 28; 6MWT = 6-minute walk test; SIS-16 = Stroke Impact Scale-16, scored from 0 to 100; SS-QOL = Stroke Specific Quality of Life Scale, scored from 1 to 5; TUG = Timed Up & Go test; USER-P = Utrecht Scale for Evaluation of Rehabilitation-Participation, scored from 0 to 100; VRT = virtual reality gait training. [b] n = 27. [c] n = 22. [d] n = 23. [e] n = 15. [f] n = 12. [g] n = 24. [h] n = 21.

To our knowledge, this is the first study that investigated the effect of a treadmill-based VRT on the level of participation in people after stroke. Participation improved both in the VRT and non-VRT groups. The VRT group improved 3.11 points per month on the USER-P Restrictions subscale vs 1.88 points per month in the non-VRT group. A large study about the course of quality of life and participation after stroke found a mean increase of 5.04 points on the USER-P Restrictions subscale between 2 and 6 months after stroke.[33] This represents a mean increase of 1.26 points per month. Compared with this previous study, the improvement in participation in the VRT group was more than twice as great, while improvement in the non-VRT group was more comparable. From a noninferiority perspective, the lower confidence bound of the mean difference between the VRT and non-VRT group is likely irrelevant and may indicate that the VRT intervention is possibly noninferior to the non-VRT intervention.

There are several possible explanations for the lack of significant between-group differences. First, the potential difference in participation might be influenced by spontaneous neurologic recovery. Previous studies showed that spontaneous recovery is an important contributor to overall functional and neurologic recovery and mainly takes place within the first 3 months after stroke.[34,35] Participants in the VRT group had, on average, a longer period since their stroke and may therefore be less prone to spontaneous recovery compared to the non-VRT group. However, the sensitivity analysis showed no confounding effect of time since stroke. Second, the contrast between the VRT and non-VRT intervention might have been too small to find significant differences.[36,37] Although the training environment clearly differed, both interventions were intended to provide functional, personalized, and progressive training. A third explanation may be that we did not use the possibility to personalize the VRT intervention optimally. We did not specifically measure underlying walking impairments at the functional level nor did we assess achievement of patient-specific rehabilitation goals related to participation restrictions. There is some evidence that VRT focusing on specific aspects of walking function, like reactive balance, can result in a more stable gait.[38] Measurement of underlying walking impairments and individual rehabilitation goals would have given the opportunity to make the training even more personalized and could have given more insight into which patients are most likely to benefit from VRT.

Although effects were not significantly different, participation improved more in the VRT group. VRT was provided using an immersive and interactive VR system with motion-capture technology that was designed for rehabilitation. This specific VR intervention was thought to promote important principles of motor learning by providing high-intensity training with task variation and real-time feedback.[13,39] These principles were confirmed in semi-structured interviews with participants after stroke. According to the participants, most advantageous training characteristics were the safe training environment, the high intensity, and the opportunities to train dual tasks, reaction time, and balance perturbations during walking. The safe training environment, together with the adjustable difficulty levels, allowed therapists to optimally challenge participants. In this way, VRT gave people after stroke more insight in their possibilities and limitations and improved confidence in their walking abilities. In addition, dual tasks and reactive balance could be easily and safely trained. The ability to practice tasks that are unsafe to practice in the real world is one of the major benefits of VR.[15] Furthermore, participants liked the game elements and variation in VR environments, which made the training more enjoyable and promoted implicit learning. Implicit learning is thought to improve movement automaticity and dual-task performance.[40] The experiences of enjoyment and immersion are in line with a study by Cano Porras et al.[41] that investigated clinical experiences with VRT in a rehabilitation population. They found that the most positive feedback obtained from patients included topics such as enjoyment, immersion, clarity, easiness of the VR system, and lack of discomfort or adverse events.

In addition, results from the semi-structured interviews gave more insight into patients' perception of how VRT influenced their walking ability and participation. Participants suggested that besides walking ability, VRT promoted improvements in cognitive function (reacting quickly and dealing with busy environments and stimuli), confidence during walking, and movement automaticity. A previous study by Fishbein et al.[42] found higher self-confidence when walking in the community after dual-task treadmill training using VR, suggesting that VRT can positively target self-confidence. Regarding cognitive function, systematic reviews showed the potential of VR for improving cognitive function in people after stroke, but until now results have yielded inconclusive evidence about the effectiveness of VR training on improving cognition.[43,44] The mentioned improvements in this domain suggest that proper measures of cognition should be included in future studies, even in a seemingly well-functioning population.

The present study had some limitations. The first limitation was a large variability in experienced participation restrictions on the USER-P at baseline. This suggests that the sample size might have been too small to determine between-group differences in the mixed-model analyses. The positive trend for greater improvement of participation in the VRT group suggests that with a higher sample size significant between-group differences might have been found. A second limitation was that the same therapists performed both the VRT and non-VRT intervention. Because the therapists knew the content and training possibilities of both interventions, they may have had more difficulty completely separating the content of both interventions and concealing whether they preferred one intervention to the other.

Conclusion

The effect of VRT was not statistically different from the effect of non-VRT on participation in community-living people after stroke. Both interventions, however, contribute to improvement in participation and can be applied in stroke rehabilitation taking into account the individual rehabilitation goals or patient preference. Although not statistically different, participation was shown to improve more in the VRT group. VRT was positively rated by people after stroke and was shown to be a well-tolerated and clinically practicable intervention, including appropriate levels of adherence and limited adverse events. These results suggest that treadmill-based VRT can be a valuable addition to stroke rehabilitation. Future studies should further explore the cost-effectiveness and added value of VRT for specific rehabilitation goals.

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Chapter 7

Feasibility and effectiveness of virtual reality training on balance and gait recovery early after stroke: a pilot study

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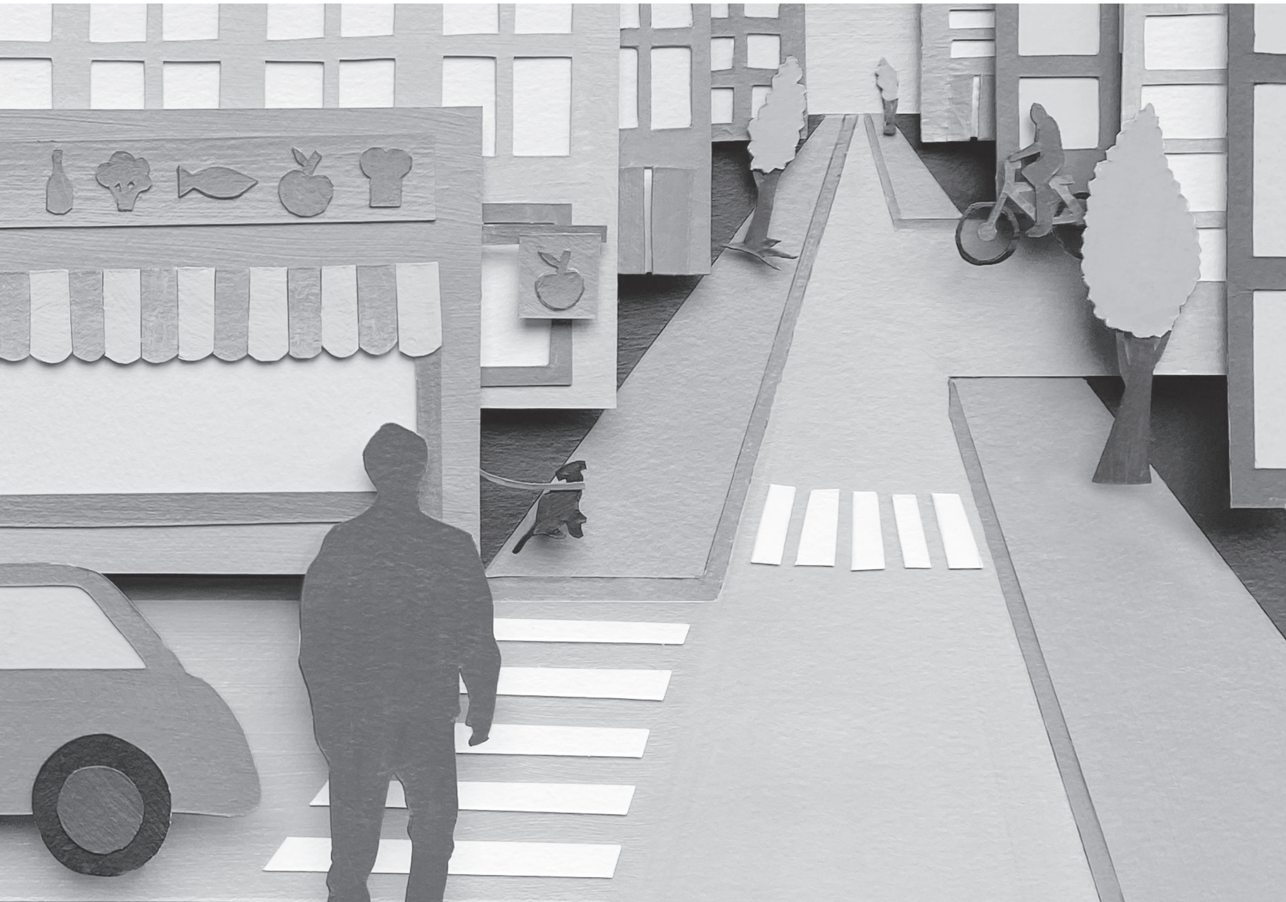

Abstract

Objective: To investigate the feasibility and effectiveness of virtual reality training for improving balance and/or gait during inpatient rehabilitation of patients within 12 weeks after stroke.

Methods: Sixteen patients within 12 weeks after stroke and dependent gait as categorised with a Functional Ambulation Category score of 2 or 3 were included in this longitudinal pilot study. Participants received 8 30-minute sessions of virtual reality training during 4 weeks as part of the regular inpatient rehabilitation program. Feasibility was assessed using compliance with the training, adverse events, experiences of the participants and the physiotherapists; and effectiveness with the Berg Balance Scale, centre of pressure velocity, Functional Ambulation Category and 10-meter walk test.

Results: Participants positively evaluated the intervention and enjoyed the training sessions. Also, physiotherapists observed the training as feasible and beneficial for improving balance or gait. Compliance with the training was 88% and no serious adverse events occurred. The Berg Balance Scale, anterior-posterior centre of pressure velocity, Functional Ambulation Category and 10-meter walk test showed significant improvement after 4 weeks of training ($P < .05$).

Conclusion: This study demonstrates that virtual reality training in patients early after stroke is feasible and may be effective in improving balance and/or gait ability.

Introduction

Balance and gait recovery are considered as key aspects in stroke rehabilitation.[1-3] To date, physiotherapy and occupational therapy focus on high intensity, repetitive and task-specific practice, which are important principles of motor learning, to elicit improvements in the early rehabilitation phase.[1,4,5] In addition to high intensity, repetitive and task-specific training, variability in practice is important for motor learning. Also, cognitive involvement, functional relevance and the presence of feedback enhance learning.[5] In current physiotherapy or occupational therapy it is difficult to meet all of these above-mentioned training characteristics as therapy may be tedious and resource-intensive.[6-9] In addition, the frequency and intensity of current therapies have been indicated as insufficient to achieve maximum recovery in the early phase of rehabilitation.[8,10] There is need for engaging, motivating and varied therapy that achieves maximal recovery.[11]

In recent years, virtual reality (VR) is introduced in the field of balance and gait rehabilitation after stroke.[12] Since VR training is characterised by individualised, high intensity training in a variety of virtual environments with a high amount of real-time feedback[13-15] it might be valuable in stroke rehabilitation. This is confirmed by recent studies.[12,15-18] However, almost all studies on the effect of VR on balance and/or gait ability were conducted in the chronic phase after brain injury.[9,12,16,17,19-23] Because of the potential relevant characteristics of VR for motor learning and neuroplasticity,[14] VR may be of even more added value during the earlier rehabilitation phase. Three studies[24-26] that investigated the effect of VR in this time period after stroke indicated a positive effect of commercially available VR systems (Nintendo Wii Fit or IREX) on balance and/or gait recovery. However, the results of these studies cannot be generalised to the whole population of patients with stroke because included participants had a relatively high functional level regarding balance and gait at the start of the VR intervention. A lack of studies including patients with lower functional status after stroke might be caused by the idea that the feasibility of using advanced VR technology may be restricted because of visual, cognitive and/or endurance impairments. These impairments are more often present in the more impaired patients early after stroke.[27-29] Because of the expected promising effects of VR training for the recovery of balance and gait in patients with low functional level early after stroke, it is important to investigate the feasibility of this innovative form of training and to determine whether the above-mentioned impairments interfere with the use of VR training early after stroke.

