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Ole Petter Norvang

Recovery After a Stroke

The Importance of Early Rehabilitation and Gait Speed

NTNU
Norwegian University of Science and Technology

Thesis for the Degree of
Philosophiae Doctor

Faculty of Medicine and Health Sciences
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Movement Science

Doctoral thesis

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Sammendrag på norsk (Summary in Norwegian)

Hvert år forekommer det 11-12000 hjerneslag i Norge. Disse kan variere fra små hjerneslag med kort varighet av symptomer til alvorlige slag med betydelige funksjonshemminger. De siste tiårene har andelen som overlever et hjerneslag økt, noe som betyr at flere lever med både fysiske og kognitive funksjonshemminger. Dette kan føre til et økt behov for hjelp i dagligdagse oppgaver, og dermed tap av selvstendighet. Tidlig intervensjon med rehabilitering kan være viktig for å gjenvinne tapte funksjoner og selvstendighet.

Hovedmålet med denne avhandlingen var å kartlegge aktivitetsnivået og gangfunksjonen hos pasienter innlagt med hjerneslag, samt endring av gangfunksjon og selvstendighet de første 3 månedene etter symptomdebut. Artikkel 1 er basert på data fra sensorer som målte aktivitetsnivået kontinuerlig for innlagte pasienter med hjerneslag. Hensikten var å se hvordan aktivitetsnivået endret seg, samt faktorer som kunne relateres til disse endringene. Resultatene viste at pasienter innlagt med hjerneslag gradvis økte totaltid i både sittende og oppreist stilling, og at denne endringen var assosiert med økt grad av selvstendighet og bedre fysisk funksjon. Samtidig viste resultatene at varigheten per mobilisering opp i sittende stilling økte, noe som var assosiert med høyere alder og mer alvorlige hjerneslag. Et spesielt fokus på eldre og mer affiserte pasienter med hjerneslag så derfor ut til å være viktig i tidlig fase for å hindre for mye tid i liggende eller sittende stilling.

I artikkel 2 og 3 så man på endring i gangfunksjonen som skjer i tidlig fase etter et hjerneslag. Resultatene viste at ganghastigheten under innleggelse, men ikke resiliens, var assosiert med funksjonell avhengighet og hjelp i dagligdagse oppgaver 3 måneder etter hjerneslaget. Ganghastighet vil kunne være et viktig måleverktøy for rehabiliteringen etter et hjerneslag. Endring i spatiotemporale gangparametere; ganghastighet, steglengde, skritt bredde, kadens, tid i ett beins stående under svingfasen, og forholdet mellom steglengde, kadens (walk ratio), og asymmetri i steglengde og tid i ett beins stående under svingfasen, ble målt under innleggelse og på kontroll etter 3 måneder. Signifikante endringer ble testet for assosiasjon med endring i balanse og gangkapasitet. Resultatene viste at endring i de fleste spatiotemporale gangparametere kunne assosieres med endring i balanse og

gangkapasitet, men at spesielt endring i ganghastighet virket å være sterkt assosiert med disse endringene.

Resultatene fra avhandlingen viser et lavt overordnet aktivitetsnivå for pasienter innlagt med hjerneslag, men med en gradvis økning av aktivitet i sittende og stående gjennom sykehusinnleggelsen. Ganghastighet under innleggelse var assosiert med selvstendighet i daglige aktiviteter 3 måneder senere og bedring i ganghastighet var også assosiert med bedring i både balanse og gangkapasitet 3 måneder senere.

Summary in English

About 11-12000 persons suffer from a stroke every year in Norway. In recent decades the prevalence of stroke has slightly increased, especially amongst the older population, with an increased survival rate leading to more people living with physical and cognitive impairments from the stroke. This is likely to lead to an increased need for help in basic Activities of Daily Living (ADL) and less independence. Early intervention with rehabilitation may be important in regaining functions and independence and may reduce the need for help in ADL.

The main aims of this thesis were to investigate activity level and gait function amongst hospitalized patients with stroke, and to assess how gait and independence changed within the first three months after symptom debut. Paper 1 is based on data from body-worn sensors measuring physical activity continuously for admitted participants, to assess changes in activity level and factors associated with these changes. Results showed that admitted patients with stroke increased their daily overall time in sitting and upright positions, and that these changes were associated with less impairment and improved physical function. Further, there was an increased duration of bouts of sitting, and this was associated with a higher age and more severe strokes. A special focus on older and more severely affected patients with stroke therefore seems to be important early after stroke to avoid prolonged sedentary time.

In paper 2 and 3, changes in gait function and activities of daily living early after stroke were studied. Results showed that gait speed, but not resilience, during admission was associated with independence in basic ADL three months after stroke. Further, changes in spatiotemporal gait parameters – gait speed, step length, stride width, cadence, time in single support, walk ratio, and asymmetry in step length and time in single support – were measured during admission and three months later, and statistically significant changes were tested for associations with changes in balance and walking capacity. Results showed that changes in most spatiotemporal gait parameters could be associated with changes in balance and walking capacity, and that gait speed seems to be strongly associated with

changes in balance and walking capacity. Therefore, improvements in gait speed from admission to three months later could be related to a safer and more efficient gait.

The results from this thesis show that the overall activity level was low for hospitalized patients with stroke, but with a daily increase in time spent sitting and upright throughout the hospital stay. Gait speed during hospitalization was associated with independence in daily activities three months later whereas improved gait speed was associated with both improved balance and walking capacity.

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Norvang OP, Hokstad A, Taraldsen K, Tan X, Lydersen S, Indredavik B, Askim T. Time spent lying, sitting, and upright during hospitalization after stroke: a prospective observation study. *BMC Neurology.* 2018; 18(1):138

Paper 2

Norvang OP, Dahl, AE, Thingstad, P, Askim T. Association between gait speed and resilience during hospitalization with independence in basic activities of daily living three months after a stroke: A prospective longitudinal cohort study. Submitted to: *Topics in Stroke Rehabilitation. June 2020*

Paper 3

Norvang OP, Askim T, Egerton T, Dahl AE, Thingstad P. Associations between changes in gait parameters, balance and walking capacity during the first three months after stroke: An observational study. *Physiotherapy Theory and Practice March 2020 Online: https://www.tandfonline.com/doi/full/10.1080/09593985.2020.1771802*

Abbreviations

ADL – Activities of Daily Living

AVERT – A Very Early Rehabilitation Trial

BBS – Bergs Balance Scale

BI – Barthel Index

BRS – Brief Resilience Scale

CI – Confidence Interval

FSS – Fatigue Severity Scale

IQR – Interquartile Range

ICC – Intraclass Correlation Coefficient

LMM – Linear Mixed Model

MAR – Missing at Random

MCAR – Missing Completely at Random

MRI – Magnetic Resonance Imaging

mRS – Modified Rankin Scale

NIHSS – National Institute of Health Stroke Scale

SD – Standard Deviation

SEE – Standard Error Estimation

SIS – Stroke Impact Scale

SPPB – Short Physical Performance Battery

SSS – Scandinavian Stroke Scale

VIF – Variance Inflation Factor

6MWT – Six-Minute Walk Trial

1. Introduction

Stroke is one of the leading causes of disability and death worldwide (V. L. Feigin et al., 2014). However, there is a trend towards a decline in stroke mortality (Sarti et al., 2003), leading to more patients with stroke and their relatives facing impairments from physical, psychological and cognitive elements after the stroke (Valery L Feigin, Mensah, Norrving, Murray, & Roth, 2015). An early and adjusted rehabilitation process is important for regaining functions and independence, as most recovery takes place in the first months after stroke (Jorgensen et al., 1995b). Safe and efficient gait to manage daily activities is considered a key factor in being independent. Therefore, focus on physical activity and mobilization starting early during hospitalization and carried out in rehabilitation centers and at home after discharge, is important. However, gait is a complex task including several factors, working together to maintain safety and efficiency. Coping with a serious event such as a stroke may greatly influence rehabilitation (Hildon, Montgomery, Blane, Wiggins, & Netuveli, 2010). Therefore, identifying factors early after a stroke that are associated with independence and independent ambulation may help in individualizing rehabilitation after stroke.

The overall aim of this thesis was to study factors related to the extent of early mobilization in the acute phase after a stroke and whether factors such as gait characteristics and resilience were associated with outcome three months later.

2. Background

2.1 Stroke

2.1.1 Definition of stroke

The World Health Organization defines stroke as "*rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin*" (Aho et al., 1980). However, this definition relies primarily on clinical symptoms and has lately been challenged by the American Heart Association and American Stroke Association. They define ischemic stroke as "*an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction"* diagnosed by a clinical assessment and imaging (Sacco et al., 2013). In this thesis, the definition by the World Health Organization, endorsed by the World Stroke Organization and European Stroke Organization will be used, as this still is the most commonly used definition.

The most common symptoms of stroke include sudden unilateral weakness, numbness, or visual loss, diplopia, altered speech, ataxia, and non-orthostatic vertigo (Hankey & Blacker, 2015). Symptoms lasting less than 24 hours and without evidence of infarction by imaging are defined as transitory ischemic attack (Sacco et al., 2013). In this thesis, included participants have suffered from symptoms lasting longer than 24 hours and have all been diagnosed with a stroke.

2.1.2 Prevalence and incidence of stroke

In 2010 it was estimated that 16.9 million people worldwide suffered from a stroke, causing 5.9 million deaths and making it one of the leading causes of death globally (V. L. Feigin et al., 2014; Krishnamurthi et al., 2013). The global incidence rate of stroke has remained relatively stable from 1990 to 2010. However, the prevalence of stroke increased slightly in the same period, mainly because of an increase in survival rate (V. L. Feigin et al., 2014). With more people surviving stroke, the need for rehabilitation increases, as patients with stroke try to regain earlier function level.

It has been estimated that about 11-12000 people suffer from stroke every year in Norway (Norwegain Directorate of Health, 2018; Norwegian Directorate of Health, 2017a). According to the Norwegian national health registry, 86% of all strokes were caused by infarctions, 13% by hemorrhages, and 1% were unclassified (Norwegain Directorate of Health, 2018). In Norway, the incidence of strokes decreased from 1995 to 2010. This was mainly caused by a decreased rate amongst the younger population, while the incidence rate amongst those aged above 75 years remained stable (Vangen-Lonne, Wilsgaard, Johnsen, Carlsson, & Mathiesen, 2015). In recent years, the mortality rate has declined dramatically. From 2012 to 2016 the number of patients dying from an acute stroke was reduced by 25%, from 59 to 44 deaths per 100 000 (Norwegian Cardiovascular Disease Registry, 2018). Several factors, such as milder strokes, better diagnostic tools, a higher percentage of patients being treated in comprehensive stroke units, and improved treatment options including thrombolysis, are likely to explain this decreased mortality rate (Katan & Luft, 2018; Norwegain Directorate of Health, 2018). The increased survival rate is likely to increase the prevalence of stroke, with more people living with stroke impairments.

In 2018, Norwegian patients with stroke had a mean age for symptom debut of 76 years. Women were older (77 years old) than men (72 years old) (Norwegain Directorate of Health, 2018) and the incidence rate of stroke is slightly higher amongst men than women. However, because women live longer than men, there are more women in the highest age group of patients with stroke in absolute numbers (Norwegian Cardiovascular Disease Registry, 2018).

2.2 Stroke treatment

2.2.1 Evidence-based stroke units

The understanding and treatment of stroke has changed during recent decades. From being considered as a chronic condition with permanent damage, it has become an acute medical condition that requires immediate and intensive medical care. Diagnostic tools have improved significantly, making the diagnostic of stroke much more accurate. This has allowed better and more precise treatment of patients with stroke, both medically and physically. Norwegian guidelines state that all patients with stroke should be treated in a comprehensive stroke unit (Norwegian Directorate of Health, 2017b), as they provide the most favorable treatment after stroke, increasing survival rates, return to home, and independence (Stroke Unit Trialists, 2013). A multidisciplinary approach focusing on early mobilization, physiological homeostasis, nutrition and fluid intake is essential to provide the best possible treatment (Indredavik, Bakke, Slordahl, Rokseth, & Haheim, 1999; Langhorne & Pollock, 2002). The focus on early rehabilitation and early mobilization after stroke is argued to be as important as the medical treatment and is well incorporated in dedicated stroke units (Indredavik et al., 1999; Langhorne & Pollock, 2002; Stroke Unit Trialists, 2013).

2.2.2 Early mobilization and physical activity during admission

It has been well established that early mobilization in medically stable patients with stroke during admission is favorable, as it has been shown to reduce complications (Herisson et al., 2016; Indredavik et al., 1999; Ingeman, Andersen, Hundborg, Svendsen, & Johnsen, 2011) and improve functional outcome after stroke (Askim, Bernhardt, Salvesen, & Indredavik, 2014; Chippala & Sharma, 2016; Franceschini et al., 2018; Hokstad et al., 2016; Ingeman et al., 2011; Shimizu, Hashidate, Ota, & Yatsunami, 2019; Yagi et al., 2017). Despite this, the amount of physical activity is low, and most time is spent in bed (Askim, Bernhardt, Loge, & Indredavik, 2012; Bernhardt, Dewey, Thrift, & Donnan, 2004). Nevertheless, recent randomized controlled trials have shown that mobilization within the first 24 hours was associated with increased dependence (Sundseth, Thommessen, & Ronning, 2012), mortality (Lynch, Hillier, & Cadilhac, 2014) and a reduction in favorable outcome (Avert Trial Collaboration group, 2015) three months later. However, secondary analysis from AVERT showed that shorter and more frequent mobilizations were associated with a better chance of regaining independence (Bernhardt et al., 2016). Given the uncertainty of potential hazard during early mobilization, the demands for more research regarding the dosage of early mobilization have been raised (Langhorne, Collier, Bate, Thuy, & Bernhardt, 2018).

Most studies on early mobilization during hospitalization have used single-day observations as a method for recording time in an upright position (Askim et al., 2012; Hokstad et al., 2015). This is, however, time consuming, person dependent and usually limited to a specific time of the day. A single-day observation of physical activity may also be biased by transitory medical challenges and time- and energy-consuming medical examinations. Recently, body-worn loggers have been introduced, allowing continuous measurement of activity for several days (Davis & Fox, 2007; Mattlage et al., 2015). These have been shown to be reliable in a hospital setting (Kramer, Cumming, Churilov, & Bernhardt, 2013). So far, only a few studies have used loggers on hospitalized patients with stroke. In an observational study for hospitalized patients with stroke, Strommen et al (2014) found that total activity level increased in the lower extremities during admission from first day hospitalized until discharge (Strommen, Christensen, & Jensen, 2014). However, it is not clear which factors are associated with time spent in sitting and upright activity during a hospital stay.

2.3 Consequences of a stroke

2.3.1 Function

According to the latest annual report from the Norwegian Stroke Register, about 85% of patients with stroke reported to have returned to their homes three months after stroke. Of these, 76% had an independent gait and 61% were considered completely independent in activities of daily living (Norwegain Directorate of Health, 2018). A higher age, more severe affection of stroke, and post-stroke complications are all associated with a worse outcome (Appelros, Nydevik, & Viitanen, 2003) and thereby less independence. Stroke can affect physical functions such as balance and gait due to paresis, paralysis, and neglect. However, a stroke is also likely to interfere with many aspects of life, physically, psychologically and cognitively. Post-stroke fatigue is one of these factors, having been associated with depression (Aarnes, Stubberud, & Lerdal, 2019; Cumming, Packer, Kramer, & English, 2016; Galligan, Hevey, Coen, & Harbison, 2016; Ingles, Eskes, & Phillips, 1999; Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006) and has shown strong correlation with disability and physical impairment (Appelros, 2006), increased impairment in activities of daily living (Glader, Stegmayr, & Asplund, 2002; Miller et al., 2013), and gait and balance (Goh & Stewart, 2019; Michael, Allen, & Macko, 2006). Therefore, a stroke may cause changes in daily living and independence, thereby affecting quality of life (Lo Buono, Corallo, Bramanti, & Marino, 2017; Ramos-Lima, Brasileiro, Lima, & Braga-Neto, 2018).

2.3.2 Resilience

A stroke is likely to have a large impact on daily living. This may have a negative impact on social functioning and well-being, as patients with stroke often experience a sense of disappointment and decreased quality of life related to unmet expectations regarding recovery (Crowe et al., 2016; Kamat, Depp, & Jeste, 2017). However, positive emotions perceive difficult situations to be less challenging as compared to persons who are anxious or depressed (Riener, Stefanucci, Proffitt, & Clore, 2011; Stefanucci, Proffitt, Clore, & Parekh, 2008). Coping skills, level of active social participation, and number of social ties may all be important in dealing with the stroke, and has been shown to improve both well-being and functioning three months after discharge (Berges, Seale, & Ostir, 2012; Kamat et al., 2017).

Resilience is a process of "bouncing back" or coping with the situation after a serious disease (Hildon et al., 2010). It has been defined as "a dynamic process of adapting well in the face of trauma, adversity, threats, tragedy or significant sources of stress" (American Psychological Association, 2014). Previous reports have suggested that resilient persons tend to use social support and keep working on goals, based on past experiences to bounce back from difficult experiences (Fontes & Neri, 2015). Resilience is closely related to quality of life and physical independence early after stroke (Liu, Zhou, Zhang, & Zhou, 2019), and has been considered as a factor contributing to improved outcomes, such as physical function also in the longer term (Edwards, Alschuler, Ehde, Battalio, & Jensen, 2017).

So far, there is a lack of knowledge on how resilience is associated with recovery among patients with stroke (Fuller-Thomson & Jensen, 2019). Understanding the role of positive emotions in persons living with stroke may provide insight into both short- and long-term recovery (Ostir, Berges, Ottenbacher, Graham, & Ottenbacher, 2008), and may therefore be an important factor to consider when doing rehabilitation after an event as serious as stroke.

2.4 Post-stroke gait

Independent ambulation is the most self-stated rehabilitation goal for patients with stroke (Bohannon, Andrews, & Smith, 1988; Duncan et al., 2007) and plays a vital role in regaining independence after stroke. Walking requires coordinated function in several physiological and cognitive subsystems, involving both motor and sensory systems. A stroke causing brain damage that affects these systems could influence gait, leading to an increased risk of falls and a higher energy expenditure due to changes in gait patterns. Because a safe and independent gait is a key factor to avoid complications such as falls, maintaining balance during walking is important. Spatial (distance parameter) and temporal (time parameter) gait parameters, often referred to as spatiotemporal gait parameters, are commonly used to measure gait, as they bring detailed information about different aspects.

