



UMEÅ UNIVERSITY

“Taking the next step”

Whole-body biomechanical gait analysis,
and user-perspectives on robotic-assisted
gait training post-stroke

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“Take small steps each day. You might not get there today, but you’ll be closer than yesterday.”
Unknown

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Abstract

Background: Stroke, and its subsequent motor function impairments may result in limited gait ability characterised by compensatory movement patterns that include deviations and asymmetries. How these movement patterns should be evaluated and quantified in order to be monitored and treated in the long term is not yet standardised. Limitations in walking quality and quantity negatively affect quality of life and lead to great costs for society if independence is lost. Improved walking ability is hence highly prioritised in stroke rehabilitation. Gait-assisting robots have been developed to enable favourable controlled, high-intensive and task-specific training. Studies evaluating the effects of robotic-assisted gait training (RAGT) have, however, shown inconsistent results. Identifying responders to treatment may facilitate further development of RAGT to improve outcomes. This requires in-depth knowledge of how specific gait movement patterns should best be identified, quantified and treated in rehabilitation. There is also a need for greater insight into how individuals experience gait training in general, and RAGT in particular, as this will likely affect the performance and outcomes of training.

Aim: This thesis aims to contribute to the discussion on how to quantify gait movement patterns post-stroke from a whole-body perspective. It will also evaluate the effects of RAGT on biomechanical measures of gait and explore the experience of high-intensive and robotic-assisted gait training in persons with impaired walking ability due to stroke.

Methods: A systematic review and meta-analysis consolidated the evidence for the effects of RAGT on biomechanical measures of gait in persons post-stroke. Two descriptive, cross-sectional studies based on kinematic gait data (31 persons post-stroke and 41 non-disabled controls) investigated potential variables to quantify post-stroke gait. The size and angular velocity of the inclination angles between the Centre of Mass (CoM) and the ankle or head, respectively, was investigated with curve analyses covering the entire gait cycle. Furthermore, misclassification rates were calculated based on leave-one-out cross-validation and logistic regression to address the combinations of kinematic variables that most correctly classify a person post-stroke when compared to controls. Finally, individual interviews were performed and analysed using qualitative content analysis to explore the experiences of high-intensive gait training, including RAGT, among persons post-stroke.

Results: The systematic review included 13 studies with a total of 412 individuals. The meta-analyses did generally not reveal significant differences between RAGT and comparator groups for biomechanical parameters. Risk of bias assessments raised concerns for several of the studies and the general quality

of evidence for these outcomes was very low. An important finding was an inconsistency of biomechanical outcome measures. Data from the primary cross-sectional studies included in this thesis indicated a bilateral lower body adaptation likely to increase the base of support and an upper body leaning towards the affected side during walking in persons post-stroke. Furthermore, core sets of 2-3 kinematic gait variables were identified from both the upper and lower body that, when combined, were most likely to differentiate post-stroke gait from gait in non-disabled controls. Finally, qualitative analysis of participants' perspectives on high-intensive gait training including RAGT revealed four categories which described: 1) A generally positive mindset when starting the gait training intervention; 2) That engaging in a high-intensive gait training programme was appreciated although experienced as mentally and physically exhausting. The role of the physiotherapist was perceived as crucial; 3) Potential barriers during RAGT, such as discomfort and lost control during walking with the robot, but also facilitators like concrete feedback and the possibility to walk longer distances, and; 4) The participants' feelings of confidence or concern for the future.

Conclusions: The systematic review demonstrated a very low certainty in current evidence for employing RAGT instead of non-robotic gait training to improve gait biomechanics post-stroke. In addition, it emphasized the lack of standardised guidelines as to which outcome measures most sufficiently quantify gait post-stroke. The cross-sectional studies included in this thesis, presenting upper and lower body kinematic variables to differentiate gait patterns between individuals with stroke and those without, highlight the advantages of adopting a whole-body perspective when evaluating gait post-stroke. Finally, interviews identified valuable aspects from the user's perspective that should be considered during further development of RAGT devices and the design of high-intensive gait rehabilitation programmes post-stroke.

Sammanfattning på svenska

Stroke, med påföljande sensoriska och motoriska nedsättningar, kan resultera i en begränsad gångförmåga som kännetecknas av avvikande, ofta kompensatoriska, rörelsemönster. Hur dessa rörelsemönster ska utvärderas och kvantifieras för att på sikt kunna följas och förändras är ännu inte standardiserat. Att inte kunna gå på det sätt eller i den utsträckning som man vill påverkar individens vardag och livskvalitet, samt leder till stora kostnader för samhället. Därför är förbättrad gångförmåga högt prioriterad inom strokerehabilitering. Gångassisterande robotar har utvecklats för att möjliggöra skraddarsydd, kontrollerad, högintensiv och uppgiftsspecifik träning. Befintliga studier som utvärderar effekterna av robotassisterad gångträning visar dock på varierande resultat, vilket väcker frågor kring hur man ska kunna identifiera de patienter som gagnas av den här typen av träning. För detta krävs fördjupad kunskap om hur specifika, avvikande gångmönster hos personer med halvsidig förlamning efter stroke bäst ska identifieras, kvantifieras och behandlas i rehabilitering. Det fordras även större insikt i hur gångträning i allmänhet och robotassisterad gångträning i synnerhet upplevs av personerna, eftersom detta i hög grad kan påverka träningens utförandet och utfall.

Målet med denna avhandling var att bidra till kunskapen om hur man med hjälp av kinematiska (rörelserelaterade) utfallsmått kan identifiera och kvantifiera gångmönster hos personer med halvsidesförlamning efter stroke. Dessutom, för att bredda perspektivet på robotassisterad gångträning, utforskas upplevelser av denna typ av träning hos personer med nedsatt gångförmåga efter stroke.

Avhandlingen består av fyra delstudier. En systematisk litteraturoversikt och meta-analys undersökte inledningsvis eventuella effekter på gångmönstret (mätt med biomekaniska utfallsmått) hos personer som haft stroke och tränat med en gångassisterande robot (delstudie I). Två deskriptiva tvärsnittsstudier (delstudie II och III) kvantifierade gångmönstret hos 31 personer med stroke och 41 kontrollpersoner med hjälp av kinematiska utfallsmått. Kurvanalys (delstudie II) användes för att undersöka två inklinationsvinklar som applicerats mellan Centre of Mass (CoM) och fotled respektive huvud. Genom dessa undersöktes om personer med stroke hade annorlunda rörelsemönster vid gång i jämförelse med kontrollpersonerna. Vidare beräknades en felklassificeringsfrekvens för olika kombinationer av kinematiska variabler (delstudie III). Detta för att identifiera vilken kombination av variabler som mest korrekt kunde särskilja en person med stroke från kontrolldatat. Slutligen genomfördes intervjuer med personer med nedsatt gångförmåga efter stroke (delstudie IV). Dessa personer hade deltagit i en sex veckor lång träningsintervention som innefattat högintensiv konventionell och robotassisterad gångträning. Intervjuerna analyserades med kvalitativ innehållsanalys.

Den systematiska litteraturöversikten (delstudie I) omfattade 13 studier med totalt 412 individer. Meta-analyser visade generellt inga signifikanta skillnader vad gäller effekten på biomekaniska mått mellan grupperna som tränat med en gång-assisterande robot jämfört med de som tränat utan roboten. Båda träningsgrupperna förbättrades lika mycket. Utöver det konstaterades metodologiska svagheter i de inkluderade studierna, samt en inkonsekvens gällande vilka biomekaniska utfallsmått som använts. Delstudie II påvisade bilaterala anpassningar av rörelsemönstret i benen bl.a. för ökad understödsyta. När personerna med stroke gick, konstaterades de även luta bälen mot sin delvis förlamade sida i betydligt högre grad än kontrollerna. Vidare identifierades kombinationer av 2-3 kinematiska gångvariabler som tillsammans bäst särskilde personer med stroke från kontrollpersonerna (delstudie III). Spatials och temporala variabler som exempelvis gånghastighet och steglängd skulle optimalt kombineras med data om ledvinkelrörelser i exempelvis bäcken eller fotled. Analyser av intervjuerna resulterade i fyra kategorier som beskrev: 1) En generellt positiv attityd vid interventionens start; 2) Upplevelsen av den högintensiva gångträningen som fysiskt och mentalt krävande, men också givande. Fysioterapeutens roll lyftes fram särskilt och betydelsen av en uppmuntrande, inkluderande och professionell kommunikation ansågs avgörande för bibehållen motivation; 3) Upplevda fördelar med den robot-assisterade träningen, såsom möjligheten att gå längre sträckor, men också svårigheterna i att finna rytm och kontroll i samarbetet med roboten; samt 4) Känslor av ökat självförtroende men även oro inför framtiden.

Det finns fortfarande kunskapsluckor att fylla för att nå optimerad utvärdering och rehabilitering av gångförmåga efter stroke. Avhandlingens litteraturöversikt visade att RAGT och konventionell gångträning generellt har samma effekt på gångmönstret hos personer som haft stroke. Standardiserade biomekaniska utfallsmått för utvärdering av gångmönster saknas fortfarande och avhandlingens tvärsnittsstudier betonade betydelsen av att gånganalyser utgår från ett helkroppsperspektiv. Intervjuerna lyfte fram värdefulla motiverande såväl som hindrande aspekter som bör beaktas i samband med design och genomförande av högintensiv gångträning samt vid vidareutvecklingen av gångassisterande robotar.

Abbreviations

A-CoMIA	Ankle-Centre of Mass Inclination Angle
BMI	Body Mass Index
BWS	Body Weight Support
CI	Confidence Interval
EMG	Electromyography
FMA	Fugl-Meyer Assessment
GC	Gait Cycle
GRADE	Grading of Assessment, Development and Evaluation
HAL	Hybrid Assistive Limb system
H-CoMIA	Head-Centre of Mass Inclination Angle
ICF	International Classification of Functioning, disability and health
MD	Mean Difference
MR	Misclassification Rate
Non-RAGT	Non-Robotic-Assisted Gait Training
o-RAGT	over-ground Robotic-Assisted Gait Training
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RAGT	Robotic-Assisted Gait Training
RCT	Randomized Controlled Trial
t-RAGT	treadmill-based Robotic-Assisted Gait Training
WHO	World Health Organization

Original Papers

This thesis constitutes the following papers. In the text, each paper will be referred to by its respective Roman numerals.

- I. Nedergård H, Arumugam A, Sandlund M, Brändal A, Häger CK. Effect of robotic-assisted gait training on objective biomechanical measures of gait in persons post-stroke: a systematic review and meta-analysis. *Journal of Neuroengineering and Rehabilitation*. 2021 Apr 16;18(1):64. doi:10.1186/s12984-021-00857-9
- II. Nedergård H, Schelin L, Frykberg GE, Häger CK. Inclination angles of the ankle and head relative to the centre of mass identify gait deviations post-stroke. *Gait Posture*. 2020/10/01/;82:181-188. doi:10.1016/j.gaitpost.2020.08.115
- III. Nedergård H, Schelin L, Liebermann DG, Johansson G, Häger CK. Towards a consensus of kinematic variables to be used for evaluation of gait post-stroke. (*Manuscript*)
- IV. Nedergård H, Sandlund M, Häger CK, Palmcrantz S. Users' experiences of intensive robotic-assisted gait training post-stroke - "a push forward or feeling pushed around?" (*Submitted manuscript*)

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Preface

The title of this thesis, “Taking the next step”, is inspired by a quote from one of the research participants. It relates to the struggle of a person post-stroke when striving to overcome the physical and mental consequences that are challenging her on an everyday basis. But it also refers to the step-by-step progress in the research fields that aim to improve post-stroke rehabilitation, as well as to my personal development as a physiotherapist and researcher.

When I began as a PhD student, I could never have imagined the frustration, feelings of hopelessness and incompetence I would occasionally experience during these years. But then again, neither could I have predicted the pleasure I would find from digging deeply into details, nor the joy of engaging in discussions with others that share the same obsession for learning more. It has been a road filled with potholes and obstacles, but also beautiful views and even a couple of downhills now and then. I have gained new insights regarding both my weaknesses and capabilities and learned to be humble for the competence of others and their efforts, struggles and engagement. Somewhere along the road, I discovered the meaning of patience and the value in doing things over and over again, taking small but persistent steps towards improving. Each step we take is part of a longer journey, taking us somewhere else than where we were before.

Introduction

Stroke is one of the leading causes of disability worldwide. Although substantial progress has been made in the last two decades concerning stroke prevention strategies and the acute treatment following a stroke, only modest improvements have been shown on motor function outcomes. While giving rise to a broad variety of body function impairments, the consequences of stroke limit a person's daily life activities and restrict their participation in society. The stroke rehabilitation field is faced with the challenge of tailoring evidence-based treatment strategies to the different needs of the individual. To accomplish that, evaluation of motor function should be broad and cover assessments ranging from the biomechanical details of movement patterns to the personal experiences of disability. This thesis strives to contribute with the next steps towards a consensus concerning the evaluation of gait ability post-stroke and expand the discussion regarding how to optimise gait rehabilitation to benefit the person afflicted by stroke.

Stroke and motor function

Stroke is commonly defined as a neurological deficit associated with an acute focal injury that persists for ≥ 24 hours or until death and is caused by a vascular disorder (either due to ischemia or haemorrhage) in the central nervous system (1). Improvements in living standards and health services, combined with more efficient stroke prevention strategies (such as control of risk factors like high blood pressure, diabetes and cigarette smoking), have resulted in a significant decrease in the age-standardised incidence of stroke from 1990 to 2010 in high-income countries (2). In line with this, the incidence rate, as well as the mortality rate due to stroke, have decreased in Sweden by nearly 40% in both men and women during the last 15 years (2004- 2018) (3). In 2018, there were approximately 25 500 new stroke cases registered in Sweden, of which 54% were men (mean age: 73 years) and 46% were women (mean age: 78 years) (4).

While the stroke mortality rate seems to have decreased more rapidly than stroke incidence, the global burden of stroke is increasing in terms of demands on health care and social care systems (2, 5). Despite the considerable progress in stroke prevention, early stroke diagnosis (e.g., using neuroimaging) and acute treatment (use of thrombolytic therapy and the development of organized stroke care in stroke units), the consequences on motor function following stroke may still be comprehensive (6, 7). About 80 million stroke survivors are currently estimated worldwide (8) and at least 140 000 Swedes live with varying degrees of disability due to stroke (9).

Disability after stroke

The reduction in arterial blood flow due to stroke causes damage to the brain tissue and neuronal networks while hindering the supply of oxygen and nutrients to the specific brain region (10). This leads to an acute onset of cognitive and physical impairments. Most often the person suffers a hemiparesis affecting unilateral sensation and movement ability. The severity of the functional impairments varies greatly between individuals and depends on the location of the injury, and the duration and extent of the reduced blood flow. Many persons survive the initial event and impairments often remain mild. For others, the damage following a stroke can be devastating. Some spontaneous recovery is most commonly further augmented by rehabilitative therapy. Long-term rehabilitation might be required and rehabilitation programmes that focus on learning new and relearning old skills often last for several months. Despite this, one-third of stroke survivors report unfavourable physical, social, cognitive and emotional functioning that affects their everyday quality of life (2, 11).