Therefore, the aim of the present study was to investigate the feasibility and effectiveness of VR training for improving balance and/or gait during the inpatient rehabilitation of patients with stroke. The specific research questions were:

- What is the feasibility, from the perspective of patients and physiotherapists, of VR training aimed to improve balance and gait ability?
- What is the effectiveness of VR training, embedded within an inpatient rehabilitation program, on balance and gait ability in people with impaired balance and dependent gait within 12 weeks after stroke?

Methods

Study design

This longitudinal pilot study involved 2 assessments, one before and one after a 4-week VR training intervention, performed within the inpatient rehabilitation program of patients with stroke at Revant Rehabilitation Centres, Breda, the Netherlands.

Participants

Patients with stroke who were following an inpatient rehabilitation program with a treatment goal to improve balance and/or gait. They received balance and/or gait training with VR as part of their regular rehabilitation program. Besides the VR training, the regular rehabilitation program could include therapy given by a physiotherapist, occupational therapist, speech therapist, psychomotor therapist, psychologist and social worker, depending on the goals of the patient with stroke. Inclusion criteria consisted of hemiplegia resulting from a stroke, a time since stroke of less than 12 weeks, a Berg Balance Scale (BBS) score of at least 20, i.e., the minimum level of balance deemed safe for balance interventions,[30] and a Functional Ambulation Category (FAC) score of 2 or 3 out of 5.[31] Exclusion criteria were patients with stroke with terminal diseases, lower-limb impairments not related to stroke, severe cognitive impairments, severe types of expressive or receptive aphasia, visual impairments, age over 80 years and experiencing epileptic seizures. All participants provided written consent to use data obtained during the rehabilitation program for research, and anonymity was assured. The study procedures follow the principles of the Declaration of Helsinki.

VR training intervention

The intervention consisted of balance and gait training using the recently developed treadmill based Gait Real-time Analysis Interactive Lab (GRAIL, Motekforce Link, Amsterdam, The Netherlands). The GRAIL comprises a dual-belt treadmill with force platform, a motion-capture system (Vicon, Oxford, UK) and speed-matched virtual environments projected on a 180° semi-cylindrical screen (Figure 7.1).[32]

Figure 7.1. Illustration of a patient performing exercises on the Gait Real-time Analysis Interactive Lab (GRAIL).

The VR training program consisted of 2 30-minute sessions of exercises on the GRAIL per week for 4 weeks. Participants wore a safety harness that was attached to an overhead suspension system but did not provide weight support. A predefined protocol of VR applications was used during the training sessions of the 4-week intervention. This predefined protocol was progressive starting with static balance exercises focussing on shifting weight, followed by training dynamic balance and, if possible, training gait ability. Each application could be individualised to the patient's ability in terms of difficulty, for example by adjusting duration, speed, the amount of simultaneous tasks and the amount of real-time visual, auditory and/or tactile feedback during the exercises. A physiotherapist, who is certified for working with the GRAIL, decided the progression of the training sessions. The physiotherapist regulated the intensity of the exercises, judged when a new and more difficult application could be used and ensured that safety and quality of movement was maintained during the training.

Outcome measures

Feasibility of the VR training intervention

The feasibility of VR training was evaluated through both structured patient interviews and structured questionnaires completed by the physiotherapists. Patients were asked about their experiences in the virtual training environment, the presence of potential side effects and their view on the design and effects of the VR intervention. These interviews were conducted after the last training session. The questions regarding the patients' experiences in the virtual environment included perception and sense of presence in the virtual environment and were partly translated and adapted from the ITC-Sence of Presence Inventory questionnaire of Lessiter et al.[33] The statements which were covered in the interviews in random order, are displayed in Tables 7.2 and 7.3.

Besides the patient interviews, feasibility was evaluated by the physiotherapists using a structured questionnaire. This questionnaire comprised the structure of the training intervention, practicality and added value of the training intervention. Statements consulting these feasibility aspects were scored from 1 (strongly disagree) to 5 (strongly agree). Also, adverse events, e.g., falls, near-falls or epileptic seizures, and compliance with the VR training, i.e., number of sessions completed, were recorded.

Effectiveness of the VR training intervention

The effectiveness of the VR training sessions was determined by measures of static and dynamic balance and gait ability. One researcher who was experienced with the tests conducted all the measurements.

Centre of pressure (CoP) velocity was assessed using the force plates underneath each belt of the treadmill. CoP velocity measurements are commonly used in studies focussing on balance in the stroke population.[34-36] Participants were asked to stand on the treadmill in most stable standing position with their head straight. Force plate data was recorded twice over 10 seconds with an analogue frequency of 1,000 samples per second. Data was down sampled to 100 Hz and then filtered using a low pass fourth order Butterworth filter with a cut-off frequency of 5 Hz. CoP velocity was measured in medio-lateral (CoPX) and anterior-posterior direction (CoPZ).[37,38]

The BBS was used to measure dynamic balance. This scale contains 14 actions from daily life to evaluate a person's ability to maintain positions or movements of increasing difficulty as the base of support is decreased.[39,40] The items of the BBS were performed without the use of walking aids, but the use of an ankle-foot orthosis, bandage or sling was permitted.

The FAC score measured functional ambulation status and distinguishes 6 levels (0−5) of gait ability on the basis of the amount of physical support required.[31] This scale has shown to be a reliable and valid measurement that is responsive to change over time.[41] Besides the FAC, the 10-meter walk test was included to measure gait ability. Participants were asked to walk 3 times 10 meters at their own comfortable speed as described by Salbach et al.[42] and the time needed was measured with a digital stopwatch. The mean of 3 measurements was considered as the comfortable walking speed. Participants that were unable to walk 10 meters without physical assistance (FAC 2) scored 0 m/s.

All assessments were performed before the start of the intervention and after the 4-week intervention.

Data analysis

Given the relatively small sample size of the present study nonparametric analyses were used. Descriptive data were reported as median with interquartile range (IQR = 1st, 3rd quartile). The Wilcoxon's signed-rank test was performed to determine changes between baseline and post-intervention values. Results were considered significant when *P* values were < .05. Participants who completed less than 75% of the training sessions were excluded from the data-analysis (patient interviews and balance and gait measures). Extreme outliers, defined as values below 1st quartile -3(IQR) or above 3rd quartile +3(IQR), were also excluded from the analysis.[43] The questionnaires regarding feasibility from the perspective of patients or physiotherapists consisted of 5 scores per statement (strongly disagree, disagree, neutral, agree, strongly agree). Results were analysed by combining the scores for strongly (dis) agree and (dis)agree resulting in 3 scores (disagree, neutral, agree) and were reported as percentage per score. All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY).

Results

Participant characteristics

Sixteen patients with stroke participated in the study (12 males and 4 females) with a median age of 61 (IQR 56, 71) years. Table 7.1 shows the demographic data and baseline clinical characteristics of the participants. Median time since stroke onset was 42 (25, 65) days and median USER (Utrecht Scale for Evaluation of Clinical Rehabilitation)[44] mobility score was 9 (7, 12) at admission for inpatient rehabilitation.

Table 7.1. Demographic and baseline clinical characteristics of the participants (N = 16)

Characteristics	Median (1st, 3rd quartile)
Age (y)	61 (56, 71)
Gender (male/female)	12/4
Type of stroke	
Haemorrhage	3
Infarction	13
Side of stroke (left/right)	5/11
Time since stroke onset (d)	42 (25, 65)
FAC score (2/3)	9/7
Admission USER	
Mobility	9 (7, 12)
Self-care	19 (14, 23)
Cognitive functioning	42 (38, 48)
Pain	0 (0, 20)
Fatigue	50 (30, 60)
Mood	40 (0, 170)

FAC = Functional Ambulation Categories; USER = Utrecht Scale for Evaluation of Clinical Rehabilitation.

Feasibility of the VR training intervention

The patients with stroke answered positively regarding their experiences in the virtual environment (Table 7.2). 93% of the participants enjoyed training in the virtual environment and were motivated for the training sessions. In addition, the participants answered that the training sessions simulated realistic movements (86%). They also felt engaged by the virtual environment and indicated that they could properly judge, based on the given feedback, whether exercises were performed correctly (86%). Participants experienced no major side effects during the training intervention, except for physical fatigue at the end of a training session which was experienced by 64% of the participants (Table 7.2).

The majority of the participants were positive about the 4-week training intervention (Table 7.3). The participants were satisfied with the frequency of 2 times per week and the duration of 30 minutes VR training; however 86% of the participants would have liked to train longer than 4 weeks. Also, 93% of the patients with stroke felt that their balance improved after 4 weeks of training and 86% thought that the VR training positively influenced daily functioning. According to all participants, the VR training is of added value to the conventional rehabilitation program. Furthermore, 50% of the patients with stroke had the impression that they performed more activities in daily life because of the virtual training intervention.

Table 7.2. Results of the patient interviews regarding the experiences in the virtual training environment and the experienced potential side effects (n = 14)

Statement	Disagree (%)	Neutral (%)	Agree (%)
I would have liked the GRAIL training sessions to be longer*	50	0	50
I felt entirely surrounded by the displayed virtual environment of the GRAIL*	7.1	7.1	85.7
I vividly remember some parts of the GRAIL training sessions*	0	0	100
I felt involved in the virtual environment of the GRAIL*	0	21.4	78.6
I paid more attention to the virtual environment than I did to my own thoughts*	7.1	0	92.9
The content of the GRAIL training sessions appealed to me*	7.1	0	92.9
I could judge well whether I performed the exercises during the GRAIL training sessions correctly	0	14.3	85.7
The GRAIL training sessions stimulated me to move during the sessions	0	7.1	92.9
My movements during the GRAIL training sessions felt realistic*	7.1	7.1	85.7
I enjoyed the GRAIL training sessions*	0	7.1	92.9
I am motivated to attend the GRAIL training sessions	0	7.1	92.9
Experienced side effects			
I felt disorientated during the GRAIL training sessions*	100	0	0
I felt dizzy during the GRAIL training sessions*	92.9	7.1	0
I felt nauseous during the GRAIL training sessions*	100	0	0
I had a headache because of the GRAIL training sessions*	100	0	0
I felt physically tired at the end of the GRAIL training sessions*	28.6	7.1	64.3
The environment on the screen was visually well tolerated	7.1	0	92.9

* Based on the ITC-Sence of Presence Inventory questionnaire of Lessiter et al.[33]

Table 7.3. Results of the patient interviews regarding the design and effects of the intervention (n = 14)

Statement	Disagree (%)	Neutral (%)	Agree (%)
The schedule and duration of the GRAIL training sessions were good	7.1	7.1	85.7
The training with the GRAIL helped me to achieve (part of) my rehabilitation aims	0	7.1	92.9
Because of the training sessions with the GRAIL I perform more activities in daily life	7.1	42.9	50
My balance was improved after the GRAIL training sessions	0	7.1	92.9
I would like to continue training on the GRAIL for a longer time period	14.3	0	85.7
Things I learned during the GRAIL training sessions have an added value for my daily functioning	0	14.3	85.7
The GRAIL training sessions are of added value to my other therapies	0	0	100

Table 7.4. Results of the structured questionnaires completed by the physiotherapists

Statement	Disagree (%)	Neutral (%)	Agree (%)
Training on the GRAIL has added value for balance recovery in inpatients	0	0	100
The frequency and duration of the GRAIL training sessions are good	0	50	50
A progression of applications focusing on static balance to dynamic balance and applications focusing on walking is good	0	0	100
The GRAIL training sessions can be properly guided	0	0	100
One clinician for the GRAIL training sessions is enough	0	50	50
The stairs in front of the GRAIL caused problems during the training sessions	50	0	50
A lot of manual support is necessary during the GRAIL training sessions	100	0	0
Training on the GRAIL has added value in daily life of the inpatients	0	0	100
The GRAIL training sessions are a valuable addition to the other therapies of inpatients	0	0	100
The GRAIL training sessions for inpatients are feasible	0	0	100

From the perspective of the physiotherapists the VR training intervention was evaluated positively and observed as feasible (Table 7.4). During the VR training sessions, the majority of the participants needed short rest periods because of endurance limitations. In some cases, extra manual support was needed during the training sessions, to provoke correct movement while performing exercises, to help participants with climbing the steps to get on the treadmill and to get participants seated on a stool that was temporarily placed on the treadmill during a short break. With little manual support of the physiotherapists all participants were able to climb the steps to get on the treadmill. The physiotherapists did not report adverse events including falls or epileptic seizures during the course of the intervention, although 3 near-falls occurred for 2 participants. These near-falls were due to tripping of the paretic leg. Because the participants were wearing the safety harness and immediately grabbed the handrails, no actual fall or injury occurred. Furthermore, compliance with the VR training sessions was 88%, with 113 of the 128 training sessions completed. Fifteen training sessions were missed because of illness of the patient or physiotherapist (n = 2), injuries of the patient not related to VR training (n = 2), early discharge (n = 6), technical issues with the GRAIL (n = 1) or unknown reasons (n = 4). Two participants did not complete 75% of the training sessions and were therefore not included in the analysis. One participant was discharged 2 weeks earlier than expected and the other participant missed 3 training sessions because of unexpected absence of the participant or the physiotherapist. In total 14 participants were included in the final analysis. Overall, the physiotherapists agreed on the benefit of the VR training intervention for balance recovery as part of the rehabilitation program. In their opinion, the benefit of the challenging training in a safe VR environment is particularly expressed in more confidence during daily life activities. Lastly, the physiotherapists advised to extend the training period because they expected that patients with stroke would still benefit VR training after 4 weeks.