2.4.1 Gait speed

Preferred gait speed may be considered a sum of several spatiotemporal gait parameters and is considered a robust and sensitive measure of health and function (Brandstater, de Bruin, Gowland, & Clark, 1983; Roth, Merbitz, Mroczek, Dugan, & Suh, 1997; Studenski et al., 2011; Wonsetler & Bowden, 2017). Previous studies have shown that gait speed is directly related to community ambulation with thresholds discriminating between the different ambulation levels (Fulk, He, Boyne, & Dunning, 2017). Gait speed below 0.8 m/s has been reported as a cut-off for community walking with moderate gait impairment (Perry, Garrett, Gronley, & Mulroy, 1995). Gait speed involves both dynamic balance and walking capacity, with a reduction in gait speed likely to be related to the others (Hak et al., 2012; Waters, Lunsford, Perry, & Byrd, 1988). Following a stroke, gait speed is likely to be reduced initially due to factors such as hemiplegia and a decreased ability of postural control. However, during the first months after stroke, gait speed has been reported to increase from admission (Wonsetler & Bowden, 2017), with a 5% change in gait speed being reported to be clinically significant (Kesar, Binder-Macleod, Hicks, & Reisman, 2011).

Gait speed is closely associated with other spatiotemporal gait parameters and it is therefore important to address speed when studying gait (Brandstater et al., 1983; Roth et al., 1997). However, gait speed does not identify the mechanisms by which an individual recovers (Wonsetler & Bowden, 2017). It has therefore been argued that gait evaluation should include characterization of the degree of asymmetry ratio (Roth et al., 1997), as spatiotemporal gait parameters and asymmetry parameters would calculate gait deviations, thereby providing further knowledge regarding recovery.

2.4.2 Hemiplegia and spatiotemporal gait parameters

Walking requires control of the trajectory of the body's center of mass over a narrow and changing base of support (Winter, Patla, Frank, & Walt, 1990). A common disability following a stroke is paresis or paralysis on the affected side, leading to a hemiplegic gait (Patten, Lexell, & Brown, 2004). This is caused either by a muscle weakness or by spasticity, or as a combination of these two (Patten et al., 2004). Hemiplegia is most likely to affect important tasks for independent ambulation, such as gait, balance and walking capacity. It can cause weight-bearing asymmetry, a smaller base of support and increased body sway (Tasseel-Ponche, Yelnik, & Bonan, 2015), all likely to affect ambulation. Most changes of motor functions are due to an impaired central nervous system, but some could be considered adaptive behaviors, causing a reduced ability to shift body weight onto the affected side (Patterson, Gage, Brooks, Black, & McIlroy, 2010; van Dijk et al., 2017) and decreased step length and time in single support on the affected side (Cruz, Lewek, & Dhaher, 2009; Mizuike, Ohgi, & Morita, 2009; von Schroeder, Coutts, Lyden, Billings, & Nickel, 1995). This is likely to lead to higher energy consumption (Wert, Brach, Perera, & VanSwearingen, 2010). During recovery after a stroke, spatiotemporal gait parameters such as gait speed are likely to recover faster than gait asymmetry (Patterson et al., 2015). A possible explanation for this is that the increased gait speed may be a compensatory strategy, whereas spatiotemporal gait asymmetry reflects hemiplegia. Therefore, measuring both spatial and temporal gait parameters has been argued to be preferable following a stroke (Wonsetler & Bowden, 2017).

An improved gait speed on an asymmetric gait is likely to lead to an increased cadence. An asymmetric gait leading to a decreased ability of single support during swing phase of the unaffected leg, will cause shorter steps. The increased gait speed is therefore likely to be caused by an increased cadence. Walk ratio, which is the ratio between step length and cadence, is likely to be related to gait efficiency, with a decreasing walk ratio often related to a less efficient gait after a stroke. There appears to be an optimal walk ratio (Egerton, Danoudis, Huxham, & Iansek, 2011b), and for healthy adults this relationship has been reported to be 0.64 cm/steps/min (Sekiya & Nagasaki, 1998). Walk ratio is being considered as an expression of central control mechanism and changes in the walk ratio can be interpreted as an indication of a more conscious control of gait (Egerton, Danoudis, Huxham, & Iansek, 2011a). For patients with stroke suffering from hemiplegia, the walk ratio is likely to decrease, as the ability of single support on the affected side decreases. Therefore, in a rehabilitation setting, a walk ratio moving toward normalization has been argued to be indicating an improved gait efficiency. Asymmetry and walk ratio are both calculated on values representing the ratio between two spatiotemporal gait parameters. This makes them less influenced by gait speed than other spatiotemporal gait parameters that are raw values of gait. An overview of the spatiotemporal gait parameters is presented in table 4.

2.4.3 Balance

Balance can be divided into three classes of human activity: maintaining a specific posture, voluntary movement, and reaction to an external disturbance (Pollock, Durward, Rowe, & Paul, 2000). It is controlled by a complex system, with several components interacting with each other and with the surroundings. During walking, these systems need to work both reactively and predictively in order to maintain balance. A deficiency in either the motor, sensory, or cognitive system, caused by a stroke, can lead to balance impairments (Zou, Sasaki, Zeng, Wang, & Sun, 2018), and thereby cause gait impairment as balance and gait are closely associated (van Meulen et al., 2016). During locomotion, the reduced ability to shift body weight onto the affected side is likely to affect gait initiation for patients with stroke, which could affect balance (Rajachandrakumar et al., 2017). Balance is likely to be associated with both spatial and temporal gait symmetry, with less asymmetry being associated with better balance (Patterson et al., 2008). This implies that balance can be considered a fundamental motor skill learnt by the central nervous system, and that like any other motor skill, postural control strategies can become more efficient and effective with training and practice (Horak, Henry, & Shumway-Cook, 1997).

2.4.4 Walking capacity and gait efficiency

Following a stroke, gait efficiency is often reduced as a result of increased gait asymmetry and reduced walking capacity. Gait efficiency reflects the energy cost of walking with oxygen consumption divided by walking speed (VanSwearingen, Perera, Brach, Wert, & Studenski, 2011). The decreased gait efficiency is likely lead to a higher energy consumption, as persistent gait impairments after stroke can increase energy expenditure (Awad, Palmer, Pohlig, Binder-Macleod, & Reisman, 2015; Bae et al., 2018; Farris, Hampton, Lewek, & Sawicki, 2015). Gait impairments will influence functional ambulation and thereby the capacity to perform walking during activities of daily living with reduced capacity during prolonged activities (Sibley, Tang, Brooks, & McIlroy, 2008). Walking capacity, often measured by the 6MWT, is frequently used as a measure of functional capacity in patients (Pollentier et al., 2010). Capacity is also affected by low cardiorespiratory fitness in patients with stroke (Mackay-Lyons & Makrides, 2004; Tang, Sibley, Thomas, McIlroy, & Brooks, 2006). This reduced ability to respond to physical demands of everyday life has detrimental effects on mobility and resistance to fatigue and it is likely to compound the functional limitations imposed by neuromuscular impairments among patients with stroke. Whereas reduced walking capacity is related to higher energy consumption and lower cardiorespiratory fitness, fatigue is related to a subjective feeling of a lack of energy (Colle, Bonan, Leman, Bradai, & Yelnik, 2006; Ingles et al., 1999). Both fatigue and reduced walking capacity are likely to influence gait efficiency, reducing walking capacity and increasing energy expenditure (Awad et al., 2015).

2.5 Summary and rationale for the thesis

In summary, there is evidence that early mobilization and physical activity is an important part of early stroke rehabilitation. However, optimal timing and intensity for initiating rehabilitation is not yet clear. The activity level is likely to change during admission as the medical condition of patients with strokes stabilizes and allows longer periods of activity.

Therefore, identifying factors associated with increased time in sitting and upright positions throughout admission could bring new knowledge on early mobilization after stroke.

The first months after stroke are the period where most recovery takes place and are therefore important in regaining independence. Identifying robust and unbiased associations with functional independence would help in guiding and facilitating stroke rehabilitation. Gait speed has been shown to be a strong indicator of physical function and to predict community walking after stroke. However, whether gait speed early after stroke can be associated with future independence in ADL is still not clear. Coping strategies following a stroke may also be associated with functional independence, as patients with stroke who have high resilience are more likely to bounce back from the stroke. Therefore, assessing the association between gait speed and resilience during admission and independence in basic ADL three months later could provide important information and focus in early rehabilitation.

Independent gait is considered as a particularly important rehabilitation goal and an important part in regaining independence after stroke. Exploring changes in spatiotemporal gait parameters during rehabilitation can tell us about gait characteristics and strategies – key factors in a safe and efficient gait. However, how these changes can be related to changes in balance and walking capacity is not yet clear. Exploring the relationship between spatiotemporal gait parameters, balance and walking capacity may improve understanding of post-stroke gait characteristics and help to optimize rehabilitation following a stroke.

3 Aims

The overall aim of this thesis was to study factors related to the amount of early mobilization in the acute phase after a stroke and whether gait characteristics and resilience were associated with outcome three months later. The thesis consists of three papers. Their specific aims were to:

Paper 1

1. Describe the amount of time spent in lying, sitting and upright (standing or walking) positions early after stroke and how these activity levels changed during the hospital stay, regarding both total time per day and duration for each mobilization.
2. Examine which factors were associated with total time and bouts of sitting and upright activity.

Paper 2

1. Examine whether gait speed assessed within the first 2 weeks after a stroke can be associated with independence in basic ADL 3 months later.
2. Examine whether resilience assessed within the first 2 weeks after a stroke can be associated with independence in basic ADL 3 months later.

Paper 3

1. Examine the associations between changes in primary and calculated spatiotemporal gait parameters with changes in balance and walking capacity during the subacute phase post stroke.

4 Material and methods

4.1 Study design

The thesis is based on data from two prospective observational studies. Paper 1 has a longitudinal design with repeated measures, measuring activity continuously during hospitalization. In paper 2 and 3, a test–retest design was applied, following one cohort for the first three months after a stroke. In paper 2, associations between gait speed and resilience during hospitalization with independence in basic ADL three months later were assessed. In paper 3, associations between changes in spatiotemporal gait parameters, balance and walking capacity in the first three months after stroke were examined.

4.2 Participants

Data in paper 1 was collected from patients with stroke admitted to the stroke unit at St Olavs University Hospital. Patients were recruited during three time periods, October-December 2013, May-December 2014, and March-August 2016. All patients accepting participation gave written consent. In line with the Norwegian regulations for informed consent, patients who were unable to consent were included if their next of kin was not opposed to their participation. Participants accepting participation wore the loggers throughout their hospital stay to obtain time spent in lying, sitting and upright positions.

Paper 2 and 3 were based on data collected from patients with stroke admitted to the stroke unit at St. Olavs Hospital from March 2012 to June 2014. Patients were recruited within 14 days after stroke onset. All patients agreeing to participate gave written consent. Included patients were invited back to the hospital three months later (± two weeks). Figure 1 shows the flow chart of the participants.

4.2.1 Eligibility criteria

The study samples consisted of diagnosed acute patients with stroke treated in a comprehensive stroke unit. Inclusion and exclusion criteria are listed in table 1. For the first paper, patients had to remain admitted for three consecutive days to be included in the study. Patients expected to be discharged within three days were excluded. In paper 2 and 3, participants had to be able to walk 10 meters without personal assistance to be included.

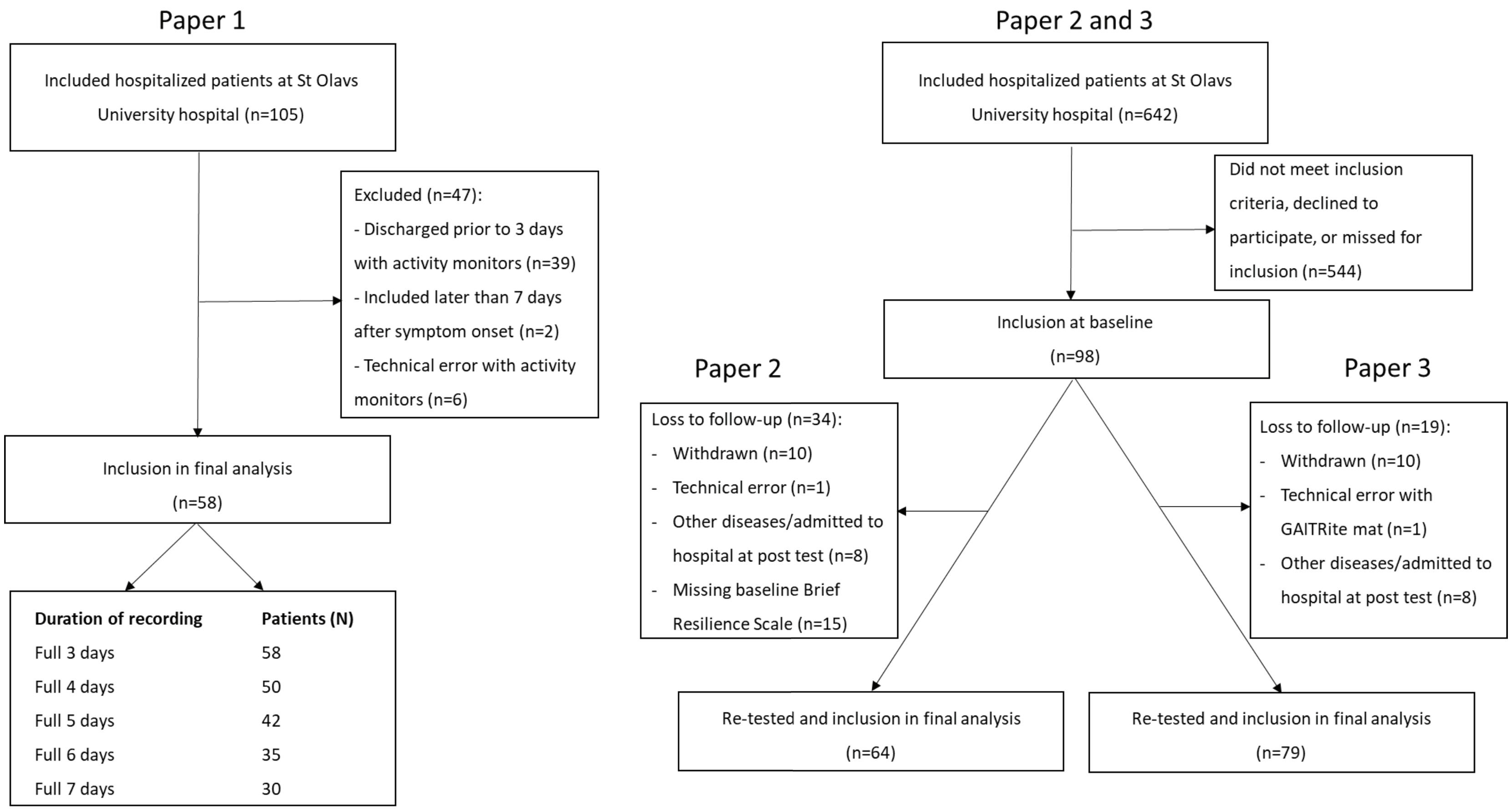

Figure 1. Flow chart of all three papers

Table 1. Eligibility criteria

Study population	Eligibility criteria	Paper
Patients with stroke admitted to the stroke unit at St Olavs University hospital between Oct-Dec 2013, May-December 2014, and March-August 2016.	**Inclusion:** Diagnosed with first ever or recurrent acute ischemic or hemorrhagic stroke, the onset of stroke had been within seven days, they spoke fluent Norwegian, and gave a written consent. **Exclusion:** Patients with terminal illness, other health conditions severely affecting ability to walk, or expected discharge within three days after inclusion were excluded.	1
Patients with stroke admitted to the stroke unit at St Olavs University hospital between March 2012 and June 2014.	**Inclusion:** Living in the municipality of Trondheim, diagnosed with first ever or recurrent acute ischemic or hemorrhagic stroke, modified Rankin Scale (mRS) score 0-3 points*, capable of walking with or without walking aid without support from another person for 10m, scored 4-6 points on the item “orientation” on Scandinavian Stroke Scale (SSS), and could provide informed consent. **Exclusion:** Life expectancy of less than six months, serious impairments prior to the stroke that could have significant impact on functional outcome, or unstable medical condition after acute stroke were exclusion criteria.	2 and 3

* mRS 0-4 in paper 2

4.2.2 Study sample

In paper 1, 105 patients were included in the study. However, 47 participants were excluded from the analysis, mainly because they were discharged prior to three consecutive days with the loggers, leaving a study sample of 58 patients with stroke. Participants were recruited within seven days after stroke onset. Because time since stroke can influence activity level, the participants were sub-grouped into three groups: 0-2 days, 3-4 days, and 5-7 days since symptom debut, to control for sub-group differences. The total National Institute of Health Stroke Scale (NIHSS) score was 6.2 (5.0) points. Those included 4-7 days after symptom onset showed significantly lower scores on NIHSS 4.6 (6.8) compared to those included within the first 48 hours (8.4 ±4.4, p=0.002). No other significant differences were found for the baseline variables.

Paper 2 and 3 were based on the same population. 642 patients diagnosed with an acute stroke and living in the municipality of Trondheim were treated at the stroke unit at St Olavs University Hospital. However, 544 patients either did not meet the inclusion criteria, declined to participate, or were missed for inclusion, leading to 98 participants included at baseline. In paper 3, 19 patients were lost to follow-up, mainly caused by withdrawn or re-admission to hospital. Therefore, 79 subjects were included in the analysis. The sample size in paper 2 was further reduced by 15 subjects because the brief resilience scale questionnaire was introduced at baseline after the study had started. Table 2 shows baseline characteristics for patients included in the analysis of the three papers.

