The Healthy Ageing Initiative
Prevention of falls and fractures

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To my friends and family, who unceasingly strive to keep me grounded and sane.
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Abstract

The world is currently experiencing a dramatic increase in the number of older individuals, an amount that is expected to double between 2015 and 2050. This increase will likely affect the prevalence of age-related functional impairments, such as those caused by fractures. Fractures are often immobilizing events leading to increased individual suffering and vast healthcare costs. Prevention of these events and detection of underlying risk factors are hence of utmost importance. Fracture prevention strategies have traditionally focused on strengthening the skeleton by improving bone mineral density, partly through the mechanical load of increased physical activity. However, research has shown that nine out of ten hip fractures are attributed to falls. While several risk factors behind falls have been identified, there is less knowledge about how aspects such as gait patterns and postural stability predict future falls. The aim of this thesis was to expand upon the current knowledge by investigating objective measures of physical activity in relation to bone parameters, and measures of gait patterns and postural stability in relation to incident falls, in a large population-based sample of 70-year-olds.

The samples investigated in the four included studies were drawn from the Healthy Ageing Initiative (HAI) cohort. Study I examined associations between physical activity, objectively measured using accelerometers, and bone parameters, measured by Dual-energy X-ray Absorptiometry and Peripheral Quantitative Computed Tomography. Study II examined how gait variability, measured using the GAITRite electronic walkway system, predicted incident falls in men and women. Studies III and IV examined how center of pressure (COP) sway and limits of stability (LOS), measured using a force platform, predicted incident falls. Independent prediction of bone parameters and incident falls were investigated using multiple linear and logistic regression models.

Study I revealed that moderate-to-vigorous physical activity and vertical peak acceleration independently predicted parameters of bone in the weight-bearing skeleton. Study II showed that women’s increased risk of falling could be explained by increased gait variability during dual-task assignments. Study III revealed that the risk of falling was increased by 75-90% for individuals in the highest quintile of COP sway. Study IV integrated COP and LOS data, showing that fall risk was increased by 9-16% per 1-unit increase in COP-LOS ratio. In conclusion, this thesis highlighted several objective predictors of incident falls among older adults. Future studies and recommendations should emphasize strategies to improve balance, muscle strength and physical activity in order to prevent falls and fractures.
Abbreviations

HAI; Healthy Ageing Initiative
BMD; Bone Mineral Density
DXA; Dual-energy X-ray Absorptiometry
pQCT; Peripheral Quantitative Computed Tomography
MVPA; Moderate-to-Vigorous Physical Activity
METS; Metabolical Equivalents
CPM; Counts Per Minute
IPAQ; International Physical Activity Questionnaire
CNS; Central Nervous System
EO; Eyes Open
EC; Eyes Closed
COP; Center of Pressure
LOS; Limit of Stability
MDLOS; Minimal Distance to LOS
sALOS; Sway-Area-to-LOS
BOS; Base of Support
COM; Center of Mass
ML; Medio-Lateral
AP; Anterior-Posterior
CV; Coefficient of Variance
TUG; Timed-Up-and-Go
MMSE; Mini-Mental State Examination
CGA; Comprehensive Geriatric Assessment
Original papers


Sammanfattning på svenska


Traditionellt har den åldersrelaterade ökningen av frakturer förklarats av samtidiga försämringar i benmassan, vilket därefter ofta har behandlats med olika läkemedel. Det har även delvis rekommenderats träning och fysisk aktivitet som ett verktyg för att bromsa åldersrelaterad minskning av benmassa. Det finns dock indikationer på att en låg bentäthet, och således osteoporos, förklarar mindre än hälften av frakturförekomsterna. Därtill har även studier visat att kvinnors ökade risk för frakturer jämfört med män inte nödvändigtvis kan förklaras av skillnader i volymetrisk bentäthet. Således är det av vikt att undersöka andra riskfaktorer för frakturer, såsom en förhöjd risk för att råka ut för ett fall. Denna logik stärks vidare av vetenskapliga fynd som påvisar att över 90% av höftfrakturer i hög ålder sker på grund av individer faller.

Ett flertal riskfaktorer för fall har idag föreslagits, såsom hög ålder, kvinnligt biologiskt kön, samt nedsättningar i gångmönster och balans. Däremot är det inte tillräckligt undersökt varför just kvinnor faller mer än män, i relation till olika fysiologiska parametrar som potentiellt kan förklara detta fynd. Vidare bygger många tidigare studier på självskaftade data från studiedeltagare och kliniska tester där testledaren gör bedömningar kring deltagarens fysiska förmåga. I detta sammanhang påvisar objektiva mätmetoder fördelar då de i mindre grad påverkas av subjektiva poängsystem och innebär en automatiserad och direkt mätning av olika riskfaktorer. Tidigare studier har även i stor omfattning baserat sina slutsatser på individers fallhistorik innan eventuella riskfaktorer har undersömts, vilket resulterar i metodologiska svagheter när framtida fall ska förutspås.
Det huvudsakliga syftet med denna avhandling har varit att göra en kartläggning över olika riskfaktorer för fall och frakturer i en äldre population, utifrån det ovan beskrivna kunskapsläget. I linje med detta har delarbete I syftat till att undersöka sambandet mellan benmassans egenskaper och objektivt uppmätt fysisk aktivitet. Delarbete II syftade till att undersöka olikheter i fallrisk mellan män och kvinnor och ställa detta i relation till variation i gångmönstret. Delarbete III ämnade närmre utreda hur subjektiva mått på balans i stående position kunde förutså framtidiga fall. Delarbete IV hade ett liknande fokus som delarbete III, men involverade även mätning av studiedeltagarnas stabilitetssytor samt undersökte eventuella skillnader i stående balans mellan kvinnor och män.

Resultaten i denna avhandling baserades på mätningar som sedan juni 2012 genomförts i HAI-studien (Healthy Ageing Initiative), vilket är en populationsbaserad kohortstudie inriktad mot olika riskfaktorer för fall, frakturer, osteoporos och kardiovaskulära sjukdomar bland 70-åringar i Umeå. De ingående delarbeteonna undersökte deltagarnas bentäthet och kroppssammansättning med röntgenapparatur, fysiska aktivitetsmönster via 7-dagars objektiv mätning med accelerometrar, stående balans via en kraftplatta, samt gångmönster via en elektronisk gångmatta. Samtliga deltagare genomgick även uppföljning för eventuella fallhändelser 6 och 12 månader efter undersökningen. Mätningarna har baserats på upptill 2400 kvinnor och män, vilket motsvarar 84% utav de tillfrågade i Umeå kommun som accepterat deltagande.

Resultaten av delarbete I visade på ett positivt samband mellan fysisk aktivitet och bentäthet, framförallt i nedre, viktbärande extremitet. Sambandet var starkast för måttlig till kraftig fysisk aktivitet, samt för aktivitet som sker i vertikal riktning. Som bäst förklarade graden av fysisk aktivitet enbart 0,8% av variationen i benmassa, varvid även andra bestämmelsesfaktorer bör tas i beaktning för att förebygga frakturer. Resultaten av delarbete II visade att kvinnor i genomsnitt har 50% högre risk råka ut för ett fall jämfört med män, samt upp till 35% högre variation i gångmönstret. Dessa fynd indikerar att kvinnor är en särskild riskgrupp för fall och därigenom potentiellt frakturer, vilket delvis kan förklaras av en högre variation i gångmönstret under progressivt svårare testsammanhang. Resultaten av delarbete III påvisade att risken för att falla var 75–90% högre för individer med stående tyngdpunktsförskjutning större än 400 mm under normala synförhållanden, och större än 920 mm med stängda ögon, jämfört med referensgrupper. Således kan objektiva mått på kroppsvaj i stående position förutså framtidiga fall, oberoende av när flera andra riskfaktorer samtidigt tas i beaktning. Slutligen visade resultaten av delarbete IV att fallrisken i genomsnitt ökade med 0–16% för varje enhets ökning i kvoten mellan kroppsvajet och den funktionella
stabilitetsytan, beroende på testförhållande. Trender i analyserna påvisade att fallrisken eventuellt kan förutspås starkare av kvoten mellan stabilitetsytan och kroppsvaj, jämfört med om enbart ytan på kroppsvajet togs i beaktning. Dock var detta inte statistiskt säkerställt och kräver vidare utredning.

Sammanfattningsvis bidrar denna avhandling till ökad förståelse för hur olika objektivt uppmätta riskfaktorer förhåller sig till fall och benmassans egenskaper hos äldre individer, vilket potentiellt även bidrar med kunskap till hur frakturer kan förebyggas. De olika aspekterna i resultaten har möjlighet att förbättra upptäckten och bedömningen av individer med ökad fallrisk, och därtill vara ett viktigt tillägg till redan etablerade, kliniska metoder. Resultaten av de ingående delarbetena bör följas upp i ytterligare studier där klinisk tillämpning och nytta bör utvärderas. Vidare skulle träning av balans, styrka och gångförmåga potentiellt kunna vara effektiva metoder för de individer där en ökad fallrisk har upptäckts. I relation till bentäthet skulle viktbärande, intensiv fysisk aktivitet potentiellt kunna vara ett positivt tillägg till samtidig medicinering, i syfte att bromsa den åldersrelaterade förlusten av benmassa hos äldre.
Introduction

"I neither deny nor affirm the immortality of man. I see no reason for believing in it, but, on the other hand, I have no means of disproving it." – Thomas Henry Huxley, 1860

The ageing population

The world’s population is growing older, a statement supported by the accelerated development in the number of older adults in virtually all parts of the world. Between 2015 and 2050, individuals over the age of 60 are expected to double in number, while at the same time we are likely to see a tripling in the number of individuals over the age of 80. This demographic change is the product of a balance shift between fertility and mortality, driven by the economical and social changes of the modern world. Combined with progresses in public health knowledge and advancements in technology, senior populations currently experience longer and often healthier lives than ever.1 Researchers argue that the upper limit of human longevity is currently unknown to us, and further progress in the frontier of survival may ascend humanity into even higher ages.2,3

This development is not without concerns however, as increased lifespans may also imply more years with disability for some individuals.4 It is common knowledge that older age leads to increased susceptibility to disease, partly as a physiological consequence of ageing. The mechanisms behind age-related deterioration of biological systems and organs have been extensively discussed elsewhere.5 In short, we humans accumulate genetic damage throughout life as we are exposed to endogenous factors such as free oxygen radicals from energy production, and to exogenous factors such as chemicals and different sources of radiation. This accumulation over time, together with impaired DNA repair mechanisms, are some of the keystones behind the progressive cellular damage that is the biological hallmark of ageing. This gradual pathological process consequently leads to detrimental physiological responses such as mitochondrial dysfunction and down-regulated nutrient sensing.5

Thus, as the physiological reserves decrease with older age, so the predisposition to disease and functional disability increase; the latter which often involves a state of general weakness, reduced muscle strength and impaired balance.6 This detrimental development can potentially manifest in the form of increased fracture incidence among older adults.7 Fractures cause suffering and may immobilize the individual, leading to increased co-morbidity, while also resulting in vast healthcare costs for society.8 As the number of older
individuals steadily increases globally, understanding the underlying mechanisms of these hazardous events and forming prevention strategies are key objectives in maintaining the health of an ageing population.