Effectiveness of the VR training intervention

Table 7.5 presents the median (1st, 3rd quartile) of the balance and gait measures before intervention and after the 4 weeks of VR training. Dynamic balance significantly improved represented by an increase of 14 (13, 17) points of the median BBS scores. In addition, static balance measured with CoPZ velocity was significantly improved by a median decrease of 0.56 (-1.34, -0.02) mm/s, although CoPX velocity did not significantly change over time. For the CoP velocity measurements one extreme outlier was observed, which was excluded in the analysis. Participants significantly improved functional ambulation with 1 point on the FAC. Twelve participants used the same walking aid during the FAC measurements before and after the training intervention. One participant changed a 4-point stick into a cane and one person walked without a walking aid at the end of the intervention instead of using a walking frame. Furthermore, walking speed improved significantly with a median of 0.20 (0.03, 0.46) m/s. The use of a walking aid during the 10-meter walk test before and after intervention was the same for majority of the participants, except for 2 participants who walked with a walking frame at start of the intervention and without a walking aid at the end of the 4-week intervention period.

Table 7.5. Balance and gait measures before and after the intervention (n = 14)

Measure	Before intervention	After intervention	Change in score	*P* value
BBS	32.00 (26.75, 36.50)	45.50 (40.25, 52.00)	14.00 (12.75, 17.25)	.001*
CoPX velocity (mm/s)[a]	1.83 (1.32, 3.50)	1.45 (0.68, 2.44)	-0.53 (-1.56, -0.36)	.084
CoPZ velocity (mm/s)[a]	2.39 (1.59, 3.75)	1.81 (1.42, 2.56)	-0.56 (-1.34, -0.02)	.023*
FAC	2 (2.0, 3.0)	3 (3.0, 4.0)	1 (0.8, 1.0)	.002*
10MWT (m/s)[b]	0.00 (0.00, 0.32)	0.46 (0.19, 0.81)	0.20 (0.03, 0.46)	.003*

All measures are presented as median (1st, 3rd quartile). BBS = Berg Balance Scale; FAC = Functional Ambulation Categories; 10MWT = 10-meter walk test; CoPX = Centre of pressure in medio-lateral direction; CoPZ = Centre of pressure in anterior-posterior direction.
* *P* value < .05 according to the Wilcoxon signed rank test.
[a] n = 12. [b] n = 13.

Discussion

This pilot study demonstrates that VR training on the GRAIL as part of the regular inpatient rehabilitation program is feasible in patients within 12 weeks after stroke. Also, our results indicate that balance and gait ability improved after 4 weeks of VR training. VR training is a potential powerful intervention for motor learning after stroke, therefore it is important to be sure that it is safe and feasible even in patients early after stroke, as shown in this study.

The patients with stroke that participated in this study were all inpatients within 12 weeks after stroke. A substantial part of these patients had severe limitations following stroke. This can be confirmed by the median values of the USER mobility and USER self-care at admission in the rehabilitation centre, which were 9 and 19 out of 35 points, respectively. These scores represent relatively poor functional status, as compared to a recent large study, including 1,310 inpatients after stroke, in which a mean physical independence (mobility plus self-care) score of 42.9 was reported.[45]

The positive findings for enjoyment and motivation, and the high compliance, indicate that the severely impaired participants could enjoy a challenging intervention like the VR training. The results for enjoyment and motivation in this study are consistent with previous studies regarding feasibility of VR in patients early after brain injury for upper[46,47] and lower extremity recovery.[48] The high level of enjoyment and motivation may have been reached because of a good balance between the difficulty of the training and the abilities of the patient with stroke.[46] Exercises on the GRAIL can easily be adjusted to the abilities and demands of the patient with stroke by changing the type of exercise, difficulty level, amount of feedback and the amount of tasks within a game. These adjustable settings provide the therapists the opportunity to search for the individual limits during the training, which is of importance for effective rehabilitation after stroke. Physical fatigue at the end of a training session was reported in 64% of the participants. The presence of fatigue indicates that participants indeed trained on high intensity with the proper amount of physical demand. This suggests that an appropriate training level could be realised for the severely impaired patients after stroke. The physiotherapists reported that in some cases extra support was needed for the participant to climb the steps to get on the treadmill, to provide manual support during the exercises or to let participants rest on a stool on the treadmill. In these cases the training sessions were more labour-intensive for the physiotherapist.

When focussing on the experienced effects of the training, both the participants and physiotherapists evaluated the training intervention as beneficial for improving balance or gait. The patients with stroke reported that balance improved after the intervention and that they experienced the VR training of added value for improving their daily functioning.

Although the majority of the participants answered that the VR training provokes improvement on functional level, 50% of the patients with stroke could not confirm that the training intervention resulted in improvements on activity and participation level.

The objective results of the present study confirm the subjective results of the VR training intervention reported by the patients with stroke. After the 4 weeks of training on the GRAIL dynamic balance, walking speed and functional ambulation improved. Median BBS and median comfortable walking speed improved with 14 points and 0.20 m/s respectively, which is substantially more than the smallest detectable change of 5.8 points for the BBS[30] and 0.15 m/s for comfortable walking speed.[49] Merely 2 of the 13 participants in this study increased less than the minimally detectable change in walking speed. Other, frequently used, physiotherapy interventions for improving balance or gait, such as circuit training, functional strength training and body weight supported treadmill training, showed comparable increases for gait speed in patients within 3 months after stroke.[50-52] It is important to notice that the VR training intervention, just like the interventions described above, was part of the regular rehabilitation program. Spontaneous recovery may have occurred in the first months after stroke.[53]

To investigate the effect of the VR training intervention on the recovery of balance and gait in patients with subacute stroke more thoroughly, the VR training needs to be compared with a dose-matched control intervention using a randomised controlled trial with a large sample size. Since the present study concerned a pilot study in which the main aim was to study the feasibility, the sample was relatively small. When conducting a controlled trial it might be considered to extend the training period beyond 4 weeks since participants indicated that they prefer a longer training period, and physiotherapists also suggest a longer training period to achieve a maximal learning effect for motor recovery. Also, it would be interesting to measure the effect of VR training on daily activity and participation level because participants in this study could not confirm whether the improvement of performance on functional level was also present on daily activity and participation level. With the use of outcome measures on participation level it can be investigated whether potential improvements induced by VR training translate to real life. In the available literature the effect of virtual training on daily life activity and participation level is not yet established.[15]

Overall our results show that even for the severely impaired patients with stroke, an appropriate training level on the GRAIL could be realised, which was experienced as motivating and challenging and did not lead to lower levels of participation. Potential visual, cognitive and endurance impairments often seen in more impaired patients after stroke did not interfere with the use of VR technology for the recovery of balance and gait in patients with stroke. In addition, our results indicate that substantial effects on dynamic balance and gait ability can be realised after a 4-week integrated VR training intervention. These results are a valuable contribution for both further research and clinical practice.

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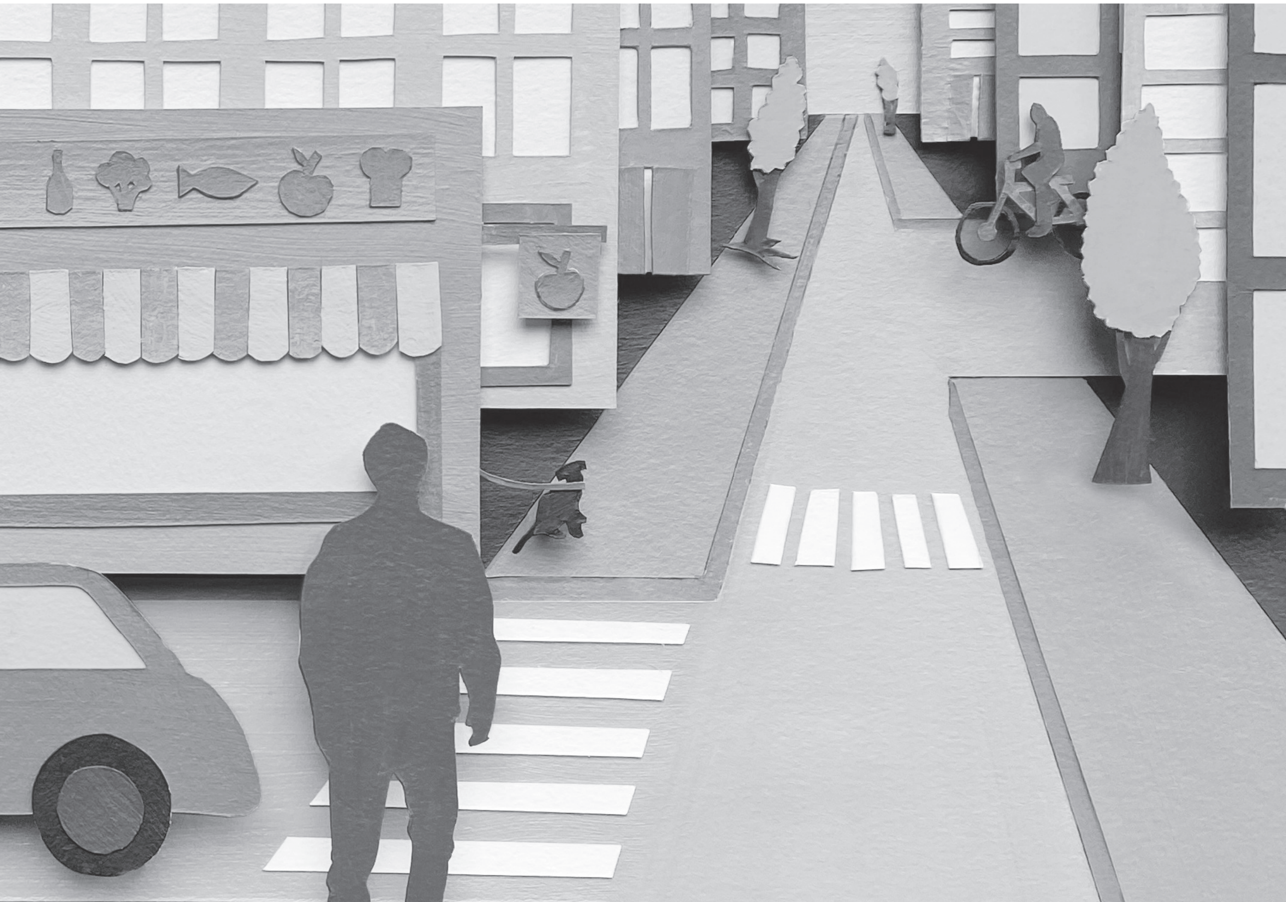
Chapter 8

General discussion



The main aims of this thesis were 1) to explore walking in relation to participation after stroke and 2) to investigate the effect of virtual reality (VR) gait training on walking ability and participation in people after stroke. This final chapter starts with an overview of the main findings of the studies presented in this thesis. Then, the main findings are discussed and directions for future research are presented. The discussion ends with 3 implications for stroke rehabilitation.

Main findings

Part I Walking ability and participation after stroke

In the first part of this thesis, walking was explored in relation to participation. Using the qualitative study in **chapter 2**, we investigated how people experienced walking in daily life after their stroke. Barriers and facilitators were identified for gait-related participation, which was described as walking with a goal on International Classification of Functioning, Disability and Health (ICF) participation level. People who were able to walk without physical support from others still described multiple barriers to gait-related participation after their stroke. Barriers were experienced regarding movement-related functions (e.g., motor impairment), cognitive functions (e.g., allocation of attention and information processing), personal factors (e.g., anxiety and insecurity), and environmental factors (e.g., terrain irregularity and busy environments). Many people reported difficulties with the performance of dual tasks during walking and could not walk fast or far enough to perform activities that they were used to doing before their stroke. Facilitators for gait-related participation were found on participation level (e.g., household responsibility) and in personal and environmental factors, such as motivation and family support. In **chapter 3**, we assessed the cross-sectional and longitudinal relation between walking ability and participation after stroke. Cross-sectionally, walking ability was significantly associated with participation and especially dynamic balance was found to be an important related factor to participation. Change in walking endurance was significantly associated with change in participation over time, suggesting a role for walking endurance to improve participation after stroke.