Table 2. Baseline characteristics in all three papers

	Paper 1 (n=58)	Paper 2 (n=64)	Paper 3 (n=79)
Age, years	75.1	75.9 (8.6)	75.4 (8.5)
Female gender, n (%)	31 (53.5)	29 (44.6)	35 (44.3)
Days hospitalized	12.1 (7.6)	6.7 (3.4)	6.5 (3.3)
Days from stroke to inclusion	2.6 (0.7)	4.3 (2.8)	4.0 (2.7)
Monitoring days	5.8 (1.5)	NA	NA
SSS at baseline test (0-58)	NA	51.8 (4.6)	51.8 (4.6)
NIHSS when admitted (0-42)	6.2 (5.0)	NA	NA
Stroke severity group, n (%)			
NIHSS <8 (mild)	46 (79.1)	NA	NA
NIHSS 8-16 (moderate)	11 (19.0)	NA	NA
NIHSS>16 (severe)	1 (1.7)	NA	NA
Type of stroke, n (%)			
Embolic	NA	51 (78.5)	65 (82.3)
Hemorrhagic	NA	4 (6.2)	4 (5.1)
Unclassified	NA	10 (15.3)	10 (12.6)
Barthel Index (0-100)	NA	85.2 (14.6)	85.7 (14.8)
mRS when admitted (0-6)	4.1 (0.7)	2.8 (0.9)	2.7 (1.0)
Fatigue Severity Scale (7-49)	NA	22.4 (11.9)	22.3 (12.0)
Gait speed, m/s	0.52 (0.36)	0.9 (0.3)	0.9 (0.3)
Bergs Balance Scale (0-56)	NA	37.4 (15.8)	37.7 (15.5)
Six-minute walk test, m	NA	385.5 (171.7)	377.3 (134.2)
Walking aids at baseline, n (%)			
None	NA	36 (55.4)	58 (73.4)
Cane	NA	7 (10.8)	7 (8.9)
Walker	NA	22 (33.8)	14 (17.7)

Mean (SD) unless otherwise stated. SSS: Scandinavian Stroke Scale, NIHSS: National Institute of Health Stroke Scale, mRS: Modified Rankin Scale.

4.3 Study setting

All participants were initially treated at the Stroke Unit at St. Olavs University Hospital, which is an evidence-based comprehensive stroke unit that emphasizes a multidisciplinary approach, early rehabilitation and independence in daily life, and with a special focus on mobilization out of bed within 24-48 hours after stroke onset in medically stable patients. The treatment was in line with Norwegian guidelines, which recently have been updated (Norwegian Directorate of Health, 2017b). Those in need of rehabilitation after discharge were transferred to a rehabilitation program or outpatient clinic and home-dwelling participants in need of follow-ups were assessed by a specialized early supported discharge team, in accordance to standard procedures in the 2010 Norwegian guidelines for management of stroke (Norwegian Directorate of Health, 2017b).

4.4 Measures

Table 3. Included variables in the papers

Measurements	Paper 1	Paper 2	Paper 3
Scandinavian Stroke Scale		X	X
National Institute of Health Stroke Scale	X		
Barthel Index		X	X
Modified Rankin Scale	X	X	X
Brief Resilience Scale		X	
Fatigue Severity Scale		X	
Short Physical Performance Battery	X		
Berg Balance Scale			X
Six-minute walk test			X
ActivPAL*	X		
Spatiotemporal gait parameters			X

*PAL Technologies Ltd, Glasgow, UK

4.5 Assessments

Baseline characteristics such as age, gender, days hospitalized, days from onset of symptoms to inclusion, the use of a walking aid, stroke severity at admission, the type of stroke, and reperfusion treatment were obtained from the medical records. Assessments of response variables and outcome variables are described in the following section and in table 5. Using the ICF classification, the measures have been grouped in terms of either body function and structure or activity and participation (World Health Organization, 2001). Activity and participation were merged into one group as a joint level of capacity and performance because the tests used here could influence both levels.

4.5.1 Body function and structure

Body function and structure assess physiological and psychological functions, and anatomical parts of the body system (World Health Organization, 2001). In the following section, the measures on body function and structure level used in this thesis are listed: Spatiotemporal gait parameters were assessed using the GAITRite mat (CIR Systems, Franklin, NJ, USA) as shown in figure 2. The mat gives a walking length of either 5.49m or 6.10m, with an additional 1m acceleration/deceleration. Each walk provided data about both spatial and temporal gait parameters, including gait speed, step length, stride width, time in single support and cadence. Further asymmetry measures and the walk ratio were calculated based on data from the GAITRite mat. Figure 3 shows the difference between steps and strides within a gait cycle and table 4 gives an overview of the different spatiotemporal gait parameters assessed during the gait analysis.

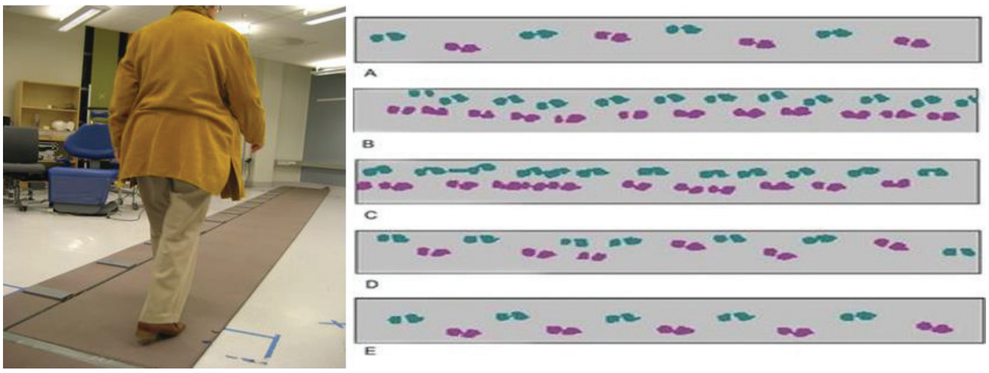

Figure 2. GAITRite mat measuring spatial and temporal gait parameters (adapted from the Trondheim Hip Fracture Trial, 2015)

One of the most common measures of stroke severity is the National Institute of Stroke Scale (NIHSS), evaluating cognitive function, orientation and response to commands, and physical and neurological function. The NIHSS has been implemented and recommended in the Norwegian guidelines for treatment and rehabilitation after stroke (Norwegian Directorate of Health, 2017b). Another test commonly used in the Scandinavian countries to assess stroke severity is the Scandinavian Stroke Scale (SSS) (Scandinavian Stroke Study Group, 1985). SSS consists of nine tasks, assessing consciousness, gaze, function in affected arm, hand and foot, orientation of time and place, language, facial palsy, and the ability to move.

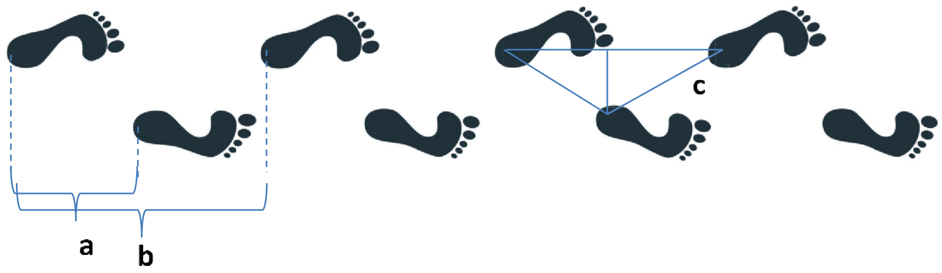

Figure 3. Spatial Gait Characteristics: a) Step length and b) stride length, c) step width

Table 4 Overview of the spatiotemporal gait parameters used during gait analysis

Spatial gait parameters	
Step length (cm)	Distance between the most rearward point of two successive footprints
Stride width (cm)	The perpendicular distance between the line connecting two heels of the same foot (cycle) and the heel of the contralateral foot
Temporal gait parameters	
Gait speed (m/s)	Distance traveled over time
Single support (%)	Period during which only one foot is in contact with the ground
Calculated gait parameters	
Cadence (steps/min)	Number of steps taken for one minute
Walk ratio (step length/cadence)	Step length divided by the cadence
Asymmetry step length (L/R)	The paretic step length divided by the nonparetic step length
Asymmetry single support (L/R)	The paretic single support time divided by the nonparetic single support

Based on the PKMAS® online definitions

4.5.2 Activity and participation

Activity includes the execution of a specific task or action for the individual. An activity limitation following a stroke will therefore involve difficulties in executing these activities. Participation refers to involvement in a life situation and restrictions in participation will involve difficulties in involvement in life situations (World Health Organization, 2001). In the following section, measures at the level of activity and participation used in this thesis are listed:

The Barthel Index is used to measure independence in daily activities (Mahoney & Barthel, 1965). The scale tests ten different activities in daily living and the sub-scores from each task are summed. Barthel Index was applied to assess independence three months after a stroke.

To objectively measure daily physical activity, the activPAL logger (PAL Technologies Ltd, Glasgow, UK) was applied. The loggers register inclination, to distinguish between the different activities. This allows continuous measurement of activities, by measuring time in different positions and then classifying the activity into lying, sitting, standing or stepping, as well as step count and postural transitions, and the logger can be worn for several days. The monitor is usually worn on the thigh but can also be worn in pairs (Taraldsen et al., 2011). One sensor was attached on the thigh of the unaffected side and one on the sternum to distinguish between lying and sitting positions. ActivPAL loggers have an internal watch that starts immediately after the monitor has been removed from the docking station. A synchronized movement on both loggers was therefore conducted before attachment and after removal from the body to create a start and stop of the measurements. However, the activPAL may have an inter-sensors time drifting. Before the start of the project, several combinations of sensors were tested for up to one week (both attached to the same thigh), which revealed time drifting for up to nearly one minute. Therefore, time drifting between the sensors was controlled every night when patients were lying for several hours, to harmonize the sensors. However, the exact time drifting and how they would affect the results was difficult to control, as this could differ between different sensors. To test the validity of the results, a virtual time drift correction was created by manipulating the time by -120 s to 120 between sensors. This was done by setting the time of the thigh sensor to be 120 seconds faster or slower without changing events in the Matlab program (Matlab R 2015B) and then repeating the method with the chest sensor. If this procedure would make significant changes to the results, the validity of the study would be weakened.

The modified Rankin Scale (mRS) is a commonly used measure of functional impairment and independence after stroke (van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988), and it was used to assess disability at different timepoints. The categories from 0-3 indicated independence in daily activities, while higher categories from 4-5 indicated dependence on others in daily activities.

Physical function may be affected in different ways following a stroke. A test commonly used to assess overall physical function is the Short Physical Performance Battery (SPPB)

(Guralnik et al., 1994; Volpato et al., 2011). It is considered a valid indicator of physical and clinical status in hospitalized elderly people and may predict length of hospital stay (Volpato et al., 2008). The SPPB consists of three different domains (balance, 4-meter gait assessment, and sit-to-stand) and gives an overview of physical function.

To study balance more closely, the Bergs Balance Scale (BBS) is applicable (Berg, Wood-Dauphinee, & Williams, 1995). This is a widely used test to objectively determine balance during a series of objective predetermined tasks, consisting of 14 items of both standing balance and movement.

The six-minute walk test is a sub-maximal test of walking capacity and endurance that has been shown to be reliable for patients with stroke (Eng, Dawson, & Chu, 2004). It measures the distance walked within 6 minutes on a defined track, usually with a length of 20-30 meters. Patients were instructed to walk as far as possible within the 6 minutes, and total distance was recorded.

A stroke may also affect function on a psychological level. The Brief Resilience Scale questionnaire (BRS) is a commonly used scale to measure resilience after a serious event as a measure of the ability to bounce back (Smith et al., 2008). The test consists of six items assessing the ability to bounce back from a serious event, each item being scored on a five-scale response ranging from “strongly disagree” to “strongly agree”.

The Fatigue Severity Scale (FSS) is a widely used method for detecting fatigue amongst patients with stroke. It comes in two versions, the FSS-7 containing seven statements about fatigue and the FSS-9 containing nine statements about fatigue. Because the FSS-7 has shown better validity and reliability than the FSS-9, it was applied here (Lerdal & Kottorp, 2011). Both the total score and an average score from the FSS are commonly reported.

Using standardized tests requires that they have previously been validated for use in the population they are to be used in, and that they provide reliable results. Table 5 presents validity and reliability for included tests used in this thesis.

Table 5. Reliability and validity for the included variables

Measurement and purpose	Test parameters	Reliability	Validity	Paper
Body structure and function				
Measurement: GAITRite **Purpose: Measure spatiotemporal gait parameters**	Measure post-stroke gait characteristics - Gait speed (m/s) - Step length (cm) - Stride width (cm) - Single support (%) - Cadence (steps/min) - Walk ratio (step length/cadence) - Asymmetry step length (%) - Asymmetry single support (%)	Intra-rater reliability: ICC 0.85-0.97 in chronic patients with stroke (Peters, Middleton, Donley, Blanck, & Fritz, 2014), and ICC 0.92 to 0.99 for most spatiotemporal gait parameters (Webster, Wittwer, & Feller, 2005) Test-retest reliability: Good to excellent for spatiotemporal gait parameters with ICC 0.85-0.93 (Bilney, Morris, & Webster, 2003)	Concurrent validity: The GAITRite system has strong concurrent validity for gait speed, cadence, and stride length at preferred gait speed (Bilney et al., 2003) Prediction validity: Spatial and temporal gait parameters collected from the GAITRite mat can be used for short-term prediction of fall risk in nursing homes (Sterke, van Beeck, Looman, Kressig, & van der Cammen, 2012)	1

Measurement: National Institute of Health Stroke Scale (NIHSS) **Purpose: Measure stroke severity**	Summary score of 13 different items assessing physical and cognitive function Total score: 0 (best) to 42 points (worst)	Inter-observer reliability: ICC 0.95 (Dewey et al., 1999; Goldstein & Samsa, 1997) Intra-observer reliability: ICC 0.93 (Goldstein & Samsa, 1997) Reliability of certain items (consciousness, facial palsy, limb ataxia, and dysarthria) has been questioned and a modified version of the scale has been introduced as more reliable (Brott et al., 1989; Dewey et al., 1999)	Criterion validity: Acceptable scale validity compared to infarction size in patients with stroke (Brott et al., 1989) Predictive validity: The NIHSS baseline score strongly predicts outcome seven days later (Adams et al., 1999) NIHSS also predicts three months outcome, with sensitivity to poor outcome, 0.71 (95% CI 0.64 to 0.79); specificity 0.90 (95% CI 0.86 to 0.94); and overall accuracy 0.83 (95% CI 0.79 to 0.87) (Muir, Weir, Murray, Povey, & Lees, 1996) NIHSS can be extracted from the medical records with a high degree of reliability	1

			(ICC 0.82) and validity (Kasner et al., 1999)	
Measurement: Scandinavian Stroke Scale (SSS) **Purpose: Measure stroke severity**	Summary score of nine different items assessing physical and cognitive function Total score: 0 (worst) to 58 points (best)	Inter-observer reliability: Mean observer K=0.76. Good to excellent reliability for most items, except moderate for the facial palsy item (Lindenstrom, Boysen, Christiansen, Hansen, & Nielsen, 1991; Luvizutto et al., 2012) and consciousness and eye movement (Barber, Fail, Shields, Stott, & Langhorne, 2004)	Predictive validity: Ability to predict mortality and dependence (Askim, Bernhardt, Churilov, & Indredavik, 2016; Christensen, Boysen, & Truelsen, 2005) ICC of 0.97 between face-to-face and retrospective SSS composite score (Barber et al., 2004)	2 and 3
Activity and participation				
Measurement: Barthel Index (BI) **Purpose: Measure functional independence**	Summary score of 10 items assessing physical function in ADL	Inter-observer reliability: Excellent inter-rater reliability Kappa=0.93 (95% CI 0.90 to 0.96) (Duffy, Gajree, Langhorne, Stott, & Quinn, 2013)	Construct validity: BI has been shown to discriminate between different patient groups (Granger, Hamilton, & Gresham, 1988)	2

in Activities of Daily Living	Total score: 0 (worst) to 100 points (best)	Good test-retest reliability of the total scores for the BI (>75%) with little bias and low random error (Green, Forster, & Young, 2001)	Prediction validity: BI can predict outcome and independence six months after stroke (Granger et al., 1988)	
Measurement: ActivPAL logger **Purpose: Measure activity during hospitalization**	Continuous measurement of time spent lying, sitting and upright	Inter-rater reliability: ICC 0.79 to 0.99 (Grant, Ryan, Tigbe, & Granat, 2006; Ryan, Grant, Tigbe, & Granat, 2006; Stanton, Guertler, Duncan, & Vandelanotte, 2016) Intra-rater reliability: ICC 0.95 (Busse, van Deursen, & Wiles, 2009) ICC siting/lying=0.99 and ICC upright= 0.99 (Sellers, Dall, Grant, & Stansfield, 2016)	Construct validity: Significant correlation (r = 0.93) between activPAL and a comparable activity monitor (Busse et al., 2009) and with small differences between the activPAL and observation (Grant et al., 2006) Concurrent validity: Similar results between monitor outcomes in ADL for activPAL monitors (Sellers et al., 2016) and for activPAL3 and video durations for sedentary and upright (Taraldsen et al., 2011)	1

Measurement: Modified Rankin Scale (mRS) **Purpose: Assess level of disability**	Degree of disability ranging from 0 (best) to 6 (worst outcome indicating death)	Inter-observer reliability: From moderate to excellent: Kappa: 0.25 to 0.74 Weighted Kappa: 0.71 to 0.93 Structured interview: K=0.62, Weighted Kappa =0.87 (Banks & Marotta, 2007; Quinn, Dawson, Walters, & Lees, 2009) ICC 0.675 (Zhao, Collier, Quah, Purvis, & Bernhardt, 2010) Intra-observer reliability: Very good, K=0.81 to 0.97, $_{w}K \geq 0.94$ (Quinn et al., 2009) Test-retest: Strong, K=0.81-0.95 (Banks & Marotta, 2007)	Construct validity: Well documented convergent and construct validity (Banks & Marotta, 2007) Content validity: There is, however, a question of validity in acute hospital settings (Zhao et al., 2010) Criterion validity: Excellent concurrent validity with Barthel Index (r= -0.89) for patients with stroke in the acute phase (Kwon, Hartzema, Duncan, & Min-Lai, 2004)	1-3

Measurement: Short Physical Performance Battery (SPPB) **Purpose: Assess physical function**	Item and summary score on three different items, consisting of balance, gait speed, and sit-to-stand. Each item scores from 0 (worst) to 4 points (best) Total score: 0 (worst) to 12 points (best)	Intra-observer reliability: Excellent with ICC 0.82-0.92 for the total sum (Medina-Mirapeix et al., 2016; Olsen & Bergland, 2017) and ICC 0.82-0.95 for the sub-scores. However, the weighted kappa was fair to low between gait speed and the other two sub-scores (Olsen & Bergland, 2017) Test-retest reliability: ICC 0.83-0.89 (Freire, Guerra, Alvarado, Guralnik, & Zunzunegui, 2012)	Construct validity: Relatively good construct validity of relation between self-perception of health and SPPB Convergent validity: The SPPB battery is related to functional and mobility factors (Medina-Mirapeix et al., 2016) Predictive validity: SPPB has predictive validity for mortality, global health improvements, difficulty in walking, and disability of the upper extremities (Freiberger et al., 2012)	1
Measurement: Bergs Balance Scale (BBS) **Purpose: Assess balance function**	Summary score from 14 items, each scored from 0 (worst) to 4 (best)	Inter- observer: ICC 0.95-0.98 (Berg et al., 1995; Blum & Korner-Bitensky, 2008)	Construct validity: Excellent correlation with mobility items of the Barthel Index (r=0.67) and adequate correlation with self-rated balance (r=0.39-0.41) (Berg et al., 1995)	3