**Fractures – epidemiology and impact**

Each year, approximately 9 million fragility fractures occur worldwide. The term “fragility” indicates that these fractures are the result of low-trauma events typically more common in older than in younger individuals, and that they occur with less mechanical force than other fractures. Traditional fragility fractures consist of hip, vertebral and wrist (Colles) fractures. Although these share a common classification, the events in which they occur may vary. For example, vertebral fractures are the most common indicator of osteoporosis, while hip and wrist fractures are likely caused by a combination of low bone mineral density (BMD) and falls. Further differences are evident when considering healthcare burden, since research has shown that hip fractures alone stand for more than 72% of all fracture-related treatment costs. Sweden holds the second highest hip fracture incidence in the world, and treatment costs for hip fractures amounted to €823 million in 2010. These costs are likely to escalate in the coming decades given the projected increase in older individuals.

Many individuals who sustain a hip fracture consequently experience increased difficulty in performing activities of daily living. As such, they are more likely to be in need of nursing home care, require a walking aid and are less able to independently walk around outdoors. Physical activity is very limited in these individuals, thus increasing their susceptibility to co-morbidities. Alas, this immobilization is severe; researchers have shown that two years after hospitalization due to hip fracture, over 50% of men and 39% of women were either dead or institutionalized.

As previously mentioned, low BMD and falls constitute two major risk factors for fractures among older adults. Each 1 standard deviation (SD) decrease in BMD generates an increased fracture risk by 1.5 – 2.5 times, while a fall to the side can increase the risk of sustaining a hip fracture by 3 – 5 times. It remains unclear whether fracture preventions benefit the most from interventions aimed at increasing BMD or reducing fall risk. Thus, the aim of the following sections is to provide an overview in these areas, and to closer examine some of the underlying risk factors that influence bone properties and fall risk.
The skeleton

Our skeletal system offers several vital functions; anatomically it provides support, movement assistance and protection of organs from injury, while physiologically it acts as a mineral reserve, producer of blood cells and storage of triglycerides. Bone itself is a complex material composed of crystallized minerals, type-1 collagen, bone cells, water and lipids. Bone can be further divided into two general subtypes: 1) cortical bone, which is compact and primarily present in the diaphyses of long bones, and acts as an outer thin layer in vertebrae and the pelvis; and 2) trabecular bone, which is spongy and primarily present in the metaphyses of long bones, and forms the central bone mass of the vertebrae and pelvis.

Bone remodeling and ageing

The bone tissue in our skeleton is constantly being remodeled. This process enables the removal of damaged bone and formation of new bone structure to maintain skeletal function and mineral homeostasis in adult humans. To achieve this, several types of bone cells synchronize and coordinate the different phases of the remodeling process: 1) osteoblasts, which are cells specialized in bone formation; 2) osteoclasts, which are responsible for the break down and removal of bone matrix; and 3) osteocytes, which are the most abundant type of bone cell and are interconnected throughout the bone to form a network via dendritic processes. Together, these cells are responsible for the remodeling and ongoing preservation of bone mass at distinct locations throughout the skeletal system. As a result of this process, almost our entire adult skeleton is replaced around every tenth year.

Initiation of the remodeling process can stem from several stimuli, such as mechanical strain that is sensed by osteocytes and subsequently transformed into a physiological signal, or through endocrinal activation of osteoblasts via parathyroid hormone receptors. Regardless, osteoclasts are recruited, followed by osteoblasts in what is defined as basic multi-cellular units (BMU), absorbing and replacing bone over the course of several weeks. During the formation phase, some osteoblasts become encased in the newly formed bone and later transform into osteocytes.

Ageing affects the tightly regulated balance between osteoblasts and osteoclasts, leading to negative bone formation since resorbed bone is no longer fully restored in the remodeling process. This eventually results in loss of bone strength due to decreased trabecular and cortical BMD as well as increased cortical porosity. It has been suggested that this decline is largely influenced by a reduction in the number of osteoblasts, a result of several potential underlying mechanisms, such as an increased number of free oxygen radicals as seen with ageing. There are also indications that bone loss due to decreased
cortical thickness and increased cortical porosity is compensated by an increased periosteal apposition of bone mass, although this effect seems to be more pronounced in men compared to women.\textsuperscript{29} Naturally there are inter-individual variations in loss of bone mass with increasing age, as BMD is influenced by factors such as sex, weight, genetic heritage and physical activity.\textsuperscript{30-33}

\textit{Impact of physical activity}

Our skeleton is designed to support movement and to endure variations in the physical load enforced upon it. To accomplish this and to mitigate potential damage, bone tissue has to adapt and respond to different mechanical forces. The magnitude of this response varies depending on volume and frequency of the mechanical load, where a high rate of strain placed upon bone is likely to result in a greater osteogenic adaptation compared to a low rate.\textsuperscript{34} Harold Frost originally theorized the concept of a "mechanostat" back in 1987, elaborating on the ability of bone to up- and downregulate bone formation in response to mechanical load.\textsuperscript{35} Within this concept, osteocytes have been proposed to act as primary sensors, able to capture the mechanical signal, e.g. produced by weight-bearing exercise, and transform it into a biological response.\textsuperscript{24}

Regular physical activity has been suggested as beneficial for achieving optimal bone growth in children and adolescents, with a proposed “window of opportunity” during pre- and peripuberty to influence peak bone mass.\textsuperscript{36} In older adults, physical activity and targeted exercise may help attenuate the age-related decline in bone mass, although the osteogenic response to mechanical loading might be affected.\textsuperscript{37} However, a recent intervention study focused on high-impact resistance exercise, revealed increases in femoral neck and lumbar spine BMD in postmenopausal women with low bone mass.\textsuperscript{38} The nature and form of physical activity and exercise likely plays a key role in achieving positive results on bone mass, regardless of age. Weight-bearing exercise and activities of high intensity with vertical impacts, such as jumping and running, is largely preferred in contrast to non-weight-bearing activities, such as swimming or cycling, and to activities of low intensity, such as walking.\textsuperscript{39-42}

However, the influence of physical activity on parameters of bone health in older individuals needs to be further evaluated in population-based samples, since intervention studies often target specific risk groups. Within this context, physical activity has traditionally been assessed using self-report instruments,\textsuperscript{43-46} thus introducing methodological issues such as self-recall bias.\textsuperscript{47} This can be avoided by using objective measurements of physical activity, such as those provided by accelerometers. These instruments are able to provide data on intensity levels as well as activity patterns.\textsuperscript{48} However, the association between objectively measured activity and parameters of bone has primarily been
evaluated in children and adolescents, whereas data on older individuals are lacking.\textsuperscript{49,50}

**Falls – epidemiology and risk factors**

An increased risk of falling constitutes one of the greatest threats to the well-being of senior populations, and falls have been argued to predict fractures even better than does osteoporosis.\textsuperscript{51} The importance of considering other risk factors besides low bone mass is also evident, as studies have shown that differences in fracture incidence between men and women are not entirely explained by inherent differences in BMD, and also since over 90\% of hip fractures are caused by falls.\textsuperscript{52,53}

Estimated medical costs for the treatment of fall-related injuries amounted to 19 billion in the U.S in 2000,\textsuperscript{54} rising to 31.3 billion in 2015.\textsuperscript{55} This escalation in healthcare expenses is likely to continue, given the projected increase in the number of older individuals and since fall incidence increases with age.\textsuperscript{56} To exemplify, the Baltimore Longitudinal Study on Aging has reported that fall prevalence increased from 21\% in middle-aged individuals, to 35\% in older individuals, with women generally experiencing higher fall rates than men.\textsuperscript{57} Aside from incurring huge medical expenses, falls may cause individual suffering, result in disability and lead to increased mortality.\textsuperscript{58,59} In light of this, it has been reported that the hospital days due to injurious falls exceed those due to breast cancer and myocardial infarction combined.\textsuperscript{60} Falls may also induce “fear of falling”, a circumstance where individuals try to avoid exposure to new falls, thus decreasing their social interactions and physical activity levels, leading to increased disease susceptibility.\textsuperscript{61}

How falls are defined is an important methodological aspect, and several definitions have been used over time. Tinetti et al. defined falls as ‘events which results in a person coming to rest unintentionally on the ground or other lower level, not as a result of a major intrinsic event or overwhelming hazard’.\textsuperscript{62} Later definitions explained falls as an ‘unexpected descent from an upright, sitting or horizontal position, the descent height being \( \leq 1 \text{m} \)’.\textsuperscript{63} The International Classification of Diseases, 10\textsuperscript{th} revision, (ICD 10) classification system currently categorizes falls by cause, one of these being ‘fall on the same level from slipping, tripping or stumbling’.\textsuperscript{64} Use of different definitions may explain the varying fall incidences that have been reported in various studies. As falls are very often self-reported by participants, appropriate definitions may be critical to results. For example, this will be the case if the aim of a study is to evaluate falls caused by internal factors, such as balance and gait disorders, while falls caused by external factors such as falling due to collisions with other pedestrians should be excluded.
The self-reported nature of fall data in most studies implies that circumstances surrounding the actual fall event have not been fully elucidated. A recent study by Robinovitch et al. investigated falls captured in real time via cameras in long-term care facilities, concluding that falls occurred primarily when patients shifted their weight inadequately, followed by trips or stumbles, bumps into external objects and through loss of support.\textsuperscript{65} It should be noted that this was investigated in institutionalized older individuals, and thus it remains uncertain how fall events objectively occur in community-dwelling and healthy seniors. Data from the National Health Interview Survey in the U.S. indicate that the proportion of indoor fall-related injuries progressively increases with age in community-dwelling adults, with women experiencing more indoor fall-related injuries than men. Furthermore, fall-related injuries that resulted from tripping also increased with age for both men and women, and common hazards related to these injuries were large objects, floor contamination, and stairs.\textsuperscript{66} Outdoor falls, on the other hand, are reportedly more common at younger ages, in men, and in individuals who are rather healthy and physically active.\textsuperscript{67}

Information on falls may be collected retrospectively by assessing fall history or prospectively through different follow-up intervals. The former is deemed weaker when assessing the risk for future falls, due to recall bias and to the fact that risk factors are not identified before the actual fall has occurred. Furthermore, retrospective study designs increase the risk of capturing risk factors that are the results of previous falls, e.g. falls that negatively influence an individual’s gait pattern or postural stability.\textsuperscript{68,69}

\textit{Regulation of sensorimotor control}

To date, several hundred risk factors for falls have been identified, some of these pertaining to intrinsic factors such as deficits in gait and postural stability, as well as related disorders.\textsuperscript{56} Understanding how sensorimotor control is regulated may facilitate comprehension of how falls are influenced by such risk factors.