Part II Virtual reality gait training

The second part of this thesis focused on the potential effects of VR training on walking ability and participation after stroke. In the systematic review with meta-analysis in **chapter 4**, we investigated the effect of VR training on balance and walking ability using pooled results of 21 studies. VR training induced stronger improvements in balance and walking ability compared with conventional therapy, both when VR interventions were added to conventional therapy and when time dose was matched. Results of this chapter demonstrated that VR training can be more effective than balance or gait training without VR for improving balance and walking ability in people after stroke. However, as the meta-analysis only included walking speed and measures of balance, further research was necessary to investigate the effect of VR training on participation level. **Chapter 5** described the protocol of the ViRTAS (Virtual Reality Training After Stroke) randomized controlled trial which compared a VR gait training with a non-VR gait training to examine the effect of VR gait training on participation in community-living people in the first 6 months after stroke. In **chapter 6**, results of the ViRTAS study have shown that treadmill-based VR gait training was a safe and well-tolerated intervention that was positively rated by people after stroke. However, the effect of VR gait training was not statistically different from non-VR gait training in improving participation in community-living people after stroke. While other chapters focused on people after stroke living in the community, **chapter 7** has shown that VR training is also safe and feasible for improving balance and walking ability during inpatient rehabilitation of people after stroke. In addition, results of this pilot study suggested that VR training is beneficial to improve balance and walking ability in severely impaired people early after stroke.

Discussion of main findings

Three main themes will be discussed in this section: ‘walking related to participation after stroke’, ‘gait training using VR technology’, and ‘application of other extended reality technology in gait rehabilitation’.

Walking related to participation after stroke

Improving participation is considered a main goal in stroke rehabilitation.[1] A previous study showed that participation restrictions are mainly present during activities that involve walking.[2] The importance of walking for participation is also reflected by the fact that 6 out of 9 ICF participation domains may require walking, including the domains 1) general tasks and demands, 2) mobility, 3) self-care, 4) domestic life, 5) major life areas, and 6) community, social, and civic life.[3]

Walking with a goal on participation level (e.g., walking to go shopping, to perform household chores, or to perform leisure activities) involves a complex level of walking as people have to be able to adjust their walking to demanding situations. For example, when walking to do the groceries one needs sufficient walking distance and walking speed to safely reach the supermarket, has to be able to maneuver through the store, has to bend to pick up objects, and has to carry groceries while walking. This walking with a goal on participation level (i.e., the 6 above-mentioned ICF participation domains) was defined in our study as gait-related participation.

A complex level of walking

Steady state walking without falling requires leg motor control to generate a stepping pattern and sufficient balance control to maintain equilibrium during walking.[4-6] However, as described above, walking in daily life involves demanding situations that require more than steady state walking. **Chapter 2** confirmed that people who could walk independently (i.e., without physical support from others) after their stroke still experienced restrictions in walking in daily life and were not satisfied with their level of participation. These results point out that more advanced aspects of walking ability are required for walking with a goal on participation level (i.e., gait-related participation).

Two advanced aspects are *walking endurance* and *walking speed*. A decreased walking distance and a decreased walking speed were both reported as limiting, by people who can walk independently, to participate in activities as they were used to before the stroke (**chapter 2**). We, therefore, conclude that both walking endurance and walking speed are required for gait-related participation. For example, one needs sufficient speed to cross a street when taking a stroll and needs considerable endurance to walk to a store for shopping or to a bus stop for visiting a friend. **Chapter 3** showed that an improvement in walking endurance was associated with an improvement in participation over time in people after stroke. This association stresses the importance of increasing walking endurance once independent walking is achieved. In line with our findings, recommendations from international guidelines described walking distance and walking speed as important therapeutic goals in people who are able to walk after a stroke.[7]

Besides walking endurance and walking speed, *walking adaptability* is a third advanced aspect that is required for gait-related participation. Walking adaptability is the ability to adjust walking to tasks and environmental demands.[5] When walking in everyday life people will encounter complex environments that involve irregular terrain, steps (e.g., curbs, doorsteps, and stairs), and obstacles (e.g., dog shit). In addition, people will encounter different weather conditions or lighting levels (e.g., darkness) and busy environments with crowds and traffic. In these environments, walking adaptability is essential to ensure correct foot placement, to avoid collisions, and to prevent falls. Besides the environment, walking needs to be adjusted to various tasks such as when performing a motor or cognitive dual task during walking (e.g., talking while walking).

Walking adaptability requires a high level of leg motor control and dynamic balance control,[6] which encompass more than the leg motor control and balance control underlying steady state walking. Dynamic balance can be described as controlling the center of mass within the base of support in order to remain upright during postural transitions and walking.[8] It involves proactive balance control to anticipate on situations that could be destabilizing and reactive balance control to restore balance in case of unexpected perturbations.[9] In case of unexpected perturbations, such as trips and slips, people have to be able to suddenly adjust their walking to prevent a fall. Also in our study, a good dynamic balance was shown to be significantly related to a high level of participation in people after stroke who could walk independently (**chapter 3**).

Gait training using VR technology

Training of walking ability should be carefully tailored to the needs and abilities of a person after stroke. During gait training, multiple motor learning principles can be applied to train the above-mentioned advanced aspects of walking ability.[10,11] The motor learning principles include task-specific and intensive training, variability, feedback, and motivation.[12] *Intensive* training with a high number of repetitions is shown to be important for effective physical therapy.[13] *Task-specific* training implies that in order to improve walking, functional and goal-directed training should be provided focusing on those walking aspects of which performance is impaired.[14] Physical therapy guidelines commonly show that intensive, progressive, and task-specific training in a functional context supports the improvement of walking ability after stroke.[7] Also, *variability* in training (e.g., variable walking speeds, positions, and difficulty levels) is important to teach people how to deal with variability within a task. This will improve retention and will help to generalize skills to learning of new tasks.[12,15] In addition, *feedback* can stimulate motor learning after stroke and is found to be beneficial during training.[16] Extrinsic feedback about the performance of a task can make people aware of how they move, which is especially important as intrinsic feedback systems may be disturbed after stroke.[17] Lastly, *motivation* is shown to be important for motor learning. An adequate balance between task difficulty and skill level of the patient increases motivation.[18] Training interventions for people after stroke should incorporate these motor learning principles as much as possible. In our studies, we investigated a high-end VR intervention because we expected this intervention to align with the above-mentioned principles.

Characteristics of the VR training

VR is generally defined as a computer-generated 3-dimensional creation of a real-life environment in which people can navigate and interact with virtual objects and events.[19] Based on this definition, different VR systems are available varying from commercial video games to high-end systems designed for rehabilitation. High-end systems can create a demanding but safe environment in which walking ability can be trained by applying the above-mentioned principles of motor learning.[20,21] Besides training, high-end VR systems with motion capturing can be used to assess walking ability and to give insight into one's walking performance in demanding environments. In the ViRTAS study, we provided VR gait training with the GRAIL (Gait Real-time Analysis Interactive Lab, Motek Medical, Amsterdam, the Netherlands), a high-end VR system consisting of a dual-belt treadmill with motion-capture system and a 180° semi-cylindrical screen for the projection of synchronized virtual environments. Why did we choose this training intervention?

The GRAIL provides opportunities to train a complex level of walking in a challenging but safe environment. Like other treadmill-based systems, the GRAIL is suitable for training of *walking endurance* and *walking speed*. A recent systematic review has confirmed that treadmill training is effective for improving walking distance and walking speed and not inferior to overground training.[22] However, we expected the GRAIL to have most added value for training of *walking adaptability*. Previous studies found beneficial effects of specific exercise interventions for walking adaptability, including dual tasking and obstacle avoidance.[23-25] A systematic review has shown that gait interventions involving dual-task training can have potential to improve dual-task walking speed after stroke.[23] Regarding obstacle avoidance, treadmill training augmented with visual obstacles on the walking surface was found to improve the ability of patients to avoid obstacles.[24,25] Although large-scale randomized controlled trials will be necessary to confirm effectiveness of specific exercise interventions for walking adaptability, the above-mentioned studies gave promising directions for training of dual tasking and obstacle avoidance. On the GRAIL, motor and cognitive dual tasking and obstacle avoidance during walking can be trained by visualizing virtual objects on the wide screen and by projecting objects on the treadmill surface. Besides dual tasking and obstacle avoidance, the VR environments of the GRAIL allow people to learn to maneuver through busy community environments with virtual traffic. In addition, by using the self-paced function of the treadmill people can adjust the walking speed and practice 'stop and go'. In the VR environments, one can also practice to make step adjustments and to walk uphill and downhill. In addition, postural transitions such as reaching during walking can be safely practiced. Yet, some aspects of walking adaptability are rather difficult to train on a treadmill system, including walking on irregular terrain and turning during walking.

Besides the suitability for walking adaptability training, we chose the GRAIL because we expected multiple principles of motor learning to be easily applied during training. Using motion-capture technology, accurate real-time *feedback* can be given about task performance and movement execution. In addition, the real-time interaction with objects and events and the elements of gamification can stimulate the *motivation* of patients.[26,27]

This gives opportunities to promote implicit learning and was expected to enhance therapy compliance and training *intensity*. However, training on the GRAIL appeared not more intensive than non-VR gait training when comparing the rate of perceived exertion and the number of steps during a training session. Although the intensity of VR gait training was comparable with a non-VR gait training, the GRAIL gives possibilities to provide *task-specific* and *variable* training (e.g., different objects, situations, and environments) in a safe environment. A therapist can easily personalize the training by choosing aspects of walking ability and adjusting difficulty. In this way, VR gives many degrees of freedom to easily tailor training to the specific needs and abilities of the person after stroke.

Effect and application of VR training

Although participation improved, on average, more after VR gait training, the effect of VR gait training on participation was not statistically different from a non-VR gait training. Also, outcome measures for balance and walking ability, walking activity, and falls-efficacy showed no significant differences between VR gait training and non-VR gait training. The VR gait training that we conducted appeared thus not superior to gait training without VR (**chapter 6**). However, these findings from the ViRTAS study contrast the rising evidence on beneficial effects of VR training in recent literature. After publication of our meta-analysis (**chapter 4**), new systematic reviews have investigated the effect of VR training on balance and walking ability after stroke. Three reviews provided evidence that VR training is more effective than training without VR to improve walking function (e.g., cadence, stride length, and gait speed).[28-30] One review included studies that provided treadmill-based VR interventions,[28] but the other 2 reviews based their results on a variety of VR interventions, including treadmill-based VR training, video games, and robot-assisted VR training.[29,30] Regarding balance, also new evidence is presented showing that VR training in combination with conventional therapy is more effective than conventional therapy alone.[31,32] However, systematic reviews to date generally focused on balance and walking function and did not investigate the effects of VR on activity and participation level after stroke. Furthermore, comparison of VR interventions in systematic reviews remains difficult as various VR systems with different training content are investigated and studies include a heterogeneity of outcome measures for measuring the same purpose.[33] VR interventions mostly differ regarding training intensity, the aspects of walking ability that can be trained, the safety of the training environment, and the extent and quality of real-time feedback that is provided with motion capturing. High-end systems can provide accurate motion capturing by advanced infrared technology (e.g., Vicon), while commercially available systems work with lower-cost camera-based trackers. Low-cost systems have generally less added value for the provision of feedback as they are less accurate and give only information about the accomplishment of a certain task, but not on how the task was performed (i.e., correct movement execution).[20] Because the amount of training and the training intensity vary greatly between studies, it is difficult to make recommendations on the dose of training that is essential to achieve meaningful improvements. In addition, the contrast between the VR intervention and control intervention differs between studies.

The ViRTAS study has shown that VR gait training is feasible and positively rated by people after stroke. Therefore, we think that VR gait training may be incorporated in the range of interventions for stroke rehabilitation despite the lack of statistically significant differences in the effect of VR gait training and non-VR gait training. Especially because the results of the VR gait training were not worse than the non-VR training. However, we learned that we should better think about for whom VR training is considered, which VR environments are used for specific therapeutic goals, and how to generalize VR training to real-world exercises and activities. The ViRTAS study included a diverse group of people who could walk independently. Physical therapists chose, based on their clinical expertise, which VR environments were used during the training intervention and adapted the difficulty level to the abilities of the patient. However, we did not measure underlying walking impairments nor did we assess the achievement of patient-specific therapeutic goals during the study. Assessment of underlying walking impairments and therapeutic goals of the participants would have given the opportunity to make the training more personalized and could have given more insight into which patients are most likely to benefit from VR gait training. As we examined VR gait training in people after stroke who lived in the community and could walk independently, results do not translate to a general stroke population. Other subgroups of people after stroke might also benefit from VR training as part of the rehabilitation program. Which people and which therapeutic goals are expected to benefit most from VR gait training?