	Total score: 0 (worst) to 56 points (best)	Intra-observer: ICC reported as 0.97 (Blum & Korner-Bitensky, 2008) and 0.99 (Alghadir, Al-Eisa, Anwer, & Sarkar, 2018) Test retest reliability: ICC 0.98 (Blum & Korner-Bitensky, 2008)	Predictive validity: Can predict length of hospital stay, discharge destination, motor ability at 180 days post-stroke and disability level at 90 days post-stroke (Blum & Korner-Bitensky, 2008), and community ambulation with a sensitivity of 79% and a specificity of 76% (Lee, An, Lee, & Park, 2016) It has also an excellent correlation with 10-meter walk test at a preferred gait speed (r=0.81) (Wang, Hsueh, Sheu, Yao, & Hsieh, 2004)	
Measurement: The six-minute walk test (6MWT) **Purpose: Assess walking capacity**	Measures the gait length (m) within six minutes of walking	Test-retest reliability: Excellent (ICC 0.96) for patients with a chronic stroke outdoors (Wevers, Kwakkel, & van de Port, 2011) and for patients with an acute stroke (ICC 0.86) (Fulk & Echternach, 2008)	Criterion validity: Strong concurrent validity (r = 0.98) between the 6MWT and using a measuring wheel (Wevers et al., 2011) A very strong correlation was also observed between the 6MWT and other	3

		However, in the subacute phase, two tests may be needed to accurately assess walking capacity (Clague-Baker et al., 2019)	gait tests (r=0.93) (Clague-Baker et al., 2019)	
Measurement: Brief Resilience Scale (BRS) **Purpose: Assess ability to cope with a serious event**	Summary score of six items of ability to bounce back Score: 6 (worst) to 30 points (best) Divide the total score by the number of answers. When answering all questions, scores between 6 points (best) and 1 point (worst)	Test-retest reliability: Few studies, but ICC 0.66 to 0.69 after one month (Leontjevas, de Beek, Lataster, & Jacobs, 2014; Smith et al., 2008) and ICC 0.62 after three months (Smith et al., 2008) Internal consistency: Consistency good with Cronbach`s alpha ranging from 0.80 to 0.91 (Smith et al., 2008)	Convergent validity: Positively correlated with resilience measures, active coping, and positive reframing. Negatively correlated with fatigue, anxiety, depression, and physical symptoms (Leontjevas et al., 2014; Smith et al., 2008) Good agreement with other resilience scales (Leontjevas et al., 2014; Smith et al., 2008)	2
Measurement: The 7-item version of the	Summary score of seven questions of degree of fatigue,	Good to excellent test-retest reliability with ICC 0.742 (Ozyemisci-Taskiran, Batur, Yuksel,	Concurrent validity: Good concurrent validity (r>0.60) with VAS and moderate with SF-36 vitality	2

Fatigue Severity Scale (FSS-7) **Purpose: Assess fatigue after stroke**	each scored from 1 (best) to 7 (worst). Total score: 7 (best) to 49 points (worst) or average score of 1 point (best) to 7 points (worst)	Cengiz, & Karatas, 2019) to ICC= 0.93 (Nadarajah, Mazlan, Abdul-Latif, & Goh, 2017) Internal consistency: Excellent internal consistency with Cronbach’s alpha >0.90 (Nadarajah et al., 2017; Ozyemisci-Taskiran et al., 2019) The FSS is reliable across diseases (Johansson, Kottorp, Lee, Gay, & Lerdal, 2014)	scale (Nadarajah et al., 2017; Ozyemisci-Taskiran et al., 2019)	

R; correlation coefficient, ICC; Intraclass correlation, k; Cohen`s kappa; $_{w}$K; weighted Cohen`s kappa, m; meter

4.6 Statistical procedures

Descriptive statistics were utilized to describe study populations in this thesis (table 2). Demographic data were assessed for normal distribution and reported as mean values and standard deviation (SD) for all participants or as numbers and proportions. However, due to a statistically significant difference between categories in demographic data in paper 1, median and interquartile range (IQR) was also reported. Residuals were visually inspected for normal distribution by quantile-quantile (Q-Q) plots and variables transformed if residuals did not follow a normal distribution. Data from the loggers were transferred via a USB docking station and processed in Matlab R 2015 B. GAITRite data were processed in the PKMAS® (version 5.07c2) (Egerton, Thingstad, & Helbostad, 2014) and transferred to Microsoft Excel. Percentage of asymmetry was calculated as the percentage of the logarithm (LN) between the left (L)/right (R) leg (100x(|LN(L/R))|) in accordance with Yogev et al, 2007 (Yogev, Plotnik, Peretz, Giladi, & Hausdorff, 2007). The statistical analyses were performed in IBM SPSS version 23 and 25 (SPSS Inc, Chicago, IL) and in Microsoft Excel 2016. A statistical significance level of $p<0.05$ was chosen for all three papers.

4.6.1 Paper 1

One-way ANOVA or Kruskal-Wallis test, depending on normality of residuals, was applied to study group differences at baseline in paper 1. To assess changes in activity levels, linear mixed models (LMM) were applied with time sitting, time upright, duration of bouts of sitting and duration of upright bouts, respectively, as dependent variables. Time (i.e., days since stroke onset) was applied as the covariate of primary interest and participant as random effect. Further, the following covariates were added, one at a time: NIHSS, age, gender, mRS pre-stroke, mRS one day post stroke, and SPPB. Two-sided p-values with a statistical significance level of <0.05, and 95% confidence intervals (CI) were reported.

4.6.2 Paper 2

Gait speed and resilience were used individually in bivariate and together in the multivariate linear regression analyses to examine whether they were associated with independence in basic ADL three months later. Age, gender, fatigue at baseline, stroke severity at admission and mRS prior to stroke were added to the multivariate model as covariates. These were selected based on clinical judgement and the literature. Correlation value was set at <0.9 and VIF<10 when controlling for collinearity.

4.6.3 Paper 3

Paired sample t-tests were used to assess changes from inclusion to three months later in spatiotemporal gait parameters, walking capacity and balance, respectively. Those showing a statistically significant change, together with correlation values between the parameters below 0.9, and variance inflation factors (VIF) <10, were applied in the bivariate and multiple regression analyses to study associations between changes in spatiotemporal gait parameters and changes in either of 6MWT and BBS. Gait speed, percentage of time in single support, walk ratio, and asymmetry measures were included as covariates in the multivariate analyses.

4.7 Ethical considerations

The studies included in this thesis were approved by the Regional Committee for Medical and Health Research Ethics in Norway, with paper 1 (REK no. 2013/1357) and paper 2 and 3 (REC number 2011/2517). Informed and written consent was obtained from all participants. In paper 1, for those who were not able to provide informed consent, their next of kin were contacted and asked if they opposed participation. The decision on whether a participant was able to provide informed consent was made by a senior physician working in the stroke unit. This procedure is in line with Norwegian consent procedures for patients unable to consent and was approved by the Ethics Committee.

There will always be a question of ethics on including participants who need their next of kin to provide written consent. However, as all three papers were based on data from observational studies, no interventions or interference with the medical care that could harm the participants should happen. Therefore, health and safety was achieved in accordance with standard procedures in the 2017 Norwegian guidelines for management of stroke (Norwegian Directorate of Health, 2017b).

5 Summary of results

5.1 Paper 1

The specific aims of paper 1 were to:

1. Describe the amount of time spent in lying, sitting and upright (standing or walking) positions early after stroke and how these activity levels changed during the hospital stay, regarding both total time per day and duration of each mobilization.
2. Examine which factors were associated with total time and bouts of sitting and upright activity.

The overall activity level for hospitalized patients with stroke was low, with most time during the day spent in bed, ranging from more than 80% of the time in a lying position on day one after stroke onset to about 58% of the time in a lying position on day 10. However, there was a corresponding increase in time spent out of bed during the hospital stay. Results from the LMM analysis showed a daily increase in time spent sitting of 22.1 minutes ($p<0.001$) and 3.75 minutes for upright ($p<0.001$). Adjusted for time from stroke onset to inclusion, there was an association between decreased time spent upright and increasing functional dependence ($p=0.002$). Further, there was an association between time spent upright and physical function showing an increase of 7.0 minutes upright for every point increase on SPPB ($p=0.007$). Severity of stroke and age were not significantly associated with changes in overall physical activity. The LMM analysis also indicated a daily increased duration of 4.3 minutes for each sitting bout ($p=0.051$). Adjusted for time from stroke onset to inclusion, the increased time sitting was associated with both a higher NIHSS score ($p=0.018$) and increasing age ($p=0.028$).

5.2 Paper 2

The aims of this study were to:

1. Examine whether gait speed assessed within the first 2 weeks after a stroke can be associated with independence in basic ADL 3 months later
2. Examine whether resilience assessed within the first 2 weeks after a stroke can be associated with independence in basic ADL 3 months later

Sixty-four participants (35 male) with a mean age of 75.9 (±8.6) years were included 4.3 (±2.8) days after a stroke. There were statistically significant improvements in the Barthel Index of 9.8 points ($p<0.001$) and gait speed of 0.2m/s ($p<0.001$) in the first three months after the stroke. Unadjusted for other covariates, the Barthel Index increased significantly by 1.60 (95% CI 0.99 to 2.21, $p<0.001$) points for every 0.1 m/s increase in gait speed at baseline. Resilience ($b=2.01$, 95% CI -5.21 to 9.23, $p=0.580$) was not associated with independence in basic ADL three months after stroke.

In the multivariate regression analysis including all variables, gait speed remained a statistically significant association with independence in basic ADL, with an increased BI of 0.82 points (95% CI 0.18 to 1.46, $p=0.013$) for every 0.1m/s increase in gait speed.

5.3 Paper 3

The aim of this study was to:

1. Examine the associations between changes in primary and calculated spatiotemporal gait parameters with changes in balance and walking capacity during the subacute phase post stroke.

Participants improved most spatiotemporal gait parameters with increased gait speed by 18% (p<0.001), took 11% longer steps (p<0.001), 1.2% more time in single support (p<0.001), increased cadence by 7% (<0.001), and walk ratio by 3% (p=0.010). Both asymmetry measures indicated decreased asymmetry after three months, but only step length asymmetry showed a statistically significant decrease, of 2.5% (p=0.004). There was a statistically and clinically significant improvement in both balance, by 10.3 points (p<0.001), and walking capacity, by 61m (p<0.001).

A statistically significant association was found in terms of an increased BBS score of 1.8 points for every 0.1m/s improvement in gait speed. Statistically significant associations were also found between increased step length, increased cadence, increased time in single support and decreased step length asymmetry with improved balance. Controlling for included spatiotemporal gait parameters in the multivariate analysis, increased gait speed was the only parameter that remained significantly associated with improved balance by 1.4 points increase on BBS per 0.1m/s increased gait speed (p=0.042).

There was an increased walking capacity of 26.5m for every 0.1m/s increase in gait speed. Further, statistically significant associations between increased walking distance and step length (6.8m increase for every extra centimeter of step length), cadence (5.1m for every step/minute increase), and percentage of time in single support (17.4m for every 1% improvement in single support) were found. There was also an increased walking capacity with decreasing spatial asymmetry of 5.1m for every 1% decrease in step length asymmetry (p=0.008). Controlling for changes in all included spatiotemporal gait parameters, the multivariate analysis showed an increased walking distance of 25.6m for every 0.1m/s increase in gait speed (95% CI 17.3 to 34.0, p<0.001).

6 Discussions

6.1 Main findings

The thesis revealed that the overall quantity of physical activity early after stroke was low, with most time spent in bed. However, there was an increase in time spent sitting and in an upright posture throughout admission. The amount of time spent upright increased as physical function improved, and the level of independence increased while the duration of bouts of sitting increased with increasing stroke severity and age. Both findings could have implications for future rehabilitation. With the knowledge from the dose-response study of the AVERT study with recommendations of shorter and more frequent mobilization (Avert Trial Collaboration group, 2015), the results indicate that a special focus should be given to the more severely affected patients who are unable to regularly change positions themselves.

Furthermore, the thesis showed that gait speed during hospitalization was associated with independence in basic ADL three months later, highlighting the importance of gait speed in recovery after stroke. This was, however, not the case for resilience, contradicting the hypothesis of an association with ADL function three months later. The thesis also showed how the post-stroke gait characteristics changed from admission to three months later. This is the time with most improvements in recovery, and the thesis revealed that most of the spatiotemporal gait parameters improved in these three months. Improvements in step length, cadence, time in single support, gait speed, and step length asymmetry were all associated with improved balance and walking capacity. However, the multiple regression analyses showed that only changes in gait speed remained significantly associated with changes in balance and walking capacity. Results from paper 2 and 3 suggest that gait speed is a relevant clinical measure related to balance, walking capacity and independence, giving valuable information to be considered in the rehabilitation process after a stroke. In the following chapter, methodological considerations of the papers will be discussed, followed by a general discussion of the results in a wider context, and with suggestions for future research.

6.2 Methodological considerations

6.2.1 Internal validity of the study

Internal validity in observational studies refers to whether the study measures what it set out to (Grimes & Schulz, 2002). Intrusion of internal validity makes the inferences of a study unreliable. All observational studies have built-in bias; the challenge for researchers is to eliminate these and judge how they might have affected results. Systematic errors, such as selection bias, information bias, and confounding factors threaten the internal validity (Grimes & Schulz, 2002). Missing data may also make results unreliable. Therefore, a clear study design is important to identify clinically important differences in treatment or behavior in observational studies (S. L. Silverman, 2009). This will be discussed in the following sections.

6.2.2. Study design

This thesis was built on two different samples of patients with stroke, both with a prospective follow-up design, thereby reducing the risk of omitting data. The design allowed us to follow patients with stroke over time and observe activity and gait during the first months, instead of collecting data from the participants' medical records. This reduced the risk of bias and allowed us to get first-hand information of the participants. In repeated testing of the same subjects, the observers' judgement may be biased by knowing a previous measurement for that specific subject (Altman, 1990). Therefore, blinding the observer is recommended to avoid detection bias and performance bias. This is especially important during experimental design (Viswanathan, Berkman, Dryden, & Hartling, 2013) but both performance bias and detection bias also need to be considered in observational studies (Juni, Altman, & Egger, 2001). In this study the same experienced physiotherapist conducted both baseline and three months' testing. This could potentially affect the results, with the observer knowing the hypothesis. In an ideal setting, a different observer would have conducted the test after three months. However, the physiotherapist did not study the results from baseline testing at three months follow-up and no participants were informed of their score, either during testing or between test settings. Using only one person during testing may also standardize test situations, thereby increase the reliability of the study.

There are, however, other variables that could bias the results. The first paper was based on a study population where all participants were assessed while admitted, with participants included up to seven days after symptom debut. Because patients with stroke are likely to be less active in the first couple of days post stroke, the relatively large inclusion window may have influenced the results, possibly biasing the results. There were, however, only small differences in baseline characteristics from those who were included in the first days after symptom debut and those included after up to one week. The choice of LMM as a statistical model was made to meet this challenge of inclusion at different timepoints, as the LMM handles missing observations. The studies reported in Paper 2 and 3 had an even larger inclusion window of up to 14 days after symptom debut, which could potentially also influence the results. However, mean inclusion time was 4.3 (2.8) days post-stroke, indicating that the majority was included within the first week. Further, participants were compared to their own measurement, thereby acting as their own controls. The relatively wide inclusion window was chosen to recruit as many participants as possible and was considered as the acute phase while participants were still hospitalized.

6.2.3 Study sample

Selection bias is due to an absence of comparability between groups being studied, and an observed outcome can be related to differences in baseline characteristics rather than representing a true effect (Grimes & Schulz, 2002). The inclusion criteria in both study samples could possibly introduce a selection bias. In the first study sample, the inclusion criteria were relatively wide, with the aim of enabling a heterogenic and representative sample of participants. However, excluding those expected to be discharged within the next three days would make it likely to exclude the healthiest and most active participants, which could potentially affect the generalizability. The reason for the three-day cut-off was to provide enough data from each participant to detect real within-person changes in activity while admitted.

Inclusion of participants for paper 2 and 3 was done between March 2012 and October 2014. In this time period, 642 hospitalized patients with stroke living in Trondheim were diagnosed with an acute stroke. Of these, only 98 subjects, representing 15% of the population, were included in the study. There could be several reasons for this low recruitment. Some patients did not meet inclusion criteria because of their poor gait, cognition, or an unstable medical condition. Additionally, some patients were missed for inclusion or discharged before inclusion and therefore not available, and some also refused participation. In the period of inclusion, several studies were conducted in the same stroke unit, which made recruitment more challenging. Unfortunately, no overview of how many potential participants were lost because of a specific reason is available. Because of this, it is difficult to rule out a selection bias. However, a comparison with the Norwegian stroke registry shows that the data can be considered representative of most patients with stroke in Norway (Norwegian Directorate of Health, 2016), and therefore representative of most patients with stroke in Norway.

The loss to follow-up in the two samples was relatively high, with a 44.8% dropout in the first paper and up to 33.7% in the third paper, which may decrease the power of the studies. With only medium-sized study populations and a relatively high dropout rate in paper 2 and 3, the power of the studies should be kept in mind when interpreting results. However, the loss to follow-up seems to have been a random selection of patients in both studies, without any significant differences in age, gender, premorbid mRS, or severity of stroke. The selection of participants and loss to follow-up therefore seems to partly be caused by practical conditions during testing and therefore not causing a selection bias.

6.2.4 Assessment tools

ActivPAL

In the first paper two loggers were used, one on the sternum and one on the thigh of the unaffected side, and data from these were merged to calculate activities registered by the two sensors. The loggers are easy to administer, have been shown to be reliable when used in pairs (Taraldsen et al., 2011), and allow us to find time spent sitting as well as lying and upright. Both the total time spent sitting and upright per day and the duration of each bout were assessed. This could show the overall activity level as well as the length of each mobilization, thereby telling us something about the change in activity for the participants throughout hospitalization. The use of two different sensors may be a source of bias, as different sensors have different time drifting. However, the virtual time drifting only showed minor changes in the results and did not change the overall results or conclusion. Another possible threat to internal validity from the loggers is that participants accepting participation knew what the activPAL had recorded, possibly influencing activity level. However, although participants were given written information about the project, no instruction regarding an increased activity level was given and the usual rehabilitation routines of the stroke unit were followed.