The term ‘sensorimotor control’ represents a very complex process. It involves the perception of a sensory stimulus via visual, vestibular or proprioceptive systems, a subsequent conversion of this stimuli to a neural signal that is transmitted to various parts of the central nervous system (CNS), where the signal is integrated, processed and transformed into a motor response. This motor response can be described as an activation of muscles and a production of force that is necessary to enable us to stand, walk or run.\textsuperscript{70} Figure 1 provides a simplified illustration and overview of how the complex sensorimotor system is regulated.
Proprioceptive input is derived from mechanoreceptors located in the deep skin, in muscle fibers as well as in the joints, which specialize in transforming mechanical stimuli into neurological signals. Muscle spindles in muscle fibers are able to sense and communicate information regarding muscle length, golgi tendon organs in joints and musculotendinous tissue primarily conveys information on muscle tension, and skin receptors sense and deliver notice from mechanical stimuli such as tactile pressure. The vestibular system is responsible for handling equilibrium and body position maintenance, and vestibular input is derived from receptor organs located in the ear. These receptor organs are able to transfer information regarding the position of head and body relative to gravity, as well as relative to movements such as rotations and head tilts. The visual system detects continuous changes in the optic flow captured by the retina. As such, it is able to convey information regarding distance to static and moving objects, as well as in what direction and at what speed an individual is moving.

Figure 1. Simplified overview of the various systems and regulators involved in sensorimotor control. Adapted from Carnivale et al. (2011).

All the information received from proprioceptive, vestibular and visual systems is integrated in the spinal cord, in conjunction with potential information from higher CNS structures. Thus, the spinal cord summarizes and formulates responses based on excitatory and inhibitory signals. Further up in the signal
processing hierarchy is the brain stem, which acts like a relay station between the spinal cord and areas of the brain. Here, motor activities are directly regulated based on input from proprioceptive, vestibular and visual systems. Acting as a primary moderator of postural control and locomotor activities, the cerebellum receives information from the spinal cord, brain stem, and motor cortex. The primary functions of the cerebellum are to compare and evaluate intended movements with resulting movements, and to provide corrective feedback. Together with the basal ganglia, the cerebellum plays a key role in coordinating and executing motor control. Lastly, the motor cortex is responsible for planning and initiating both complex and discrete movements.19,71

It is thus understood that seemingly normal everyday activities, such as standing upright or walking, are in fact possible due to a complex integration and regulation of neurological signals from multiple systems, and a production of an adequate motor output. When everything is working correctly in a healthy individual, the sensorimotor system produces stable gait patterns and adequate postural control, while impairments in these systems may lead to increased instability and possibly falls. Individuals may be able to compensate for impairments in a single system, e.g. an individual with sensory loss in the feet due to neuropathy may rely more on visual input for postural control. However, this compensation may negatively impact the individual’s ability to perform normal activities when it is dark. Thus, to determine an individual’s fall risk, it is important to measure and evaluate the function of several sensorimotor systems.73,74

Postural sway
Researchers often use the term ‘postural stability’ when investigating associations between an individual’s balance ability and the risk of falls, fractures or disability. This term relates to the ability of an individual to maintain their body’s center of gravity within the base of support (BOS) during static positions and dynamic movements.75 Postural stability can be objectively determined by quantifying postural sway, measured as deviations of the center of pressure (COP) from a pre-specified point of origin. Postural sway can be described as the resulting oscillation when the sensorimotor system attempts to compensate for shifts in the body’s center of mass (COM).76

Several non-instrumented tests exist that include assessment of postural stability, such as the Berg-Balance Scale, Short Physical Performance Battery and Timed-Up-and-Go tests.77-79 However, these tests involve subjective scoring systems and provide general estimates on postural stability performance, whereas instrumented tests provide objective, and more detailed data. Instrumented tests commonly involve the use of force plate devices, which may
also reduce test performance variability.\textsuperscript{80,81} Using force plate devices, researchers have suggested that multiple global COP variables are of interest. These variables relate to measures such as 1) total area covered by the COP deviations in mediolateral (ML) and anteroposterior (AP) directions; 2) total path length, determined by the two-dimensional COP excursion and total distance covered; and 3) sway velocity, which is the COP path length divided by total trial time. Test protocols for postural control can include monopedal or bipedal stances while also integrating eyes open (EO) or eyes closed (EC) conditions. Furthermore, test durations are recommended to be between 20 and 60 s, and both firm and unstable surfaces can be used.\textsuperscript{81}

It is well known that postural sway increases with age, accompanied by greater muscle activity in the lower extremities as the sensorimotor system attempts to maintain posture equilibrium.\textsuperscript{82,83} Reductions are also seen in anticipatory-compensatory control mechanisms with age. Anticipatory postural adjustment strategies are used to support posture preservation in response to an external perturbation, whereas compensatory postural adjustments exist to regain posture after the perturbation has occurred. Ageing may cause the anticipatory postural adjustment mechanism to be delayed, resulting in a greater compensatory response, which may explain the increase in postural sway seen in older individuals.\textsuperscript{84}

Several pathological disorders may cause increased postural sway. Diabetes type-2 patients can experience impaired sensation in feet soles due to neuropathy, and Parkinson’s disease patients often experience postural abnormalities partly due to loss of dopamine-producing nerve cells in the basal ganglia.\textsuperscript{85,86} Regardless of whether postural sway is impaired by disease progression or by ageing in general, falls and fall-related injuries such as hip fractures may be the traumatic end result. The link between objectively measured postural sway and falls has been investigated previously, and researchers have suggested several parameters to be predictive of falls, such as mean ML COP length during EO and mean COP velocity on firm surface during EC.\textsuperscript{87} However, the results of these studies have been deemed inconclusive, and prospective studies with larger sample sizes are warranted. Furthermore, there is a need to evaluate adequate cut-off points from objectively measured postural sway parameters in order to provide clinicians with better tools in determining a patient’s fall risk.

\textit{Limit of stability}

As initially mentioned in the previous section, postural stability is upheld by maintaining the center of gravity within the BOS.\textsuperscript{75} While large COP deviations indicate that an individual may experience impaired postural stability, it is plausible to assume that the actual loss of balance and potential fall do not occur
until the COP crosses the BOS boundary. As such, BOS can be characterized as the theoretical maximal stability area, enclosed by the feet in a bipedal stance and stretching in anteroposterior directions from heels to toes. This area is however likely to be functionally smaller in reality, limited by factors such as ankle muscle strength, various pathologies and sensorimotor impairments. In regard to this, a functional ‘limit of stability’ (LOS) has been proposed that describes the boundary in which an individual is able to maintain their COP and uphold postural stability. The size of the LOS area may thus play an important part in determining fall risk.

Functional LOS is reported to decrease with age, declining about 16% in size per decade after the age of 60. This decline has been suggested to coincide with a reduced ability in older individuals to quickly process information regarding movement initiation and control. Furthermore, visual conditions influence functional LOS estimations to a greater degree in older than in younger individuals, indicating that stability boundaries are also determined by other factors besides strength and flexibility. Individuals with multiple sclerosis and Parkinson’s disease show decreased functional LOS compared to healthy controls, which are reasonable findings since these disorders influence CNS regulation of postural stability. There are some indications of a possible link between LOS measurements and fall prediction, as it has been shown that individuals with multiple previous falls have significantly smaller stability boundaries. However, the evidence regarding how LOS estimations can predict future falls is currently lacking.

LOS can be determined by different assessment protocols, both spatial and temporal in nature. The latter often involves using time-to-boundary as the determinant of postural stability and has increased in popularity over the years. However, it has been implied that time-to-boundary protocols likely overestimate functional stability boundaries where the stability margins are defined around the outer limits of the feet, while in reality these margins are likely smaller than the BOS and more elliptical in nature. As such, researchers have proposed a low-speed leaning protocol using circular motions to overcome these limitations and produce an adequate measure of functional LOS.