Disability in general, and disability after stroke in particular, is a multifaceted phenomenon that affects the person in a number of ways. It should therefore be defined from a broad perspective that includes biological, individual and social factors. The World Health Organization (WHO) has developed a universally applicable classification and assessment tool that provides a coherent view of health and disability, namely the International Classification of Functioning, disability and health (ICF) (12). The classification system is used for identification of health care and rehabilitation needs and for measuring the effect of rehabilitation interventions from a comprehensive perspective. The framework identifies three domains of a health condition: 1) body function and structure (physiological/psychological functions and anatomical structure), 2) activity (execution of a task), and 3) participation (involvement in a life situation) (Figure 1). Disability implies dysfunction (impairment, activity limitation and/or participation restriction) in one or several domains and is also closely associated with the context involving environmental and personal factors.

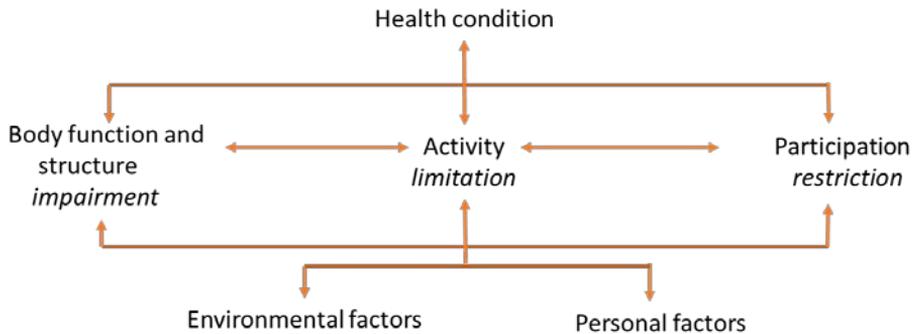


Figure 1. The domains included in the International Classification of Functioning, disability and health, WHO.

The ICF domains interact and are closely connected. Activity limitations (like difficulties in walking, standing etc.) are related to, although not completely dependent on, the level of motor function impairments (such as muscle weakness, impaired movement control and perception) included in the domain of body structure and function (13). Limitations in body function and activities are likewise associated with eventual restrictions in participation (for instance possibilities of taking part in social activities). Furthermore, environmental (for instance physical barriers like stairs, social attitudes, climate) and personal factors (such as gender, education, adaptability and coping skills, cognition and learning ability) are equally important. These form the physical, social and attitudinal circumstances that influence how the consequences of disability are experienced by the individual.

Pathways to recovery; “true recovery” or compensation?

The onset of motor disability due to stroke generates powerful body engagement in the development of alternative ways of performing daily activities (14, 15). Essentially, any motor function improvement is driven by neural reorganization enabled by the concept of plasticity, that is the ability of the cells in the central nervous system (CNS) to modify their structure and function in response to a variety of external stimuli (16, 17). These structural-anatomical or functional changes in the brain either serve to find alternative means to activate the same muscles used for the task before the injury, then referred to as “true recovery”, or to use alternative muscles in compensatory movement strategies (18, 19). Both approaches result from a motor learning process that involves neural reorganization, which is changes in genes, synapses, neurons and neural networks within specific brain regions that are connected to the damaged area of the brain (20). Functional neuroimaging methods and brain mapping have

provided insights into the underlying remodelling and re-organization processes for functional recovery. Some degree of neural reorganization, although rarely complete, is nearly almost achieved following stroke (21). There is, however, an ongoing debate about which areas are activated and the contribution of different areas in terms of beneficial re-organization for functional recovery (22). When performing a task, persons with good recovery post-stroke are suggested to have brain activation patterns that are similar to those who are not disabled, whereas impaired persons continue to recruit larger portions of secondary motor areas.

As mentioned above, motor learning is an essential component of post-stroke recovery (23). Learning might be controlled and directed specifically to stimulate “true recovery”, but it may also be the driver for a variety of more or less self-taught movement adaptations. In fact, the development of compensatory strategies to perform daily activities in the presence of lost function is one of the most reliable behavioural consequences of brain damage (24). Individual joint movements can be combined in many different ways to perform a specific task and compensatory movement strategies post-stroke involve the use of the unaffected limb or alternative muscle groups on the affected side to overcome functional constraints (16, 25). Another strategy is described in agreement with Bernstein’s theories of human movement behaviour, where the solution for problems in controlling coordination consists of reducing the number of independent elements to control (26). For the person post-stroke, this is observed in reduced joint involvement in the affected side, proximal motor control and uncoupling of successive joint movements. These adaptations enable increased movement control with higher accuracy and lesser energy demands (27). Different compensatory strategies are associated with different functional and structural changes in the brain. For example, major restructuring and neuronal growth in the contra-to-lesion hemisphere is associated with the reliance on the less-affected limb commonly observed after unilateral cerebral damage (23, 28).

From the viewpoint of a person post-stroke, the distinction between “true recovery” versus compensation may not be important as long as the consequences of disability are minimized and the quality of life is restored. This distinction is nevertheless of fundamental importance when aiming to understand the mechanisms of stroke recovery and the development of successful therapies within post-stroke rehabilitation.

Rehabilitation and timeline

Based on the knowledge of the biology of recovery, a common framework has been suggested to define five different phases post-stroke (16) (see Figure 2). The framework outlines critical timepoints post-stroke, advocating that the time

perspective may be of specific importance to guide the choices of treatments to maximise the potential of restorative interventions.

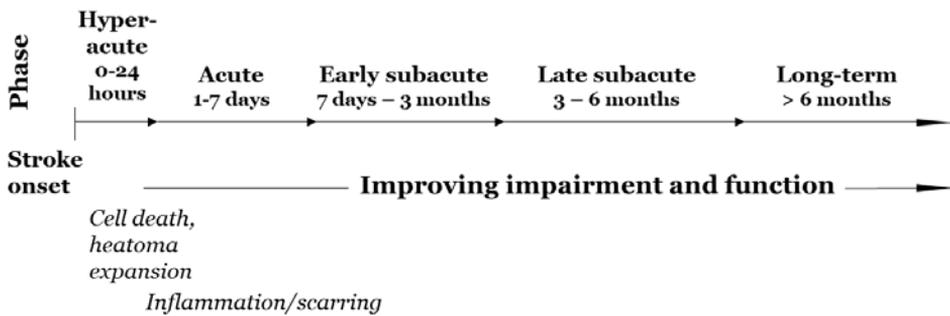


Figure 2. The phases post-stroke presented on a timeline

The current understanding of brain repair processes implies that the majority of behavioural recovery, and rapid changes in general, occurs during the first weeks-to-months post-stroke (16). During this early phase post-stroke, some improvements in motor recovery seem to occur irrespective of type and amount of therapy treatment (29), although research indicates that optimised training during this phase may stimulate neural reorganization even more. For instance, Biernaskie et al. (30) found that a 5-week period of rehabilitation initiated 30 days after cerebral infarcts were far less effective in improving functional outcome and in promoting the growth of cortical dendrites than the same regimen initiated 5 days post-infarct. Nevertheless, it is still not defined exactly when the brain is most responsive to the sensorimotor input or targeted application of stimuli that is suggested to promote plasticity (31). Studies have reported the possibility of different brain regions being variously responsive to treatments during different phases post-stroke (32). There is thus still much to be learnt regarding when and how the therapy should be designed and carried out to most efficiently stimulate neural reorganization.

Strong evidence indicates a lifelong ability of the human brain to reorganize itself to encode new experiences and improve functional abilities (24, 33, 34). Any experience or occasion for learning may stimulate anatomical and structural changes in the brain (32). We learn and remember and change our thoughts and behaviours continuously throughout our lifetime. Therapy promoting neural restructuring should, therefore, be valuable at any age and any phase post-stroke. There may be time windows in which directing reactive plasticity is particularly effective following a brain lesion. Even if neural reorganization seems not to be limited to age or time post-stroke, it has been suggested that time delays in rehabilitation may allow for a greater establishment of self-taught compensatory

behaviours of which some may interfere with rehabilitative training efforts (20). For example, the reliance on the non-affected body side may limit the propensity of individuals to engage in behaviours that improve the function of the impaired body side.

Post-stroke rehabilitation, both in the acute inpatient ward and in the outpatient setting, combines stimulation of “true recovery” and compensatory strategies to achieve improvements in function, independence, and quality of life (8, 34-36). There is a need for an improved understanding of the mechanisms that drive recovery of post-stroke impairments and disabilities, as well as their associated time limitations (37, 38). The differentiation between functional recovery in terms of restitution of impairments, and the development of adaptive strategies resulting from a learning process is complex and yet to be further explored.

Gait ability and gait rehabilitation post-stroke

In the late subacute phase, three months after stroke onset (Figure 2), about 80% of persons afflicted by stroke experience walking problems (39). In a comprehensive prospective study including over 800 persons after stroke rehabilitation in Copenhagen, Denmark, 18% were not able to walk at all, 11% walked with assistance and 50% could walk independently (40). The recovery of walking is affected by multiple factors such as the received rehabilitation, location and extent of the lesion (41). Despite regaining the ability to walk, post-stroke muscle weakness, pain, spasticity and impaired balance control can lead to reduced tolerance to activity, fear of falls and a sedentary lifestyle. During the first year post-stroke, 70% of community-dwelling persons fall (42), and most falls have been shown to occur due to loss of balance during walking (43). Assessments of daily activities related to walking have shown that the number of steps taken per day for community-dwelling persons with mild-to-moderate impairments in a long-term phase post-stroke has high individual variety (60-6000 steps/day) (44, 45). The mean value (3000 steps/day) is however far below the daily steps count for age-matched sedentary healthy older individuals (5000-6000 steps/day).

Gait ability has been reported to be of high importance in the everyday lives of persons post-stroke since it affects aspects like mobility and self-care as well as the community and social life (46, 47). It is therefore not surprising that improved gait ability is one of the most commonly stated goals in post-stroke rehabilitation (48, 49), and that persons who undergo rehabilitation programmes spend more time practising walking compared to all other activities (50). Walking straight, at a steady pace and without fear of falling are considered desirable skills (46). Inability to walk independently is an identified predictor for discharge to nursing homes (51) and an increased probability of death (52). Walking endurance also

seems to be related to the community reintegration of persons who have suffered a stroke (53, 54) and is assumed to provide some protective effects against common secondary complications such as e.g., cardiovascular disease or osteoporosis (55).

Investigating gait

Walking is described as a balanced forward progression of alternating weight-bearing limbs (56). Among non-disabled persons, this is an automatized movement involving a cyclic process that requires comprehensive interactions between the muscles, bones and the nervous system (57). One gait cycle (GC) defines the period from initial contact, when the foot first touches the floor, through the stance and swing phase of the same foot, and to the next occurrence of initial contact with the same foot (Figure 3).

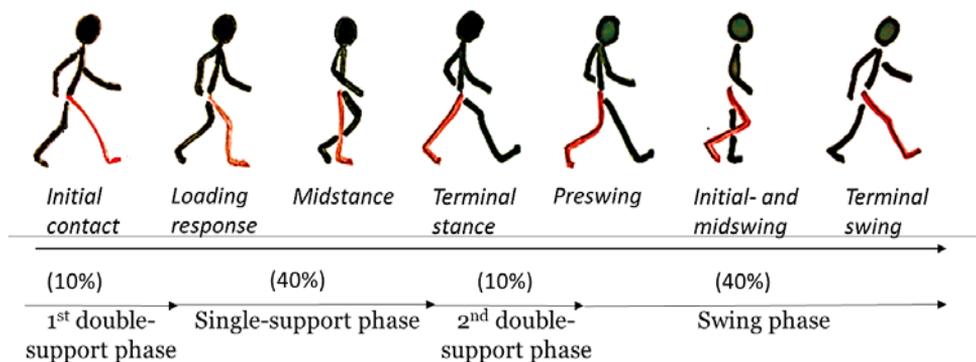


Figure 3. Description of the sequences of events and phases of one gait cycle for non-disabled individuals.

In non-disabled gait, the stance phase constitutes 60% of the GC; of which the 1st double-support constitutes 10%; the single-support 40%; and the 2nd double-support phase 10% of the GC. Equilibrium comprising of stabile postural control, smooth weight shifting and coordinated muscle activity are essential throughout and during repeated GCs (56, 58). A symmetric movement pattern characterizes normal gait and occurs when the spatial and temporal parameters of both body sides are the same during the entire GC (59). A genetically determined spinal circuit that is capable of generating the basic locomotion pattern forms the central program together with various descending pathways to stop, trigger and steer. The feedback system is combined with muscle and skin afferents and the vision, audition and vestibular senses. Proprioceptive input can adjust the timing and degree of activity of the muscles and thereby adjust the locomotion pattern during

the different phases of the GC (60). Stability in the stance phase, foot clearance before the swing phase, pre-positioning of the foot for initial contact, adequate step length and energy conservation are all factors suggested necessary for normal gait (57).

The central pattern generators are networks of nerve cells in the spinal cord that, independent of sensory input, activate different motor neurons in a suitable sequence and intensity to generate the basic motor pattern for rhythmic stepping (61). The contributions from the cerebral cortex, basal ganglia, brainstem and cerebellum are the basis for the unique walking pattern in humans (62). Information from the peripheral sensory system and descending inputs from the motor cortex may shape the stepping function and enable balanced walking in different environments and under various circumstances. Injury to the central nervous system, such as a stroke, causes disturbances in the balance between the automatic and executive gait pattern control. The earlier gait, automatised and performed with little effort, then becomes a performance that requires a substantial degree of awareness and attention.

Investigating gait requires observation of several spatial (related to distance), temporal (related to timing), kinematic (motion without regard to forces or moments) and kinetic (forces and moments affecting motion) factors during the different phases of gait. Improved insight into the complex interaction between neuromuscular impairments and post-stroke gait may help to standardise the evaluation of gait movement pattern quality and influence the clinical decision-making process. Knowledge of deviations in gait pattern function is also fundamental when striving to identify gait rehabilitation interventions that stimulate neural reorganization (8, 18, 36, 38). There is hence a need for a consensus regarding which outcome measures that most efficiently discriminate post-stroke gait from the gait of non-disabled persons and that distinguish “true recovery” from compensation (63-66).