A strength of using the loggers is that they give an objective measurement of the activity level continuously, enabling them to measure the activity level for days. This makes them less time consuming, costly and vulnerable to bias, such as post-stroke complications, than single-day observations (Kramer et al., 2013; Taraldsen et al., 2011). The measurement was chosen to be a 24-hour measurement and not just daytime activity. This would increase time lying, as this also included nighttime when most participants slept. This was done because some participants had a disrupted circadian rhythm, which might be more common during hospitality. In a confusing situation after a stroke, a regular sleeping routine may be hard to achieve. Excluding nighttime could therefore underestimate the activity level for some of the participants. Ideally, loggers discriminating directly between time sleeping and awake would have been preferable, but this was not possible during the testing period.

Barthel Index

The Barthel Index was used to assess independence in basic ADL after stroke. However, results in the second paper suggest a ceiling effect after three months. Baseline characteristics suggested that participants were only mildly to moderately affected by the stroke, raising the question of whether other tests of more complex or instrumental tasks, such as the items regarding communication and daily activities in the Stroke Impact Scale (SIS), could have given a different result. In a study comparing different batteries assessing daily activities, BI was concluded to be reliable in measuring basic daily activities (Green et al., 2001). Testing more challenging tasks, such as with the SIS, could have provided additional information, but the BI is a well-known test for clinicians that makes it comparable to other studies, and provide internal validity in this study.

Gait and gait speed

Assessing post-stroke gait characteristics was done using the GAITRite mat in paper 3. However, the relatively wide inclusion criteria allowed for patients with stroke in need of a walking aid. Using a walking aid while walking on a GAITRite mat will influence spatiotemporal gait parameters, thereby possibly biasing the results. For instance, it is likely that using a walking aid would increase gait speed, compared to walking without. An experienced physiotherapist evaluated the necessity for the walking aid, such as a cane or a walker. Only when safety was threatened was this permitted. Another challenge regarding the use of a walking aid was that the need for it could change within the follow-up time. This follows as a natural recovery from the stroke but made the comparison between baseline and post-test more challenging. It is likely that the use of a walking aid could influence gait speed, asymmetry, and efficiency, as a walking aid provides stability and therefore improves gait parameters. The change in need for a walking aid could possibly underestimate improvements between the two timepoints, with the use of a walking aid affecting the spatiotemporal gait parameters at baseline but not at follow-up. In longitudinal clinical research this will always be a challenge when doing within-subject measurements, as recovery after an injury or a disease continues (Taris & Kompier, 2003). However, to capture the heterogeneity in the stroke population, a variety of patients with a stroke. To test whether the results would have changed if only participants without the need of a walking aid had been included, post hoc analyses were performed, assessing only those not in need of a walking aid at any given timepoint. To a large degree, results from this showed the same trends.

Testing gait on a GAITRite mat gives us detailed information about the gait. However, whether this gait is representative of walking outside the laboratory is questionable. The testing on the GAITRite mat was conducted in a protected area without other people, with stable and bright lighting, and on a completely flat surface. Therefore, results found here may not necessarily correspond completely with gait outside the laboratory. Repeated measurement demands, however, that the conditions are as identical as possible.

Therefore, the use of the GAITRite mat was arguably valid in the study of changes in gait over time.

Spatiotemporal gait parameters represent different aspects of gait. One of these aspects is variability. Both asymmetry and variability are common and important measures in the study of falls, and improvements in both variability and asymmetry could represent a decreased risk of falling. In this thesis, asymmetry measures were chosen because of the expectation that most participants would have a hemiplegic gait. However, the baseline assessment suggested lower asymmetry. Therefore, in retrospect, variability measures could have supplemented these results with additional information.

Gait speed is a well-documented marker for health and function (Cummings, Studenski, & Ferrucci, 2014), is considered an easy-to-administer measurement in a clinical setting and has been highlighted as a strong predictor of physical function (Brandstater et al., 1983; Roth et al., 1997; Studenski et al., 2011; Wonsetler & Bowden, 2017) and walking recovery (An, Lee, Shin, & Lee, 2015). In paper 1, gait speed was based on results from the 4m walk test in SPPB. All the 58 participants performed the SPPB and the average gait speed was calculated from these results. However, although all participants had a total SPPB score above zero, not all participants managed to perform the walk test. The choice to include all participants in the calculation of the average gait speed would therefore underestimate the real gait speed, challenging the internal validity. This was done because the overall SPPB was considered a more precise measure of physical function, thereby including all participants.

There is a relatively large difference in gait speed between the two study samples, raising the question of bias. In the first study, a stopwatch was used, whereas the GAITRite mat measured gait speed in the other two. When using two different techniques, one cannot completely rule out a detection bias. However, the difference in impairment between the two different samples while admitted is likely to partly explain the different gait speeds. In the first study sample the participants had an increased impairment and walked more slowly, compared to the other study sample used in paper 2 and 3. Therefore, it is possible that the study sample in paper 1 walked more slowly because of their decreased function, compared to the second study sample. Another explanation was the way gait speed was calculated in paper 1, where the average gait speed was reported to be 0.52 (0.36) m/s. However, this also includes those with a gait speed of zero. As mentioned, this was done to correspond with the overall SPPB score where all 58 participants were included. However, this also means that the reported average gait speed was lower than for those finishing the walk test. Excluding those not able to perform the walk test (n=13) would have given an average gait speed of 0.65 (±0.27) m/s.

BBS

The BBS is widely used by clinicians as a test of balance. However, most tasks in the BBS test balance standing, whereas the association in these analyses was of balance and gait. Therefore, whether the BBS is specific enough might be questionable. Previously, a method measuring balance during walking has shown inter- and intra-patient variations in metric values that cannot be explained by BBS scores (van Meulen et al., 2016). Using different balance assessments during walking, such as the Tinetti test or the BESTest, could possibly have given different results. However, the BBS is widely used in both research and clinically, making it a well-known tool to assess balance.

6.2.5 Statistics

A linear mixed model was used to assess changes in activity level during hospitalization. This has been shown to be robust in dealing with non-independent data on repeated measurement. A challenge in clinical research is that participants are admitted and discharged differently. In Paper I, the time of recruitment also varied from day 1 to 7 after onset of symptoms. The LMM has a major advantage compared to other regression analysis with its ability to deal with missing values (Harrison et al., 2018). It will remain unbiased as long as data are missing at random (MAR) or missing completely at random (MCAR). It is questionable whether delayed recruitment and early discharge should be treated as MAR here, with less affected and more active patients diagnosed and recruited later and discharged first. However, apart from the difference in NIHSS, no significant differences were found between those recruited in the first and the last days. With a relatively large standard deviation in NIHSS and the small sample size in the group recruited in the last days of inclusion, a systematic difference between the groups is highly debatable. Other factors such as weekends and inconclusive MRI findings might just as well have delayed inclusion in the study. Regarding discharge, factors such as other medical conditions, cognition and living conditions might influence how fast a patient with a stroke would be discharged. Even though the use of LMM might be questionable, the missing data due to delayed recruitment and early discharge were considered to be missing at random and the LMM was therefore considered to be the most appropriate statistical analysis to use.

Confounding is a mixing of effects with attempts to relate an exposure to an outcome but that actually measures the effect of a third factor (Grimes & Schulz, 2002). If not accounted for, the estimated associations between an exposure and outcome may partly be explained by the confounding factor, thereby risking a Type I error and threatening the internal validity (Glasser, 2014). However, adjusting for possible confounders can be challenging and depends on the sample size. Factors often related to activity level after a stroke are age, gender, and pre-stroke mRS (Strommen et al., 2014), functional independence (Veerbeek, Kwakkel, van Wegen, Ket, & Heymans, 2011), fatigue (Aarnes et al., 2019) and stroke outcome (Appelros et al., 2003). Whereas age has been shown to be associated with all outcomes, gender is still debated as a confounder in functional independence (Veerbeek et al., 2011). Pre-stroke mRS was also adjusted for, as pre-stroke impairment level was likely to influence the ability to be physically active also after the stroke. Physical function was adjusted for in the first paper and severity of stroke in both the first and second paper, as it was likely that patients with a more severe stroke and with physical disabilities were less active during hospitalization.

Regression analysis are beneficial because they allow adjustments for different covariates. However, adjusting for several covariates in the same analysis could cause statistical challenges. Generally, as a rule of thumb, no more than n/10 variables should be added in the regression analysis to avoid making a type I error of rejecting the null hypothesis

(Altman, 1990). In paper 2 and 3, several covariates were discussed. Previous research has shown that fatigue is closely related to depression (Aarnes et al., 2019; Galligan et al., 2016). Depression was therefore considered as a possible covariate in paper 2 but were left out because of the relatively small sample size.

Adding covariates could lead to multicollinearity, where at least two variables are highly correlated with each other. This would not affect the overall fit of the model, but would affect p-values of correlated values, thereby affecting the interpretation of the effect of individual variables (Vatcheva, Lee, McCormick, & Rahbar, 2016). In paper 2, the analysis showed low correlation and VIF values allowing the multiple regression analysis to be conducted as planned. The same limits were set in paper 3, but here several spatiotemporal gait parameters breached the limit of multicollinearity with correlation values above 0.9 and variance inflation factors (VIF) above 10. Therefore, the multivariate regression analyses were adjusted by excluding step length, stride width, cadence and single support asymmetry to avoid multicollinearity. Walk ratio and asymmetry measures may be less influenced by gait speed than other spatiotemporal gait parameters because they are based on the ratio between gait parameters. This makes them more robust to the influence of gait speed and may add additional information about post-stroke gait characteristics.

The medium sample size also influenced the analysis. In paper 2, functional independence was treated as a continuous variable instead of being dichotomized. Previously, cut-off values for Barthel Index have been reported for patients with stroke (Cumming et al., 2016; Jorgensen et al., 1995a). However, dichotomizing variables risk losing power. The medium sample size, and the linear relationship between the dependent and independent variables, a multiple linear analysis was considered more appropriate and therefore chosen.

Mean values were applied in the analyses. This might have masked the diversity of the results and could possibly mask trends within the samples, thereby also challenging the external validity. However, normal distribution was tested for the variables before deciding to use mean values and found a normal distribution with relatively few outliers in the outcome variables.

6.3 Discussions of the main results

6.3.1 Quantification of early rehabilitation and physical activity during admission

Focus on early rehabilitation following a stroke has been highlighted as equally important as medical treatment (Indredavik et al., 1999; Langhorne & Pollock, 2002; Stroke Unit Trialists, 2013). Results from this thesis showed that the general activity level was low, with most of the time spent in bed. During hospitalization, a daily increased amount of time sitting of more than 22 minutes and an increased time in upright of almost 4 minutes was found. These were not associated with severity of stroke, which may indicate that patients with stroke, regardless of stroke severity, were mobilized as soon as medically stable. This mirrors the importance of early mobilization in dedicated and evidence-based stroke units and their mobilization routines. The increased time sitting was important, as previous research has shown a 4% deterioration on the mRS score three months after a stroke (Askim et al., 2014). The daily increase of less than 4 minutes upright may seem small. However, as participants spent an average of 12 days hospitalized, the activities in an upright position could possibly increase by almost 50 minutes, allowing rehabilitation in independent ambulation, balance, and walking capacity. Therefore, the increased time sitting and upright may be considered as clinically important.

The AVERT study questioned timing and duration of early mobilization. However, secondary dose-response analysis from the AVERT data, Bernhardt et al (2016) found that shorter and more frequent mobilizations early after stroke were favorable for a better outcome three months later (Bernhardt et al., 2016). Results from this thesis showed an association between increased duration of bouts of sitting and higher age and more severe symptoms, indicating that older and more severely affected patients with stroke were sitting for a longer time than younger and less affected patients. It is likely that the younger and less affected patients were capable of changing positions themselves, highlighting the importance of an awareness when treating older and more severely affected patients to avoid prolonged duration of bouts and increased risk of sedentary behavior (Askim et al., 2014). The analysis also revealed that increased time spent upright was associated with both improved physical function and being less dependent. With improved physical function, the participants could move around by themselves, not relying on help from the hospital staff.

6.3.2 Gait speed as a measure of associations

In paper 2, the results showed an association between gait speed in the acute phase and basic ADL function three months after stroke in both the simple and the multiple regression analyses. Gait speed may also be looked upon as a sum of spatiotemporal gait parameters (Brandstater et al., 1983; Roth et al., 1997; Wonsetler & Bowden, 2017). Results from paper 3 showed that gait speed increased from the acute phase to three months later. However, as the results showed, gait speed was closely related to other spatiotemporal gait parameters, violating the assumptions of collinearity. Therefore, the multivariate regression analyses between changes in spatiotemporal gait parameters and changes in balance and walking capacity were done after removing step length and cadence from the analysis. The results showed that gait speed was the only gait parameter that sustained a statistically significant association to changes in balance and walking capacity. One may ask whether the increased gait speed represents a clinically significant improvement, as gait speed during hospitalization is relatively high. However, an improvement in gait speed of 0.2m/s has previously been reported as a clinically significant improvement after a stroke (Fulk et al., 2011; Tilson et al., 2010). Therefore, results from both papers are considered to highlight the importance of measuring gait speed as a measure of gait recovery.

6.3.3 Resilience was not associated with independence in basic ADL

Resilience can be looked upon as an ability to cope with diseases or injuries. Previously, resilience has been argued to be a considerable factor in rehabilitation (van Rijsbergen, Mark, Kop, de Kort, & Sitskoorn, 2019), as resilience has been shown to predict functional outcome when suffering from neurological diseases (A. M. Silverman, Molton, Alschuler, Ehde, & Jensen, 2015) and act as a predictor of quality of life (Lo Buono et al., 2017).

However, results showed no associations with independence in basic ADL. Despite the relatively wide inclusion criteria, the study had a relatively well functioning group of participants. It is therefore possible that resilience could have been associated with independence in basic ADL later in the rehabilitation process where the participants had returned to their home and started adapting to the new situation or in a study sample including more severely affected patients with stroke, than ours.

6.3.4 Changes in the post-stroke gait characteristics and its association with balance and walking capacity

Several gait parameters have been studied to assess the gait characteristics. Following a stroke, hemiplegic patients are likely to have an asymmetric gait, with a decreased ability to shift body weight onto the affected side (Patterson et al., 2010; van Dijk et al., 2017). Results from this thesis showed an improvement in spatiotemporal gait parameters, leading to a less asymmetric gait with longer steps and more time of the gait cycle spent in single support. Changes in most spatiotemporal gait parameters were associated with improved balance, including step length and time in single support. A higher percentage of time in single support on the affected side would allow a longer swing phase of the unaffected leg, thereby achieving longer steps. This has previously been shown to lead to less spatial gait asymmetry (Lewek, Bradley, Wutzke, & Zinder, 2014), and the results of a decreased step length asymmetry being associated with improved balance confirms this. All significant improvements in spatiotemporal gait parameters were also associated with improved walking capacity. Improvement in post-stroke gait characteristics will lead to a more efficient gait with less asymmetry and a lower energy expenditure, which is likely to be associated with improved walking capacity.

The change in single support asymmetry was, however, not statistically significant. This, together with only gait speed sustaining the associations in the multivariate analyses, may raise the discussion of whether improvements are due to compensatory strategies or to actual improvements in the post-stroke gait characteristics. An increased gait speed and a lack of improvement in temporal asymmetry could suggest that the increased gait speed was due to a compensatory strategy. At the same time, improvements in most spatiotemporal gait parameters and their association with both balance and walking capacity suggest an actual improvement of gait characteristics. Improvement of temporal asymmetry may need more time after a stroke and the lack of association could therefore be due to the relatively short follow-up time in the project. It is possible that some participants improved their gait caused by compensatory strategies whereas others improvement is due to an improved gait. However, the overall interpretation of the results suggests an improvement towards a safer and more efficient gait.

6.4 External validity of the study

External validity is the ability to generalize from the study to the reader's patients, in other settings, populations, and in other times (Glasser, 2014; Grimes & Schulz, 2002). Included participants were all recruited from the stroke unit at St Olavs University hospital, and it is possible that changes in physical activity, gait and function were limited to patients treated there. However, the stroke unit follows national guidelines for treatment and early rehabilitation after stroke (Norwegian Directorate of Health, 2017b). These guidelines are being followed by other Norwegian hospitals and are also likely to correspond with guidelines in other western countries.

Baseline characteristics show only a light to moderate severity of stroke, a moderate modified Rankin Scale, a high Barthel Index, and a baseline gait speed close to 1.0m/s, all pointing in the direction of a relatively well functioning group of participants even early after stroke. This could suggest that the participants were not representative of patients with stroke in general, but rather a selected group, threatening external validity. However, comparing the baseline characteristics with data from the Norwegian Stroke Registry showed similar results, with most patients with stroke scoring 0-5 points on the NIHSS while hospitalized and an mRS score <3 of after three months (Norwegian Directorate of Health, 2016). Therefore, one would argue that the selection of participants is likely to be representative of most patients with stroke. However, although the data were similar to the national stroke registry regarding median age, days hospitalized, and stroke severity, no participants were below the age of 60 years in the study samples. Further, in the national stroke registry, about 17% had an NIHSS score above 10, indicating a more severe stroke.

(Norwegain Directorate of Health, 2018). Hence, findings from these analyses may not be representative of younger stroke survivors and of patients with stroke with more severe stroke outcome.

7 Conclusion

In conclusion, the research constituting this thesis has shown that early physical activity was low during admission and that the increased level of daily activity was mainly in sitting. An important finding was that prolonged duration of bouts of sitting was associated with a higher age and more severe strokes, highlighting the importance of paying extra attention to this group in the early phase after a stroke to reduce sedentary behavior. Both functional outcomes and spatiotemporal gait parameters improved significantly from baseline to three months after stroke. Most spatiotemporal gait parameters were associated with improvements in balance and walking capacity, while gait speed during admission was associated with independence in basic ADL three months later. These findings provide important information about activity during hospitalization and three months later that should be considered in rehabilitation to regain independence and independent ambulation after a stroke.

8 Clinical implications

The results showed a gradually increased time spent both sitting and upright. However, the association found between increased time in upright positions and improved function suggests that patients with stroke depending on personal assistance in transfer to a sitting or an upright position should be given extra focus to ensure shorter and more frequent periods of upright activity. For older and more severely affected patients with stroke who are less capable of changing position, this focus would be particularly important, to avoid prolonged durations of bout, sedentary time, and further complications.

Factors associated with independence in basic ADL would help in guiding early rehabilitation. The results showed that gait speed was associated with functional independence, further highlighting the importance of measuring and focusing on gait speed during the earlier stages of stroke rehabilitation.