Postural sway and LOS parameters are key factors to consider when determining an individual’s postural stability, and it may thus be of interest to investigate how these parameters relate and co-vary with to fall risk. This can potentially be achieved by estimating the region representing postural sway and the region representing the limit of stability region, and subsequently by investigating the ratio between these parameters. In this regard, the extent of the postural motion would be compared to the maximum stability tolerance of an individual. Such parameters have attained some attention in previous
research, where it was determined that older age negatively influenced the ratio between the postural sway region and the stability boundary region.\textsuperscript{90}

\textit{Gait patterns and variability}

While measurements of postural sway during quiet standing may be considered as assessments of static balance, measurements of gait can instead be classified as an evaluation of dynamic balance. The sensorimotor system is highly involved in the maintenance of stable gait patterns, integrating visual, vestibular and proprioceptive input into closely controlled motor commands, which results in coordinated muscle activity and proper joint movements required for steady ambulation. Human gait, a seemingly normal everyday activity that may be taken for granted in healthy individuals, is thus actually quite the remarkable feat, manifesting as the motoric output generated by the control and coordination of several physiological systems.\textsuperscript{74}

Originally, research into the field of gait dynamics typically revolved around averages of spatial and temporal stride properties. It was later detected that human gait actually express fluctuations between strides, and that these fluctuations can differ between individuals.\textsuperscript{96,97} As such, researchers initiated closer examinations of these stride-to-stride fluctuations, their meaning and their potential significance. It was subsequently revealed that increases in these gait pattern fluctuations could be associated with certain diseases, establishing gait variability as a promising research item in risk prediction and disease progression.\textsuperscript{98} However, all individuals, regardless of health status and age, express gait variability to a certain degree. As such, “normal” spatial and temporal variations in gait patterns could possibly be viewed as a sign of healthy dynamic balance control, reflecting sensorimotor compensations for sudden shifts in the COM during ambulation. There are indications that both too little and too much gait variability is associated with a history of falls, further suggesting that a certain amount of variation is needed in performing normal, stable locomotion.\textsuperscript{99}

One of the primary aspects driving variations in gait patterns as a research area forward has been its relationship to falls. This association was detected in a study almost 40 years ago, where it was revealed that patients who had sustained a fall without injury showed an increased variability in step length.\textsuperscript{100} These early findings have since been expanded upon by numerous studies either confirming the results or providing detailed analyses and further discussion on which gait parameters that are of clinical interest.\textsuperscript{99,101} Gait variability parameters have subsequently been proposed as better predictors of prospective fall risk compared to regular gait measures such as average gait speed and average stride length.\textsuperscript{102} More recent population-based data suggests that specific parameters of gait variability, such as step length and the double-
support phase, are predictors of multiple falls only. However, the authors acknowledged that this might be the result of them not assessing gait variability during more challenging tasks. In this sense, researchers have shown interest in the concept of multitasking during gait measurement protocols, which adds a cognitive aspect when exploring the relationship between gait and fall risk. Dual-task conditions are believed to challenge an individual’s executive functions, defined as the ability to organize and perform cognitive and motoric processes simultaneously. These functions are known to be reduced in older individuals, and may thus be an important link to consider when investigating associations between gait variability and fall risk among the elderly.

**Muscle strength and physical activity**

It is also worth recognizing other aspects related to fall risk beside assessments of postural stability and variations in gait, such as estimations of muscle strength. It has been previously reported that decreased muscle strength in the lower extremities is associated with the occurrences of falls, while it can also influence other fall-related risk factors such as static and dynamic balance ability. These findings were further confirmed in a prospective study revealing that decreased muscle strength increased the risk of fall-related fractures in older women independent of bone density measurements and hormonal status. Additionally, several measures of lower extremity muscle strength were collectively analyzed in a meta-analysis, revealing that muscle weakness can potentially increase the risk of falls by 76%. The same study highlighted that associations were also seen between falls and upper extremity muscle strength, commonly assessed by testing an individual’s grip strength. The interaction between muscle strength and fall risk is not fully understood and the mechanisms are likely complex. To exemplify, ankle muscle strength can influence postural stability and thus possibly affect the risk of falling, although some studies indicate that muscle strength and postural stability predict fall risk independently of each other, probably because they likely constitute two different neurological capacities.

Some studies have also aimed to evaluate the relationship between physical activity and falls, although the results have been inconsistent. In a large prospective cohort study, self-reported moderate-to-vigorous physical activity (MVPA) was associated with roughly 35% reduced fall risk. Another study discordantly reported no association between average physical activity and falls, and also revealed that an individual classified as having low physical activity sustained more falls when exposed to more activity. It has additionally been reported that men under 80 years of age with low activity sustained fewer falls compared to those who were more active, while the opposite was true for men above the age of 80. The effect of physical activity on fall risk may thus be mediated by age. Overall the relationship between physical activity and falls
seems complex and warrants further investigation. Furthermore, physical activity can potentially influence the relationship between falls and other independent risk factors, such as measures of gait and balance.\textsuperscript{115}
Thesis rationale and aims

Prediction of fall risk and subsequent prevention of falls and fractures is an important research area given the increasing proportion of older individuals. The current level of knowledge can advantageously be expanded upon by prospective and population-based evaluation of data in combination with the use of objective measurement technologies. In light of this, the following objectives were the focus of this thesis:

1. Physical activity may help preserve bone mass in older individuals who are susceptible to age-related decreases in BMD and thus osteoporosis. However, physical activity data on older individuals have predominantly been self-reported. Furthermore, these studies have traditionally used DXA measurements on bone parameters, whereas pQCT data, and thus detailed analyses of trabecular and cortical bone mass, are lacking. The aim of study I was to examine how objective measures of physical activity influence bone parameters, as measured by pQCT and DXA, in a population-based cohort of elderly women and men.

2. Women experience more fractures than men, partly explained by a higher prevalence of bone fragility in women, although an increased risk of falling may also contribute to this observation. The underlying mechanisms to these sex differences in fall rates have not been fully elucidated. It is also unclear whether gait variability, a known risk factor for falls, differs between men and women. Thus, the aim of study II was to determine if older women are more prone to falling than older men, and if so, whether this increased risk is associated with variability in gait patterns.

3. Impaired postural stability has been proposed as a risk factor for falls among older individuals, although prospective data on falls relative to objective measures of postural stability are lacking. Furthermore, associations between posturography and falls need to be evaluated in a population-based sample. Study III aimed to investigate if objective measures of postural sway can predict incident falls.

4. To predict incident falls, it may additionally be important to consider an individual's functional stability limits. Study IV followed upon study III, and aimed to investigate how population-based, integrated LOS and postural sway data predict incident falls. An additional aim was to investigate if these measures differ between older men and women.
Materials and Methods

The methodological framework of this thesis is based on measurements and procedures used within the Healthy Ageing Initiative (HAI) study, led by researchers Anna Nordström and Peter Nordström at Umeå University, Sweden. While the HAI study includes several tests and assessment instruments, this section will focus on procedures and equipment relevant to the thesis rationale and aims.

The Healthy Ageing Initiative study

The HAI study was initiated in June 2012 with the aim to evaluate both traditional and potentially novel risk factors for falls, fractures and cardiovascular disease. The HAI study is currently ongoing with nearly 4000 participants examined at the time of writing this thesis, and several scientific papers have been published as a result.\textsuperscript{116-121}

The HAI study is population-based and uses two inclusion criteria: 1) residence in the Umeå municipal area and 2) age of 70 at the time of testing.

Eligible individuals are contacted using information drawn from population registers and receive written information about the research project. They are subsequently contacted by telephone and may either accept or decline to participate. The HAI study holds a participation rate of approximately 84% since the start in 2012, calculated as those who receive information about the study and complete the examination. Alternatively, the participation rate is about 70% when also considering individuals who are not contactable due to an incorrect accounting address or telephone number.

Participants arrive at the hospital clinic for testing at prescheduled times during morning or afternoon. They are instructed to be fasting, and upon arrival they receive verbal and written information about the tests. Participants subsequently provide written consent and commence the testing procedure, beginning with reporting of cardiovascular disease history, previous fractures and smoking. Participants perform anthropometric measurements such as height and weight, followed by body composition and bone density measurements and blood sample collection. After a small meal, participants complete a comprehensive questionnaire that includes items regarding lifestyle, habitual physical activity levels, nutrition, fall history, depression and cognitive function. Testing is continued with measurements of postural stability, gait patterns and functional movement ability. The examination is subsequently completed after tests of cognitive ability and preparation of objective physical
activity assessment. The total testing time for each participant estimates to roughly 3 hours. After testing is completed, participants are assigned accelerometers in order to collect objective physical activity data for 7 days, after which they return for a pre-scheduled visit. During this shorter visit, participants receive information regarding their tests results, including physical activity patterns. Each participant is followed up with a phone interview 6 and 12 months later, where he or she reports any new falls that have occurred.

The HAI study has been approved by the Regional Ethical Review Board in Umeå (dnr 2012-85-32M, supplement to dnr 07-031M) and is conducted according to the principles stated in the World Medical Association’s Declaration of Helsinki.

**Dual-energy X-ray absorptiometry (DXA)**

Study I involved measures of body composition, including areal BMD (aBMD, g/cm²), using a Lunar iDXA device (GE Healthcare Lunar, Madison, WI, USA). The DXA technology involves generating two x-rays at different energy levels. As these x-rays pass through a subject’s body, they are attenuated differently depending on the body tissue, enabling the device to determine the body composition. The radiation dose exposed upon the subject is low, the highest reportedly reaching 0.013 mSv for lumbar spine scans in adults, hence increasing the clinical utility of DXA.¹²²,¹²³

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*Figure 2. The iDXA device used in the HAI study.*
Study I included measurements of aBMD in the left femoral neck, in the lumbar spine (L1-L4) and in the left radius. Total scan time was approximately 20 minutes, including the whole-body measurement segment. The iDXA device was calibrated using a phantom each morning ahead of measurements and all scans were performed on the same device by 1 out of 3 research nurses. Research involving iDXA measurements have reported coefficients of variance (CV) of 0.4% for the lumbar spine and 1.4% for the femoral neck.124

Peripheral Quantitative Computed Tomography (pQCT)
Study I also involved measurements of volumetric BMD (vBMD mg/cm³) using a pQCT device (XCT-2000; Stratec Medizintechnik, Pforzheim, Germany). This technique provides a three-dimensional quantification of true volumetric BMD and enables separate analysis of cortical and trabecular bone. As with the DXA, the technique is based on measuring the attenuation coefficient of X-rays passing through bone mass, although pQCT also provides further information regarding bone geometry and structure. The radiation dose of <0.003 mSv per scan slice is also negligible.125

Figure 3. The pQCT device used in the HAI study.