In observational gait analysis, the human eye is highly sensitive to detecting deviations from normal. To quantify specific details in the gait movement pattern, however, an instrumented gait analysis is necessary. Several types of motion capture systems are available today. Markerless methods, such as 2D or 3D video systems, allow tracking without the participants being limited by physical markers. Inertial motion tracking systems consisting of accelerometers and gyroscopes and magnetometers, for instance, can also be used in a variety of environments. Still, the marker-based, 3D optoelectrical motion tracking systems are often referred to as the gold standard (67) due to their superior accuracy compared with other systems (68). An infrared camera system registers the positions and motions of reflective markers that are placed on the skin in relation to anatomical landmarks. The system thus enables registration of time-distance

variables (spatial-temporal data) and overtime recordings of joint motions (kinematics) described in the three planes of space, including linear and angular motions, velocities and accelerations. The camera system covering a specific walkway is also often used in combination with synchronised force platforms that add information on joint moments and powers (kinetics), and with dynamic electromyography that registers muscle activity. Even though the interpretation of the collected data might leave room for some amount of subjectivity, the actual data is based on objective, accurate and reliable measurements. The system requires a special lab and equipment, as well as educated staff and time resources for gathering and analysing the biomechanical data. These factors limit the availability of such systems within common clinical contexts. Since the information gathered through an instrumented gait analysis has been proven valuable, continuous efforts are made in developing easily applicable and low-cost alternative motion tracking systems such as the markerless and inertial systems mentioned above, but also devices for recordings of spatial and temporal parameters of gait such as foot switches, in-shoe pressure sensors or pressure mats etc. (68-70).

Instrumented gait analysis has most commonly focused on lower limb movements. Importantly though, recent research suggests that upper limb movements along with movements of the trunk and/or the centre-of-mass (CoM) should be included in gait analysis (71-74). Such parameters are suggested to be related to factors of importance for gait ability such as balance control (75), energy expenditure and functional ability during gait (76). Reliable and valid outcome variables representing a wider perspective are hence requested to expand the understanding of post-stroke gait.

The hemiparetic gait and post-stroke gait rehabilitation

The hemiparetic gait pattern is characterised by a reduced gait speed due to decreased step/stride length, along with spatial and temporal asymmetry and an increased GC time (58, 67, 77-79). Evidence indicates that persons post-stroke walk with decreased postural stability and increased mediolateral and anteroposterior trunk movements (73). The typical reciprocal motion of the arms is absent or reduced, sometimes being flaccid or placed in a silent position of elbow flexion and deviating shoulder abduction/adduction (67, 80). These deviations in the hemiparetic arm have been reported to interfere with balance and safe ambulation (81). Weakness in ankle dorsi and plantar flexors, hip flexors, knee extensors and knee flexors of the affected leg is correlated with both self-selected and fastest possible gait speed (82). A shorter stance time and longer swing time of the affected leg characterise the pattern of temporal asymmetry, while spatial asymmetry is most commonly associated with a shorter step length of the non-affected leg (although the opposite also has been observed) (83, 84).

Circumduction and hip elevation to achieve foot clearance during the swing phase, prolonged knee flexion at the stance phase or hyperextension during the late single-support phase, are commonly observed strategies to overcome decreased muscle strength, impaired motor control and balance (67, 79, 85). Additionally, muscle co-activation in both the affected and non-affected lower limb is a common compensatory strategy providing mechanical stability by stiffening the joints (67, 86).

Gait performance can not be separated from its functional purpose in facilitating a large range of daily life tasks (13). Indoor ambulation requires the ability to walk on different floor textures, turn around, avoid obstacles, ascend and descend stairs, adopt and maintain different positions while at the same time reaching for or using different objects etc. All these tasks may seem simple from the perspective of a skilled, independent, non-disabled person, but request a lot from a person afflicted by gait impairments. Human walking requires, in addition to the necessary body functions, the capacity to process information about the physical and social environment (13). Normal walking implicates complex interactions with the physical and social environment while proceeding towards a predefined goal. This puts high demands on awareness, focus and distributive attention and shortcomings in the information process increases the risk of falls.

Responding to an increased understanding of the mechanisms behind recovery and neuroplasticity, a paradigm shift seems to have occurred in the research area of gait rehabilitation post-stroke (87). It is currently recommended that rehabilitation methods should strive to stimulate the nervous system's ability to recover a normalised movement pattern, rather than encourage compensation for impaired mobility, motor control, and balance (6, 18, 36, 38). The rehabilitation programme should provide for improvements and retraining of posture, static and dynamic balance, muscle strength, movement control and coordination (13). Walking exercises that stimulate weight bearing on the paretic limb, aerobic function, balance control, and functional strengthening appear to be most efficient for improving gait ability (88). Intensive and task-specific training that implicates active patient participation and is performed in an enhanced training environment with the use of biofeedback and mental imagery has so far been suggested to stimulate neuroplasticity and improve functionality in all phases post-stroke (6, 20, 88-92). Ideally, the gait rehabilitation programme should incorporate a combination of activities that promote a large number of steps and a range of different walking tasks (stepping and walking forward, backwards and to the sides) on different surfaces and with additional challenges stimulating simultaneous information processing.

The post-stroke gait rehabilitation programme should be tailored to the specific needs of the individual, hence actively engage the person in the design, goal

setting and performance of the training programme (92-94). The experiences of individuals who participate in gait rehabilitation post-stroke are however rarely reported. Reviews that have explored experiences of general physical rehabilitation among patients and stroke survivors, describe barriers related to environmental (i.e., access, transport, cost) or self-perceived physical abilities, embarrassment, fear of falls or fear of recurrent stroke (93-95). Disempowerment, fatigue, boredom and frustration have also been reported as negative experiences. The same reviews emphasize aspects such as meaningfulness, partnership, patient education, communication and collaborative goal-setting. Additionally, factors like accessibility, availability and professional support have been reported to be related to patient satisfaction after hospital discharge.

High-intensive robotic-assisted gait training

As a response to the call for high-intensive and task-specific training, the field of medical technology has developed gait-assisting robots. These are advocated to provide intensive quality treatment at a lower cost and effort, reducing the physical strain on physiotherapists while increasing the number of steps that the person undergoes during one training session (96-98). The electromechanical devices assist the stepping cycles by supporting body weight while automating the gait process through the facilitation of movement in one or several lower limb joints (99). They allow early verticalisation and enable safe and highly repetitive gait training that is otherwise particularly difficult to perform for non-ambulatory persons post-stroke (13). Yet another feature of robotic-assisted gait training (RAGT) is the enabling of training intensity to restore an adequate level of cardiorespiratory efficiency (99). Persons post-stroke generally suffer poor cardiovascular fitness, including a decline in general mobility followed by a reduction in quality of life (100). Considering that cardiovascular disease is the leading prospective cause of death in people with chronic stroke (101), this is a feature of importance.

An increasing amount of different gait-assisting robotic devices are commercially available and are generally categorised according to the support they provide (102). Treadmill-based RAGT (t-RAGT) is either performed with end-effector robots that drive two footplates that simulate the phases of the gait or with exoskeleton orthoses (see Figure 4) that move the lower body extremity joints in coordination with the phases of gait (99). T-RAGT is most commonly used in combination with body weight support. Overground RAGT (o-RAGT), on the other hand, is provided by wearable powered exoskeletons. These allow a person to walk overground on hard and flat surfaces while enabling the user to experience increased proprioceptive input compared with stationary treadmill training (103).



Figure 4. Treadmill-based RAGT performed with an exoskeleton, the Hybrid Assistive Limb® (HAL; Cyberdyne, Tsukuba, Japan).

RAGT systems are suggested to enable intensified gait training which is assumed to 1) positively affect gait ability and balance, 2) enable gains in cardiovascular function, and 3) stimulate the restoration of motor skills which should generate a gait movement pattern closer to that of non-disabled persons (104-106). Trials that have evaluated the effects of RAGT have, however, reported inconsistent results. Reviews have revealed that RAGT in combination with conventional physiotherapy may have a slightly better or similarly positive effect on gait speed and ambulation when compared with conventional gait training alone (97, 107-114). The possible effects of RAGT on the gait movement pattern have, however, not yet been thoroughly investigated, and the mechanisms underlying potential functional gains achieved through RAGT in individuals post-stroke are still poorly understood (16, 112, 113, 115). Little is, for instance, known about the effect of assistance control strategies on neural reorganisation. The robotic-assisted movements have been argued to require less neural activation than actively engaged voluntary movements of limbs, even when individuals are unable to actually move the limb (116). This could eventually counteract the positive effects of RAGT. Additionally, as neural reorganisation and improved motor control is a product of personal learning, reviews have highlighted the need for evaluations of the patients' expectations and experiences from training with a gait-assisting robot (97, 107, 108). A deeper understanding of the experienced barriers and facilitators would enhance the design of improved rehabilitation. Insights into different perceptions of performing RAGT could also reveal possible explanations for the reported differences in the outcomes concerning this type of training.

The effect of gait rehabilitation interventions using the ICF framework

The American Physical Therapy Association (APTA) presented in 2018 a core set of outcome measures related to walking to be used for adults with neurological conditions undergoing rehabilitation (117). The core set included the Berg Balance Scale (118), the Balance Confidence Scale (119) and the Functional Gait Assessment (120). The 10-meter Walk Test (121) was recommended for assessing gait speed and the 6-Minute Walk Test (122) for assessing changes in walking distance. All these outcome measures have shown acceptable clinical utility and provide valuable information regarding a person's gait ability. Yet their results are narrowed to evaluate gait ability on one ICF level alone, namely the activity level. Nevertheless, gait training interventions have the potential to improve gait-related outcomes across all domains of the ICF (body function and structure, activity and participation) (16). It would hence be ideal, or even necessary, to use a variety of outcome measures representing each ICF domain when evaluating gait rehabilitation interventions (88, 123). To aid the discovery of new and more targeted treatments, the Stroke Recovery and Rehabilitation Roundtable (2017) published a consensus-based recommendation for standardized measurements of sensorimotor recovery in stroke trials (38). The recommendations are aligned with the ICF, taking all the domains into account. The Fugl-Meyer assessment (124), specifically developed to assess motor recovery after stroke, was recommended to incorporate the domain of body structure and function. The need for complemented kinematic and kinetic measures was however also strongly acknowledged. Research has shown that gait improvements post-stroke are not linearly related to the underlying impairments. Improved muscle strength does not automatically induce improved gait function (88) and increased gait speed is not necessarily generated by a more close to normal gait movement pattern (125). Measuring activity limitations alone does not capture specific movement strategies, and the measurement fails to distinguish whether the improvements achieved are due to "true recovery" or compensation (16, 18, 19, 24, 38, 126).

Neuroplasticity drives normalisation of the quality of gait and is suggested to be strongly reflected by measures of inter-limb coordination, such as, e.g., symmetry between the affected and non-affected side in spatiotemporal, kinematic and kinetic parameters of gait (38, 67). To fully understand the effects of a gait training intervention from a wider perspective the evaluation should be broadened to include details of the specific gait movement pattern (ICF: body structure and function), as well as the activity level and the subjective experience of walking and participating in gait rehabilitation programmes (127). No individual treatment is likely to apply to every patient (37). A broadened perspective will enable the identification of responders and non-responders of a

given intervention and facilitate the development of efficient, individually adapted gait rehabilitation treatments.

Rationale for this thesis and study aims

Post-stroke gait rehabilitation faces challenges in meeting the needs of a population with a comprehensive variety of cognitive and physical impairments and severity levels. The assumption of universally applicable treatments has been questioned and attention is instead suggested to focus on identifying responders to treatments based on individual prerequisites/determinants (38). The steps towards achieving this include a broadened knowledge concerning 1) quantification of deviating gait movement patterns using a whole-body perspective and 2) experiences of gait rehabilitation that may influence the efficiency of such an intervention.

These factors are the main concerns of this thesis which initiates from a biomechanical perspective, using a magnifying glass when striving to evaluate gait performance by detecting relevant details in body function and structure during walking post-stroke (Paper I-III). Within the research area of post-stroke gait and biomechanics, the importance of identifying specific gait movement patterns manifested in biomechanical measures has been emphasized while striving to separate between compensatory movement patterns and a “closer-to-normal” movement pattern suggesting “true recovery” (16, 18, 19, 24, 38, 126).

Even though it most certainly makes all our assumptions more problematic, we cannot separate the objective measures used to evaluate gait from the subjective experiences of walking and training gait. The fourth and final study of this thesis thus shifts the focus from the biomechanical details to explore the perceptions of participating in a high-intensive post-stroke gait rehabilitation intervention that included RAGT.

Study	Knowledge gaps	Aims
I	Effects of RAGT have been investigated in several reviews presenting functional outcomes. No review has however addressed the evidence for possibly superior effects of RAGT compared with non-robotic treatments on specific gait movement patterns.	Summarize the evidence for potentially superior effects of RAGT on biomechanical measures of gait post-stroke when compared with non-robotic gait training alone.
II	There is a need for a whole-body perspective when quantifying gait post-stroke. Gait movement patterns thus need to be more comprehensively investigated to not only include lower limb movements.	Investigate the coordination between the upper and lower body and body symmetry during gait post-stroke, while exploring the discriminative ability of an upper and lower body inclination angle in relation to the centre of mass.
III	Instrumented gait analysis post-stroke is becoming more common in research and clinics. Consensus regarding the most relevant and informative descriptors of gait has been advocated critical for evaluation and rehabilitation post-stroke.	Identify core sets of combined kinematic variables to most efficiently differentiate post-stroke gait from the gait of non-disabled persons.
IV	Trials performing RAGT post-stroke report inconsistent results. Reviews have requested knowledge on how to optimise training and whether there are responders and non-responders to treatment. One key factor is an immersed knowledge about the experience of high-intensive gait training including RAGT.	Describe the experiences of individuals who participated in a high-intensive gait training programme that included RAGT in a long-term phase post-stroke.

Materials and Methods

This thesis comprises four studies in which quantitative and qualitative methods have been used to elicit and interpret data to answer different research questions. The cross-sectional studies (Paper II and III) were conducted at the U-motion laboratory, Department of Community Medicine and Rehabilitation, Physiotherapy, Umeå University. The interview study (Paper IV) was part of a randomized controlled trial (RCT) investigating the effects of the Hybrid Assistive Limb (HAL) system on gait ability in persons post-stroke. Data collection was performed at the University Department of Danderyd Hospital and the Department of Clinical Sciences, Karolinska Institute, Stockholm.

Table 1. Design and overview of the papers

	Study type	Data set	Data collection	Analysis
Paper I	Systematic review and meta-analysis	Data from 13 RCTs, including 412 persons in a subacute or long-term phase post-stroke	Data search and process following the PRISMA guidelines	Cochrane RoB2 and the GRADE criteria. Meta-analysis (random-effects model)
Paper II	Cross-sectional	31 participants in a long-term phase post-stroke, 41 controls	Instrumented gait analysis at the U-motion laboratory, Umeå University	Functional Data Analysis
Paper III				Leave-one-out cross-validation and logistic regression
Paper IV	Qualitative in the context of an RCT	13 participants in a long-term phase post-stroke	Semi-structured interviews performed at Danderyd Hospital, Stockholm	Qualitative content analysis

GRADE = Grading of Assessment, Development and Evaluation; PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis; RCT = randomized controlled trial; RoB = risk of bias

Datasets, participants and study contexts

A systematic review with meta-analysis investigating the effects of RAGT (Paper I)

The research question and eligibility criteria for the review were framed using the PICO approach (representing the patient population [P], the interventions [I], the comparator group [C], and the outcome [O]) (128), and the protocol was published in PROSPERO (CRD42020168846). Studies of interest were RCTs that involved adult participants (≥ 18 years of age) in an acute, subacute or long-term phase post-stroke and investigated the effects of RAGT assessed with biomechanical measures of gait.