In people who are able to walk independently, we experienced that the greatest added value of VR training on the GRAIL is covered by 2 aspects. First, VR gait training can contribute to improve self-confidence during walking. In the safe training environment, people are optimally challenged to train their walking and can experience that they are capable of adjusting their walking to demanding situations. In addition, real-time feedback conveyed to a person during the training can help to give better insight into one's walking performance. Second, walking adaptability (e.g., stepping tasks, obstacles, and dual tasks) can be safely trained on high-end dual-belt treadmill systems such as the GRAIL. Especially the training of perturbations is of added value because unexpected perturbations that people might experience in daily life (such as trips and slips) are difficult to safely practice during overground training. Trips and slips can be simulated by sideways movements of the treadmill platform and by unilateral belt acceleration and deceleration. In people after stroke, 3 studies already provided evidence that perturbation-based balance training on a movable platform could improve reactive balance,[34-36] which is important for an adequate walking adaptability. In addition, a pilot study has shown that perturbation-based gait training could enhance gait stability in people after stroke.[37] A future study, called HEROES (Home-based ExeRgaming fOr Enhancing resistance to falls after Stroke), will further investigate whether perturbation-based gait training combined with home-based exergaming can improve resistance to balance perturbations and reduces falls in people after stroke. To make sure that results translate to real-life environments, VR training could precede or could be combined with outdoor gait training or home-based exercises.

Besides people after stroke who can walk independently, we suggest 2 other subgroups that are expected to benefit from VR training. **Chapter 7** has shown that VR training on the GRAIL is safe and feasible for regaining balance and walking ability during inpatient rehabilitation. For this group of more severely impaired people after stroke who may not be able to walk independently, repetitive but variable training can be given in a controlled and safe environment to enhance functional recovery. Difficulty level can be gradually increased to create a progressive training and may also easily be decreased if necessary. In addition, challenging situations can be practiced that would be unsafe to practice in the real world. At the same time, the VR environments with game elements make training enjoyable and may distract people’s attention away from pain or frustration. The controlled environment together with the high level of enjoyment stimulate people to perform a high number of repetitions, which is important for effective therapy.[11,13] In addition, the amount of stimuli in VR environments can be adapted which enables gait training in stimulus poor environments for people who cannot tolerate much stimuli. The VR environments give opportunities to gradually increase the amount of stimuli over time to improve stimulus processing. Lastly, we expect VR gait training to be suitable for people after stroke who are restricted by cognitive impairments during walking. One can train dual tasks and attention-demanding tasks when walking in a safe environment. The VR environments with real-time feedback can make people more aware of their performance and can promote implicit learning. Implicit learning is thought to improve dual-task performance and may be especially beneficial for people after stroke who have difficulty with processing explicit verbal instructions.[38,39]

Experiences of implementing VR technology

New technologies need to be properly investigated and when research results are positive they should be carefully implemented to be well embedded in clinical practice. Various theoretical models and frameworks are available to guide implementation, to understand factors that influence implementation, and to evaluate implementation.[40] Though the

GRAIL was already in use as part of clinical care, our research project contributed to further acceptation and application of VR within rehabilitation of people after stroke. What did we experience important for successful implementation of VR training?

- Most important, clinicians should embrace the technology and should be keen on using the system in their clinical practice. Several passionate clinicians who are motivated to use the technology can lead implementation and actively stimulate other colleagues to adopt the technology (so-called early adopters). For implementation of the GRAIL, an internal workgroup was set up consisting of physical therapists from pediatric and adult rehabilitation units.
- In addition, patients should be actively and early involved in the implementation process to make sure that the system suits the goals and wishes of patients. Systems and applications are often developed by experts, e.g., engineers, technicians, designers, developers, who are not involved in rehabilitation. Wishes and experiences of patients and clinicians should be aligned with possibilities of the systems so that user-friendly and effective training applications can be co-created.
- Furthermore, clinicians, e.g., physical therapists, should be able to experiment with new technology in order to experience which applications or settings are appropriate for which patients and therapeutic goals. Guidelines and training protocols can help to facilitate clinical expertise. Ideally, these training protocols are exchanged between institutions that use the same technology to learn from each other. After installation of the GRAIL, 2 national user groups were raised to share experiences and expertise to help implementing the GRAIL in Dutch rehabilitation care. One group focused on practical application of the GRAIL and shared experiences and solutions for practical issues. The second group aimed to unite knowledge and expertise on training content, research, and data collection.
- Lastly, it is important to have easily accessible support to make sure that clinicians can properly learn how to work with new technology and can get help quickly. Otherwise clinicians will get disappointed and frustrated when due to (technical) problems with the system they cannot provide the treatment for the patient as planned. This increases the risk that they stop using the system. Most VR systems, especially the high-end ones, require adequate technical support in case of deficits and for structural maintenance of both software and hardware.

Application of other extended reality technology in gait rehabilitation

High-tech VR training systems such as the GRAIL are yet only accessible for a small proportion of the people after stroke who receive rehabilitation in a rehabilitation center. Also other extended reality technology is available for use in gait rehabilitation. Yet, systems differ in the motor learning principles that are applied and the aspects of walking that can be trained. Regarding VR, commercial video games may be used to stimulate people's motivation and to increase training intensity in the home environment. However, video games are usually restricted to balance training and not developed for rehabilitation purposes. In addition, head-mounted VR devices can give some additional opportunities for training of walking adaptability (e.g., dual tasks) in people who can walk safely while wearing a head-mounted device. However, just like video games, head-mounted VR devices have generally less options to create purposive, safe, and interactive training with accurate feedback.

Besides VR, augmented and mixed reality systems can be interesting for gait training. Augmented reality allows people to respond to virtual objects that are superimposed over the real environment using head-mounted devices or projections on the walking surface.[41] The projection of visual context on the walking surface enables training of walking adaptability.[42] Using instrumented treadmills with augmented visual context, such as the C-mill (Motek Medical, Amsterdam, the Netherlands), walking adaptability can be trained in a safe environment.[43] Although the C-mill has less possibilities than the GRAIL, the system provides high-intensity, task-specific, and variable training with real-time feedback and is accessible for more rehabilitation facilities because of lower costs. Training with projections of visual context can also be performed in an overground setting, such as the Interactive Walkway.[44] Furthermore, head-mounted mixed reality devices, such as the HoloLens (Microsoft Corporation, Redmond, Washington, USA) might give future opportunities for training of walking ability in combination with other tasks in the home environment. Mixed reality combines elements of both VR and augmented reality and in this way produces interaction between 3-dimensional virtual objects and real-world objects and environments.[45] However, this technology is still emerging and further research has to be conducted to see which devices are safe, effective, and suitable for people after stroke.

As multiple systems are available and new technology is rapidly evolving, it is important to think about which technology or system should be used in which patient population and for which therapeutic goals. It should be remembered that using technology is not an end in itself; it is a means to an end. The choice for a certain technology should be based on the aspects of walking ability that need to be trained and the motor learning principles that should be applied. In addition, physical and cognitive abilities of the person after stroke and the availability of support from family and friends should be considered. Training using extended reality can be provided in combination with other gait training interventions.

Directions for future research

The ViRTAS study was the first to explore the effect of VR gait training on activity and participation level in people after stroke. However, more research is necessary to further examine effects of VR on daily life participation, to gain better insight into training content, and to explore which people after stroke benefit from VR gait training. Although we provided some suggestions for subgroups of people after stroke who may benefit from VR training, future research could better characterize the people after stroke for whom VR training can best be considered. Proper assessments prior to VR training can help to focus the training on those aspects of walking that people have difficulty with by using specific elements of VR (e.g., training of dual tasks or obstacle avoidance). When training is more personalized based on assessments and therapeutic goals, VR gait training will likely generate more added value. Future research should give more insight into which VR systems with which training applications and difficulty levels should be used for specific therapeutic goals. Randomized controlled trials are perhaps not the best methodology to provide more insight into training content. N-of-1 trials or prognostic studies might be more appropriate to explore the difficulties that people experience with walking and to learn how to direct the content of VR training accordingly.

We believe that VR has also great potential for the assessment of walking ability. Using motion-capture technology, the walking performance of a person after stroke can be monitored and visualized using graphs or VR representations. It is also possible to monitor how people respond to objects and events in the VR environments. Challenging environments of high-end VR systems give safe options to explore how good a person can cope with demanding situations. People who seem to walk fine in a simple and predictable hallway, may reveal difficulties with dual tasking or adjusting speed when walking in a demanding VR environment. In this way, VR systems are expected to give insight into which advanced aspects of walking ability may require further attention in rehabilitation. Future research will be necessary to figure out how VR environments should be used to assess the advanced aspects of walking in a standardized manner.

Implications for stroke rehabilitation

On the basis of the findings from this thesis and clinical experience, we formulated 3 main implications for the rehabilitation of people after stroke. First, we suggest to add VR training to the existing gait interventions. We expect VR to be especially of added value when the possibilities of VR gait training are used to train specific aspects of walking ability (e.g., dual tasks or perturbation training) and when it suits the goals and abilities of the patient.

VR gait training appeared not superior to gait training without VR in a diverse group of people after stroke who can walk independently. Yet, gait training on a high-end VR system was feasible and positively rated by people after stroke and provides opportunities to train specific aspects of walking ability in a challenging but safe environment. VR gait training may, therefore, be incorporated in the range of interventions for stroke rehabilitation but should be carefully considered depending on the therapeutic goals and the characteristics of the patient.

Second, we advise clinicians to be aware that people after stroke who are physically able to walk independently can still have considerable difficulty with gait-related participation. Using both quantitative and qualitative methods, this thesis showed that people after stroke experience multiple difficulties when walking with a goal on participation level. This gait-related participation requires a complex level of walking as people have to be able to adjust their walking to tasks and environmental demands. Clinicians should have attention for this complex level of walking during the rehabilitation of people after stroke.

Third, we recommend to thoroughly examine the factors that underlie the difficulties with gait-related participation. Especially walking adaptability seems important to consider for examination. To assess walking adaptability, physical therapists could use interviews, observations, and performance-based instruments (e.g., Mini Balance Evaluation Systems Test). In addition, extended reality technology makes it possible to examine walking adaptability in demanding environments and to give both therapists and patients insight into aspects of walking that are difficult. For example, perturbations and obstacles can be provided during walking to objectify how good a person can respond to unexpected situations. By targeting training on those aspects of walking that people show difficulty with, people can best learn how to face these challenges in their own community and will improve their participation.