As independent gait is one of the most common rehabilitation goals, a safe and efficient gait is crucial to regain independence. Results from this study suggested that changes in most spatiotemporal gait parameters could be related to changes in both balance and walking capacity. Changes in gait speed seemed to be the strongest gait parameter for association with both balance and walking capacity and could therefore be a clinical measurement when monitoring the safety and efficiency of gait after stroke. Measuring gait speed is an easy-to-administer task and may be used as a measure of physical function during rehabilitation in hospitals, rehabilitation centers and outpatient clinics, and possibly as a measure of physical function three months after a stroke.

9 Suggestions for further research

Although paper 1 gives important knowledge about the physical activity pattern amongst patients with stroke, the optimal timing, frequency and intensity is yet to be found. Future research should therefore focus on how to optimize physical activity in the acute phase in order to improve recovery and independence in the long term after stroke. Further, longitudinal studies following patients with stroke up to one year after stroke to study correlation on physical activity and covariates, such as age, gender, and pre-stroke mRS, would add important knowledge to paper 1 and could help in developing specific rehabilitation interventions.

Paper 2 and 3 were based on the same population, following patients with stroke three months after stroke. The follow-up time may have been too short to detect long-term changes and associations. The first months after a stroke is the period when most recovery takes place, but factors such as temporal gait asymmetry may need more time to change. Independent ambulation requires a safe and efficient gait, and a longitudinal study lasting for up to one year could have given us additional information about how the different characteristics of the gait develop over time.

The GAITRite mat was applied to study changes in gait and the BBS to study balance. However, maintaining balance during gait requires control of the trajectory of the body`s center of mass over a narrow and changing base of support. The ability to move the body`s center of mass in the mediolateral direction is highly likely to be affected by hemiplegia, thereby affecting the safety of the gait. Therefore, a study including the use of an accelerometer worn on the lower back could add further knowledge on changes in both gait and balance that could help develop and improve person-adjusted interventions.

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Paper I

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RESEARCH ARTICLE Open Access

Time spent lying, sitting, and upright during hospitalization after stroke: a prospective observation study

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Abstract

Background: Early mobilization has been an important part of acute stroke unit treatment. However, early and intense mobilization within the first 24 h post stroke may cause an unfavorable outcome. Recently, objective measurements using body-worn sensors have been applied, enabling continuous monitoring of physical activity in the hospital setting. This study aimed to use body-worn sensors to quantify the amount of physical activity and how activity levels changed over time during hospitalization in patients with acute stroke. We also wanted to investigate which factors were associated with upright and sitting activity.

Methods: This was a prospective study including patients admitted to hospital within seven days after onset of stroke. Physical activity was measured by two sensors (ActivPALs from PAL Technologies Ltd., Glasgow, UK), one attached on sternum and one on the thigh of the unaffected side, monitoring continuously from inclusion until discharge. Data were processed in Matlab R 2015B and provided information about daily time in lying, sitting, and upright positions, and daily average duration of sitting and upright bouts. A linear mixed model was used to analyze changes over time.

Results: 58 patients were included (31 women, mean (SD) age; 75.1 (12.0)). Patients were hospitalized for 12.1 (7.6) days and had a mean score on the National Institute of Health Stroke Scale of 6.2 (5.5) points. Time spent sitting and time spent upright increased per day during hospitalization by 22.10 min (95% Confidence interval (CI): 14.96, 29.24) and 3.75 min (95% CI: 1.70, 5.80) respectively. Increased time upright was associated with improved Modified Rankin Scale scores (– 38.09 min, 95% CI: -61.88, – 14.29) and higher Short Physical Performance Battery scores (6.97 min, 95% CI: 1.99, 11.95), while prolonged bouts of sitting were associated with more severe stroke (4.50 min, 95% CI: 0.80, 8.19), and older age (1.72 min, 95% CI: 0.20, 3.26).

Conclusions: Patients increased their daily time spent sitting and upright during the initial hospital stay after stroke. Prolonged bouts of sitting were associated with older age and more severe strokes. Hence future research should investigate the benefit of interventions aimed at breaking up sitting time after stroke.

Keywords: Stroke, Early rehabilitation, Accelerometer, Physical activity

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Background

One of the core elements of care for dedicated comprehensive stroke units is acute medical treatment combined with early rehabilitation [1–3]. Early rehabilitation with mobilization out of bed during hospitalization has shown to be associated with better functional outcomes for patients after stroke [4–8]. This may reduce the loss of muscle mass, increase muscle strength [6, 9], avoid complications [3, 4, 10], exploit the plasticity of the brain [11], improve neurological functioning [12], and improve gait function [13]. Although time spent out of bed early after stroke varies significantly between hospitals [14–16], the amount of physical activity is generally low during hospital stays [17, 18].

Optimal timing and intensity of early mobilization is, however, not clear, as previous studies have shown an association between mobilization within the first 24 h and a negative trend towards increased dependency [12, 19] and increased mortality [20]. On the other hand, short and frequent mobilizations have been associated with improved outcome [21].

Most studies of physical activity during hospitalization have been single-day observational studies during daytime hours. Recently, objective measurements using body-worn single sensor activity monitors have been applied, enabling continuous monitoring of physical activity over time [22, 23]. So far, only a few studies have used activity monitors to distinguish between different activities in the acute phase for stroke patients [24]. In one of these studies, Strømmen et al. (2014) found significantly increased activity in the lower extremities for hospitalized stroke patients from the first day until discharge [25]. The increased activity was significantly associated with lower severity of stroke, whereas decreased activity was found with increasing age [25]. However, the study did not discriminate between times spent in different positions, which is crucial when measuring physical activity in the acute phase after stroke. Applying two single sensors from the ActivPAL sensor system, one on the chest and one on the thigh, makes it possible to quantify the amount of time spent in different positions. This method has previously been proved valid for stroke patients [26].

The main aim of this study was to describe the amount of time spent in lying, sitting and upright (standing or walking) positions early after stroke and how these activity levels changed during the hospital stay, both regarding total time per day and duration for each mobilization. Another aim was to examine which factors were associated with total time and bouts of sitting and upright activity. Our primary hypothesis was that patients would gradually increase time spent in an upright position, and thereby increase the duration of each upright bout.

Method

Design

This study used a prospective observation design, measuring physical activity continuously with two activity monitors for three to seven consecutive days during hospitalization.

Study setting

All patients were treated in an evidence-based comprehensive stroke unit that emphasizes a multidisciplinary approach and early rehabilitation. The treatment focused on independence in daily life. All patients, regardless of participation, received routine medical treatment, including rehabilitation, in accordance with Norwegian guidelines for treatment and rehabilitation after stroke [27].

Study population

Patients were recruited during three time periods, October–December 2013, May–December 2014, and March–August 2016. Patients admitted to Trondheim University Hospital, Norway, with diagnosed first ever or recurrent acute ischemic or hemorrhagic stroke were eligible for inclusion if the onset of stroke had been within seven days, they spoke fluent Norwegian, and if they gave written consent. In line with the Norwegian regulations for informed consent, patients who were unable to consent were included if their next of kin not opposed participation. Patients with terminal illness, other health conditions severely affecting their ability to walk, or expected discharge within three days after inclusion were excluded.

Measurements

The ActivPAL Professional sensor system (from PAL Technologies Ltd) consists of a three-axis accelerometer that collects continuous data with a sampling frequency of 10 Hz, and with a battery capacity of up to 14 days. The primary outcome for this study was whether time spent lying, sitting or upright changed during the hospital stay. It has previously been shown that this activity monitor provides valid data for time spent lying, sitting, standing and walking [28, 29] and that placement on the thigh and sternum provides good validity for postures and transitions compared to video observations [26]. The 24-h period was measured from the time the activity monitors were attached. Duration of sitting bouts was estimated according to the following ratio: time spent in sitting/number of transitions from lying to sitting, while duration of upright bouts was estimated correspondingly. A time threshold for transitions was set at 1.5 s to eliminate unreliable event records.

The Short Physical Performance Battery (SPPB) (ranging from 0 to 12, where 12 is the best score) was used to assess physical function. The test consists of three different mobility tasks, and has been found to be both valid and reliable for assessing physical function amongst elderly people [30]. Gait speed was calculated based on the walking task of the SPPB. An experienced nurse or physiotherapist performed the test.

Global function was defined using the Modified Rankin Scale (mRS) (ranging from 0 to 6, where 0 is normal function and 6 denotes death) [31] at admission and after the first day in hospital. The mRS measures independence in activities of daily living.

The National Institutes of Health Stroke Scale (NIHSS) was used to measure severity of the stroke. The scale is widely used and has proved both valid and reliable [32].

Both mRS and NIHSS were scored by an experienced clinician within the first day after the patient's admission and recorded together with age, gender, number of days from first symptom to admission date, and number of days at the hospital, which were collected from the medical record.

Procedure

All patients accepting participation had two ActivPAL activity monitors attached, one at the sternum and one at the unaffected thigh, to distinguish between lying, sitting and upright position. If neither of the lower extremities were affected by the stroke, the activity monitor was attached to the right thigh. Patients were instructed to follow the standard rehabilitation routines without paying attention to the equipment. Both activity monitors were removed 14 days post stroke unless the patient had been discharged earlier. Data from the activity monitors were transferred via a USB docking station, and processed in Matlab R2015 B. The valid body and leg data had an individual start and stop time defined and used to measure a count for a full 24-h day, and the activity was coded in reference to the body position. To distinguish the different positions, data from the two sensors were synchronized and recoded according to body position (lying, sitting, and upright).

State durations were calculated by accumulating time intervals for lying, sitting, and upright and state transitions between these positions per 24-h measurement. Time upright was calculated by merging time standing and time walking. A validation procedure was performed to control for possible time drifting of the sensors.

Statistical analysis

Demographic data were reported as mean values and standard deviation (SD) for all patients, and for three subgroups categorized by time from onset of symptoms to inclusion. Baseline characteristics were compared for those included within the first two days after stroke, those included 3 to 4 days after stroke and those included 5 to 7 days after stroke. This was done using a one-way ANOVA or Kruskal-Wallis test, depending on normality of residuals, which was judged by visual inspection of Q-Q plots. To assess changes in activity levels, we used linear mixed models (LMM) with time sitting, time upright, duration of sitting bouts and duration of upright bouts, respectively, as dependent variables, patients as random factor, and days since stroke as covariate. Next, we included the following covariates, one at a time: NIHSS, age, gender, mRS pre-stroke, mRS one day post stroke, and SPPB. Because the time spent lying, sitting and upright totaled 24 h, only time spent sitting and upright were used in the mixed model analysis. Two-sided p-values less than 0.05 were considered statistically significant, and 95% confidence intervals (CI) are reported where relevant. Statistical analyses were done in SPSS 23.

Results

The flow of patients is shown in Fig. 1. Of the 105 patients who met the inclusion criteria, 47 were excluded, mainly because of early discharge.

Fifty-eight patients (31 female) were included in the analysis. Patient characteristics are presented in Table 1. Mean (SD) time from onset of symptoms to inclusion was 2.6 (1.7) days, and patients wore the activity monitors for 5.8 (1.5) days. The NIHSS score was 6.2 (5.0) points. Those included 4–7 days after symptom onset showed significantly lower scores on NIHSS as compared to those included within the first 24 h ($p = 0.002$).

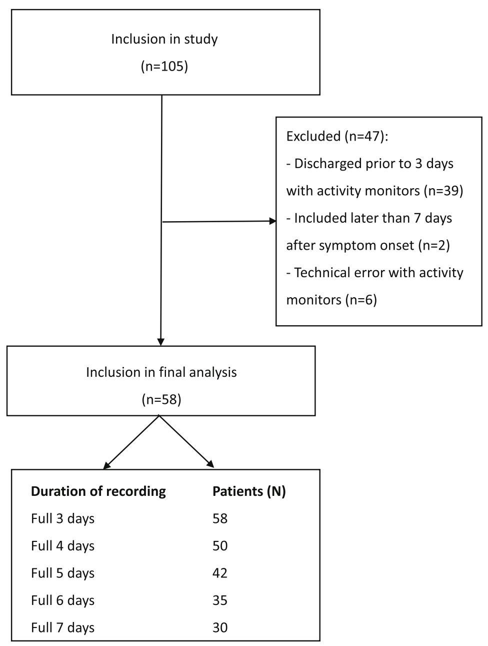

Fig. 1 Flow chart

Table 1 Demographic data for included patients ($N = 58$)

	Included 0–2 days from symptoms ($n = 19$)	Included 3–4 days from symptoms ($n = 24$)	Included 5–7 days from symptoms ($n = 15$)	Total ($n = 58$)
Female gender, *n* (%)	11 (57.9)	11 (45.8)	9 (60.0)	31 (53.5)
Age (years)	72.9 (10.0)	76.6 (13.1)	75.3 (12.1)	75.1 (12.0)
Monitoring days	5.8 (1.6)	5.8 (1.6)	6.0 (1.3)	5.8 (1.5)
Days hospitalized	10.6 (4.6)	10.0 (4.6)	12.6 (5.5)	12.1 (7.6)
Days from stroke to inclusion	0.9 (0.3)	2.4 (0.5)	5.0 (1.3)	2.6 (1.7)
NIHSS when admitted	8.4 (4.4)	8.4 (4.4)	4.6 (6.8)	6.2 (5.0)
Median (IQR)	7.0 (6.0–13.0)	4.0 (3.0–7.0)	3.0 (2.0–5.0)	5.0 (3.0–8.0)
Stroke severity groups, *n* (%)				
Mild (NIHSS < 8)	13 (68.4)	19 (79.2)	14 (93.3)	46 (79.1)
Moderate (NIHSS 8–16)	6 (31.6)	5 (20.8)	0 (0.0)	11 (19.0)
Severe (NIHSS > 16)	0 (0.0)	0 (0.0)	1 (6.7)	1 (1.7)
mRS prior to stroke	1.6 (1.1)	1.6 (1.1)	1.2 (0.9)	1.7 (1.2)
Median (IQR)	1.0 (1.0–2.0)	2.0 (2.0–3.0)	1.0 (1.0–2.0)	2.0 (1.0–2.3)
mRS when admitted	4.1 (0.5)	4.1 (0.5)	4.1 (0.7)	4.1 (0.7)
Median (IQR)	4.0 (4.0–4.0)	4.0 (4.0–5.0)	4.0 (4.0–4.0)	4.0 (4.0–4.3)
Gait speed (m/s)	1.7 (1.6)	1.5 (0.9)	1.2 (1.2)	1.5 (1.2)
SPPB	5.1 (3.8)	5.1 (3.8)	3.9 (3.5)	4.4 (3.5)
Median (IQR)	5.0 (1.0–7.0)	3.5 (2.0–7.0)	4.0 (0.0–7.0)	4.0 (1.0–7.0)

Mean (SD) unless otherwise stated
NIHSS National Institute of Health Stroke Scale, *mRS* modified Rankin Scale, *SPPB* Short Physical Performance Battery

No other significant differences were found for the baseline variables.

Figure 2 illustrates the combinations of activities for each day, showing an increase in time spent out of bed during the hospital stay. Time spent upright remained low throughout the observation period.

Results from the LMM analysis (Table 2) show a daily increase in time spent sitting of 22.10 min ($p < 0.001$) and 3.75 min upright ($p < 0.001$). Adjusted for time, we found that decreasing time spent upright was associated with increasing dependency, measured by mRS the first day after stroke ($p = 0.002$). An association was also found between time spent upright and physical function showing an increase of 6.97 min upright for every point increase on SPPB ($p = 0.007$). Neither severity of stroke nor age significantly influenced changes in overall physical activity.

Although not significant, LMM analysis indicated a daily increased duration of 4.32 min for each sitting bout ($p = 0.051$). Adjusted for time, this increase in time was associated with both a higher NIHSS score ($p = 0.018$) and increasing age ($p = 0.028$).

Discussion

In this study, we found that stroke patients increased their time spent sitting and upright during the initial hospital stay, with a corresponding decrease in time spent in a lying position. The duration of sitting bouts also increased over time, while the duration of upright bouts remained constant. Furthermore, overall increased time spent upright was associated with increasing independency (mRS) and improved physical function (SPPB), while prolonged sitting bouts were associated with higher age and more severe stroke.

Despite a statistically significant increase in time spent upright during the hospital stay, we may ask whether an estimated 3.75 min's more upright activity per day was a clinically significant change. This means that time spent

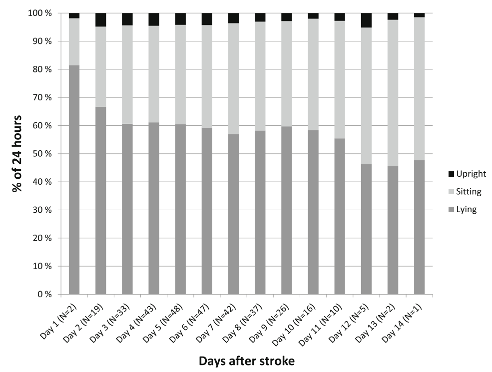

Fig. 2 Percentage of time spent in different positions within every 24 h

Table 2 Linear mixed model regression with activity level as dependent variable

	Time sitting (minutes)			Time upright (minutes)			Duration of bouts in sitting (minutes)			Duration of bouts in upright (minutes)		
Covariate	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value
Time stroke to inclusion (days)[a]	22.10	14.96, 29.24	< 0.001	3.75	1.70, 5.80	< 0.001	4.32	−0.25, 8.66	0.051	0.14	−0.08, 0.36	0.212
NIHSS	0.19	−10.53, 10.91	0.972	−2.34	−5.97, 1.28	0.201	4.50	0.80, 8.19	0.018	−0.08	−0.35, 0.19	0.547
Age (years)[b]	3.09	−1.26, 7.44	0.160	−0.47	−1.99, 1.04	0.534	1.72	0.20, 3.26	0.028	−0.08	−0.19, 0.03	0.133
Female gender[b]	− 35.23	− 141.08, 70.60	0.508	−12.55	−48.93, 23.83	0.492	21.10	−16.95, 59.14	0.271	−0.90	−3.52, 1.71	0.493
mRS_pre strole[b]	− 2.48	−47.02, 42.06	0.912	1.72	−13.60, 17.03	0.823	9.52	−6.39, 25.43	0.236	0.09	−1.00, 1.19	0.867
mRS_post stroke[b]	− 66.98	−140.22, 6.27	0.072	−38.09	−61.88, − 14.29	0.002	6.83	− 20.29, 33.96	0.616	−0.73	−2.57, 1.11	0.432
SPPB	12.21	−2.92, 27.33	0.111	6.97	1.99, 11.95	0.007	−3.23	−8.78, 2.33	0.250	0.18	−0.20, 0.55	0.358

[a]Unadjusted
[b]Adjusted for days since stroke

upright will increase by almost 40 min during a 10-day hospital stay. A previous study has shown that every 5-min increase in time spent in bed was associated with a 4% deterioration on the mRS score three months later [6]. Hence, the daily increase in time spent upright could potentially have a great impact on functional recovery over time.