Concerning inclusion criteria of the studies, no distinctions were made according to the type of stroke (haemorrhagic or ischemic), nor the functional ability or gender of the participants. RAGT should be performed in either an inpatient or outpatient setting, using an end-effector or exoskeleton for either treadmill or overground gait training. Studies that combined RAGT with other non-robotic therapies such as conventional physiotherapy or functional electrical stimulation (FES) were considered eligible for inclusion. Importantly though, all studies had to comprise at least one comparator group performing active, non-robotic gait rehabilitation. Non-weight bearing interventions that used non-interactive devices for delivering continuous passive motion, e.g., an isokinetic apparatus for passive knee flexion (129), were excluded. Likewise were studies that used devices for seated or standing lower extremity training (e.g., the MotionMaker™ (130), the Rutgers Ankle (131) or the Active Knee Rehabilitation Orthotic Devices (AKROD) (132)). The instrumented gait analysis had to be performed while walking without the assisting robot in either a laboratory or a clinical setting. The devices used for registering biomechanical gait parameters could be e.g. a 3-dimensional (3D) or 2-dimensional (2D) motion capture system, an optoelectrical or inertial system, a pressure mat, force shoes, or a magnetic or acoustic tracking system etc. The outcome measures of interest were parameters related to temporal and spatial information, kinematics and/or kinetics of gait. Studies that performed the gait analysis immediately after only a single training session were excluded, as well as studies using biomechanical outcomes measured solely by clinical testing, such as gait speed evaluated with a stopwatch or cadence reported from observations.

Kinematic evaluation of gait (Paper II and III)

For data collection in the cross-sectional studies, 31 persons post-stroke were recruited via two clinics for one assessment each at the U-motion laboratory, Umeå, Sweden. Inclusion criteria were: 35-85 years of age; >3 months post-

stroke; unilateral hemiparesis following an ischemic or hemorrhagic stroke; ability to walk indoors without aids; comprehension of written and verbal information in Swedish. Participants were excluded if they had any impairments other than stroke that may have influenced their gait performance. A control group consisting of 41 non-disabled persons were recruited among staff, acquaintances and local organizations. Individuals with musculoskeletal or neurological movement problems were excluded from the control group.

Table 2. Participant characteristics. Measurements are reported in Medians (Q₁, Q₃) unless otherwise stated.

	Post-stroke (n = 31)		Controls (n = 41)
	Moderate-Severe	Mild	
Time since stroke, months	25 (15, 49)	13 (8, 24)	N/A
Brain lesion side R/L (n)	6/7	9/9	N/A
Affected side D/ND (n)	7/6	10/8	N/A
Sex, male/female (n)	8/5	10/8	21/20
Age, years	71 (61, 75)	72 (60, 75)	68 (58, 73)
Height (cm)	169 (166, 177)	168 (165, 178)	174 (168, 181)
Body Mass Index*	27.5 (27.5, 29.3)	27.5 (24.4, 28.9)	24.5 (23.3, 26.6)
Statures per Second*	0.5 (0.3, 0.6)	0.6 (0.4, 0.7)	0.76 (0.7, 0.8)

R = Right, L = Left, D = Dominant, ND = Non-Dominant, N/A = not applicable. Statures per second describe speed in relation to height. * indicates significant differences between persons post-stroke and controls (Mann-Whitney Test; p<0.05).

Based on power calculations from pilot data on controls and persons post-stroke (power 80%, alpha 0.05), we estimated that 30 persons post-stroke would be needed for the study. The control data were collected for the purpose of this and other studies on gait (133, 134). Data from all available controls (n = 41) were included in the analyses since larger samples are often assumed to better represent the population. The groups did not differ significantly regarding characteristics such as age, sex and height. Furthermore, the theoretical properties of the statistical analyses of Paper II (related to error control) hold for unequal sample sizes.

The interview study exploring experiences of gait training (Paper IV)

The qualitative study was undertaken within the context of an RCT that investigated the additional value of training with a RAGT-system, HAL, in a long-term phase post-stroke. The study reported no additional value of RAGT on walking (assessed with the 6-Minute Walk Test) when compared with non-RAGT (135). Participants were 18-70 years old with stroke-related hemiparesis of the lower limb after an ischemic or haemorrhagic first-ever stroke (diagnosed by a stroke physician and verified by computer tomography or magnetic resonance imaging) 1-10 years earlier. For further details on the inclusion criteria and randomisation process that preceded the data collection, see Palmcrantz et al. (135).

Participants (n=20) had, together with specifically trained physiotherapists, performed high-intensive gait training including gait training on a treadmill with the assistance of the HAL exoskeleton for 6 weeks (3 sessions/week). The training was performed at a rehabilitation centre. Each session included 1) conventional gait and mobility training (limited to 30 min of training time), and 2) HAL training for a maximum of 1 h and 30 min (including approximately 30 min of donning and doffing the exoskeleton and harness). The HAL exoskeleton was attached to the participant's body with straps around the waist and the thigh and lower leg of the affected side. The HAL device assisted stepping cycles by supporting body weight and facilitating the gait process. It was used in combination with a harness (body weight support) to prevent falls and unburden the weight of the suit (9 kg) (136). Settings for assistance and support from HAL were individualised and continuously adjusted for each participant. Parameters such as gait speed, and time and distance of walking intervals, were monitored and reported, which enabled regular follow-ups on the performance and progression of the participant. The high-intensive conventional gait training was led by experienced physiotherapists and performed in accordance with the current best evidence-based practice and included overground walking with assistance, treadmill walking and training of gait function, strength and balance.

Because of unforeseen logistical reasons related to the transportation of the HAL suits, two participants were excluded halfway through the training period. Another two participants dropped out due to medical reasons. Hence, 16 participants completed the training period. Interviews were performed with 13 participants since three were excluded due to severe aphasia. The group were represented by men (n=8) and women (n=5) of different ages (range 37-70 years), as well as the full range in levels of walking independence according to the inclusion criteria (able to walk but in need of manual support or close supervision

due to lower extremity paresis). They took part in the study 13-49 months after stroke onset.

Data collection and data processing

Screening process, risk of bias ratings and quality assessments (Paper I)

Nine scientific databases (PubMed, Web of Science, EBSCO (Cumulative Index to Nursing and Allied Health Literature [CINAHL], Allied and Complementary Medicine [AMED], Academic Search Elite, Sports Discus), Scopus, ProQuest (Sports Medicine & Education Index) and the Cochrane Central Register of Controlled Trials (CENTRAL)) were systematically searched with terms and strategies adapted to the specific database. Retrieved abstracts and titles were exported to EndNote X9 (Clarivate analytics Software; Philadelphia, USA) for a manual screening process that followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement guidelines (137, 138). Screening of titles and abstracts was performed independently by two reviewers to reduce the risk of rejecting any relevant studies in adherence with the criteria that had been elaborated in the protocol. Only studies that did not clearly match the inclusion criteria were excluded in this stage of the screening process (e.g., populations such as individuals with Parkinson's disease, traumatic brain injury, etc.; study designs such as case studies, cross-sectional studies, etc.; different types of robots, like robots for training the upper limb, etc.; types of reports such as conference papers, reviews, etc.). In case of initial disagreements, the reviewers discussed the studies until a consensus was reached. When studies were not available as full texts, the author of the study was contacted via the e-mail address reported in connection to the abstract, or via ResearchGate.

After the final full-text screening of potentially eligible articles, data were independently extracted from the remaining records by two different reviewers. The reviewers met and compared results to verify a similar interpretation of the reported data in the included studies. The updated and comprehensive Cochrane risk of bias 2 tool (139) was employed to assess the risk of bias across studies. Risk of bias assessment followed the PRISMA guidelines (137) and was first performed independently by two reviewers for each study, then compared and discussed between the reviewers. To assess as objectively as possible, an additional reviewer was involved in the discussion when estimating the domain of bias due to missing outcome data because of somewhat unclear reporting concerning the number and reasons for missing outcome data.

In addition, the level of evidence for the biomechanical gait parameters of interest was corroborated using the GRADE (Grading of Assessment, Development and

Evaluation) criteria (140). According to the criteria, assessment of the certainty of evidence for each outcome was based on several factors, including eventual concerns regarding the risk of bias as well as other aspects, such as indirectness of the evidence, inconsistency of findings and imprecision of effect estimates across studies or potential publication bias (140). Concerns about these aspects downgraded the evidence by one (serious) or even two (very serious) levels.

Instrumented gait analysis and clinical motor assessment (Paper II and III)

The clinical Fugl-Meyer assessment (FMA; a scale to assess sensorimotor impairments in persons post-stroke (124)) and an instrumented gait analysis was performed in the U-motion laboratory at Umeå University, Sweden. In accordance with a full-body model, single spherical reflective markers (n=72, diameter of 12 and 19 mm) were affixed with skin-friendly double-sided adhesive tape, and rigid clusters were attached with Velcro straps, on defined anatomical locations of the body (for details see Frykberg et al. (133)). The two same test leaders applied markers for the entire control group and 25 persons post-stroke, and a third test leader applied the markers for the six remaining persons post-stroke. Marker placement adhered to a strict protocol and the third test leader performed a pilot test under supervision of the first test leader before the complementing data collection. The participants were asked to walk barefoot on a 10 m walkway for six to ten trials at a comfortable speed. Assistive devices or personal support were not allowed, but if necessary the test leader walked beside the participant to minimize risk for falls. During the middle 3 meters of the walking distance, an eight-camera three-dimensional motion capture system (Oqus®-cameras, Qualisys, Gothenburg, Sweden) emitted and captured infrared light reflected by the markers, and recorded motion data. One recording typically included 2-4 GCs for each leg, of which all were to be used in the forthcoming analyses. Two-dimensional cameras (Canon Legria HV40) were positioned beside and in front of the walkway, providing a frontal and sagittal plane view for post-testing control.

Motion capture files with recordings were tracked in Qualisys Track Manager Software (version 2.2, Qualisys AB, Gothenburg, Sweden). Markers were captured, 3D coordinates constructed, markers identified and trajectories interpolated. Data were low pass filtered (15Hz, fourth-order bidirectional low-pass Butterworth digital filter) and transformed in Visual 3D processing software (Professional version 5.02.23, C-motion Inc., Germantown, Maryland, USA).

Several kinematic variables consisting of information on frontal, sagittal and transversal plane motions (abduction/adduction, flexion/extension and

rotations) were extracted from the processed data in Visual 3D. The variables used in Paper III are presented in Appendix, Table A. Where necessary, the GC was divided into four phases according to Table 3.

Table 3. Presentation of events and reference points related to the phases of the gait cycle. Every phase was time-normalised in analysis in Paper II.

D1	1 st double-support phase	From Initial contact => Toe-off on the opposite leg
Single	Single-support phase	From Toe-off on the opposite leg => Initial contact on that same leg
D2	2 nd double-support phase	From Initial contact on the opposite leg => Toe-off
Swing	Swing phase	From Toe-off => Initial contact of the same leg

Paper II investigated two frontal plane inclination angles: the *A-CoMIA* (lower body inclination angle) based on previous work from Chen and Chou (141), and the novel *H-CoMIA* (upper body inclination angle). The size and angular velocity of the inclination angles were followed during the entire GC (events presented in Table 3). Frontal plane A-CoMIA was defined as the angle between a vertical axis and the axis emanating from the estimated Centre of Mass (CoM), both passing through the centre of the ankle joint (Figure 5). This ankle centre point was specified as the midpoint of the lateral-medial malleoli in a standing position, and estimated by the shank markers (shank cluster, tuberositas tibiae and lateral malleolus). Earlier studies investigating the ankle-CoM inclination angle have used the lateral malleolus marker alone to form the inclination angle (141). By placing the point in the middle of the ankle instead we suggest that our method more closely represents the CoP projection (142), and makes the point less sensitive to rotations that may cause assessment errors. The position of the CoM was derived by a weighted sum of the positions of all 15 rigid segments in the kinematic model (Visual3D 6-DOF) (143). Additionally, the frontal plane H-CoMIA was computed, which depicted the angular relation between the estimated CoM and the vertical axis passing through the centre point between the two temporal head markers (Figure 5). The larger the inclination angle, the further away were the ankle or head, respectively, from the position of CoM.

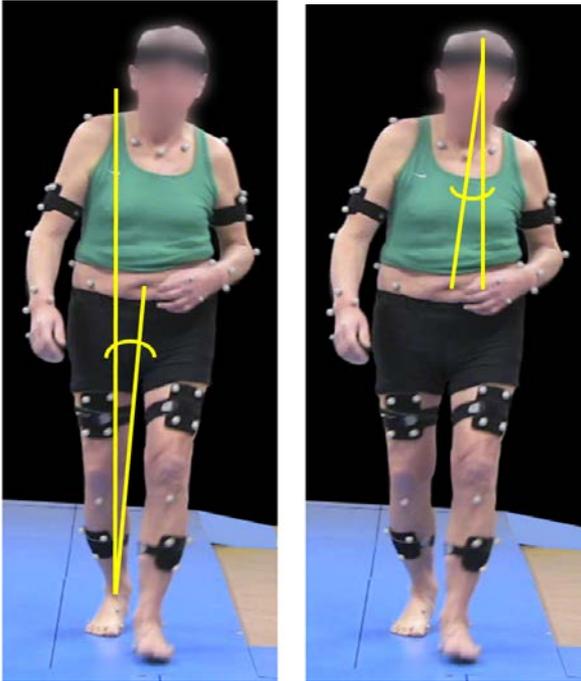


Figure 5. The A-CoMIA (lower body) and H-CoMIA (upper body) inclination angles

Since we were also interested in analysing the discriminative ability of the inclination angle variables in relation to stroke severity level, we divided the post-stroke group into two subgroups according to their FMA motor score. This resulted in one subgroup with mild impairments ($n=18$; FMA score ≥ 80), and one subgroup with moderate-to-severe impairments ($n=13$; FMA score ≤ 79).

Semi-structured interviews and qualitative content analysis (Paper IV)

Semi-structured interviews were performed during the last week of the RCT's intervention period (after 10-18 training sessions) by two physiotherapists who were not otherwise involved in the intervention. They were carried out in a quiet and private room at the rehabilitation centre and conducted directly after an exercise session. An interview guide had been designed to collect comprehensive information regarding the expectancies, experiences, perceived barriers and facilitators, and eventual effects associated with the received high-intensive gait training and the training with HAL. Interviews lasted between 21-63 minutes and were audio-recorded. Recordings were transcribed verbatim, some by one of the authors and some by an independent person. A code number was used to de-identify the transcripts.