Using the pQCT, scans were performed in participants’ non-dominant radius and tibia, estimating the following bone parameters: cortical and trabecular vBMD (mg/cm³), cross-sectional area (CSA, mm²), cortical thickness (mm) and periosteal and endosteal circumferences (mm). Trabecular CSA and vBMD were measured at metaphyseal scan sites located at 4% of total bone length in the
distal-proximal direction, while cortical CSA, vBMD, thickness and periosteal and endosteal circumferences were measured at scan sites located in the diaphysis located at 66% of total bone length in the same trajectory. Scan settings involved a slice thickness of 2.0 mm with a 0.5 mm voxel size. Scan analysis applied thresholds of 180 mg/cm$^3$ for trabecular scans and 280 mg/cm$^3$ for cortical scans. A secondary measurement was performed if participants accidently moved during the scan. Total scan time was approximately 15 minutes. As with the DXA, a phantom was used to calibrate the pQCT device each morning ahead of measurements and all measurements were performed on the same machine by 1 out of 3 research nurses. Reported CVs for the pQCT are 0.3% for cortical density and 1.6% for trabecular density.\footnote{126}

**Actigraph GT3X+**

Objective measures of physical activity were used and analyzed across all four studies included in this thesis, although it was also the main focus of study I. These measurements were obtained with the Actigraph GT3X+ (Actigraph, Pensacola, FL, USA) and analyzed using the Actilife software version 6.11.2 (Actigraph). The Actigraph GT3X+ is a portable accelerometer, 4.6 × 3.3 × 1.5 cm in size, capable of measuring accelerations in the dynamic range of ±6 G in the following three dimensions; the vertical (y), the mediolateral (x) and the anterior-posterior axes (z). This accelerometer uses micro-electro-mechanical technology to convert the mechanical signals into electrical signals. Captured acceleration signals are stored on a resilient flash drive and are subsequently filtered using a standard proprietary algorithm in order to eliminate potential accelerations outside the human spectrum.\footnote{127} Finally, accelerations are summarized into "counts" which are used when analyzing and describing different aspects of accelerometer-based physical activity and sedentary data. More information regarding technical specifications are available at: www.actigraphcorp.com.

Participants in all four included studies were instructed to wear the Actigraph GT3X+ at the non-dominant hip for seven days and to remove it only for water-based activities and bedtime. Participants were further instructed to maintain their current lifestyle in order to provide a representative sample of their normal physical activity. If they reported having forgotten to wear the device, or if the device for some reason had malfunctioned, a second measurement period was offered. All activity data were collected in 30 Hz, transformed into epoch lengths of 60 s, and processed through wear-time validation protocols using the Actilife software. Non-wear time was defined as ≥ 60 min of consecutive zero activity
with a total tolerance of 2 minutes of activity spikes above this threshold. This definition facilitated the exclusion of sleep times from the analyses. In studies III and IV, measurements were also excluded if participants had worn the accelerometer for less than 4 days and less than 10 hours per day.

Figure 4. Example of accelerometer data output from the Actigraph GT3X+. Yellow lines represent activity intensities, such as vigorous (top line), moderate (middle line) and light (bottom line) physical activity. The green lines represent activity in the medio-lateral axis (x) and the blue lines represent activity in the vertical axis (y). The anterior-posterior axis (z) is not shown in this example.

Activity intensity and non-activity were classified according to Freedson et al. and thus divided into the following cutoffs based on counts per minute (CPM): sedentary (1-99 cpm), light (100-1951 cpm), moderate (1952-5724 cpm) and vigorous (25725 cpm). These cutoffs have been previously determined in participants introduced to exercise protocols on a motorized treadmill while measuring direct oxygen consumption. Light activity equals to 1.1-2.9 metabolic equivalents (METS) and may relate to daytime activities such as slow walking, working at a desk or low-intensity household duties. Moderate activity equals to 3-5.9 METS and is generally represented by brisk walking, gardening or bicycling. Vigorous activity equals to ≥ 6 METS and may contain directed exercise efforts such as jogging and aerobics, as well as strenuous gardening with a markedly increased heart rate.

Study I also investigated peak axial accelerations, defined as the maximum number of activity counts achieved in x, y or z axes during one minute throughout the whole measurement period. The results of studies II and III were adjusted for total physical activity by combining the total number of counts.

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* Note: The description of wear-time validation in study paper I, section 2.4 - Assessment of physical activity should read “Periods ≥ 60 min characterized by zero activity were marked as non-wear time...” Similarly, the description in study paper II, Assessment of physical activity section should read “… define nonwear time as periods ≥ 60 minutes at 0 CPM...”

of all three axes. The results of study IV were adjusted for moderate-to-vigorous physical activity per day.

**Fall assessment**

Studies II-IV investigated prospective falls as the primary outcome. Participants’ fall histories were collected during the examination and prospective falls were collected in the cohort during follow-up 6 and 12 months after the examination. The participants were contacted by telephone, where a research nurse asked them the following question: “Have you experienced a fall on the same level during the past six months?” To qualify, falls had to be low-energy events where the participants unexpectedly came to rest on the ground by themselves. Thus, falls from e.g. higher levels such as from standing on top of a chair, or related to external influence, such as bicycle accidents, were not recorded.

**GAITRite**

Objective measures of gait patterns were the main study focus of study II. Temporal and spatial gait parameters were collected using the GAITRite walkway system (CIR Systems, Sparta, NJ, USA). This electronic walkway contains pressure-activated sensors situated 1.27 cm apart, which directly measures the timing and two-dimensional geometric positions of footfalls. These measures are subsequently used to calculate gait parameters such as step velocity, step length and potential asymmetries between left and right sides.\textsuperscript{131}

![Figure 5. The 8.6-meter-long GAITRite Walkway System used in the HAI study.](image)

Study II was performed on an 8.6 m long, and 0.88 m wide walkway, collecting gait data with a scan rate of 120 Hz. Participants were asked to remove footwear
and start 1 m ahead of the walkway in order to avoid acceleration effects. Each participant performed a total of three progressively challenging walk trials. The first trial consisted of walking at normal speed. In the second trial, they were instructed to walk as fast as possible while still maintaining control. The third trial introduced dual-tasking, as participants walked with normal speed and simultaneously counted backward from 100 in decrements of 1.

The investigated gait parameters are detailed in the GAITRite technical manual\(^1\) and shortly outlined in Table 1. The GAITRite software application (GAITRite version 3.8E) calculated means and standard deviations of these parameters for each trial. Subsequently, CVs were manually calculated by dividing the standard deviation with the mean and multiplying by 100, in order to obtain gait variability percentages.

Table 1. Description of gait parameters investigated in study II.

<table>
<thead>
<tr>
<th>Gait variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spatial Definitions</strong></td>
<td></td>
</tr>
<tr>
<td>Step Width (cm)(^2)</td>
<td>Measured from the midpoint of the current footprint to the midpoint of the previous footprint of the opposite foot.</td>
</tr>
<tr>
<td>Stride Width (cm)</td>
<td>Measured from the midpoint of one footprint to the progression line formed by two consecutive footfalls of the opposite foot.</td>
</tr>
<tr>
<td>Step Length (cm)</td>
<td>Measured from the heel center of the current footprint to the heel center of the previous footprint of the opposite foot.</td>
</tr>
<tr>
<td>Stride Length (cm)</td>
<td>Measured as the line of progression between heel points of two consecutive footfalls of the same foot.</td>
</tr>
<tr>
<td><strong>Temporal Definitions</strong></td>
<td></td>
</tr>
<tr>
<td>Step Time (sec)</td>
<td>Measured as the time passed from first contact from one footfall to the first contact of the opposite foot.</td>
</tr>
<tr>
<td>Stance Time (sec)</td>
<td>Measured as the time between initiation of heel contact and toe-off of the same foot.</td>
</tr>
<tr>
<td>Stride Time (sec)</td>
<td>Measured as the time passed between the first contacts of two consecutive footfalls of the same foot.</td>
</tr>
<tr>
<td>Stride Velocity (cm/sec)</td>
<td>Acquired by dividing Stride Length by Stride Time.</td>
</tr>
<tr>
<td>Swing Time (sec)</td>
<td>Measured as the time passed between floor contacts, between toe-off and heel contact for the same foot.</td>
</tr>
<tr>
<td>Double Support Time (sec)</td>
<td>Measured as the total summarized time of two occurrences when both feet are in contact with the floor during a complete gait cycle.</td>
</tr>
</tbody>
</table>

\(^1\) In study paper II, descriptions of gait parameters are referenced to Hollman et al. 2011. However, they described the step width parameter differently. In our study, the correct definitions are given here in table 1, in accordance with how gait parameters are described in the GAITRite Technical Manual.
**Force plate device**

Studies III and IV investigated objective measures of postural stability, involving assessment of COP sway lengths and LOS using a force plate device (Wii, Nintendo, Kyoto, Japan). This force plate contains four vertical force sensors capable of delivering COP-derived data at ~60 Hz. The equipment was linked to a personal computer via Bluetooth connection ‘E1310E(00***)’ using drivers identified as ‘Manage Library for Nintendo’s Wiimote v1.7.00 by Brian Peek’. Data were obtained by custom-written software labeled “Balans-test”, programmed in Visual Studio by Göran Westling, Umeå University, Department of Integrative Medical Biology. The software sampled the data at 100 Hz after interpolation and force signals were exported to MATLAB R2014b (Mathworks, Inc, Natick, MA, USA). Data were finally filtered using a 3rd degree 10 Hz Butterworth filter and down-sampled to 20 Hz.

The measurement procedure was initiated by LOS assessment with each participant positioned in a stationary stance on the force plate device. They were instructed to lean as far away as possible from the initial static postural position, performing a circular motion during 60 seconds while holding onto provided hand grips. Feedback was provided on a front-placed monitor, displaying a visual representation of their functional LOS during the whole procedure. Participants were instructed to only use ankle joint motions when leaning and avoid hip involvement. Measurements were repeated if participants stepped in any direction, used hip strategies for leaning or generally did not follow the instructions. With LOS assessment complete, each participant performed a total of two static balance trials of 60 s each; one with EO condition and one with EC condition. Measurements were performed in a quiet stance where participants were instructed to stand upright, relax and maintain forward vision while avoiding any body movements. Measurements were repeated if instructions were not followed. Study III investigated total postural sway length (cm), while study IV investigated postural sway area (cm²), minimal distance between sway area and LOS border (MDLOS, centimeters) and the ratio between sway area and LOS polygons (SALOS, 0-100). Figure 6 illustrates how the parameters in study IV were calculated.
Figure 6. Illustration of investigated postural stability parameters. The red polygon represents the participant’s postural sway area, the geometric form produced by the total COP sway length. The blue polygon encompasses the participant’s functional limit of stability and the green, dotted line represents the location and length of the minimal distance between sway area and stability limits. The ratio between the red and blue polygons are additionally calculated. The light-blue lines represent the participant’s COP excursion when attempting to establish their LOS.

**Measurements of muscle strength and physical function**

Studies III and IV additionally included measurements of muscle strength and physical function. Handgrip strength was assessed using a hydraulic hand dynamometer (Jamar; Patterson Medical, Warrenville, IL, USA). This is a relatively safe and common way to measure muscle strength in epidemiological studies involving older adults and participants with chronic diseases. Handgrip measurements of muscle strength are also known to correlate strongly with lower extremity strength. Participants were instructed to hold the hand dynamometer in their non-dominant hand and keep the elbow in proximity to the waist in a 90° angle. They performed two consecutive attempts at pressing the dynamometer with maximal effort, whereas the highest score was recorded and used in further analyses.