On the other hand, we found no association between stroke severity and time spent out of bed. This finding might be explained by the fact that activity measures during hospitalization also mirror the mobilization routines in the wards [33], showing that patients are mobilized out of bed as soon as they are medically approved, independent of the patients' ability to mobilize themselves.

The duration of each sitting bout also increased by more than 4 min per day during the hospital stay. More surprisingly, the increased duration of sitting bouts was associated with higher age and more severe stroke, while no associations were found for bouts in upright activity. These findings might be explained by the ability of less affected and younger patients to change position more often by themselves. This is interesting because it adds further knowledge to the ongoing debate regarding the intensity of early mobilization. Also, clinicians should be aware that patients with the most severe strokes who are not able to move independently are at increased risk of sedentary behavior, which might be harmful, thereby increasing the risk of poor outcome [6].

Our results show that stroke patients on average spend a significant proportion of each 24 h in a lying position (Fig. 2). Considering the 24-h monitoring, patients would normally spend at least 30% of the time sleeping. Still, patients spent almost 30% of the remaining time in bed. This corresponds with the high amount of time spent lying previously reported early after stroke [14, 17, 25]. One factor that could influence the low overall activity amongst our participants is the exclusion of those expected to be discharged within three days after inclusion, as these patients are likely to be more active. However, as we aimed to study change in physical activity over time, patients with short monitoring time had to be excluded.

The major strength of the present study was the prospective study design with continuous monitoring of activity, from two activity monitors, over 24 h for several days during the hospital stay. This allowed us to discriminate between lying, sitting and upright positions, which is of major importance in the acute phase after stroke. The use of such a protocol has been validated in the stroke population earlier, showing a high accuracy compared to video observation [26]. In contrast to observation of activity by, for example, behavioral mapping during daytime hours, usually for 9–10 h [7, 14, 17], continuous monitoring will account for out-of-bed time during 24 h. It is also a strength that all included patients received evidence-based treatment in a comprehensive stroke unit combining acute medical treatment and early rehabilitation. Therefore, we know that our patients were mobilized according to recommendations in the national and international guidelines [27, 34], increasing the validity of the study.

A limitation of this study was the wide window for inclusion, ranging from one to seven days post stroke. This criterion was chosen for practical reasons, as recruitment was delayed during weekends and because the diagnosis was delayed in some patients (if the MR images were inconclusive or if patients were not admitted to hospital immediately after the first stroke symptoms). Nevertheless, apart from a significant difference in NIHSS between early and late admission to hospital, indicating that patients with the most severe symptoms are admitted to hospital earlier, we found no significant differences in the demographic data at baseline. However, the variation in time from onset of stroke to inclusion is accounted for in the LMM analysis. Our prolonged recruitment period (2013–2016), with three different time periods may also have influenced our results. The same routines were, however, applied for all stroke patients in the acute stroke treatment in the time periods. Therefore, all included patients, regardless of when they were recruited, should have received treatment focused on early rehabilitation. Another limitation is the lack of possibility to draw a causal relationship between the clinical parameters and the activity categories. Our secondary analysis indicate that the clinical parameters were influencing the activity levels. However, it is also possible to reverse this relationship, and to argue that the activity levels might influence the clinical parameters. Hence, it is important to have this possible bilateral relationship in mind when interpreting the results. Finally, the accelerometers used in this project do not discriminate between active and passive mobilization, and based on our inclusion criteria, mobilization may have been conducted with or without support from another person. This could influence both length and frequency of mobilization, as an active mobilization is naturally more tiring for the patient. However, in a comprehensive stroke unit, hospital staff are trained to activate stroke patients as soon as medically accepted, to encourage active rehabilitation. This means that even though some patients receive more support than others, all patients should be challenged according to their functional level.

Clinical implications

Our study supports previous findings showing that stroke patients spend most of their time in a lying or sitting position [7, 17, 25, 28], during hospitalization. The association between increased time spent upright and improved function indicates a need to pay specific attention to patients who depend on support to be able to transfer to an upright position to ensure frequent and short periods in upright activity throughout their hospital stay as recommended [21]. As older and more severely affected stroke patients may not be able to change position as often as independent patients, hospital staff also should pay extra attention to these patients when mobilizing them to a sitting position, to reduce sedentary time and avoid complications.

Conclusion

This study showed that time spent in sitting and upright positions increased throughout the hospital stay in patients admitted to hospital following a stroke. We found that these changes were associated with improved physical function and a higher degree of independence. There was also an increased duration of bouts spent sitting during hospitalization, with longer bouts associated with increasing age and more severe strokes. Future research should focus on defining the optimal dose of activity in the acute phase in order to improve function in the long term after stroke.

Abbreviations

CI: Confidence Interval; IQR: Inter Quartile Range; LMM: Linear Mixed Model; MRS: Modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; SD: Standard Deviation; SPPB: Short Physical Performance Battery

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Availability of data and materials

Due to Norwegian regulations and conditions for informed consent, the dataset is not publicly available.

Authors' contributions

AH and TA planned the study. AH and OPN recruited, and AH and OPN tested patients. BI was medically responsible for the included patients. OPN, KT, and XT planned and processed data. OPN, SL, and TA performed the statistics by analyzing the data. OPN and TA interpreted the results. The manuscript was written by OPN and TA. All authors critically reviewed and approved the manuscript before it was submitted.

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Ethics approval and consent to participate

The study was approved by the Central Regional Committee for Medical and Health Research Ethics (REK no. 2013/1357) and approved by a member of the local stroke patient organization (Landsforeningen for slagrammede). Informed consent was obtained from those able to agree. For those not being able to provide informed consent, their next of kin was contacted and asked if they opposed participation. The decision of whether or not a participant was able to provide informed consent was made by the senior physician. This procedure is in keeping with Norwegian consent procedures for patients unable to consent, and was approved by the Ethics Committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Correction to: Time spent lying, sitting, and upright during hospitalization after stroke: a prospective observation study

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The original version of this article [1] unfortunately contained errors. The authors wish to correct the Gait speed (m/s) values in Table 1 and add a corresponding table footnote. Below is the correct version of the table.

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Table 1 Demographic data for included patients ($N = 58$)

	Included 0–2 days from symptoms ($n = 19$)	Included 3–4 days from symptoms ($n = 24$)	Included 5–7 days from symptoms ($n = 15$)	Total ($n = 58$)
Female gender, *n* (%)	11 (57.9)	11 (45.8)	9 (60.0)	31 (53.5)
Age (years)	72.9 (10.0)	76.6 (13.1)	75.3 (12.1)	75.1 (12.0)
Monitoring days	5.8 (1.6)	5.8 (1.6)	6.0 (1.3)	5.8 (1.5)
Days hospitalized	10.6 (4.6)	10.0 (4.6)	12.6 (5.5)	12.1 (7.6)
Days from stroke to inclusion	0.9 (0.3)	2.4 (0.5)	5.0 (1.3)	2.6 (1.7)
NIHSS when admitted	8.4 (4.4)	8.4 (4.4)	4.6 (6.8)	6.2 (5.0)
Median (IQR)	7.0 (6.0–13.0)	4.0 (3.0–7.0)	3.0 (2.0–5.0)	5.0 (3.0–8.0)
Stroke severity groups, *n* (%)				
Mild (NIHSS < 8)	13 (68.4)	19 (79.2)	14 (93.3)	46 (79.1)
Moderate (NIHSS 8–16)	6 (31.6)	5 (20.8)	0 (0.0)	11 (19.0)
Severe (NIHSS > 16)	0 (0.0)	0 (0.0)	1 (6.7)	1 (1.7)
mRS prior to stroke	1.6 (1.1)	1.6 (1.1)	1.2 (0.9)	1.7 (1.2)
Median (IQR)	1.0 (1.0–2.0)	2.0 (2.0–3.0)	1.0 (1.0–2.0)	2.0 (1.0–2.3)
mRS when admitted	4.1 (0.5)	4.1 (0.5)	4.1 (0.7)	4.1 (0.7)
Median (IQR)	4.0 (4.0–4.0)	4.0 (4.0–5.0)	4.0 (4.0–4.0)	4.0 (4.0–4.3)
Gait speed (m/s)[a]	0.46 (0.40)	0.59 (0.33)	0.58 (0.38)	0.52 (0.36)
SPPB	5.1 (3.8)	5.1 (3.8)	3.9 (3.5)	4.4 (3.5)
Median (IQR)	5.0 (1.0–7.0)	3.5 (2.0–7.0)	4.0 (0.0–7.0)	4.0 (1.0–7.0)

Mean (SD) unless otherwise stated

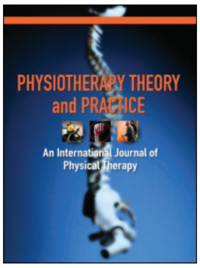
NIHSS National Institute of Health Stroke Scale, *mRS* modified Rankin Scale, *SPPB* Short Physical Performance Battery

[a]These values includes all 58 participants, both those who completed the 4 meter walking test, and those unable to do so (*n*=13). A gait speed of 0 m/s were imputed for participants who not were able to walk 4 meters

Paper II

This article is awaiting publication and is therefore not included.

Paper III



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Associations between changes in gait parameters, balance, and walking capacity during the first 3 months after stroke: a prospective observational study

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Associations between changes in gait parameters, balance, and walking capacity during the first 3 months after stroke: a prospective observational study

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ABSTRACT

Background: Independent ambulation is a common rehabilitation goal after stroke, requiring adequate balance and efficiency of gait. Spatiotemporal gait parameters are expected to improve in the first 3 months and their association with balance and efficiency of gait may provide useful insights into the recovery of safe and independent mobility.
Objective: Examine the associations between changes in spatiotemporal gait parameters, balance, and walking capacity during the first 3 months after stroke.
Methods: This prospective observational study included participants diagnosed with stroke. Within the first 2 weeks after stroke onset and again 3 months (±2 weeks) later, gait was assessed using a GAITRite mat at self-selected gait speed, balance using the Berg Balance Scale (BBS), and walking capacity using the 6-minute walk test (6 MWT). Changes in gait parameters, balance, and walking capacity were assessed using paired sample t-tests, and linear regression analyses were used to assess associations between changes in spatiotemporal gait parameters, BBS, and 6MWT.
Results: Seventy-nine participants (mean (SD) age 75.4 (8.5) years; 44 men) were included. Gait parameters, balance, and walking capacity all improved during follow-up. The bivariate regression analyses showed associations between improvements in all gait parameters, except walk ratio, with improvement in balance, and in all gait parameters with improvement in walking capacity. Only gait speed was associated with balance (13.8 points, 95% CI 0.5, 27.8, $p = .0042$) and walking capacity (256 m, 95% CI 173,340, $p < .001$) in the multivariate analyses.
Conclusion: Improved spatiotemporal gait parameters were associated with improved balance and walking capacity within the first 3 months after stroke.

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Gait; balance; walking ~~capacity~~; stroke; rehabilitation

Introduction

For older people, the ability to walk without the fear of falling is strongly associated with health-related quality of life (Stenhagen, Ekstrom, Nordell, and Elmstahl, 2014). With most spontaneous recovery taking place the first months after stroke (Jorgensen et al., 1995), an early and adjusted rehabilitation is important to regain independence. Following stroke, independent ambulation is reported to be the most frequent self-stated rehabilitation goal (Bohannon, Andrews, and Smith, 1988; Duncan et al., 2007). Walking with adequate postural stability to be safe and avoid falls and a level of gait efficiency that enables a functional level of walking capacity should be a focus in post-stroke rehabilitation (van Ooijen et al., 2015).

Gait speed is well documented as a marker for health and function and is one of the most common and recommended overall measures of gait for older adults (Cummings, Studenski, and Ferrucci, 2014). Following a stroke, most people improve their gait speed during the first 3 months (Fulk, He, Boyne, and Dunning, 2017; Wonsetler and Bowden, 2017), and this improvement is associated with improved community ambulation (Lord et al., 2004; van de Port, Kwakkel, and Lindeman, 2008). However, improved community ambulation also relies on adequate balance and walking capacity (van de Port, Kwakkel, and Lindeman, 2008).

Gait speed is a nonspecific measure and tells us little about gait quality and strategies. Although gait speed is closely associated with other gait parameters, such as cadence, step length, time in single support and asymmetry (Brandstater, de Bruin, Gowland, and Clark, 1983; Roth et al., 1997; Wonsetler and Bowden, 2017), increased speed may not always be the result of improved quality of gait as faster walking may be achieved through developing compensatory strategies

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(Nadeau, Betschart, and Bethoux, 2013). Compensatory strategies may lead to lower safety or efficiency when walking (Olney and Richards, 1996; Weerdesteyn, de Niet, van Duijnhoven, and Geurts, 2008) and lead to reduced overall capacity and increased risk of falling. Exploring the relationship between other gait parameters and both balance and walking capacity may improve understanding of the importance of quality of gait (Thingstad et al., 2015), and guide rehabilitation following stroke.

Balance is a complex system, involving both motor, sensory, and cognitive components, interacting with each other and with surroundings. A deficiency in any of these systems following a stroke can lead to balance impairments (Zou et al., 2018), and may be related to gait impairments. Previous studies have reported decreased step length and time in single support on the affected side early after stroke (Cruz, Lewek, and Dhaher, 2009; Mizuike, Ohgi, and Morita, 2009; von Schroeder et al., 1995). This spatiotemporal gait asymmetry indicates decreased ability to shift body weight onto the affected side (Patterson et al., 2010; van Dijk et al., 2017). During walking, this reduced ability to shift body weight onto the affected side may be related to the same deficits in motor and/or sensory control systems involved in maintaining balance. Reduced balance control has previously been shown to be associated with gait asymmetry (Hendrickson et al., 2014). However, while most spatiotemporal gait parameters improve early after stroke, gait symmetry may require more targeted rehabilitation for many stroke patients (Patterson et al., 2015; Rozanski et al., 2019).

Gait efficiency is related to energy cost of walking. Following a stroke, compensatory strategies resulting from persistent gait impairments may increase energy expenditure (Awad et al., 2015; Bae et al., 2018; Farris, Hampton, Lewek, and Sawicki, 2015), leading to fatigue (Michael, Allen, and Macko, 2006), and affect walking capacity. For example, improved step length on the affected side may lead to less asymmetry and improve efficiency (Awad et al., 2015). Walk ratio, the ratio of step length to cadence, may be related to gait efficiency as there appears to be an optimal stride length–cadence relationship (Egerton, Danoudis, Huxham, and Iansek, 2011). For stroke patients, an improvement in walk ratio toward that reported for healthy adults (Sekiya and Nagasaki, 1998), would indicate that step length has increased relative to cadence, which may imply improvements in gait efficiency.

Several studies have investigated changes in spatiotemporal gait parameters after stroke (Forrester et al., 2014; Lee, 2015; Verma, Arya, Garg, and Singh, 2011). Spatiotemporal gait parameters have also been associated with both balance (Dobkin et al., 2014; Rose et al., 2018) and walking capacity (Awad et al., 2015; Farris, Hampton, Lewek, and Sawicki, 2015) in cross-sectional and longitudinal studies.

However, investigating how changes in spatiotemporal gait parameters are associated with changes in balance and walking capacity will add further to this enquiry and could provide useful insights into the recovery of safe and efficient gait following a stroke. The aim of this study was therefore to examine the associations between changes in primary and calculated spatiotemporal gait parameters with changes in balance and walking capacity during the subacute phase post stroke. We hypothesize that changes in gait speed, step length, time in single support, and single support asymmetry would be most highly associated with changes in balance, as improvements in these spatiotemporal gait parameters would suggest an improved ability to shift body weight from side to side. In addition, we hypothesize that gait speed, step length, cadence, step length asymmetry, and walk ratio would be most highly associated with walking capacity, as improvements in these spatiotemporal gait parameters would suggest a more efficient gait with less energy expenditure.

Methods

Design

This study used a prospective observation design, with an initial assessment within 14 days and a follow-up assessment 3 months (±2 weeks) post stroke. The study was approved by the Central Regional Committee for Medical and Health Research Ethics (REC number 2011/2517). Informed and written consent was obtained from all participants. As this was an observational study in a comprehensive stroke unit, health and safety were obtained in accordance with standard procedures in the 2010 Norwegian guidelines for the management of stroke (Norwegian Directorate of Health, 2017).

Study setting

All participants were being managed in an evidence-based comprehensive stroke unit that emphasized a multidisciplinary approach and early rehabilitation, with a special focus on early mobilization and independence in daily life. Those in need of rehabilitation after discharge were transferred to a rehabilitation program in accordance with standard procedures in the 2010 Norwegian guidelines for the management of stroke (Norwegian Directorate of Health, 2017). According to the guidelines, patients discharged directly at home received further rehabilitation according to their individual needs. This typically consists of 45 minutes of physiotherapy per week in the patient's home or at an outpatient clinic.

Study population

Between March 2012 and October 2014, people admitted to the stroke unit at Trondheim University Hospital, Norway, were screened for eligibility. Those living in the municipality of Trondheim, diagnosed with first ever or recurrent acute ischemic or hemorrhagic stroke were eligible for inclusion if, within 14 days post stroke, their modified Rankin Scale (mRS) score was 0–3 points (able to walk without personal assistance), they were capable of walking with or without walking aid and without support from another person for 10 m, scored 4–6 points on the item "orientation" on Scandinavian Stroke Scale (SSS) (correct on two out of three on time, place, and situation), suffered from stroke impairments scoring from 0 to 57 points on SSS (max score 58 points), and were capable of providing informed consent. Having a life expectancy of fewer than 6 months, serious impairments prior to the stroke that could have a significant impact on functional outcome or unstable medical condition after acute stroke were exclusion criteria.

Measurements

An experienced physiotherapist (MSc) with more than 9 years of experience from assessment and treatment of patients in an acute stroke unit conducted all assessments. The severity of stroke was scored using the SSS (Askim, Bernhardt, Churilov, and Indredavik, 2016). Activities of daily living (ADL) score were measured with the Barthel Index (Mahoney and Barthel, 1965) and degree of independence with the modified Rankin Scale (mRS) (van Swieten et al., 1988), in order to describe the functional level of the sample and make it possible to be comparable to the general stroke population and other study samples.