Analysis of the transcripts was performed using qualitative content analysis with an inductive approach, as described by Graneheim and Lundman (144). The recordings were listened to and transcripts were read repeatedly to get a sense of the content of the interviews. Transcripts were then exported to the MAXQDA qualitative analysis software (Release 20.4.0; VERBI Software GmbH; www.maxqda.com) for further processing. Meaning units related to the study aims were identified (word, sentences, or paragraphs containing aspects related to the aim and to each other through content and context) in consensus between authors. These were manually condensed and labelled with codes (short descriptions of the content) (145). Based on patterns of similarities and differences, the codes were sorted to form subcategories with similar manifest content. These were further arranged in descriptive categories with a higher level of abstraction (144, 146). The codes, subcategories, and categories were continuously reflected on and discussed among the co-authors that also moved back and forth between the transcripts, codes and categories through the process of analysis. Examples of interview text, codes, subcategories and categories are presented in Table 4.

Table 4. Examples of meaning units, codes, subcategories and categories.

Meaning unit	Code	Subcategory	Category
The lactic acid squirts out of your eyes. But it's just the muscles working hard.	Draining but worth it	Mentally and physically challenging	Being pushed to the limit
I knew exactly what to do and it got boring	It got boring	Predictable with lack of variation	

Statistical analyses

Meta-analyses (Paper I)

When a minimum of three studies with relevant data and adequate homogeneity (regarding population, interventions and chosen outcome measures) were available, a meta-analysis using a random-effects model (due to heterogeneity in effect sizes) was performed with Review Manager 5 (Copenhagen: The Nordic Cochrane Centre, Cochrane) software. The threshold for statistical heterogeneity was an I^2 value $>40\%$ (147). Since the outcomes were presented in the same units, effect measures were expressed as mean differences (MD) with corresponding

95% confidence intervals (CI). Velocity during the assessment (self-selected versus fastest possible), and the type of RAGT employed in the intervention group (t-RAGT or o-RAGT), as well as the time for publication (before or after 2015), gave rise to subgroup analyses of cadence and gait speed. In one study (148) two intervention groups performed RAGT. One used additional direct transcranial stimulation during the training, while the other group received sham transcranial direct stimulation. Since the results in these two groups did not differ significantly, they were pooled in the synthesis. Where meta-analysis was not possible, a descriptive synthesis was performed and findings presented in a narrative form.

Functional Data Analyses (Paper II)

A functional interval-wise testing approach; a method from the statistical area of Functional Data Analysis (149), was employed in Paper II to address movement differences between body sides, and between persons post-stroke and controls. This method has previously been implemented on movement curves investigating hip, knee and hip movement during drop-jumps after anterior cruciate ligament injury (150). Curves illustrating mean values and distributions across individuals were performed separately for each of the four phases of the GC. The procedure identified intervals during each phase of the gait where the groups (i.e., persons post-stroke vs. controls and persons with moderate-to-severe impairments vs. persons with milder impairments) differed significantly. The affected side in persons post-stroke was compared with the non-dominant side of controls and vice versa. An adjusted p-value function was used to ensure that the probability of falsely rejecting an interval was controlled, i.e., below the chosen significance level. A corresponding test for paired samples was applied for analyses of symmetries between the affected and non-affected side of persons post-stroke, and the non-dominant and dominant side of controls. The statistical analyses were performed in R (R Core Team; 2014) (151), and the significance level was set at 0.05.

Calculations of misclassification rates (Paper III)

The statistical approach applied in Paper III consisted of two main steps, briefly presented below, and inspired by the set-up in Schelin et al. (2017) (152). Analyses were performed in R (R Core Team; 2014) (151).

Step 1: Kinematic variables with significant differences between groups (persons post-stroke and controls) were identified using a linear regression model also including the variables age, sex and Body Mass Index (BMI).

Step 2: Core sets consisting of either one or combinations of 2, 3 or 4 variables were systematically investigated using a leave-one-out cross-validation and logistic regression to estimate a misclassification rate (MR) of each core set. A logistic regression model based on the variables in the core set was used to calculate the probability that the person (that was left out) belonged to the group of persons post-stroke. The MR was estimated as the proportion of wrongly classified individuals from the leave-one-out cross-validation. The lower the MR, the higher the probability of classifying the person correctly. The threshold used for classification was 0.5, implying that the person was classified as post-stroke for an estimated probability above 0.5.

Ethics

The Regional Ethical Review Board in Umeå, Sweden approved the cross-sectional studies (Dnr. 2011-199-31). In accordance with the Helsinki Declaration, the participants received written and verbal information before signing a consent form prior to participating. The risks for participation were considered to be minimal, yet some precautions were taken. The test leaders were physiotherapists with long experience of working with stroke patients. If deemed necessary based on the participants' gait ability, the test leader could walk closely alongside the participant to minimize the risk of falls. At least two researchers were always present during the gait analysis, and participants were informed of the possibility to withdraw from the assessments at any time without a specific reason. No incidents occurred during assessments.

The qualitative study was part of an RCT (published protocol on [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02545088); NCT02545088) (135). The trial was carried out at the University Department of Rehabilitation Medicine, Danderyd Hospital and Department of Clinical Sciences, Karolinska Institute in Stockholm, Sweden, and was approved by The Swedish Ethical Review Authority (Dnr: 2015/1216-31). Participants were presented with verbal and written information about the study by the study coordinator before giving their informed consent to participate.

Results

The effect of RAGT on biomechanical measures of gait (Paper I)

Of the 2857 studies retrieved from searching nine different databases, 13 studies (involving 264 male and 148 female participants) met the inclusion criteria and were included in the review. The results of the literature search are presented in detail in the published systematic review (153). The populations' mean age in each study ranged from 52 to 69 years. Sample sizes ranged from 12-63 participants and more than half of the studies involved samples of 30 participants or less. Three studies included participants in a subacute phase post-stroke (3 - 4 months since onset), while the other ten studies included persons in a long-term phase post-stroke (10-96 months since onset). Gait ability among the persons post-stroke varied from being independent to walking with an assistive device and/or personal assistance when starting the intervention. Comparator groups performed conventional gait training, overground gait training and/or treadmill gait training with or without body weight support. Similar training duration and frequency were reported for the intervention and comparator groups. The content and intensity concerning power output during training were however vaguely reported, especially for the comparator group where the interpretation of "conventional gait training" or "traditional gait training" may differ. Details of the included studies' interventions and gait analysis assessments are presented in Tables 5 and 6.

Table 5. Details of the interventions

Author (year)	Device for RAGT	Intervention setting	Comparator group setting	Training intensity
Bang 2016	Lokomat	t-RAGT	Treadmill gait training	60 min, 5 d/week, 4 weeks, 20 sessions
Buesing 2015	Stride Management Assistance, SMA	o-RAGT	Overground or treadmill gait training, functional mobility training	45 min, 3 d/week, 6-8 weeks, max 18 sessions
Calabró 2018	EKSO	o-RAGT and overground gait training	Overground gait training	45 min + 60 min/d, 5 d/week, 8 weeks, 40 sessions
Geroin 2011	Gait Trainer (GT1)	1) t-RAGT with BWS and transcranial direct current stimulation 2) t-RAGT with BWS and sham transcranial stimulation	Overground gait training	50 min/session, 5 d/week, 2 weeks, 10 sessions
Hidler 2009	Lokomat	t-RAGT with BWS	Conventional gait training	45 min (90 min), 3 d/week, 24 sessions
Hornby 2008	Lokomat	t-RAGT with BWS	Treadmill gait training with BWS	30 min, 12 sessions
Husemann 2007	Lokomat	t-RAGT with BWS + Conventional gait training	Conventional gait training	2x30 min/day, 5 d/week, 4 weeks, 40 sessions
Lee 2019	Gait Enhancing and Motivating System (GEMS)	o-RAGT + t-RAGT	Treadmill gait training + overground gait training	45 min/d, 3 d/week, 4 weeks, 10 sessions
Lewek 2009	Lokomat	t-RAGT with BWS	Treadmill gait training with BWS	60 min, 3d/week, 4 weeks, 12 sessions
Ogino 2020	Gait Exercise Assist Robot (GEAR)	t-RAGT with BWS + limb range motion exercise	Treadmill gait training	60 min/day, 5 d/week, 4 weeks
Srivastava 2016	Active Leg Exoskeleton, ALEXII	t-RAGT + FES, no BWS	Treadmill gait training with BWS	40 min, 5 d/every other week, 15 sessions
Tanaka 2019	Stride Management Assistance, SMA	o-RAGT	Conventional gait training	60-120 min/day, 10 sessions
Westlake 2009	Lokomat	t-RAGT with BWS	Treadmill gait training with BWS	max 60 min, 3 d/week, 4 weeks, 12 sessions

BWS = body weight support; d = days; t-RAGT = treadmill-based robotic-assisted gait training; o-RAGT = overground robotic-assisted gait training;

Table 6. Details of assessments

Author (year)	Timepoint of assessments	Walking condition for assessment	Velocity during analysis	Gait analysis system	Walking device during gait analysis
Bang 2016	Baseline and post training	4.6 m walkway, no info on the number of trials	No info	GAITRite	Not reported
Buesing 2015	Baseline, midpoint and post training, and at a 3-months follow-up	GAITRite walkway and 5 feet before and after, 3+3 trials	Self-selected and fastest velocity	GAITRite	Assistive device allowed
Calabró 2018	Baseline and post training	10 m walkway, 2 trials	Self-selected velocity	Accelerometer	Not reported
Geroin 2011	Baseline and post training	12 m walkway, 3 trials	Fastest velocity	GAITRite, Bertec	Orthoses allowed
Hidler 2009	At baseline, midpoint and post training, and at a 3 months follow-up	Overground walkway, no further info	Self-selected velocity	GAITRite or GaitMat	Not reported
Hornby 2008	At baseline, post training and at a 6-months follow-up	10 m, overground, >5 trials	Self-selected and fastest velocity	GaitMat II	No physical assistance, orthoses if needed
Husemann 2007	At baseline and post training	10 m walkway, no info on the number of trials	Fastest velocity	In-shoe plantar pressure measurement system, Parotec system.	Assistive device allowed
Lee 2019	At baseline and post training	8 m walkway, 5 trials	Self-selected velocity	3D motion capture system with 6 infrared cameras	Not reported
Lewek 2009	At baseline and post training	10 m walkway, overground, >5 trials	Self-selected velocity	8-camera motion camera system	Orthoses allowed
Ogino 2020	At baseline and post training, at a 1-month and 3-month follow-up	Walk on treadmill, no further info	Self-selected velocity	KinemaTracer, 3D motion analysis system	Handrail or brace allowed
Srivastava 2016	At baseline and post training	Overground, no further info.	Self-selected velocity	Qualisys 8-camera motion capture system	Not reported
Tanaka 2019	At baseline and post training	8.4 m walkway, overground, >2 trials	Fastest velocity	WalkWay MW-1000	Assistive device allowed
Westlake 2009	At baseline and post training	5.3 m walkway, ≥ 3 trials	Self-selected and fastest velocity	GAITRite	Assistive device allowed

Quality assessment

A summary of the risk of bias ratings is reported in detail for each included study in the published review (153). High concerns were revealed for two studies due to the lack of relevant information concerning the randomisation process (154) or because the randomisation was based on the participants' hospital record numbers (155). Another issue identified in several studies was the risk of bias due to missing outcome data. One study (156) absence of reasons for participants' withdrawal, and in the studies where reasons were reported they were likely to be related to consequences of the training, e.g., fear of falling, skin lesions, leg pain due to training, pitting oedema or self-reported exercise intolerance (155, 157-160). Dropouts were excluded from the analysis in all these studies except for one (160). Finally, the frequent absence of study protocols or pre-specified analysis plans raised some concerns about selective reporting of results. In addition, the analyses performed in one study did not conform to the registered protocol (161), and another study (162) reported within-group analyses exclusively.

Quantitative analysis

At least one temporal gait parameter, most commonly gait speed (n=10) or cadence (n=8), was analysed by the studies included in the systematic review. Due to risk of bias, indirectness of evidence owing to variations in intervention and gait analysis settings, and imprecise findings with insignificant differences between small population groups (6-25 participants/group), the certainty of evidence (GRADE evaluation) was very low for all temporal parameters. Neither the meta-analysis of gait speed (mean difference [MD] 0.00 m/s; 95% confidence interval [CI] -0.05, 0.05; $I^2 = 93\%$) (Figure 6), nor that of cadence (MD 1.44 steps/min; 95% CI -2.34, 5.22; $I^2 = 92\%$) indicated overall significant differences between the intervention and comparator groups after the training period. The absence of differences remained in meta-analyses performed on subgroups based on velocity during gait assessment (self-selected or fastest possible), the type of RAGT (t-RAGT vs. o-RAGT) or time of publication (earlier: 2007-2014 vs. later: 2015-2020). Regarding other temporal parameters (gait cycle/stride duration, step time, stance/swing time/percentage of GC), nearly all studies reported no significant differences between groups, indicating that both groups improved to an equal extent.

Among spatial parameters, GRADE implied a very low certainty of evidence for a significantly greater increase in stride length (MD 2.88 cm; 95% CI 0.46, 5.25; $I^2 = 66\%$) and step length on the affected side (MD 2.67 cm; 95% CI 1.55, 3.80; $I^2 = 65\%$) following RAGT, when compared with non-robotic gait training (see Figure 6).

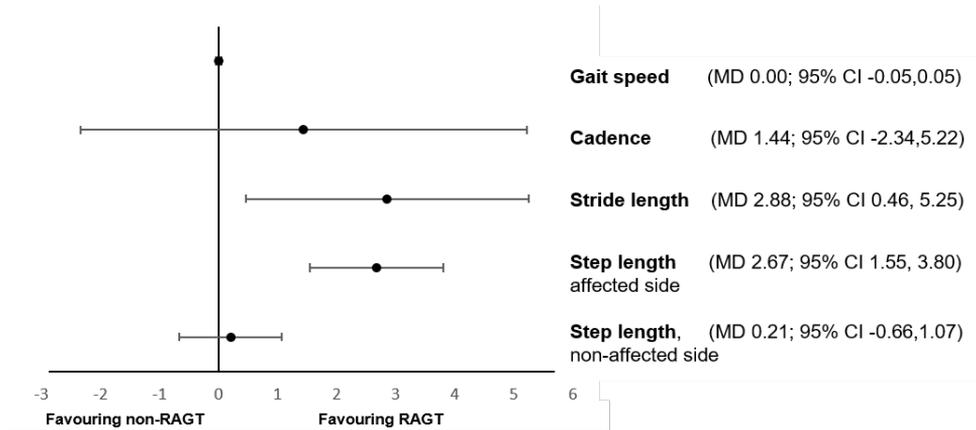


Figure 6. Forest plot illustrating the aggregated effect of RAGT when compared to non-robotic gait training.