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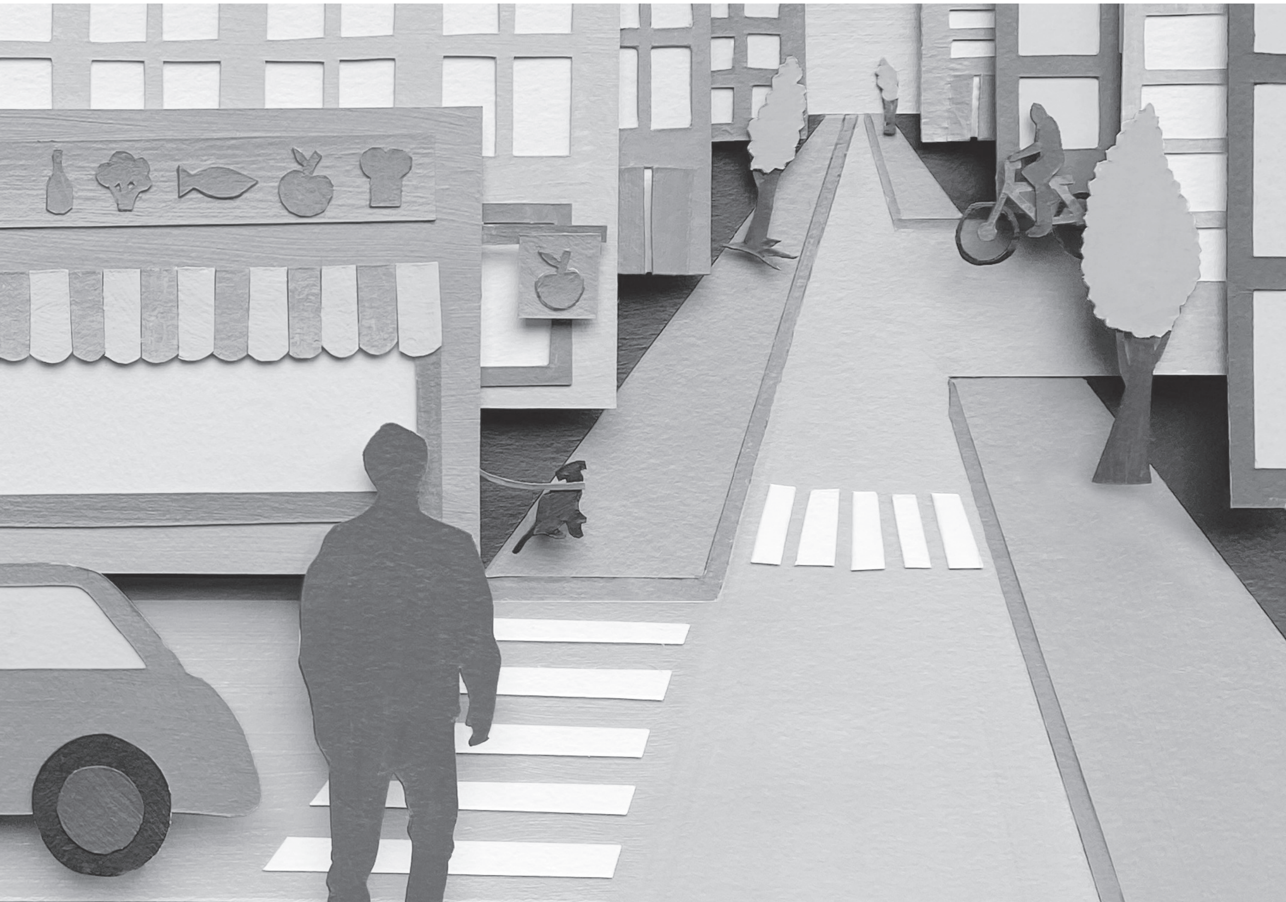
Summary



A stroke can lead to severe physical and cognitive impairments. As a result of these impairments, many people experience problems with walking after a stroke, such as when walking on irregular terrain or walking in a busy shopping area. Because of these problems with walking people are restricted in their social functioning, also referred to as participation. They can experience difficulties with work, hobby's, household tasks, and doing the groceries, for example. In stroke rehabilitation, therapeutic goals are therefore often focused on improving walking and participation in daily life.

Virtual reality (VR) offers new training opportunities to improve walking ability. High-end VR systems, such as the GRAIL (Gait Real-time Analysis Interactive Lab), can create a challenging but safe training environment in which real-life situations can be simulated. The GRAIL consists of a dual-belt treadmill with motion-capture system and a large semi-cylindrical screen for the projection of virtual environments. Using reflective markers that are placed on the body, people can interact with the virtual environment and receive real-time feedback. When walking on the treadmill, people can be challenged to perform dual tasks and to respond to unexpected perturbations (e.g., acceleration or sideways movement of the treadmill).

The use of VR is increasingly studied in stroke rehabilitation, varying from commercial video games to high-end VR systems designed for rehabilitation. Favorable effects of various VR systems have been found for improving balance and walking function (e.g., walking speed, step length, and cadence) after stroke. However, results of previous studies about the effect of VR training on walking ability were inconsistent and studies lacked outcomes on the level of participation. It is, therefore, yet unknown whether VR training can contribute to improvement in walking ability and participation of people after stroke.

This thesis is divided in two parts. In the first part, walking is explored in relation to participation after stroke. More insight in the problems that people after stroke experience with walking and participation, and the association between both, can help to further direct the content of gait rehabilitation. In the second part, the effect of VR gait training on walking ability and participation after stroke is investigated. The studies in this second part focus on the feasibility and effect of VR to improve walking ability and to reduce participation restrictions in people after stroke.

The thesis starts with an introduction (**chapter 1**) about the consequences of stroke on walking ability and participation. In addition, VR is introduced as a possible intervention to enhance walking ability.

Part I Walking ability and participation after stroke

Chapter 2 presents the results of a qualitative study aimed to explore the barriers and facilitators for gait-related participation from the perspective of people after stroke. In this study, gait-related participation was defined as walking with a goal on participation level. We conducted 21 semi-structured interviews to investigate what hinders people or holds them back from walking or performing gait-related activities. We also asked people what makes it easier or stimulates them to walk or to perform gait-related activities. The interviews were audio-recorded, transcribed, and analyzed using thematic analysis. People who had the capacity to walk independently described multiple barriers to gait-related participation after their stroke. These barriers were experienced in movement-related functions, cognitive functions, mobility, personal factors, and environmental factors. Facilitators for gait-related participation were found on participation level and in personal and environmental factors, such as motivation and family support. These findings emphasize that it is important to focus rehabilitation not only on the physical aspects of walking but to also consider cognitive functions and personal and environmental factors.

Chapter 3 describes the relationship between walking ability and participation in community-living people after stroke. Data was used from 52 people after stroke of whom walking ability and participation were measured at the start and end of a 6-week gait training intervention. Walking ability was expressed as walking endurance, functional mobility, walking activity, and dynamic balance. Participation was measured with the Restrictions subscale of the Utrecht Scale for Evaluation of Rehabilitation-Participation (USER-P). The cross-sectional results at the start of the intervention showed that walking endurance, functional mobility, and dynamic balance were significantly associated with participation. However, in the multiple regression analysis only a better dynamic balance was independently related to a higher level of participation. The relationship between walking ability and participation was also explored over time. Longitudinally, improvement in walking endurance during the 6-week training intervention was positively associated with improvement in participation. This positive association indicates that training walking endurance may contribute to improvements in participation.

Part II Virtual reality gait training

In **chapter 4**, a systematic literature review is performed to investigate whether balance or gait training using VR is more effective than conventional balance or gait training in people after stroke. We included 21 studies that compared the effect of training with and without VR. The results for the outcomes gait speed, Berg Balance Scale, and Timed Up & Go test were pooled using a meta-analysis. The pooled results showed that VR training is more effective than balance or gait training without VR for improving balance or gait ability in people after stroke. Based on the included studies, we could not determine whether the effects of VR training on balance and gait function translated to an improved participation in daily life and could be sustained over time. Therefore, the recommendation was done for future research to study the effect of VR training on participation level with a longer follow-up period.

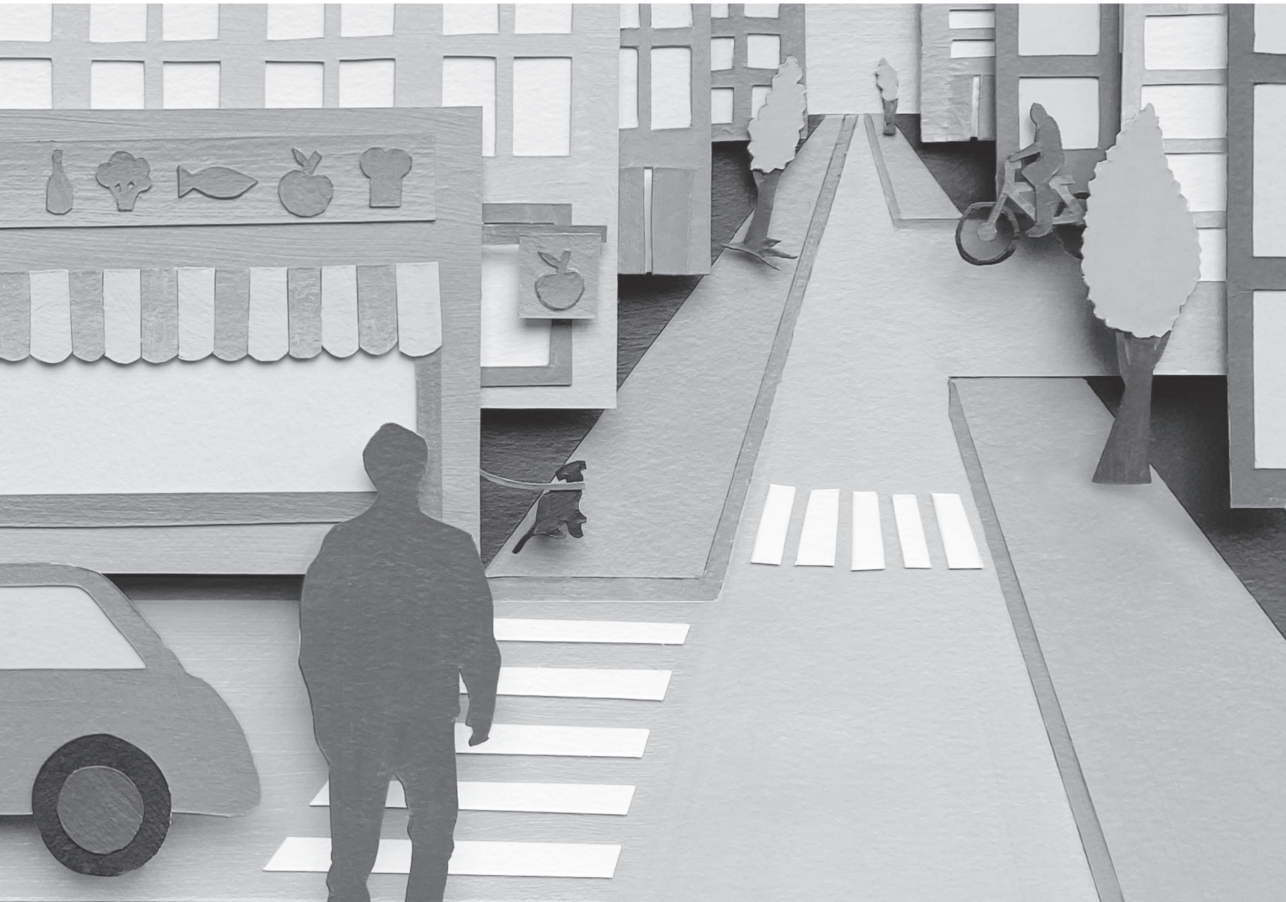
Chapter 5 describes the protocol of the ViRTAS (Virtual Reality Training After Stroke) study. In this randomized controlled trial, we examined the effect of VR gait training on participation in community-living people after stroke. In addition, the effect of VR gait training on walking ability, walking activity, functional mobility, dynamic balance, subjective physical functioning, falls efficacy, anxiety and depression, fatigue, and quality of life was investigated. The VR gait training was performed on the GRAIL (30 minutes treadmill training combined with VR). To study the effect of VR gait training, the training was compared with a non-VR gait training consisting of conventional treadmill training (10–15 minutes) and functional gait exercises (15 minutes). Participants were randomly assigned to one of the interventions and received 12 training sessions of 30 minutes during 6 weeks. Participation was measured with the Restrictions subscale of the USER-P at baseline, post intervention, and 3 months post intervention. The Restrictions subscale asks people about the experienced participation restrictions in daily life.

Subsequently, **chapter 6** presents the results of the ViRTAS study. A total of 55 people after stroke were included, of which 28 received the VR gait training and 27 the non-VR gait training. The study showed that both training interventions contribute to improvement in walking and participation after stroke. The VR gait training was, however, not more effective than the non-VR gait training for improving walking ability and participation. This suggests that both interventions can be applied in stroke rehabilitation taking into account the individual rehabilitation goals or patient preference. The VR gait training was shown to be a safe and well-tolerated intervention with limited adverse events. We performed semi-structured interviews to explore the experiences of people after stroke with this new intervention. Participants experienced the VR gait training as enjoyable, challenging, and intensive. After the training intervention, people experienced improvements in their balance ability, the ability to perform dual tasks, walking speed and walking endurance, and they felt more confident during walking. These findings suggest that VR gait training is a valuable addition to stroke rehabilitation.

Chapter 7 describes a pilot study about the feasibility and effectiveness of VR training for improving balance and walking ability early after stroke. This study focused on people within 12 weeks after their stroke who are not able to walk independently. Because people are often restricted by visual, physical, cognitive, and endurance impairments early after stroke, it is important to explore whether training using high-end VR technology is feasible in this group. Sixteen people after stroke received 8 VR training sessions on the GRAIL as part of their inpatient rehabilitation program. The VR training appeared safe and feasible based on a high training compliance, the absence of serious adverse events, and positive experiences of both patients and physical therapists. In addition, significant improvements in balance and walking ability were found after 4 weeks of VR training. This study showed that VR training on the GRAIL is suitable for severely impaired people early after stroke.