Physical function was assessed with the Timed-Up-and-Go (TUG) test, commonly used in clinical practice to examine leg strength, gait ability and overall mobility in patients. In this test, each participant was asked to rise unaided from an armchair and walk forward 3 meters until he or she reached a line marked on the floor, then to turn around and return to a seated position in
the chair. Research nurses provided instructions and measured total testing time using a stopwatch.

**IPAQ-SF questionnaire**

In study I, participants also completed the International Physical Activity Questionnaire Short Form (IPAQ-SF). This instrument asks individuals to appraise the duration of their physical activities relative to different intensity levels (walking, moderate- and vigorous intensity) during the past seven days. The estimated duration and intensity should be connected to activities in the following domains: 1) leisure time activity, 2) gardening and domestic activities, 3) work-related activity and 4) transport-related activity. Responses are subsequently recoded into MET-minutes data in accordance with IPAQ guidelines.133

**MMSE**

Studies II-IV investigated cognitive function as a covariate using the Mini-Mental State Examination (MMSE).134 In this test, participants are asked to solve different tasks and answer various questions related to six cognitive domains. The MMSE is practical to use within the clinical context and takes approximately 5-10 minutes to administer. Individual scores for each section of the test are summarized and the maximum score is 30.

**Additional covariates**

 Anthropometric data across all the studies were obtained using a gauge (Holtain Limited; Crymych, Dyfed, UK) for height measurements and a scale (HL 120; Avery Berkel, Fairmont, MN, USA) for weight measurements. Body Mass Index (BMI) was calculated as weight divided by height squared. Additionally, study II included information on participants’ educational levels, accessed from the Statistics Sweden Database.

**Statistical analysis**

All studies presented descriptive data using means and standard deviations (M ± SDs). Group comparisons, such as differences between men and women and fallers and non-fallers, were investigated using the student’s t-test. Categorical variables were analyzed using Pearson’s chi-square test. Study I performed a sensitivity analysis using Pearson’s correlation coefficients (r), when comparing different measures of physical activity. Study III additionally investigated the test-retest reliability of objective postural sway measurements, using a two-way mixed effects model including reporting of intraclass coefficients (ICC 3,1).
Multiple linear regression models were used in study I to investigate how objective and self-reported physical activity independently predicted parameters of bone. These models were adjusted for sex, height and weight, and potential associations were presented as standardized $\beta$-coefficients. Studies II-IV all used multiple logistic regression models to investigate various independent predictors of incident falls. These models were adjusted for a rich set of covariates including: objective measures of physical activity, muscle strength, educational level, cognitive function, physical function, disease history, smoking and previous falls. Prediction of incident falls were presented as odds ratios (ORs) with 95% confidence intervals (95% CIs).

In study I, all analyses were performed with SPSS version 22.0 (IBM, Armonk, NY, USA). In studies II-IV, all analyses were performed with Stata version 13.1 (StataCorp, College Station, TX, USA).
Results

Presented here are the key findings of studies I-IV. Please see each individual paper, attached at the end of this thesis, for more in-depth information regarding the results.

Results of study I

This study investigated how accelerometer-derived physical activity independently predicted various parameters of bone. Of the initial 1227 participants, 1197 completed seven days of accelerometer measurements with a mean accelerometer wear time of 5719 ± 871 min, roughly 13 hours per day. The other 30 participants were excluded from all analyses due to device malfunction, or because they had forgotten to wear the device. Men and women differed in the majority of objective physical activity measurements; men showed significantly higher accelerometer values as compared to women (p ≤ 0.05 for all), except for moderate activity intensity and medio-lateral and anterior-posterior peak acceleration. For pQCT analyses, a total of 36 participants were excluded primarily due to metal artifacts from fracture treatment. All measured bone parameters were significantly lower in women (p ≤ 0.001 for all).

The multiple linear regression models revealed the following results:

- Vigorous physical activity showed the strongest association with femoral neck aBMD only (β = 0.09, p ≤ 0.001).
- Both moderate and vigorous physical activity showed positive associations to cortical area (β = 0.07, p ≤ 0.001) and trabecular vBMD (β = 0.06, p ≤ 0.001) in the tibia.
- Vertical peak accelerations were positively associated to cortical area and trabecular vBMD parameters in the tibia (β = 0.09 for both, p ≤ 0.001 for both). Associations with these bone parameters were weaker when investigating medio-lateral peak accelerations (β = 0.07 for both, p ≤ 0.05 for both), and they were non-significant when investigating anterior-posterior peak accelerations.

Results of study II

This study primarily investigated whether variability in gait patterns independently predicted incident falls, and secondarily, if this is related to differences in fall rates between men and women. Of the original 1421 participants, 1390 completed all three gait trials, and common dropout reasons
were 1) use of walking aid, 2) weight <50 kg, and 3) severe instability. At the time of this study, 1350 participants had been followed up 6 or 12 months after the examination, and 148 of these (11%) reported at least one incident fall. There was a total of 88 women and 60 men ($p = 0.01$) among these fallers. Total physical activity did not differ significantly between men and women.

Women predominantly expressed higher CVs compared to men during all tests, a pattern that was more pronounced as trials progressed to become more challenging. To exemplify, all gait variability parameters were significantly higher in women than in men during dual task trials ($p < 0.01$ for all). Similarly, fallers showed higher gait variability than non-fallers in 8 out of 10 gait parameters ($p < 0.05$ for all) during dual task trials. Results from analyses on each separate gait parameter are detailed in study paper II, table 2 and table 3.

Results from the multiple logistic regression models revealed the following:

- The unadjusted model showed that women were 58% more likely to experience a fall compared to men (OR 1.58, 95% CI 1.12 – 2.23)
- Adjusting for multiple covariates, including educational level, physical activity, smoking, disease history and cognitive function did not significantly attenuate this increased risk.
- Each SD increase in total physical activity reduced the risk of falling by 30% (OR 0.70, 95% CI 0.56 – 0.87), although this risk reduction was non-significant in the final model.
- Adjusting for gait variability, such as step width CV, in the final model resulted in women no longer showing a significantly higher risk of falling compared to men.

**Results of study III**

This study investigated how objective measures of postural sway independently predict incident falls. Complete data on postural sway and prospective falls were available for 1877 participants, and 255 of these (~14%) reported having fallen at least once between the examination and follow-up. Fallers were more often women (54.5%, $p = 0.046$), had lower muscle strength ($p = 0.002$) and performed more poorly in the TUG test ($p = 0.002$). Fallers showed a 10% increase ($p = 0.003$) in postural sway during EO trials, and 14% increase ($p = 0.005$) during EC trials, as compared to non-fallers. EO trials revealed a more non-linear distribution of falls over different quintiles of postural sway, compared to EC trials, as shown in figure 1 in study paper III.

These quintiles were subsequently added and analyzed in multiple logistic regression analyses, revealing the following:
• EO-trial participants with postural sway in the 5th quintile, roughly above 400 mm, showed 90% increased risk of falling (Crude OR 1.90, 95% CI 1.27-2.84) compared to participants in the 1st quintile.
• This risk remained significantly elevated after adjusting for sex, weight, history of falls, smoking and cardiovascular disease, cognitive function, objective physical activity, muscle strength and TUG test performance (OR 1.75, 95% CI 1.09-2.79).
• Analyzing EC trials resulted in similar odds ratios. Postural sway in the 5th quintile, roughly 920 mm, increased the risk of incident falls by 65% (OR 1.65, 95% CI 1.07-2.55) in the unadjusted model and by 90% (OR 1.90, 95% CI 1.12-3.22) in the fully adjusted model.
• Sensitivity analyses revealed that the test-retest reliability for the force plate equipment was moderate for EO trials (ICC3,1 = 0.60) and excellent for EC trials (ICC3,1 = 0.94).

Results of study IV
This study examined how functional LOS influenced the relationship between postural sway and incident falls, including 2396 participants with complete data for these measures. In total, 337 participants (14.1%) reported having fallen when followed up 6 and 12 months after the examination. Additionally, 20.3% of these had also previously reported a history of falls prior to the baseline examination. Incident falls were more common in women (p = 0.033), and fallers had higher BMI (p = 0.006), lower muscle strength (p = 0.001) and worse TUG test performance (p = 0.002). Results from the EO trials revealed that fallers had 23% increased sway area (p = 0.007), 4% lower MDLOS (p = 0.011) and 34% increased SALOS ratio (p < 0.001). Similar results were seen when analyzing the EC trials. Integrated postural sway and LOS parameters were subsequently analyzed in multiple logistic regression models.

• In EO trials, the odds for a fall increased by 6% per each cm² increase in sway area (OR 1.06, 95% CI 1.02-1.11) and by 16% per 1-unit increase in SALOS ratio (OR 1.16, 95% CI 1.07-1.25), as seen in the unadjusted model. Additionally, each cm increase in MDLOS decreased the risk of falling by 10% (OR 0.90, 95% CI 0.83-0.97).
• The odds ratios where slightly attenuated for sway area and SALOS ratio in the fully adjusted model, while MDLOS no longer predicted incident falls. When analyzing EC trials, investigated parameters predicted incident falls slightly weaker than in the EO trials.
• While investigated as a covariate in fully adjusted models, having fallen in the 12 months prior to baseline examination was the strongest predictor of incident falls (ORs 2.23 – 2.24, p < 0.001 for all).
Discussion

The proportions of older individuals are on the rise globally, and it is thus plausible to assume that there will be an increase in age-related disabling trauma such as fragility fractures. Improved prediction and prevention of these events will be of utmost importance to avert individual suffering and reduce future burden on already hard-pressed healthcare systems. Although increased fracture risks have traditionally been linked to low BMD, it has been shown that a T-score of -2.5, and thus osteoporosis, explains less than 50% of fracture incidences. Moreover, the majority of fractures among older adults occur as a result of falls. This thesis provides additional insights into risk factors for falls, such as how differences in gait variability can partly explain women’s increased risk of falling compared to men, and how population-based objective data on postural stability can predict prospective fall risk.