Seven studies (148, 155, 156, 158, 161, 163, 164) used a variety of ratio calculations to investigate either temporal or spatial symmetry. With very low evidence (GRADE), the meta-analysis of temporal symmetry revealed a greater, statistically significant improvement in the symmetry ratio in the RAGT groups when compared with the non-robotic gait training groups (MD 0.09; 95% CI 0.04, 0.15; $I^2 = 90\%$). This difference was however not detected in the meta-analysis for spatial asymmetry (MD -0.01; 95% CI -0.07, 0.04; $I^2 = 79\%$).

Kinematic data were seldom investigated in the included studies. The overall (GRADE) certainty of evidence was found to be low, and no between-group differences were reported for the kinematic parameters. No eligible RCTs evaluating kinetic gait data following RAGT were found during the search.

Kinematic assessments of gait

Size and angular velocity of the A-CoMIA (Paper II)

Results from the FDA performed in the first cross-sectional study indicated that both the size and velocity of the A-CoMIA differed in persons post-stroke when compared to controls (Figure 7A-D). The A-CoMIA was significantly larger in persons post-stroke on both sides when compared to controls during the majority of the GC (~70% of the GC in the affected, and ~90% of the GC in the non-affected side of the body) (Figure 7A). In the midswing phase, a mean angle of 7° (range 5°-15°) was found in the affected side in persons post-stroke when compared with mean 5° (range 4°-7°) in the non-dominant side in controls. In the midstance phase the difference was less, although still significant with a mean angle of 4°

showed very low variability when compared to persons post-stroke, but was yet significantly asymmetrical during ~50% of the GC.

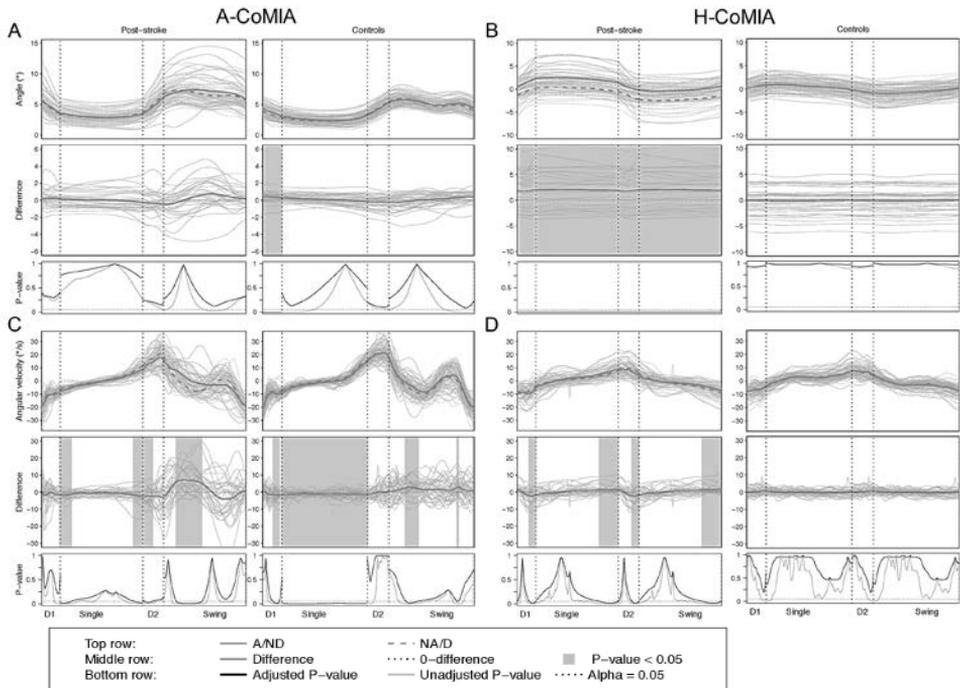


Figure 8. Body symmetry: Within-group comparisons of the A-CoMIA and H-CoMIA (A-B), and the angular velocity of the inclination angles (C-D), throughout the entire gait cycle. The affected (A) side is compared to the non-affected (NA) side in persons post-stroke and the non-dominant (ND) side is compared to the dominant (D) side in controls. The grey areas within the plots demonstrate significant asymmetry. Figure explanations in the box are valid for A-D. Attribution according to CC license: "Figure 3A-D", by Nedergård et al. 2020.

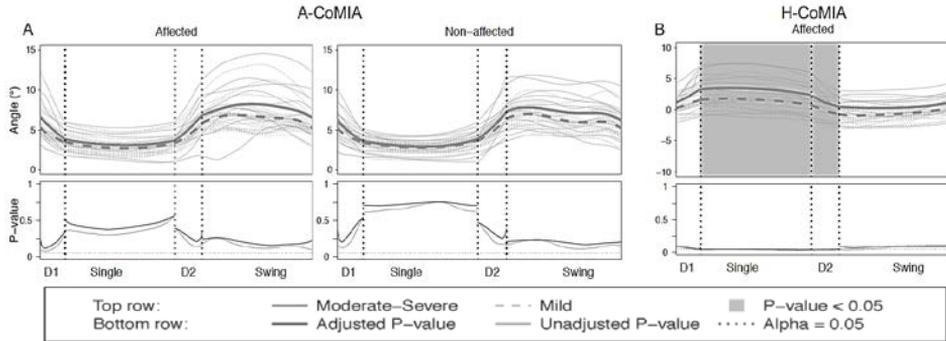


Figure 9. Subgroup comparisons of the A-CoMIA and H-CoMIA ($^{\circ}$). Persons post-stroke with mild impairments were compared to persons with moderate-to-severe impairments. The grey areas within the plots demonstrate significant differences between groups. Attribution according to CC license: "Figure 3A-D", by Nedergård et al. 2020.

Size and angular velocity of the H-CoMIA (Paper II)

When the H-CoMIA in the affected side in persons post-stroke (mean 2° ; range 1° - 8°) was compared to the corresponding inclination angle in the non-dominant side of controls (mean 1° ; range -2° - 3°), it was significantly larger during the stance phase of the affected side (Figure 7B). The head and upper trunk were asymmetrically positioned towards the affected side of the body during the entire GC (Figure 8B). The angular velocity of H-CoMIA was asymmetrical at the end of each phase of the GC: slightly lower towards the affected side at the end of the double-support phases, but higher at the end of the single-support and swing phase (Figure 8D).

When compared to persons with milder impairments (Figure 9B), the H-CoMIA in persons with moderate-to-severe impairments was significantly larger in the affected side during the single-support and 2nd double-support phase in the affected side. This would reflect a change in the upper body position during walking related to stroke severity level.

Core sets of kinematic variables (Paper III)

The statistical approach applied in Paper III consisted of two main steps. Initially, a linear regression model was used for all outcome variables to test if there was a difference or not between persons post-stroke and non-disabled persons while controlling for age, sex and BMI. The kinematic variables with non-significant group differences were excluded from the subsequent analyses. Results are

presented in Table 7, with further details and descriptive statistics in Appendix, Table A.

Table 7. Variables of interest analysed in Step I. The variables that differed significantly between persons post-stroke and controls were included in the subsequent analysis.

Included		Excluded
Spatial and temporal gait variables		
<i>Step length</i>	<i>Duration of 1st dbl-support</i>	
<i>Stride length</i>	<i>Duration of 2nd dbl-support</i>	
<i>Stride width</i>	<i>Swing time</i>	
<i>Self-selected gait speed</i>	<i>Step time</i>	
<i>Cadence</i>	<i>Stride time</i>	
<i>Duration of stance phase</i>	<i>Temporal symmetry</i>	
<i>Duration of single-support</i>	<i>Spatial symmetry</i>	
ROM joint angles		
<i>Pelvis sagittal ROM</i>	<i>Thorax frontal ROM</i>	<i>Thorax sagittal ROM</i>
<i>Hip sagittal ROM</i>	<i>Thorax transversal ROM</i>	<i>Pelvis transversal ROM</i>
<i>Hip frontal ROM</i>	<i>Shoulder sagittal ROM</i>	<i>Pelvis frontal ROM</i>
<i>Hip transversal ROM</i>	<i>Shoulder frontal ROM</i>	
<i>Knee sagittal ROM</i>	<i>Shoulder transversal ROM</i>	
<i>Ankle sagittal ROM</i>	<i>Elbow sagittal ROM</i>	
ROM Index		
<i>Hip sagittal ROMI</i>	<i>Ankle sagittal ROMI</i>	<i>Pelvis sagittal ROMI</i>
<i>Hip frontal ROMI</i>	<i>Shoulder sagittal ROMI</i>	<i>Hip transversal ROMI</i>
<i>Knee sagittal ROMI</i>	<i>Elbow sagittal ROMI</i>	<i>Shoulder frontal ROMI</i>
		<i>Shoulder transversal ROMI</i>
MAX joint angles		
<i>Hip transversal MAX</i>		<i>Pelvis sagittal MAX</i>
<i>Knee sagittal MAX</i>		<i>Pelvis frontal MAX</i>
<i>Shoulder frontal MAX</i>		<i>Pelvis transversal MAX</i>
		<i>Hip sagittal MAX</i>
		<i>Hip frontal MAX</i>
		<i>Ankle sagittal MAX</i>
		<i>Shoulder sagittal MAX</i>
		<i>Shoulder transversal MAX</i>
		<i>Elbow sagittal MAX</i>
Lower and upper body inclination angles		
<i>A-COMIA, stance</i>		<i>H-COMIA, swing</i>
<i>A-COMIA, swing</i>		
<i>H-COMIA, stance</i>		
Gait deviation scores		
<i>Gait Profile Score (GPS)</i>		
<i>Gait Deviation Index (GDI)</i>		
<i>Arm Posture Score (APS)</i>		
Stroke specific gait variables		
<i>Hip extension, swing</i>		<i>Hip abduction, swing</i>
<i>Knee flexion, swing</i>		<i>Ankle dorsiflexion, swing</i>
<i>Ankle plantarflexion, terminal stance</i>		<i>Hip abduction, non-affected side, stance</i>
		<i>Knee extension, single-support</i>

When calculating the MR for single variables, the lowest (hence also the best) rate was identified for the *Duration of single-support* (MR = 0.10) and the *Duration of 2nd double-support phase* (MR = 0.11) (Table 8). This corresponds to a 90% and 89% probability, respectively, of correctly classifying a person as post-stroke or control based on these specific variables.

Table 8. Presentation of the five lowest misclassification rates (MR) for one variable alone, or for core sets of 2-3 variables in combination.

Variables		MR
One variable	<i>Duration of single-support</i>	0.10
	<i>Duration of 2nd double-support</i>	0.11
	<i>Stride length</i>	0.13
	<i>Self-selected gait speed</i>	0.15
	<i>Step length</i>	0.17
Core sets of two variables	<i>Step length</i> AND <i>Pelvis sagittal ROM</i> OR <i>Stride length</i>	0.06
	<i>Self-selected gait speed</i> AND <i>Pelvis sagittal ROM</i>	0.07
	<i>Duration of single-support</i> AND <i>Ankle sagittal ROM</i>	
	<i>Duration of single-support</i> AND <i>Ankle plantar flexion, terminal stance</i>	
	<i>Duration of 2nd double-support</i> AND <i>Knee flexion in swing</i>	
Core sets of three variables	<i>Stride length</i> AND <i>Pelvis sagittal ROM</i> AND <i>Shoulder sagittal ROM Index</i> OR <i>Step length</i> OR <i>Knee sagittal ROM</i>	0.04
	<i>Self-selected gait speed</i> AND <i>Pelvis sagittal ROM</i> AND <i>Shoulder sagittal ROM Index</i> OR <i>Knee flexion MAX</i> OR <i>Arm Posture Score</i> OR <i>Cadence</i>	
	<i>Stance time</i> AND <i>Pelvis sagittal ROM</i> AND <i>Knee flexion MAX</i> OR <i>Swing time</i>	
	<i>Duration of 2nd double-support</i> AND <i>Ankle plantar flexion, terminal stance</i> AND <i>Shoulder abduction MAX</i>	

ROM = range of motion; MAX = Maximum

For core sets containing a combination of two variables, the MR improved to 0.06 (highest MR = 0.42). The best MR was shown for *Step length/Stride length* in combination with *Pelvis sagittal ROM* (anterior/posterior pelvis tilt). This combination of variables classified 94% of the persons correctly. The other core sets that contained two variables generated an MR of 0.07 and was represented by one temporal variable combined with one joint angle position variable.

Core sets of three kinematic variables combined improved the MR to 0.04 and classified 96% of the persons correctly. Each of the combinations that generated the lowest MRs included at least one joint angle variable, most often *Pelvis sagittal ROM*, and 1-3 additional spatial or temporal variables. Adding a fourth variable did not decrease the MR further.

Experiences of high-intensive gait training including RAGT (Paper IV)

From analyses of the interviews in Paper IV, four different categories emerged, each formed by three to five different subcategories. These are presented in **Table 9**.

Table 9. Categories and sub-categories describing the experiences of a high-intensive gait training programme including RAGT.

Categories	<i>A rare opportunity for possible improvements</i>	<i>Being pushed to the limit</i>	<i>Walking with both assistance and constraints</i>	<i>Reaching the end and taking the next step on your own</i>
Sub-categories	Always striving to improve	Mentally and physically challenging	Facility-bound rehab	Moving on with confidence
	Accepting and trying to maintain functioning	Supported by encouragement, feedback and individual adjustments	Restrained by the HAL-suit and harness	Appreciating the exercise
	Anticipating a chance for progress	Predictability with lack of variation	Difficult to walk with a natural flow	Feeling resignation and being lost
			Assistive but strenuous	
			Pain and discomfort as barriers	

When enrolling in the programme, the expectations were optimistic among participants. They had acknowledged a need for physical training to improve or maintain function. However, since they were in a long-term phase post-stroke, access to stroke-specific rehabilitation was described as limited. The offered intervention included both professional support and access to a novel technological innovation. It was hence considered *a rare opportunity* that might positively affect their functional abilities: **“To see what was going to happen, which is what I was after from the beginning when I heard about this robot”** (P1). The applied technology was generally met with careful curiosity. Participants described being hopeful, although not without some doubts related to the operation of, and technology behind, the robotic device: **“They're looking at some measurements with curves. I've got electrodes on my leg. So they can see some pulses there somehow. I don't know if it helps me, so to speak, but... I guess they're the ones working with it”** (P2).

Although the high intensive gait training with and without robotic assistance was perceived as mentally and physically exhausting, *being pushed to the limit* during training was generally appreciated among the participants. Making a strong physical effort was considered extraordinary in a positive way, making the hard training worthwhile: **“It has taken its toll. Two hours, three times a week. No, it's been really good, actually. I feel like I've had to actually make an effort”** (P3). Perceived barriers were the lack of variation due to task specificity. Individually adjusted gait training exercises and challenges combined with continuous and concrete feedback (e.g., speed and distance of walking) motivated participants to greater efforts. Being in focus, and feeling personally included was considered essential for engagement. Furthermore, the professional, supportive and encouraging role of the physiotherapists leading the training was described as crucial: **“I hope it has taught me something. At least X (physiotherapist) and Y (physiotherapist) have. I don't think the robot itself is as essential as the physiotherapists”** (P4).