Finally, **chapter 8** discusses the main findings of this thesis. We also present suggestions for future research and clinical implications for stroke rehabilitation. Our research showed that people who have the physical capacity to walk independently can have considerable difficulty with walking and participation in daily life. Various aspects of walking ability are important for gait-related participation, including the ability to adjust walking to environmental demands. This adjustment of walking is extra difficult for people after stroke. VR training can provide opportunities to train advanced aspects of walking ability in a challenging but safe environment. We, therefore, suggest to incorporate VR gait training in the range of interventions for stroke rehabilitation. VR gait training can then be carefully considered depending on the therapeutic goals and the characteristics of the patient. Future research should aim to gain more insight into the content of VR interventions and the use of VR for specific therapeutic goals.

Nederlandse samenvatting



In Nederland krijgen jaarlijks ongeveer 40.000 mensen een beroerte (herseninfarct of hersenbloeding). Een beroerte kan leiden tot ernstige fysieke en cognitieve beperkingen. Als gevolg van deze beperkingen ervaren veel mensen problemen met lopen, zoals in een drukke winkelstraat of bij het lopen over een ongelijk trottoir. Door deze problemen met lopen worden mensen beperkt in hun maatschappelijk functioneren, hun participatie. Zij ervaren bijvoorbeeld moeilijkheden tijdens werk, boodschappen doen en het uitvoeren van huishoudelijke taken en hobby's. In de revalidatie na een beroerte zijn therapeutische doelen dan ook vaak gericht op het verbeteren van loopvaardigheid en participatie in het dagelijks leven.

Virtual reality (VR) biedt nieuwe mogelijkheden om het lopen na een beroerte te trainen. Geavanceerde VR-systemen, zoals de GRAIL (*Gait Real-time Analysis Interactive Lab*), kunnen een uitdagende maar veilige omgeving creëren waarin situaties uit het dagelijks leven worden nagebootst. De GRAIL bestaat uit een tweedelige loopband, een systeem voor bewegingsregistratie en een groot scherm waarop virtuele omgevingen worden geprojecteerd. Door middel van reflectieve markers die op het lichaam geplakt worden kan de persoon op de loopband interactie hebben met de virtuele omgeving en direct feedback krijgen. Tijdens het lopen op de loopband kunnen mensen uitgedaagd worden door het uitvoeren van extra taken en het reageren op plotselinge verstoringen (bijvoorbeeld een versnelling of zijwaartse beweging van de loopband).

De afgelopen jaren is er steeds meer wetenschappelijk onderzoek gedaan naar het inzetten van VR in de revalidatie na een beroerte, variërend van commerciële videospellen tot geavanceerde VR-systemen. Gunstige effecten van verschillende VR-systemen zijn gevonden voor het verbeteren van de balans en loopfunctie (o.a. loopsnelheid, staplengte en stapfrequentie) na een beroerte. Eerdere onderzoeken zijn echter niet eenduidig over het effect van VR-training op loopvaardigheid en namen geen uitkomstmaten mee op het niveau van participatie. Het is daarom nog onbekend of VR-training kan zorgen voor een verbetering van loopvaardigheid en participatie bij mensen na een beroerte.

Dit proefschrift bestaat uit twee delen. In het eerste deel is het lopen onderzocht in relatie tot participatie na een beroerte. Het inzichtelijk maken van de problemen die mensen na een beroerte ervaren met lopen en het maatschappelijk functioneren en de samenhang tussen beide kan helpen om de looprevalidatie verder vorm te geven. In het tweede deel is het effect van VR-training op loopvaardigheid en participatie na een beroerte onderzocht. De studies in dit tweede deel richten zich op de haalbaarheid en het effect van het inzetten van VR voor het verbeteren van het lopen en het verminderen van participatiebeperkingen bij mensen na een beroerte.

Het proefschrift start met een introductie (**hoofdstuk 1**) waarin de gevolgen van een beroerte op loopvaardigheid en participatie worden beschreven. Daarnaast wordt VR geïntroduceerd als mogelijke training voor het verbeteren van loopvaardigheid.

Deel I Loopvaardigheid en participatie na een beroerte

Hoofdstuk 2 geeft de resultaten weer van het kwalitatief onderzoek naar de ervaren belemmerende en bevorderende factoren bij het lopen en het participeren in het dagelijks leven na een beroerte. In 21 semigestructureerde interviews is aan deelnemers gevraagd wat het voor hen moeilijk maakt of wat hen tegenhoudt om te lopen of loop-gerelateerde activiteiten uit te voeren na de beroerte. Ook is gevraagd wat het makkelijker maakt of wat hen stimuleert om te lopen. De interviews werden opgenomen, getranscribeerd en geanalyseerd via een thematische analyse. Ondanks dat de meeste mensen in staat waren om zelfstandig te lopen, eventueel met hulpmiddelen, ervaarden zij meerdere belemmerende factoren voor het lopen in het dagelijks leven. Deze belemmerende factoren werden met name ervaren in bewegingsgerelateerde functies, cognitieve functies, mobiliteit, persoonlijke factoren en omgevingsfactoren. Bevorderende factoren werden gevonden op het gebied van participatie en in persoonlijke factoren en omgevingsfactoren, zoals motivatie en ondersteuning van familie. Deze bevindingen benadrukken dat het belangrijk is om tijdens de revalidatie niet alleen op het fysieke aspect van het lopen te focussen, maar ook op de cognitieve functies, persoonlijke factoren en omgevingsfactoren die het lopen beïnvloeden.

Hoofdstuk 3 beschrijft de relatie tussen loopvaardigheid en participatie bij zelfstandig wonende mensen na een beroerte. Hiervoor zijn de gegevens gebruikt van 52 mensen na een beroerte bij wie loopvaardigheid en participatie werden gemeten bij de start en het einde van een 6-weekse looptraining. Loopvaardigheid werd in kaart gebracht door middel van loopafstand, functionele mobiliteit, loopactiviteit en dynamische balans. De participatiebeperkingen die mensen ervaren als gevolg van de beroerte werden gemeten met de Beperkingenschaal van de Utrechtse Schaal voor Evaluatie van Revalidatie-Participatie (USER-P). Uit de cross-sectionele resultaten bij start van de training bleek dat loopafstand, functionele mobiliteit en dynamische balans significant geassocieerd waren met participatie. In de multipele regressieanalyse was echter alleen een betere dynamische balans onafhankelijk gerelateerd aan een beter niveau van participatie. In de longitudinale analyse was verbetering in loopafstand gedurende de 6-weekse training geassocieerd met een vermindering van participatiebeperkingen in het dagelijks leven. Deze associatie suggereert dat het trainen van het uithoudingsvermogen van het lopen kan bijdragen aan het verbeteren van participatie.

Deel II Looptraining met virtual reality

In **hoofdstuk 4** is het systematisch literatuuronderzoek beschreven waarin is onderzocht of balans- en looptraining met VR effectiever is dan reguliere balans- of looptraining voor mensen na een beroerte. De resultaten van de 21 geïncludeerde studies werden samengevoegd in een meta-analyse met loopsnelheid en balans, gemeten met de *Berg Balance Scale* en de *Timed Up & Go* test, als uitkomstmaat. De meta-analyse laat zien dat VR-training effectiever is dan training zonder VR voor het verbeteren van balans en loopvaardigheid bij mensen na een beroerte. Op basis van de gevonden studies kon niet worden bepaald of de effecten van VR-training op balans en loopvaardigheid zich vertalen naar minder beperkingen in het dagelijks leven en of de effecten op lange termijn behouden blijven. De aanbeveling voor toekomstig onderzoek was daarom om het effect van VR-training te onderzoeken op participatie en daarbij gebruik te maken van een lange follow-up periode.

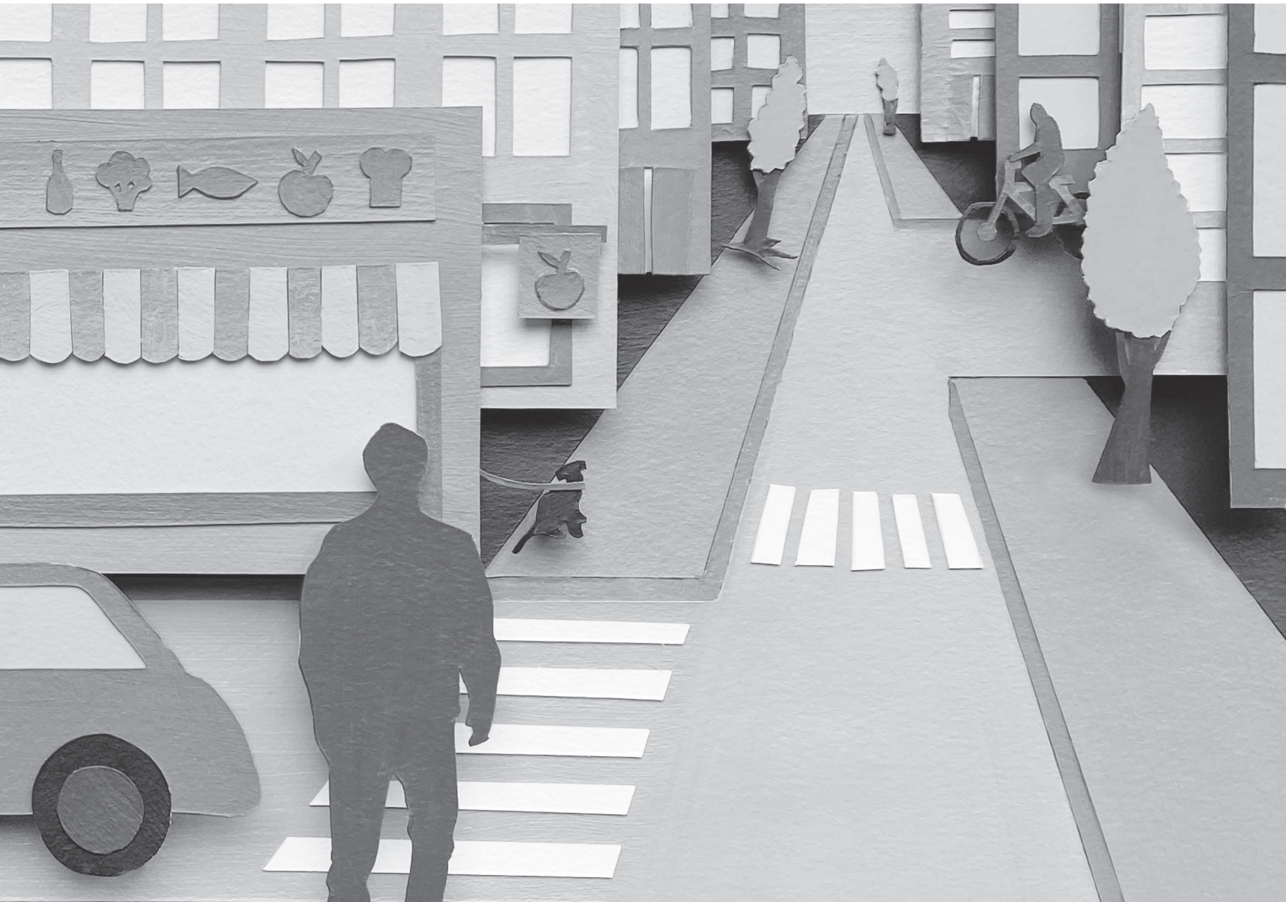
Hoofdstuk 5 beschrijft het onderzoeksprotocol van de ViRTAS (*Virtual Reality Training After Stroke)* studie. Dit is een gerandomiseerd gecontroleerd onderzoek. Het primaire doel van de ViRTAS studie was om het effect van looptraining met VR te bepalen op participatie van mensen na een beroerte. Daarnaast werd het effect van VR-looptraining onderzocht op loopvaardigheid, loopactiviteit, functionele mobiliteit, dynamische balans, subjectief fysiek functioneren, valangst, angst en depressie, vermoeidheid en kwaliteit van leven. De VR-looptraining vond plaats op de GRAIL (30 minuten loopbandtraining gecombineerd met VR) en werd vergeleken met een looptraining zonder VR. Deze training bestond uit conventionele loopbandtraining (10–15 minuten) en functionele loopoefeningen (15 minuten). Deelnemers werden gerandomiseerd in een van beide trainingsinterventies en volgden 12 trainingssessies van 30 minuten verdeeld over 6 weken. Participatie werd gemeten met de Beperkingenschaal van de USER-P bij start van de interventie, het einde van de interventie en na 3 maanden follow-up. De Beperkingenschaal vraagt mensen in welke mate zij zich beperkt voelen in hun participatie in het dagelijks leven.