Preventing fractures: targeting bone loss and falls

Low bone mass and increased fall risk constitute two of the primary risk factors for fractures in older adults, and there is an important relationship between these to consider. The bone mass in our skeleton is the composite material required to be solid enough to withstand potential mechanical forces without breaking. It is thus natural to assume that high BMD equals lower risk of fracture, as confirmed by several longitudinal prospective studies. Clinical trials have shown promising results in improving BMD and reducing fracture risk using pharmaceutical interventions such as bisphosphonates, while studies focusing primarily on exercise and physical activity reveal a statistically significant, although relatively small relationship with BMD. These findings are supported by the results of study I, where objective measures of physical activity were significantly associated with parameters of bone in the weight-bearing skeleton, although at best only explaining 0.8% of the variability in bone properties.

Parallel to bone mass in the fracture cause spectrum, falling represent the dynamic event where the properties of the bone material are exposed to potentially hazardous mechanical forces, ultimately breaking and resulting in a fracture. This is especially true for hip fractures, which in more than 90% of cases are caused by falls. While the effects of exercise and physical activity on bone parameters in older adults are modest at best, it may be more advantageous to instead target falls using similar interventions. Randomized controlled trials that greatly challenge the balance ability of participants and include a high total amount of exercise, have in this regard reported a 40% reduction in fall rates, thus introducing a promising prospect in fall and fracture
Ultimately, fracture prevention efforts would likely benefit the most from a holistic approach, e.g. screening for low bone mass with eventual pharmaceutical intervention, and parallel quantification of fall risk followed by adequate intervention forms, such as physical exercise. One such effort is the comprehensive geriatric assessment (CGA), which is a multidimensional diagnostic process that geriatric clinics use to determine the frailty of an older individual. This assessment considers the medical, psychological and physical conditions of the individual, including identification of fall risk and osteoporosis, which in the end results in a multidisciplinary intervention effort. Researchers have shown that implementation of CGA increases the likeliness that older individuals will be able to live independently in their own homes by 25%, while it also reduces mortality by 24%.141

Differences in fall risk between women and men

This thesis focused primarily on investigating risk factors for falls, one of these being differences in fall rates between older women and men. Several studies have reported that women are more prone to falling than men, findings that are confirmed by study II, where unadjusted analyses showed that fall risk was increased by 58% in women. It has been reported that these sex differences in fall risk gradually even out during the later stages of life, since the frequency of falls progressively increase more among men when they reach a very old age.144 Subsequent reports have also indicated a difference in fall localization between men and women, as men tend to experience more outdoor falls and women on the other hand experience more indoor falls.66,67,145 However, there has been no general consensus on the specific mechanisms underlying women’s increased fall risk. In this regard, study II revealed increased gait variability in women compared to men, progressively increasing from between 10-15% in fast speed trials to 15-35% in dual-task trials. We suggest that this higher gait variability could contribute to the higher risk of falls in women than in men, and thus potentially also to women’s higher prevalence of fractures. These novel findings are partly supported by the results of other studies, where fallers showed increased gait variability during dual-task protocols.104,146 Additionally a recent study reported that executive functions decrease more in women than in men with increasing age, lending some explanation to the results of study II.147

Study IV partly examined potential differences in postural stability between men and women, and similar to study II, also reported an increased risk of falls among women. However, men showed a larger sway area and an increased Sₘ/LOS ratio compared to women during the EC trial, a finding that can be interpreted as reduced postural control. While this discovery is in line with the results of other studies,83,148 it is also a contrasting finding since fall risk was found to be increased among women in study IV. As such, the sex differences in
postural stability found in study IV did not directly translate into an increased risk of falls. One possible explanation is the lack of a cognitive dual-task regimen in postural stability testing protocols, similar to what was performed during gait measurements in study II. It has also been reported previously that increased body sway relates to increased fall risk only in men, but not in women, suggesting the existence of different sex-specific mechanisms that mediates the relationship between falls and postural stability.149 Interestingly, we found directly contrasting results in a post-hoc analysis stratified by sex from the data sample in study IV, where increased sway area and SLOS ratio were related to increased fall risk in women only (data not shown). The higher age range and smaller sample size in the other study might offer some explanation to these disparities, although further studies are warranted to examine this relationship more thoroughly.

**Postural stability parameters as predictors of incident falls**

The results of studies III and IV indicate that several measures of postural stability are viable in predicting future falls. To exemplify, having a total postural sway length greater than 400 mm during EO trials and 920 mm during EC trials resulted in a 75-90% higher fall risk, while each cm² increase in postural sway area incrementally increased the risk of falling by 4-6%. Although these parameters are strongly related, they employ different characteristics, as sway length is calculated by the total COP excursion and sway area is the resulting geometrical form encompassing the zone in which these excursions occur. Both parameters have merits, as the sway length cutoffs presented in study III could have clinical value in predicting fall risk, and the sway area in study IV forms the basis of comparing ratios between postural sway and LOS. Nonetheless, this thesis shows that static balance testing is viable in fall predictions, even though most falls likely occur during dynamic situations.65

Determining postural stability while progressing through conditions of normal vision to no vision challenges participants to maintain postural control while relying less on visual input, an important segment in the sensorimotor system.72 Potentially, this could reveal dysfunctions in balance and enhance the identification of individuals at risk for falling, although this could not be concluded in either study III or IV. However, there was a clear difference between EO and EC trials in fall distribution over different quintiles of postural sway, as visualized in figure 1 in study III. This suggests a non-linear relationship between postural sway and fall risk during EO status, although the underlying reasons for this nonlinearity is unknown and needs further elucidation. The sudden increase in fall rates in the fifth quintile, corresponding to >400 mm in COP sway length, provides a basis for further investigations into clinical utility of postural sway cutoffs. Examining postural stability during EO
conditions is relevant since falls are likely to happen in everyday situations where individuals keep their eyes open. Although a counter-argument could be that many falls occur indoors during evenings or nighttime due to inadequate vision,\textsuperscript{150} thus strengthening the rationale for postural stability measurements during no-vision conditions. Additionally, it has been reported that EC trials have improved ability to detect individuals with risk for multiple falls.\textsuperscript{151} It has also been shown that aspects of impaired vision, such as decreased depth perception, independently predict the risk of future falls, emphasizing the importance of an adequate eyesight.\textsuperscript{152} However, there were no indication that elimination of visual input significantly influenced the relationship between postural stability and fall risk in either studies III or IV.

Study IV evaluated integrated postural sway and LOS parameters such as minimal distances between sway area and LOS boundaries, as well as the ratio between sway area and the LOS area. While some of these parameters have seen some previous research attention, there may be methodological issues in LOS assessment to consider, and previous research has not included clinical outcomes, such as incident falls.\textsuperscript{94,95} The rationale behind the examination in study IV was to holistically approach postural stability assessment and broaden the scope beyond traditional measures such as COP sway length. All parameters predicted falls in unadjusted models, and the majority of associations were only slightly attenuated in fully adjusted models, including covariates such as muscle strength, physical activity and cognitive function. This indicates that examination of postural sway in relation to functional stability limits provides valid measures of fall prediction. Interestingly, the integrated \textit{sa LOS} ratio measure showed a tendency towards stronger fall risk prediction in comparison to sway area, producing crude odds ratios from EO trials of 1.16 and 1.06 respectively, although this potential difference could not be statistically confirmed. As such, future studies should evaluate if there is any additional benefit in fall risk prediction when employing postural sway directly in relation to functional stability limits.

**Physical activity in bone maintenance and fall risk reduction**

The aforementioned modest associations between measures of physical activity and parameters of bone reported in study I are consistent with other studies on older adults,\textsuperscript{44,45} despite evidence pointing to physical load as a determinant in bone mass remodeling.\textsuperscript{34} In line with these results, it has been suggested that habitual physical activity levels among older individuals do not generate enough mechanical force,\textsuperscript{153} and may thus be generally insufficient in producing clinically relevant effects on bone properties. Others have argued that the adaptability of bone to mechanical load may be impaired by age-related factors, such as women's menopause, hence resulting in a reduced osteogenic
response. Furthermore, ageing might generally lead to an attenuated ability of bone tissue to sense mechanical strain, which is the proposed role of osteocytes.\textsuperscript{154} As is the case with many other cell types, the number of osteocytes decrease with age through apoptosis,\textsuperscript{155} which might progressively inhibit the capacity of bone tissue to sense mechanical strain and produce an adequate physiological response through bone remodeling. Studies that do find positive effects of physical training on BMD in older adults tend to generally involve high-impact exercises, in an attempt to produce adequate levels of mechanical load.\textsuperscript{38} Such an approach is supported by the findings of study I, where peak accelerations, particularly in the vertical plane, showed some of the strongest associations with measured bone parameters.

In a recent meta-analysis, it was revealed that individuals with high levels of physical activity had a 29\% lower risk for any fracture compared to individuals with very low activity.\textsuperscript{156} Following the previous argumentation, it is plausible to assume that this relationship is affected by other underlying factors besides modest improvements on bone properties. In this regard, increasing physical activity and exercise in older populations has the potential to prevent falls, a relationship which could partly be driven by influences on postural stability and gait control.\textsuperscript{112,115,140} This is supported by the findings of study II, where each SD increase in physical activity lowered the risk of falls by approximately 30\% in partially adjusted regression models. This association was attenuated in the fully adjusted model, lending some credibility to the aforementioned notion that gait parameters may influence the relationship between physical activity and falls.

While habitual physical activity produces many known health benefits, it should also be noted that the connection to fall risk is complex. It has been reported that increasing levels of physical activity may lead to greater fall exposure in older individuals, and the outcome may vary depending on factors such as age, if the individual's initial activity level is very low and the eventual existence of mobility limitations.\textsuperscript{113,114,157} This complexity indicates the need for further studies including a broad perspective on mediating factors, and to exercise caution when generally recommending physical activity to individuals with potentially increased fall risk.

**Methodological considerations**

The methodological focus of this thesis has involved the examination of objective measurements in relation to prospective falls and associations to parameters of bone. While there are many advantages to using objective assessments and to follow-up on future falls, several considerations should also be addressed.
Study II reported a prospective fall rate of 11%, a fall rate that later increased to 14% in studies III-IV, which is lower compared to what other studies have reported for older adults. One possible reason for this disparity is the follow-up periods of 6 and 12 months used in the current studies, potentially leading to difficulties in fall recollection for some participants. Studies using similar follow-up times have also reported similar fall rates, while these have been reportedly higher when closer intervals have been implemented. Of course, the relatively low fall rate compared to other investigations in geriatric populations may also originate from the homogenous age range of participants included in the HAI study. Other studies with a wider age spread may detect an increased fall risk due to including considerably older individuals, since it is well known that fall risk increase with age. The 70-year-old individuals included in the HAI study might be considered as “young” and relatively healthy among senior citizens, supported by the fact that they were community-dwelling and relatively physically active. Nonetheless, studies II-IV were clearly able to discriminate fallers from non-fallers using objective measures of gait and postural stability.