The RAGT was specifically described as *walking with both assistance and constraints*. Even though the RAGT was perceived as strenuous participants considered the device assistive and acknowledged walking further and faster with the help of the robot. Discomfort or pain, and feelings of being restricted in movement during RAGT was described as affecting the experience negatively. **“It pinches a little here and there... It's tightened so that it's secured. So it's kind of awkward to wear it”** (P5). Also, walking with a natural rhythm in cooperation with the robotic device was often considered a struggle. Especially in the beginning, the device was experienced as difficult to synchronize with: **“It**

has a life of its own. Apparently you stand and think and everything you have on your back starts bouncing” (P4). Gradually though, the participants became more familiar with the movement pattern and forward progression initiated by the robot.

When *reaching the end of the intervention* many participants had experienced gains during walking with the robot. If these were not transferable to their abilities without the robot, in their everyday life and home environment, the result could be considered a source of disappointment. Together with those who had experienced no improvements, they described feeling abandoned by the health care system when the intervention ended: **“Yes, it would have been good to continue... but... then you get pushed out into the cold again”** (P6). Other participants, however, described gains in muscle strength, balance and everyday independence: **“I notice it in slightly different ways but... when I stood up like that there is a big difference... I am much more steady and like now I just walk with a walking stick”** (P7). These participants felt greater trust in their abilities and were motivated to continue training on their own.

Discussion

The systematic review showed low evidence for a superior effect of RAGT on biomechanical measures of gait when compared to non-robotic gait training. It also confirmed the earlier reported (38, 65, 66, 165) lack of consensus as to which gait variables are best used for the investigation of motor coordination during walking. The size and velocity of the lower and upper body inclination angles, introduced in Paper II, were investigated throughout the GC. These were able to discriminate between persons post-stroke and controls. The upper body inclination angle also discriminated between persons with mild and moderate-to-severe impairments. Furthermore, core sets consisting of 2-3 kinematic variables were identified. The core sets contained spatial (*Stride length/Step length*) or temporal variables (e.g., *Self-selected velocity* or *Duration of single-support*) in combination with joint motion data such as, e.g., *Pelvis sagittal ROM* (anterior/posterior tilt), *Ankle sagittal ROM* (plantarflexion/dorsiflexion) or *Shoulder sagittal ROM* (flexion/extension). The sensitivity, responsiveness over time and functional significance of the inclination angle variables, as well as several of the kinematic variables included in the core sets, remain unclear and need to be further studied. A whole-body perspective including both lower and upper body is, however, emphasized and demonstrated as relevant in post-stroke gait evaluations.

The lack of superior effect of RAGT, when compared to non-robotic gait training that was demonstrated in the systematic review, is to be further discussed. The explanations for the neutral results may be multifactorial and derived from the several challenges associated with designing and conducting well-controlled rehabilitation trials post-stroke (127). The physical support during stepping provided by the gait-assisting robots may also not be enough to stimulate the pursued neural reorganization. The robotic device should additionally encourage a high level of active participation, smoothly synchronise with the intentions of the wearer and enable training in different environments without renouncing necessary physical support and safety. Furthermore, interviews showed that, for a positive experience and engagement, the high-intensive gait training should involve motivational and supportive communication, individualized goal-setting, concrete feedback and a variation of gait-specific exercises.

Quantifying gait performance

To focus attention on the ICF domain of body structure/function and identify specific movement pattern deviations constitutes the first step towards eventually favouring “true recovery” in post-stroke gait rehabilitation. However, no core set of biomechanical variables for the investigation of post-stroke gait has been recommended. The most commonly used biomechanical measures when

investigating the effects of RAGT, for instance, were shown to be gait speed and cadence (153). These measures are well investigated and commonly used in a clinical setting. On their own, however, these variables do not reflect the specific gait movement pattern used during walking (16, 123, 166, 167). Different compensatory movement patterns can be adapted to facilitate a faster gait speed or higher cadence. The calculations of MRs suggest that self-selected gait speed alone seems to correctly classify persons post-stroke with a probability of 85%, whereas for cadence the corresponding probability was 68%. These variables should preferably be evaluated in combination with kinematic and/or kinetic variables (16, 123, 166, 167) that provide more detailed information on specific movement patterns. By adding data on the pelvis' range of motion in the sagittal plane (*Pelvis sagittal ROM*), the probability of correctly classifying persons post-stroke increased to 93%. Adding yet another kinematic variable (e.g., *Knee MAX flexion* or *Shoulder sagittal ROM*) increased the probability even more (96 %). Since *Pelvis sagittal ROM* was found in two-thirds of the presented core sets, our analyses suggest that this specific variable seemed to be of certain value when being combined with other kinematic variables to discriminate post-stroke gait. Since the pelvis constitutes the connection between the trunk and upper body, muscular control at the pelvis has been suggested as highly relevant for dynamic balance and weight transmission during walking (168). Impaired trunk and hip muscle strength, combined with adaptations following distal limb impairments, most likely results in the deviating pelvis motions (such as increased anterior/posterior tilt) that seem to characterise stroke-specific gait (169, 170).

The investigated body inclination angles were able to discriminate persons post-stroke from controls and may hence be useful when evaluating the consequences of impairments. The A-CoMIA (lower body inclination angle), defined as the angular relation between the ankle and CoM in the frontal plane, has previously been found to be larger among older people during the single-support phase (141). We investigated the inclination angle throughout the entire GC and found that it was bilaterally larger during most of the GC when compared with non-disabled controls. During the stance phase, the foot is essentially fixated to the floor and therefore changes in the A-CoMIA during this phase are derived from a horizontal motion of the CoM. This is however not necessarily the case during the swing phase when both the ankle and the CoM position are in motion and thus together affect the size of the inclination angle. Considering previous reports of a normal and symmetrical CoM position during the swing phase in persons post-stroke (76), the observed larger A-CoMIA during the same phase among our participants seems to be generated by the changes in footpath rather than the CoM position. One explanation could be a deviating hip abduction/adduction due to upward pelvic movement (hip hiking) or circumduction commonly observed in persons post-stroke (67, 171). Interestingly, the A-CoMIA was equally large on the non-affected side during the same phase, supposedly as a reflection of the

coupling between legs (172, 173). A strive for symmetry may result in an adaptive movement pattern that includes the non-affected side of the body, which advocates for the importance of considering the possibility of bilateral deviations when evaluating gait post-stroke.

A greater stride width and increased lateral displacement of CoM during the stance phase, as suggested by our results, is suggested to increase the velocity of the mediolateral motion of CoM (76), hence also influence the angular velocity of A-CoMIA. In addition, the progression of the trunk over the paretic foot would supposedly cause a rapid weight shift and CoM motion towards the more stable, non-paretic side when possible (174). Analyses showed alternating higher, but also lower A-CoMIA angular velocities during different phases of the GC when comparing person post-stroke and controls (Figure 8). The deviations in the angular velocity are assumingly caused by complex associations between breaking force parameters and kinematic movement strategies (175).

The H-CoMIA (upper body inclination angle) revealed asymmetrical motions in the upper body during the entire GC. Persons post-stroke aligned their upper trunk and head more towards the affected side of the body in relation to the CoM position. The H-CoMIA could also differentiate persons with milder from those with moderate-to-severe impairments according to the FMA. The trunk has been found to play an important role in ensuring necessary head control for visual and vestibular function during walking (176, 177) by filtering oscillations prior to reaching the head (178). Since persons post-stroke have been reported to have an increased lateral sway of the lower trunk towards the non-affected side (179), the orientation of the head and upper trunk towards the affected body side could be a counteracting strategy to maintain balance.

The results of both cross-sectional studies investigating the kinematics of post-stroke gait confirm a relevant whole-body engagement where the trunk and upper limb are suggested to actively take part in compensatory strategies to improve body weight distribution and balance during walking (73, 80). The core sets of kinematic variables that received the lowest MRs included at least one variable connected to the kinematics of the trunk (Pelvis sagittal ROM) or upper limb (commonly shoulder). Trunk impairments post-stroke are bilateral and commonly reported (73), while upper limb function affects 50-70% of persons in the acute (180), and about 40% in the long-term phase post-stroke (181). These factors influence gait performance and should hence be part of post-stroke gait evaluations.

Robotic-assisted gait training - biomechanical and user-perspective

Gait speed and independence, both measurements that investigate effects related to the ICF activity domain, have been reported unchanged or slightly more improved after RAGT when compared to non-RAGT (97, 107-114). We, therefore, chose to synthesise the evidence for the effects of RAGT on biomechanical measures of gait, covering the ICF domain of body function and structure. Since RAGT provides for several more repetitions of steps with a close to normal gait movement pattern when compared to conventional gait training (96 -98, 135) the training should be more efficient when aiming to stimulate “true recovery” (104-106). However, the review found no significant differences between intervention groups as these improved to an equal extent. The lack of significant benefit from RAGT may suggest that the optimal gait rehabilitation intervention or gait-assisting robot is yet to be developed.

To increase the stimulation of neural activity and reorganization following RAGT, several essential factors have been advocated such as the enhancement of active wearer participation (108, 182) and an adaptable robotic interference that also allows for individual adjustments (62, 65, 132, 133). Different technologies for movement intention detection are commonly used in exoskeletons to enable active wearer participation and individual adjustments. Still, the sensitivity of several of these systems seems to be under development (13). While using the robot, a smooth and natural walk with a close to normal gait movement pattern is highly dependent on the interaction between the wearer and the robotic device (183). The HAL system uses recordings of bio-electrical signals (electromyography; EMG) that are triggered by the wearer’s voluntary muscle activity to time the output of force to facilitate movement (136). In the interviews, participants described some difficulties in finding a rhythmical and balanced gait. The device was even perceived as taking over the gait and reducing the control of the wearer. Other studies exploring the perceptions of walking with a gait-assisting robot have also reported a similar conflict in the relation between the device and the wearer (184, 185). Since tension, stress and the perception of lost control have been suggested to affect active training engagement negatively (115), the experience of feeling safe and in control during RAGT should be prioritized.

The allowance of sufficient degrees of freedom to minimize motion restrictions in body joints and also enable other aspects of gait, such as balance, to be incorporated in RAGT has previously been emphasized (62, 65, 132, 133). The reported relevance of adapting a whole-body perspective during the evaluation of gait ability also suggests that a wider perspective is of importance in post-stroke gait rehabilitation. RAGT is often performed on a treadmill with the use of a harness and supporting handrails. These aids constrict the movement of the trunk and upper limbs during RAGT and may negatively affect efforts to facilitate

a gait movement pattern that is as close to normal as possible. The balance between providing sufficient safety and support while at the same time encouraging active whole-body engagement is a dilemma since these factors are not easily combined. The participants in our interview study described feeling physically restricted by the device and harness. Some even experienced pain due to pressure or abrasions caused by the equipment. Due to the multiple tight straps and the perceived heavy weight of many gait-assisting robots, studies have reported perceived discomfort for the wearer (186, 187). Additionally, donning and doffing of the robotic device was considered time-consuming. This too has been reported earlier (188), and in combination with the training's high physical and mental demands, is a factor that increases the risk of fatigue. The gait-assisting devices and associated equipment need to be easy to apply and designed to feel less restrictive. Enabling a whole-body engagement while still providing for necessary support, is a challenge for future development in the area of gait robotics.

Engagement and appreciation of a rehabilitation programme are dependent on positive facilitators to overcome eventual barriers. Fatigue has been identified as a common and debilitating post-stroke symptom (189) and a potential barrier to any physical activity following stroke (93, 190, 191). Considering that, the feasibility of physically demanding training could be questioned. Nevertheless, research suggests that a high-intensive exercise programme can be implemented and appreciated in a post-stroke population (93, 192, 193). Our participants described the training as rewarding despite, or even because of, being pushed to the limit both physically and mentally. A person-centred focus that includes individualised goal setting along with personalized physical and psychological support has been suggested as crucial for engagement in any training (93-95, 192, 194). Good communication between the physiotherapist and the participant undertaking therapy has been reported to foster hope, motivation and greater satisfaction during rehabilitation (93, 192, 195). In line with this, participants in the interview study described the physiotherapist's support and feedback as being even more important for a positive experience than the actual content of the training. They considered individually-tailored exercises and goal setting as essential and experienced the lack of variation in the training to be a potential barrier to active engagement. The repetitive nature of this type of training does nevertheless generate advantages such as simultaneous detection of well-defined gait parameters like gait speed, walking intervals and distances (132). These may serve as concrete reference points, enabling feedback and evaluation of progression to serve as possible motivators (193, 196) and thus strengthen the value of this type of training intervention. Yet repetitive training is at risk of being perceived as monotonic and predictable. Good and consistent information and collaborative goal setting are hence of particular relevance for continued motivation (93). To be more stimulating, high-intensive and task-specific

training should preferably be performed in an enhanced environment and complemented with other physiotherapy treatments (197). This would also facilitate variability in performance which has been suggested to ease transferability and adaptability of movements from the training context to other circumstances that are relevant for the person (180).

Finally, the RCT in which context Paper IV was conducted, did not find a significant improvement for the 6-Minute Walk Test after six weeks of RAGT combined with conventional gait training (135). The interviews did however reveal that several of the participants described meaningful improvements in strength and mobility even though these were not necessarily transferable to their daily lives. The discrepancy between the clinically assessed gains and the subjective reports from participants mirror the complexity in the evaluation of gait ability. We can only base our results on the assessments we make and the outcome measures we use. These should therefore be thoroughly considered and attempt to cover all the domains of the ICF in order to provide a comprehensive evaluation.

Methodological considerations

Datasets, participants and study contexts

The heterogeneity in study populations in combination with a wide range of definitions and/or calculations in data analysis limited the possibilities for generalizing the results of the systematic review. The included studies differed concerning the intervention itself (the robotic device used, feedback delivered, and content, duration, intensity and frequency of the training etc.), the methods for gathering gait data (various systems for gait analysis, allowance of walking aids during assessments, variations in walking distances etc.) and the reporting of biomechanical outcome measures.

Factors such as age, cognition and functional abilities have been suggested to be associated with post-stroke rehabilitation outcomes (198). The small sizes of the study populations included in the primary studies of this thesis limited possibilities for subgroup analyses. Also, the populations' characteristics (e.g., time since stroke and stroke severity level) are aspects that should be considered. The FMA motor scores of the participants, for instance, indicated a relatively high-functioning gait ability among the participants. This may affect the likelihood of generalising the studies' results to other post-stroke populations.

Data collection and data processing

The systematic review adhered to a protocol pre-registered in PROSPERO. The systematic and broad electronic search resulted in the inclusion of 13 relevant RCTs published until the 19th of January 2021. Despite the comprehensive search,

one of the studies was found manually when searching reference lists of relevant papers. We can therefore not dismiss the risk of missing other relevant studies during our database search. Also, the review excluded studies in languages other than English and that may have limited the possibility of including additional studies. Research has however reported that English-language restrictions in meta-analyses do not affect calculated treatment effects (199).