Gait was assessed using either a 6.10 m or a 5.49 m GAITRite® mat (CIR systems Inc. Franklin, NJ, USA). To measure gait asymmetry, the ratio between left and right foot was calculated for both step length and single support time. Walk ratio was calculated as the ratio between step length/cadence. Participants were instructed to walk back and forth at a self-selected gait speed, along the walkway which included 1 m at either end for acceleration/deceleration. Walking aids, such as a cane or a walker, were permitted only when necessary for safety reasons. The GAITRite mat has previously shown to be both valid (Bilney, Morris, and Webster, 2003) and reliable (Menz et al., 2004; Webster, Wittwer, and Feller, 2005) for assessing gait.

Berg Balance Scale (BBS) was applied in accordance with the tests manual guide (Berg, Wood-Dauphinee, Williams, and Gayton, 1989) to assess balance. The scale ranges from zero (worst) to 56 (normal balance) points and has been shown to be a reliable and valid measure of balance after stroke (Berg, Wood-Dauphinee, Williams, and Maki, 1992). A change of six points on the BBS is considered the minimal important change (MIC) early after stroke (Saso, Moe-Nilssen, Gunnes, and Askim, 2016).

The 6-minute walk test (6MWT) was used to assess walking capacity using a 20 m track following a standard protocol (Guyatt et al., 1985) where participants were instructed to walk as far as they could in 6 minutes. They were permitted to take a break during the test but informed that the timer would still be running. After each minute, participants were informed of the time remaining. The need for walking aid during testing was a joint decision between participant and physiotherapist and was only for safety. The 6MWT is a widely accepted method for measuring walking capacity (Butland et al., 1982), with a minimal clinically important change between 14.0 m and 30.5 m for adults with pathology (Bohannon and Crouch, 2017).

Data and statistical analysis

Data from the GAITRite mat were processed in the PKMAS® (version 5.07c2) (Egerton, Thingstad, and Helbostad, 2014) and transferred to Microsoft Excel 2016 and IBM SPSS Statistics version 25 for analysis. Demographic data were reported as mean values and standard deviation (SD) for all participants unless otherwise stated. Residuals were visually inspected for normal distribution by Q–Q plots and variables transformed if residuals were not normally distributed. Asymmetry was calculated as the percentage of the logarithm (LN) between the left (L)/right (R) leg $(100x(|LN(L/R))|)$ providing a measure of percentage of asymmetry (Yogev et al., 2007). An average of the spatiotemporal gait parameters from the two walks was calculated. Paired sample t-tests were applied to investigate changes over 3 months in spatiotemporal gait parameters, walking capacity, and balance. Those showing a statistically significant change were applied in bivariate and multiple regression analyses for associations between changes in spatiotemporal gait parameters and changes in either of 6MWT and BBS. Because spatiotemporal gait parameters may influence each other, we set cutoff values for correlations between the parameters at below 0.9 and variance inflation factors

(VIF) >10 for inclusion in the multivariate analysis to avoid collinearity. Therefore, only gait speed, percentage of time in single support, walk ratio, and asymmetry measures were included in the multivariate analysis.

Results

A total of 98 people met the inclusion criteria and were recruited for the study. By 3 months, ten had declined further participation, eight were re-hospitalized and not available, and one participant was lost to follow-up due to technical error. Seventy-nine people (44 men, 55.7%) were therefore included in the final analysis. Table 1 shows demographic and functional data at baseline. Participants were discharged either to a rehabilitation center (n = 24, 30.4%) or home (n = 55, 69.6%) in accordance with their physical and cognitive level. At baseline, fourteen participants used a walker, six participants used a cane or a unilateral crutch, and one participant used bilateral crutches (Table 1). After 3 months, only three participants were still in need of a walker, four participants used a stick or unilateral crutch, and one participant used bilateral crutches.

Table 1. Demographic and functional data at baseline (n = 79). Mean (SD) unless otherwise state.

	Mean (SD)
Age (years)	75.4 (8.48)
Days hospitalized	6.5 (3.3)
Male gender, N (%)	44 (55.7)
Types of stroke	
Embolic stroke, N (%)	75 (94.9)
Hemorrhagic stroke, N (%)	4 (5.1)
Modified Rankin Scale (0–6)	2.7 (1.0)
Barthel index (0–100)	85.7 (14.8)
Scandinavian Stroke Scale (0–58)	51.8 (4.6)
Bergs Balance Scale (0–56)	37.7 (15.5)
6-minute walk test (meters)	400.9 (177.8)
Walking aid at baseline tests	58 (73.4)
None, N (%)	7 (8.9)
Cane, N (%)	14 (17.7)
Walker, N (%)	

SD: Standard Deviation

Table 2 shows changes in the spatiotemporal gait parameters, balance, and walking capacity from the acute phase to 3 months later at self-selected gait speed. Participants increased their gait speed by 18% (0.2 m s^{-1}, p < .001), with 11% longer steps (6.6 cm, p < .001), spent 1.2% longer time in single support (p < .001), and increased their cadence by 7% (7.7 steps/min, p < .001). Walk ratio improved by 3% from 0.58 to 0.60 (p = .010). Both asymmetry measures indicated a decreased asymmetry after 3 months, but only step length asymmetry showed a statistically significant decrease (2.5%, p = .004). There was a statistically and clinically significant improvement in both balance (10.3 points, p < .001) and walking capacity (61 m, p < .001).

Table 3 shows the associations between changes in spatiotemporal gait parameters and changes in balance from the acute phase to 3 months later. The bivariate analyses showed a statically significant association, with an increased BBS score of 1.8 points for every 0.1 m s^{-1} improvement in gait speed. We found small, but statistically significant associations between increased step length, increased cadence and decreased step length asymmetry with improved balance. For percentage of time in single support, a 1% improvement was associated with an increased BBS score of 1.3 points. Controlling for all included spatiotemporal gait parameters in the multivariate analysis, a significant independent association was only found between increased gait speed and improved balance: 1.4 points increase on BBS per 0.1 m s^{-1} increased gait speed (95% CI 0.05 to 27.79, p = .042). The multivariate regression analysis had an R^2 value of 0.17 and changes in gait speed explained about a third of the variation in BBS change.

Table 4 shows the bivariate and the multivariate analysis of association for changes in spatiotemporal gait parameters and changes in walking capacity from the acute phase to 3 months later. In the bivariate analysis, for every 0.1 m s^{-1} increase in walking speed from baseline, there was a 26.5 m improvement in walking distance as

Table 2. Changes in spatiotemporal gait parameters, balance, and walking capacity from the acute phase to 3 months later at self-selected gait speed.

	Baseline	3 months	Mean change	
	Mean (SD)	Mean (SD)	Mean (95% CI)	p-value
Gait speed (m s^{-1})	0.9 (0.3)	1.1 (0.3)	**0.2 (0.1, 0.2)**	**<0.001**
Step length (cm)	55.7 (12.9)	62.3 (13.1)	**6.6 (4.5, 8.6)**	**<0.001**
Stride width (cm)	8.1 (3.1)	7.6 (3.5)	−0.5 (−1.2, 0.2)	0.129
Single support (%)	33.9 (3.6)	35.1 (3.0)	**1.2 (0.5, 1.8)**	**<0.001**
Cadence (steps/min)	96.5 (16.7)	104.2 (12.0)	**7.7 (5.0, 10.4)**	**<0.001**
Walk ratio (step length/cadence)	0.58 (0.11)	0.60 (0.11)	**0.02 (0.01, 0.03)**	**0.010**
Asymmetry step length (%)	7.4 (9.3)	4.9 (4.1)	**−2.5 (−4.1, −0.8)**	**0.004**
Asymmetry single support (%)	5.9 (6.5)	4.8 (4.7)	−1.1 (2.4, −0.2)	0.098
Bergs Balance Scale (range 0–56)	37.7 (15.8)	48.0 (10.0)	**10.3 (7.9, 12.6)**	**<0.001**
6MWT (m)	380 (133)	441 (143)	**61 (41, 79)**	**<0.001**

SD: Standard Deviation, CI: Confidence Interval, 6MWT: 6-Minute Walk Trial; p-value <0.05.

Table 3. Bivariate and multivariate associations between changes in spatiotemporal gait parameters and changes in balance from acute phase to 3 months later.

	Bivariate analysis			Multivariate analysis		
	Coefficient (95% CI)	Standardized coefficient	p-value	Coefficient (95% CI)	Standardized coefficient	p-value
Step length (cm)	**0.5 (0.3, 0.8)**	**0.4**	**<0.001**			
Cadence (steps/min)	**0.3 (0.2, 0.5)**	**0.4**	**0.001**			
Gait speed (m s^{-1})	**18.1 (8.3, 27.8)**	**0.4**	**<0.001**	**13.8 (0.5, 27.8)**	**0.3**	**0.042**
Single support (%)	**1.3 (0.5, 2.1)**	**0.3**	**0.003**	0.3 (−1.0, 1.5)	0.1	0.684
Walk ratio (step length/cadence)	22.4 (−17.6, 62.3)	0.1	0.268	11.1 (−27.8, 50.0)	0.1	0.572
Asymmetry step length (%)	**−0.3 (−0.7, −0.1)**	**−0.2**	**0.036**	−0.2 (−0.6, 0.2)	−0.1	0.354

CI: Confidence Interval; *p*-value <0.05.

Table 4. Bivariate and multivariate associations between changes in spatiotemporal gait parameters change in walking capacity from acute phase to 3 months later.

	Bivariate analysis			Multivariate analysis		
	Coefficient (95% CI)	Standardized coefficient	p-value	Coefficient (95% CI)	Standardized coefficient	p-value
Step length (cm)	**6.8 (5.2, 8.3)**	**0.7**	**<0.001**			
Cadence (steps/min)	**5.1 (3.7, 6.5)**	**0.7**	**<0.001**			
Gait speed (m s^{-1})	**265 (209, 322)**	**0.7**	**<0.001**	**256 (173, 340)**	**0.7**	**<0.001**
Single support (%)	**17.4 (11.1, 23.7)**	**0.6**	**<0.001**	1.0 (−6.8, 8.8)	<0.1	0.792
Walk ratio (step length/cadence)	**349.8 (1.6, 698.1)**	**0.2**	**0.049**	−49.9 (−311.5, 211.6)	<-0.1	0.705
Asymmetry step length (%)	**−5.1 (−8.9, −1.4)**	**−0.3**	**0.008**	−0.8 (−3.9, 2.4)	<-0.1	0.619

CI: Confidence Interval; *p*-value <0.05.

measured by the 6MWT. The analysis showed a statistically significant association between increased walking distance and step length (i.e. 6.8 m increase for every extra centimeter of step length). This was also the case for cadence, where an increase in 5.1 m in 6MWT for an increase in cadence of one step/minute. For percentage of time in single support, a 1% improvement was associated with an increased walking capacity of 17.4 m. There was an increase in walking capacity with decreasing spatial and temporal asymmetry, with associations being statistically significant. Controlling for changes in all included spatiotemporal gait parameters, the multivariate analysis showed an increase in walking distance of 25.6 m for every 0.1 m s^{-1} increase in gait speed (95% CI 17.3 to 34.0, $p < .001$). The increase in gait speed accounted for 72% of the variation in change of walking capacity and the multivariate analysis had an R^2 of 0.56.

Discussion

Our results support clinically meaningful improvements in gait, balance, and walking capacity during the first 3 months after stroke. Improvements in step length, cadence, gait speed, percentage of time in single support, and step length asymmetry were all associated with the improvement in balance. Improvements in step length, cadence, gait speed, percentage of time in single support, walk ratio, and step length asymmetry measures were associated with the improvement in walking capacity. However, in the multivariate analysis, only change in gait speed was significantly associated with the changes in balance or walking capacity.

Improvements in many of the spatiotemporal gait parameters are thought to enable safer and more efficient gait. The improved gait speed of 0.2 m s^{-1} is considered clinically significant early after stroke (Fulk et al., 2011; Perera, Mody, Woodman, and Studenski, 2006; Tilson et al., 2010) and a gait speed above 0.8–1.0 m s^{-1} is considered safe in community ambulation. (Studenski et al., 2003). The increased step length and percent of time in single support are suggestive of an improvement in motor control with less time needed in double support (Kollen et al., 2005; Kwakkel, Kollen, and Twisk, 2006). Our results showing decreased step length asymmetry are in accordance with our hypothesis as we expected that early motor recovery would decrease asymmetry. However, single support asymmetry did not change significantly, possibly because it is slower to improve (Rozanski et al., 2019). The increased walk ratio in our study may suggest a more efficient gait, with the ratio moving toward the level of healthy adults (Sekiya and Nagasaki, 1998). The lack of improvement in single support asymmetry and the sustaining associations in multivariate analyses between gait speed and balance and walking capacity raises a question whether our findings are due to compensatory strategies. However, most of the other spatiotemporal gait parameters improve and are associated with both improved balance and walking capacity. Gait speed may be considered as the sum of spatiotemporal gait parameters and may have affected associations between other spatiotemporal gait parameters and balance and walking capacity. We would, therefore, argue that the results found here represent an improvement toward a safer and more efficient gait. It is possible that some participants improve because of compensatory strategies whereas others improvement is due to an improved gait. This aspect could be interesting to study in future studies.

The bivariate analysis shows several associations between changes in spatiotemporal gait parameters and changes in balance. A higher percentage of time in single support on the affected side allows for a longer swing phase of the unaffected leg and would help achieve longer steps. These improvements are also likely to be reflected in the spatial (step length) asymmetry measure (Lewek, Bradley, Wutzke, and Zinder, 2014). There was an association between decreased step length asymmetry and improved balance, suggesting that balance improves as step length asymmetry decreases. When including all gait parameters in the multivariate analysis, most associations disappeared apart from the association between gait speed and balance. Gait speed may therefore effectively be the "sum" of all the other gait parameters (Brandstater, de Bruin, Gowland, and Clark, 1983; Roth et al., 1997; Wonsetler and Bowden, 2017). We hypothesized improved step length would be associated with improved balance. However, because our model breached limits of collinearity, step length was excluded from the multiple analysis. The low R^2 value of 0.17 in the multiple regression model suggests that there are other factors explaining more of the changes in balance. Gait and balance are both complex tasks that rely on the functioning of multiple systems, such as improved vestibular function (Tramontano et al., 2018); improved postural stability (Puckree and Naidoo, 2014); and improved muscle strength (Lund et al., 2018), and it is likely that these systems also can be associated with changes in balance.

The bivariate analysis showed that improvements in several spatiotemporal gait parameters were associated with improved walking capacity. The improvements in spatiotemporal gait parameters are likely to lead to a more efficient gait, with a decreased energy expenditure during walking (Awad et al., 2015; Bae et al., 2018; Farris, Hampton, Lewek, and Sawicki, 2015). It has also previously been shown that walking distance achieved during prolonged walks, such as the 6MWT, is strongly associated with gait speed (Awad et al., 2015). Results from our multivariate analysis show that only changes in gait speed sustained associated with increased walking capacity when including all the variables. This suggests that they were not independently associated with 6MWT when gait speed is also included in the model. The multivariate analyses excluded step length and cadence because of collinearity. However, without breaking the limits, there seems to be collinearity between speed and the other measures that were included in the model. The model had an R^2 of 0.56, showing that improvements in speed over a short 10 m walkway are reflected in improvements in speed over longer distances.

There are some methodological limitations to consider in this study. Our inclusion criteria of being able to walk 10 m without personal assistance will have excluded participants with severe physical impairments from the stroke. The baseline mRS of 2.7, the relatively high BI of 85.7, and a gait speed at baseline close to 1.0 m s^{-1} all suggest that participants were only mildly to moderately affected by the stroke. However, the relatively large standard deviations for both spatiotemporal gait parameters, balance, and walking capacity suggest a heterogeneous group of participants within this mobile cohort. Our results are also in line with data from the Norwegian Stroke Registry from 2017, showing comparable results for stroke severity, functional impairment, and independence in ADL (Norwegian Directorate of Health, 2017).

Participants were permitted to use a walking aid, if necessary, for safety, when walking unassisted on the GAITRite mat and during the 6MWT. The need for a walking aid could be expected to change from the acute phase to 3 months later for several participants. It is likely that the use of a walking aid could influence both gait speed, asymmetry, and efficiency and could question the reliability of the walking tests. The first 3 months after stroke is the period with most spontaneous recovery takes place and it is therefore likely that the need for a walking aid changed. Because we wanted to include a representative group of participants, we chose to include participants in need of a walking aid in the acute phase. This could, however, represent a possibly measurement bias of our results. Therefore, we tested the bivariate and multivariate analysis when excluding those in need of a walking aid at baseline (n = 58). In both analyses, all coefficients pointed in the same direction between improved spatiotemporal gait parameters and improved balance, but improved gait speed was no longer associated with improved balance in the multivariate analysis. This was also the case between improved gait speed and improved walking capacity, with a borderline significance level (p = .060) in the multivariate analysis. The lack of associations is possibly caused by the smaller sample size. However, single support asymmetry changed from a non-significant association to a significant association of −5.60 m (−10.25 to 0.94, p = .020) with changes in walking capacity. A possible explanation for this change of direction for the coefficient is that the walking aid helped maintain postural stability and therefore masked associations. The post hoc analyses were conducted to control whether the results were affected using walking aids. However, excluding participants in need of walking aids did not change our results.

The BBS is a common, reliable, and valid measure of balance after stroke (Berg, Wood-Dauphinee, Williams, and Maki, 1992). However, most tasks in the BBS are of standing balance. With balance control during gait requiring the ability to adjust relative to the surroundings (Zou et al., 2018) there is a question whether BBS is task-specific enough to capture balance during walking. A measure of balance during walking might have shown different results.

The change of GAITRite mats was done because of an error with the first mat. The only difference between the mats was their length. Although the length of the mat could lead to more steps, we do not expect the change of GAITRite mats to threaten the overall reliability of the study.

Clinical implications

Results from this study show that changes in spatiotemporal gait parameters are associated with changes in both balance and walking capacity over the first 3 months after stroke. Changes in gait speed may be considered as a "sum" of the changes across several gait parameters and is an easy and low-cost parameter to measure. Therefore, assessing gait speed may be helpful when monitoring the safety and efficiency of gait after stroke.

Conclusion

The observed spatiotemporal gait parameters improved from the acute phase to 3 months later. Most were associated with improved balance and walking capacity. The associations suggest that improvements in spatiotemporal gait parameters can reveal the safety and efficiency of gait. The analysis shows that improved spatiotemporal gait parameters do explain improved walking capacity better than improved balance.

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Disclosure statement

The authors report no conflict of interest.

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