While the participation rate of 84% is high, it is difficult to conclude whether there were any differences in health status between those who participated and those who chose not to. Furthermore, some individuals lacked contact information and thus did not receive any invitation to the HAI study. Unfortunately, no analysis of non-response has been performed, which could have provided important information on the generalizability of results. Our current belief, however, is that the sample investigated in the HAI study is fairly representative of people aged 65 to 75 in the Umeå municipality, although this is speculative.

Studies II-IV presents some of the largest datasets on gait variability and postural stability to date. This provided ample opportunity to investigate these parameters in relation to fall risk and perform analyses stratified by sex. There are many advantages to objectively quantify gait and postural sway, such as the avoidance of subjective scoring systems and crude determinations of individual balance ability. Objective instruments benefit from investigation of test-retest reliability, and should preferably include homogenous groups to reduce confounding effects from factors such as wide age ranges. In light of this, study III involved sensitivity analyses of the force plate device, showing a moderate and excellent test-retest reliability for EO and EC conditions, respectively. However, it has also been suggested that objective instruments examining postural stability needs further evaluation for clinical utility, preferably by including prospective follow-up on outcomes, as was done in studies III-IV. It should also be acknowledged that common clinical tests, like the TUG-test, SPPB and Berg Balance Scale are less expensive compared to
electronic walkway and force platform instruments, while still providing prediction of fall risk to some extent.\textsuperscript{161,162} Further studies are thus needed, in order to evaluate whether there are any advantages to using objective measures in fall prediction over common clinical tests and fall risk assessment tools.\textsuperscript{163}

Another important challenge to overcome in objective postural stability assessment is how to determine an individual’s “true” stability limit, as this methodological issue will impact fall risk prediction. It has been suggested that an individual’s functional LOS is likely smaller than the theoretical maximum stability boundary, limited by factors such as joint mobility and muscle strength.\textsuperscript{88} Study IV attempted to facilitate this by letting participants use provided hand grips and thus potentially lean closer to their “true” stability limit, although joint-muscular limitations and fear of falling could still have influenced the results.

Study IV also revealed that participants with falls reported prior to baseline examination were more than twice as likely to report a new fall during follow-up, compared to participants with no fall history. This intriguing finding is supported by other studies,\textsuperscript{164,165} and indicates the importance of also involving simpler methods in fall risk assessment besides objective measurements. However, it should be noted that parallel analysis of retrospective and prospective fall data might be subject to recollection bias, as participants with multiple falls may experience difficulty in separating when the events actually occurred.\textsuperscript{166} Furthermore, far from all participants report a history of falling, while they could still be at risk due to eventual impaired postural stability or gait variability. As such, objective measures and fall history assessment would likely complement each other well and provide increased precision when determining fall risk.

To some extent, the primary results of study III and IV might be subject to “first trial” effects, since participants only performed one postural stability trial for each condition. It has been reported that participants become habituated when performing repeated measurements, which leads to reduced test-retest variability.\textsuperscript{167} On the other hand, falls are often in reality unexpected events, so it can be argued that measuring postural stability in unprepared participants during the initial trial reflects natural conditions.

The multiple logistic regression models in studies II-IV were adjusted for several covariates, including objective measures of physical activity, assessment of cognitive function, and both previous and prevalent diseases such as cardiovascular disease and diabetes. However, no information on musculoskeletal conditions or neurological deficits were available. These circumstances are known to increase fall risk and could have provided
important data for fall risk prediction. Furthermore, no information was available for medicine use besides antihypertensive medication and statins, and it has previously been shown that psychotropic agents such as antidepressive medicine may increase fall risk. Alas, there are several factors that were not controlled for in this thesis, factors that could have possibly enhanced the explanation why older people fall and potentially sustain fractures.

The objectively determined physical activity intensities used in this thesis were based on cut points established by Freedson et al., with a ≥1952 CPM threshold for MVPA. These are some of the most commonly used cut points in physical activity research, thus enabling comparison between the findings of this thesis and a majority of the existing literature. However, these cut points were originally validated in younger adults, while the capacity for physical activity might be different in older individuals, potentially warranting lower thresholds when establishing MVPA. In a recent systematic review, it was established that the Freedson cut point is valid in older adults who are likely to attain the recommended 30 min of physical activity per day. Using the Freedson cut point, it was shown in study IV that 66% of participants reached the WHO cut point of 150 min MVPA per week. Study I additionally presented data that the participants of HAI were more physically active compared to age-matched individuals in the U.S. This taken together with the earlier discussion on the health status of HAI study participants may indicate that the Freedson cut points are viable in this cohort of 70-year-olds. Furthermore, using cut points established for older adults by Copeland and Esliger resulted in >80% of participants meeting the 30 min of MVPA per day criteria, while using Freedson cut points, the corresponding number was roughly 40% (data not shown). It has been previously discussed that using either too low or too high cut point thresholds may over- or underestimate how many individuals that actually reach sufficient physical activity levels. Additionally, studies II and IV used non-threshold parameters for the objective physical activity parameters and instead assessed the total accelerations of all three axes, thus completely avoiding this potential issue.

To summarize, this thesis investigated risk factors of falls and fractures in a large-population based cohort of older individuals aged 70 years. This examination was enabled by the use of direct measurements, objective risk quantification, and by following up on falls prospectively. Additionally, several risk factors were included and considered, from both objective measurements and traditional clinical tests, enabling statistical analyses with adjustments for a rich set of covariates. The findings of this thesis should be expanded upon to further improve current methods of fall and fracture prediction, which could potentially improve preventive efforts in the ageing population.
Conclusions

Study I
This study revealed significant associations between primarily moderate to vigorous physical activity intensities and bone properties, after adjusting for height, weight and sex. Additionally, associations were stronger for peak accelerations in the vertical axis compared to the other axes. This indicates that older individuals require at least moderate physical activity in vertical directions, such as from activities involving jumping or light running, in order to produce impacts that influence their bone health positively.

Study II
This study showed increased gait variability among participants with incident falls compared to non-fallers, particularly during multitasking. Additionally, women similarly showed increased gait variability during dual-task trials as compared to men, and the increased fall risk among women could be partly explained by these differences in gait. The results identify older women as a particular risk-group for falls where interventions to improve gait and balance might be appropriate to reduce fall risk.

Study III
This study revealed that fall risk was increased by 75-90% in individuals with an objectively measured postural sway in the 5th quintile compared to the 1st quintile. The cut offs for this markedly increase in fall risk corresponded to 400 mm during EO trials and 920 mm during EC trials. The results indicate that postural sway, as measured by a force plate, is potentially clinically relevant in fall risk determination and that fall risk might increase non-linearly when maintaining EO status.

Study IV
This study indicates that the addition of LOS to postural sway measurements provides valid prediction of fall risk and broadens the perspective on determinants of postural stability. During EO trials, the ratio between COP area and LOS increased fall risk by 16% for each unit increase, while each cm² increase in sway area increased fall risk by 6%. These results were slightly weaker for EC trials and mildly attenuated when adjusting for multiple confounders. Further research is required to determine any potential benefit of integrating LOS and COP parameters for fall predictions.
Scientific contribution and future research

With regard to risk factors for falls and fractures, this thesis has expanded upon the current level of knowledge in the following ways: First, the included studies were all population-based and contained some of the largest datasets to date on gait patterns and postural stability. This, in addition to including prospective follow-up on falls, enabled objective quantification of fall risk and identified several independent risk factors to consider for future prevention efforts. Second, the sample size also enabled stratification by sex to examine underlying mechanisms as to why women experience more falls, and in the long run potentially more fractures, as compared to men. Novel findings have been presented in this regard, indicating that older women’s increased risk of falls compared to men is mediated by increased gait variability, particularly when multitasking. These findings present underlying factors that may be targeted in future intervention efforts to reduce women’s increased tendency to fall. Third, cutoffs for increased fall risk were identified by objective quantification of postural sway during normal vision may be of particular interest in this regard, where fall risk was considerably, and also nonlinearly, increased in the highest COP sway quintile. The identified cutoffs could be of potential value for clinicians when assessing fall risk in older adults. Fourth, statistical analyses included a rich set of covariates, including objective physical activity, cognitive ability, physical capacity, history of disease and previous falls. As such, the predictors of falls that were identified are independently determined and relatively robust in relation to other potential risk factors. This also enabled parallel fall risk quantification by several additional measures, which broadens the perspective and holistically provides a likely needed overview to understand the multiple aspects surrounding why individuals experience falls. Fifth, even though the associations between parameters of bone and physical activity were modest, these findings underline that habitual physical activity need to be of at least moderate intensity and preferably be performed in vertical directions to potentially decelerate bone loss in older adults.

The findings of this thesis enable new and potentially promising avenues of investigation for prevention research related to falls and fractures in older populations. Thus, it would be of interest to investigate whether interventions aimed towards improvements in balance and strength could decrease objectively quantified postural instability, and thus potentially reduce the associated fall risk. Furthermore, it would also be of value to further pursue the concept of dual-tasking in relation to gait and postural stability measurements, which potentially enhances the identification of individuals with or without increased fall risk. Interestingly, some studies have begun implementing the
concept of dual-tasking during exercise intervention programs in order to explore any additional benefits for older adults to simultaneously train cognitive and physical functions. Additionally, it would also be interesting to further explore the accuracy of fall risk predictions, by combining multiple risk factors together, both from objective and traditional measures, and to determine how much of the variance in fall rates that can be explained by the included elements. This knowledge could potentially benefit and further improve upon clinical interventions, such as the CGA for individuals with increased risk for falling. In line with this reasoning, it would be very valuable to analyze longitudinal data on bone parameters parallel to determinants of fall risk, together with associated risk factors and to follow up on fragility fractures. Not only would this potentially deepen our understanding as to how much each of these factors contribute in the fracture process, it would also provide clinicians with information on how to better prevent disability related to fractures in the increasingly older populations.
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The author in his preferred environment. Picture taken in September 2017 at the peak of Hamperokken, Tromsø, Norway.

Foto: Andreas Hult