Standardized marker placement, and rigid clusters used in data collection for Paper II and III, were employed to increase reliability and precision during the instrumented gait analysis. The use of skin-attached markers may nevertheless have affected data due to soft tissue artefacts. In addition, particularly for persons with severely impaired gait, there was a risk that markers would fall off during the test because of, e.g., high impact during initial contact or feet touching during the swing phase. The test leader also sometimes accompanied the person walking to reduce the risk of falls and therefore occasionally blocked markers from the sight of the cameras. Since an eight-camera system was used this was however seldom a cause of problems during the data processing and did not result in loss of data.

The laboratory environment for gait analysis, including the specific walkway, was not similar to normal environments familiar to the participants. Due to a whole-body marker setup that required minimal clothing, the person may also have been uncomfortable and conscious of being recorded during walking. These factors could have influenced the way participants walked. Another confounding factor to consider was the use of self-selected gait speed. This reflects the spontaneous speed that a person is comfortable with during a gait test. In line with our results, a slower gait speed is generally reported among persons post-stroke when compared with non-disabled persons. Even though studies have shown some kinematics during gait in persons post-stroke to be unrelated to gait speed (171, 200), it cannot be ruled out that our results may be associated with gait speed more than with stroke-specific impairments.

Gait movement patterns can be influenced by factors such as familiarization and fatigue due to performing several trials. Fatigue may also have affected the participants during the interviews performed in Paper IV. Several of the participants were already affected in their communication skills due to their stroke. The extensiveness of the interview guide that consisted of a relatively large number of questions covering several areas of interest, and the timing of the interview directly after a training session, increased the risk of fatigue. This might have affected the comprehensiveness of the answers by some participants.

Statistical analyses

Paper II presented curve data following the entire GC, whereas the data for Paper III constituted discrete time points. The latter limits information relating to potential deviations or if they are isolated to specific phases of the GC. Additionally, when calculating MRs, only the variables that significantly differed between groups were included in the subsequent steps of the analysis process. This gave rise to a risk of excluding variables that could have been of importance but were not significant due to a potential lack of power. There is also a possibility that the default threshold of 0.5 that was used in Step II analysis may have influenced the estimated proportion of wrongly classified individuals from the leave-one-out cross-validation, although we consider this to be highly unlikely.

The current statistical approach used in Paper III aimed to identify potential core sets of variables for discussion and further study. The focus was not on checking model assumptions, interpreting parameter estimates, and comparing models in other ways than their classification ability. The presence of multicollinearity due to highly correlated variables within the same model might be affecting the results since their combination may represent the same underlying process. While we have not a priori eliminated collinear variables based on conceptual conjectures, we are aware that this could result in redundancy in the discrimination process.

Qualitative content analysis

In qualitative content analysis data are systematically and stepwise organized into categories based on identified similarities and differences in the context of the codes (144). An inductive approach was chosen to enable access to information from the study participants without imposing preconceived theories or hypotheses. To strengthen the study's trustworthiness, aspects of credibility, dependability, transferability and conformability were addressed (201). For credibility, examples of the abstraction and interpretation processes are provided in the presentation of the results. Dependability determines the consistency and repeatability of findings with regard to time and circumstances (201). As with the aspect of transferability mentioned above, the dependability was reinforced through comprehensive descriptions of the selection and characteristics of the participants, the context of the data collection, as well as the process of data analysis. Conformability was addressed by involving all authors in the analysis process. Each author contributed with a slightly different knowledge base and pre-understanding related to their experiences from clinical neurological/stroke rehabilitation (all were physiotherapists with experiences of physical and neurological rehabilitation) and rehabilitation research (4 - 30 years of experience in quantitative and qualitative rehabilitation research). The coding,

forming of sub-categories and further abstraction was continuously discussed between the authors. Agreements between transcripts and codes, sub-categories and categories, were frequently controlled during the analysis process.

Transferability should be addressed to strengthen the trustworthiness of qualitative studies (201). In Paper IV, the study participants represented men and women of different ages with a variation concerning time since stroke (although all in a long-term phase post-stroke) and body side afflicted by stroke. The functional ability of the participants varied, but all were able to walk shorter distances independently or with minor assistance. The results may therefore differ from the experiences of those who are not able to walk at all, and of those in an acute or subacute phase post-stroke. Participants had also responded to a study advertisement or been asked to participate while having contact with primary caregivers due to their functional impairments. These factors may imply recognition of limitations, an active standpoint and a positive attitude towards physical training that could differ from the standpoint in persons that perform similar training as a compulsory part of their rehabilitation programme. Furthermore, this study was performed in one rehabilitation centre using one specific exoskeleton, namely the HAL system. The market today comprises several gait-assisting devices. The experience of walking with a gait-assisting robot possibly differs depending on the device used for training.

Taking the next step: implications for future research and the clinic

Time since stroke onset (for timeline see Figure 2) has been suggested to greatly influence the possibilities of achieving gains in motor function (202). Still, the non-significant differences between the intervention and comparator groups (where the intervention groups improve to an equal extent) in our review and other reviews looking at post-stroke motor control trials (127), suggest that persons post-stroke benefit from training irrespective of time after the event. What is still to be investigated is how the aspect of time since stroke influences the impact of physical rehabilitation on neural reorganisation.

Standardised guidelines for assessing and reporting gait variables, including a core set of informative and sensitive biomechanical variables to be used in post-stroke gait analyses, would enable the pooling of results to guide further improvements in gait rehabilitation. These guidelines should encompass several aspects of gait, consider bilateral motor coordination and the engagement of the lower limbs as well as the trunk and upper limbs. A core set of biomechanical variables would also guide the development of reliable and valid motion tracking systems that are easily used within a clinical context and allow for assessments in a variety of environments.

A whole-body engagement during walking advocates for a broadened perspective both in the evaluation of gait and in gait rehabilitation interventions. Streamlining gait-assisting devices and associated equipment to make them easy to apply and to feel less restrictive while also engaging the upper limb and trunk without renouncing necessary support is a challenge for future development in the area of gait robotics. The design and application of a gait-assisting robot should be guided by a human-centric approach that acknowledges both the human neural and musculoskeletal system, as well as psychological aspects (203).

High-intensive gait rehabilitation with or without robotic assistance can be implemented and appreciated among persons post-stroke. Not just despite, but in some individuals because of the physical and mental challenges it implies. To be more stimulating, task-specific training should preferably be performed in an enhanced environment and complemented with other physiotherapy treatments (197). This would also facilitate variability in performance which has been suggested to ease the transferability from the training context to other circumstances that are more relevant for the persons in their daily life (180).

Finally, the relationship and communication between the physiotherapist and the person undertaking rehabilitation should not be underestimated. In fact, the role of the physiotherapist may be even more important for the rehabilitation outcomes than the applied programme or technology itself. One of our interviewed participants said: "It's the little things that matter. It doesn't have to be robots for millions of Swedish krona". The participant wanted to highlight that making the person feel actively involved in the training through individual goal-setting and inclusion in the decision-making processes, and to offer hope, support and encouragement, way surpassed the access to high-technological assistance.

Conclusions

- The systematic review (Paper I) identified a very low certainty for the current evidence for employing RAGT instead of non-RAGT to improve gait ability as measured with biomechanical measures post-stroke. Standardised guidelines for biomechanical quantification of gait post-stroke would enable pooling of results and evaluations that provide more detailed information on the potential effects of gait training interventions in general, as well as the influence on gait movement patterns in particular. In the long term, identification and understanding of post-stroke gait deviations contribute to an improved gait rehabilitation (with or without robotic devices) to better target “true recovery” and decrease the impact of compensatory gait patterns post-stroke.
- The proposed upper and lower body inclination angles (Paper II), presented with curve analyses covering the entire GC, served to discriminate between persons post-stroke and controls. The increased lower body inclination angle (*A-CoMIA*) in persons post-stroke implies a bilateral lower body adaptation that generates symmetric interrelationships between the CoM and the ankle during gait. Also, the *H-CoMIA* revealed asymmetrical motions in the upper body whereby persons post-stroke leaned more towards the affected side with their head and upper body during most of the GC. Further exploration is warranted of the angular velocities of the inclination angle variables and of the sensitivity, responsiveness over time and functional significance of these variables, as well as their relationships to other gait parameters.
- A core set combining a few crucial kinematic variables (Paper III) may sufficiently evaluate post-stroke gait and should receive more attention in future research and rehabilitation. Core sets of 2-3 variables suggest that spatial or temporal variables may be combined with data related to specific joint motions to correctly classify 93-96% of persons post-stroke. Our results contribute towards a consensus of instrumented gait evaluation post-stroke, which could substantially facilitate future diagnosis and monitoring of rehabilitation progress.
- Participating in a high-intensive gait training programme that included RAGT was perceived as a rare opportunity among persons in a long-term phase post-stroke (Paper IV). Even though the intervention induced tough mental and physical requirements, it was generally considered rewarding. Support, feedback and the engagement of the physiotherapists were recognised as crucial aspects. As participants

described the training as monotonous and sometimes even boring, the high-intensive and task-specific training should preferably be performed in an environment enriched with stimuli and complemented with other physiotherapy treatments. The perception of the equipment being uncomfortable, and difficulties in finding flow and rhythm during walking with the robotic device, highlight the need for further tailoring of the device and associated equipment so that it becomes easier and more comfortable to wear and use.

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Appendix

Table A. Presentation of the variables included in Step I of the analysis (Paper III). P-values below 0.005 are reported as 0.00.

Variables and short descriptions		p-value	
Spatial and temporal parameters			
Step length	toe off => initial contact, (cm)	0.00	
Stride length	initial contact => initial contact on the same leg (cm)	0.00	
Stride width	the distance between the heels of the two feet during double-support (cm)	0.00	
Gait speed	velocity normalized to height; statures per second	0.00	
Cadence	steps per minute	0.00	
Duration of single-support	opposite toe-off => opposite initial contact; % of GC; A or ND	0.00	
Duration of stance phase	initial contact => toe off; % of GC; A or ND	0.00	
Duration of swing phase	toe-off => initial contact; % of GC; A or ND	0.00	
Duration of 1 st double-support	initial contact => opposite toe-off; % of GC; A or ND	0.00	
Duration of 2 nd double-support	opposite initial contact => toe-off; % of GC; A or ND	0.00	
Step duration	% of GC; A or ND side	0.03	
Stride/GC time	seconds	0.00	
Temporal symmetry	The ratio value; A/NA or ND/D	0.00	
Spatial symmetry	The ratio value; A/NA or ND/D	0.00	
Range of angular motion (ROM)			
The difference between the highest and lowest values of the angular joint motion curve during the GC.			
Sagittal plane	Elbow	flexion/extension	0.00
	Shoulder	flexion/extension	0.00
	Thorax	flexion/extension	0.21*
	Pelvis	anterior/posterior tilt	0.00
	Hip	flexion/extension	0.00
	Knee	flexion/extension	0.00
	Ankle	flexion/extension	0.00
Frontal plane	Shoulder	abduction/adduction	0.04
	Thorax	abduction/adduction	0.00
	Pelvis	depression/elevation	0.27*
	Hip	abduction/adduction	0.00
Transversal plane	Shoulder	external/internal rotation	0.04
	Thorax	external/internal rotation	0.00
	Pelvis	ipsilateral/contralateral rotation	0.62*
	Hip	external/internal rotation	0.02

Variables and short descriptions			p-value
Range of angular motion Index (ROMI) The difference between the highest and lowest values of the angular joint motion curve during the GC and comparison between body sides. Ratio value: A/NA or ND/D.			
Sagittal plane	Elbow	flexion/extension	0.02
	Shoulder	flexion/extension	0.00
	Pelvis	anterior/posterior tilt	0.20*
	Hip	flexion/extension	0.00
	Knee	flexion/extension	0.00
	Ankle	flexion/extension	0.00
Frontal plane	Shoulder	abduction/adduction	0.24*
	Hip	abduction/adduction	0.03
Transversal plane	Shoulder	external/internal rotation	0.07*
	Hip	external/internal rotation	0.10*
Maximum joint angle The highest value of the angular joint motion during the GC			
Sagittal plane	Elbow	flexion/extension	0.27*
	Shoulder	flexion/extension	0.14*
	Pelvis	anterior/posterior tilt	0.76*
	Hip	flexion/extension	0.08*
	Knee	flexion/extension	0.00
	Ankle	flexion/extension	0.42*
Frontal plane	Shoulder	abduction/adduction	0.03
	Pelvis	depression/elevation	0.22*
	Hip	abduction/adduction	0.05
Transversal plane	Shoulder	external/internal rotation	0.76*
	Pelvis	ipsilateral/contralateral rotation	0.19*
	Hip	external/internal rotation	0.04
Maximum inclination angle The greatest value of upper or lower body inclination angle during the stance or swing phase of the GC			
H-CoMIA, stance	Upper body inclination angle defined as the angle between the estimated CoM and the frontal head marker; the maximum value during the stance phase		0.00
H-CoMIA, swing	Upper body inclination angle during the swing phase		0.30*
A-CoMIA, stance	Lower body inclination angle defined as the angle between the estimated CoM and the mid-ankle; the maximum value during the stance phase		0.00
A-CoMIA, swing	Lower body inclination angle during the swing phase		0.00

Variables and short description		p-value
Deviation scores		
A summarized deviation score derived from comparing the joint angles ROM of each subject and the average of the controls during one GC.		
Gait Profile Score (GPS)	Identifies a scaled distance between 9 lower limb and trunk gait variable scores for a subject and the average of the same 9 gait variable scores for a control group.	0.00
Arm Posture Score (APS)	Identifies a scaled distance between 6 upper limb gait variable scores for a subject and the average of the same 6 gait variable scores for a control group.	0.00
Gait Deviation Index (GDI)	Identifies a scaled distance between 15 lower limb and trunk gait feature scores for a subject and the average of the same 15 gait feature scores for a control group.	0.00
Stroke specific parameters		
Joint position angles that are suggested to specifically characterise the post-stroke gait movement pattern		
Hip extension, swing	The highest value of hip extension in A/ND side during the swing phase	0.01
Hip abduction, swing	The highest value of hip abduction in A/ND side during the swing phase (circumduction)	0.50*
Hip abduction, stance	The highest value of hip abduction in NA/D side during the stance phase (hip hiking)	0.69*
Knee flexion, swing	The highest value of knee flexion in A/ND side during the swing phase	0.00
Knee extension, single-support	The highest value of knee extension in A/ND side during the single-support phase (knee overextension)	0.52*
Ankle plantarflexion, terminal stance	The highest value of ankle plantarflexion in A/ND side during push-off	0.00
Ankle dorsiflexion, swing	The highest value of ankle dorsiflexion in A/ND side during the swing phase	1.00*

*Exclusion from further analyses because of non-significant differences between groups. Abbreviations: GC = gait cycle; A = affected body side in persons post-stroke; ND = non-dominant body side in controls; NA = non-affected body side in controls; D = dominant body side in controls; CoM = centre of mass, GVS = gait variable score

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