Vervolgens presenteert **hoofdstuk 6** de resultaten van de ViRTAS studie. In totaal namen 55 mensen na een beroerte deel aan de studie, waarvan 28 mensen werden ingedeeld in de VR-looptraining en 27 mensen in de looptraining zonder VR. Uit de studie bleek dat beide looptrainingen zorgen voor een verbetering van het lopen en minder beperkingen in het dagelijks leven bij mensen na een beroerte. De VR-looptraining gaf echter geen statistisch significant betere resultaten dan de looptraining zonder VR. Dit suggereert dat beide trainingen kunnen worden toegepast tijdens de revalidatie na een beroerte, rekening houdend met de individuele revalidatiedoelen en de wensen van de patiënt. De VR-looptraining bleek veilig en praktisch haalbaar met een beperkt aantal ongewenste voorvallen. Door middel van semigestructureerde interviews hebben we de ervaringen van de deelnemers met deze nieuwe trainingsvorm in kaart gebracht. Deelnemers vonden de VR-looptraining leuk, uitdagend en intensief. Na de training ervaarden zij verbeteringen in hun balans, loopsnelheid en loopafstand en het uitvoeren van extra taken tijdens het lopen. Ook hadden zij meer vertrouwen in het lopen. Op basis van deze bevindingen concludeerden we dat VR-looptraining een waardevolle aanvulling kan zijn bij revalidatie na een beroerte.

Hoofdstuk 7 beschrijft de pilot-studie naar de haalbaarheid en effectiviteit van VR-training voor het verbeteren van balans en loopvaardigheid in een vroege fase na een beroerte. Deze studie richtte zich op mensen die minder dan 12 weken ervoor een beroerte hadden gehad en nog niet geheel zelfstandig konden lopen. Omdat deze groep vaak nog laag belastbaar is en beperkt wordt door diverse visuele, fysieke en cognitieve problemen, is het belangrijk om te bekijken of trainen met geavanceerde VR-systemen haalbaar is. Zestien mensen na een beroerte kregen 8 keer VR-training op de GRAIL als onderdeel van het klinische revalidatieprogramma. De VR-training bleek veilig en haalbaar. Ernstig ongewenste voorvallen vonden niet plaats, de aanwezigheid bij de trainingen was goed en de ervaringen van zowel patiënten als fysiotherapeuten waren positief. Balans en loopvaardigheid verbeterden na 4 weken VR-training. De studie laat zien dat VR-training op de GRAIL geschikt is voor mensen met aanzienlijke beperkingen kort na een beroerte.

Tot slot worden in **hoofdstuk 8** de belangrijkste bevindingen van dit proefschrift bediscussieerd. Daarnaast presenteren we suggesties voor vervolgonderzoek en klinische implicaties voor de revalidatie na een beroerte. Ons onderzoek liet zien dat mensen die fysiek in staat zijn om zelfstandig te lopen na een beroerte, toch aanzienlijke beperkingen kunnen ervaren bij het lopen in het dagelijks leven. Verschillende aspecten van het lopen zijn belangrijk voor het maatschappelijk functioneren, waaronder het kunnen aanpassen van het lopen aan verschillende situaties en omgevingen. Het aanpassen van het lopen is voor mensen na een beroerte vaak extra moeilijk. Looptraining met VR kan mogelijkheden bieden om deze aspecten van het lopen te trainen in een uitdagende maar veilige omgeving. We bevelen daarom aan om VR-looptraining op te nemen in het scala aan interventies voor de revalidatie na een beroerte. Het inzetten van VR-looptraining kan dan zorgvuldig overwogen worden op basis van de therapeutische doelen en kenmerken van de patiënt. In vervolgonderzoek is het van belang om meer inzicht te krijgen in de inhoud van VR-interventies en het gebruik van VR voor specifieke therapeutische doelen.

Dankwoord



Het is zover, mijn proefschrift is af! Graag wil ik iedereen bedanken die betrokken is geweest bij mijn promotietraject in welke vorm dan ook. Een aantal mensen wil ik graag in het bijzonder noemen.

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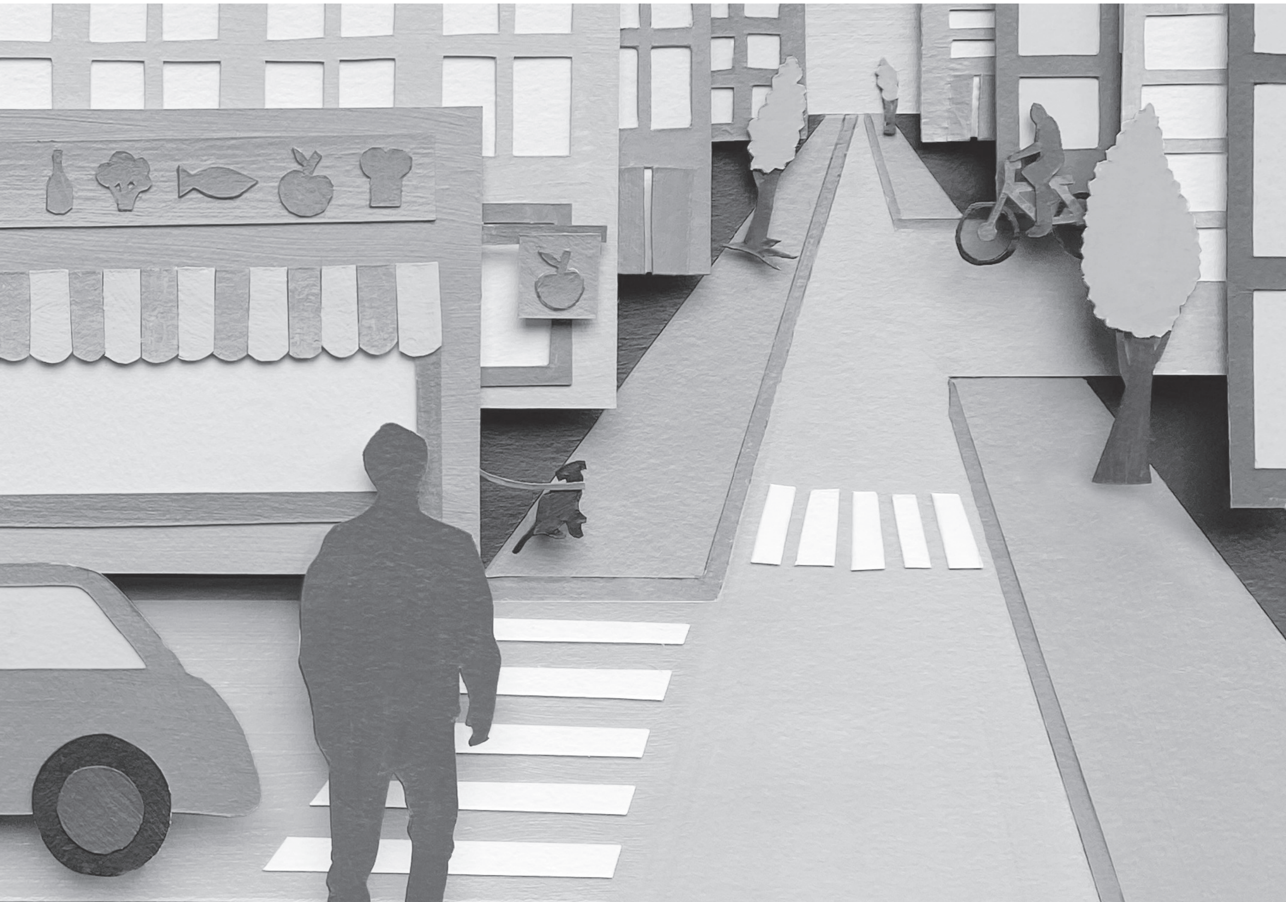
About the author

Curriculum Vitae

List of publications



Curriculum Vitae

Ilona de Rooij was born on May 30, 1993, in Liempde, the Netherlands. In 2011, she finished secondary school at Jacob-Roelandslyceum in Boxtel (Gymnasium). Thereafter, she started the Bachelor Biomedical Sciences, major Human Movement Sciences at Maastricht University. In 2015, she obtained her master's degree in Human Movement Sciences. During her master Ilona focused on rehabilitation and performed her research internship at Revant Rehabilitation Centres. This internship resulted in the publication of her first research article. After the internship, she continued her career as a research assistant.

In 2017, Ilona started her PhD trajectory at Revant and the Center of Excellence for Rehabilitation Medicine Utrecht (a collaboration between University Medical Center Utrecht and De Hoogstraat Rehabilitation). During her PhD she performed the ViRTAS study under supervision of dr. Ingrid van de Port, dr. Jan-Willem Meijer, and prof. dr. Anne Visser-Meily. In 2020, she won the best presentation award at the Dutch Congress of Rehabilitation Medicine. Ilona is currently working as a researcher at Revant Rehabilitation Centres where she supervises research and innovation projects, performs clinical data analyses, and coordinates the GRAIL lab.

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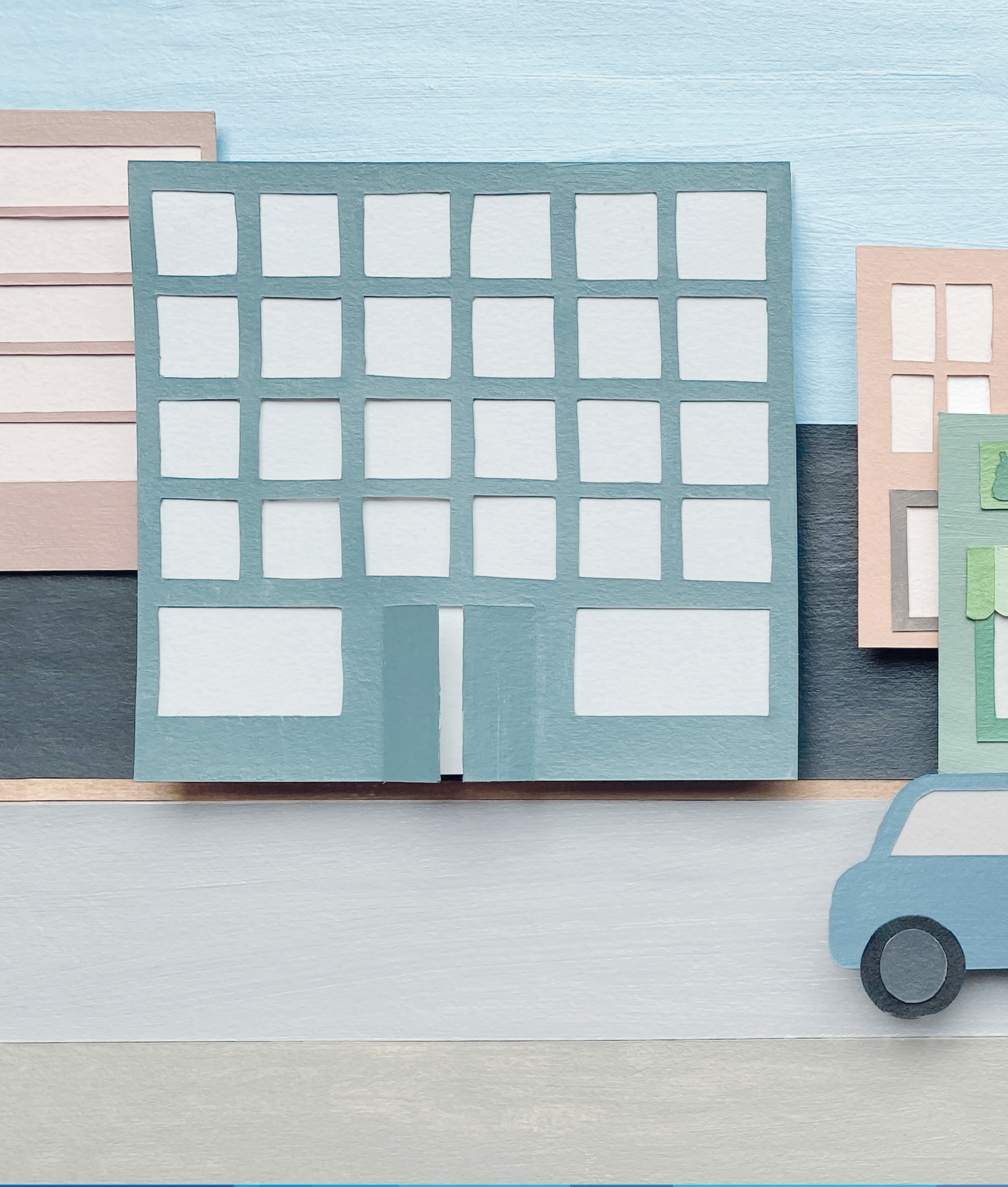

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