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Gait speed, physical activity, cognitive function and dementia

Associations in cross-sectional and longitudinal studies and validity of a physical activity questionnaire in very old people

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To my little light

Table of Contents

Abstract

Dementia and cognitive impairment are leading causes of disability in older people (≥ 65 years) and gait speed decline seem to be an early indicator of these conditions, sometimes preceding clinical symptoms. Dementia may be delayed or prevented with management of risk factors, such as low physical activity. However, few studies have investigated associations of gait speed and physical activity with cognitive function and dementia in very old people (≥ 80 years) and a physical activity questionnaire adapted for use in this population is lacking. The overall aims of this thesis were to explore the associations of gait speed and physical activity to cognitive function and dementia in very old people, and to determine the validity of a novel self-reported physical activity questionnaire adapted for very old people (IPAQ-E 80+).

Associations of gait speed with dementia and cognitive function were investigated in a population based cohort of people aged ≥ 85 years, in cross-sectional (n=1317) and longitudinal (n=296) analyses. Gait speed was measured over 2.4 meters and cognitive function was measured with the Mini-Mental State Examination (MMSE). Associations of physical activity at baseline with dementia, cognitive function and gait speed were studied in a cohort of 541 people aged ≥ 80 years at the time of follow-up. Physical activity was measured using a six level questionnaire and categorized into low, medium and high. Cognitive function was measured with the MMSE and executive function with the Frontal Assessment Battery. ActivPAL accelerometers were used to assess the validity of IPAQ-E 80+ in 76 participants aged ≥ 80 years.

Cross-sectional linear regression analyses showed that gait speed was associated with cognitive function in very old people with and without dementia. An interaction analysis showed that walking aid use attenuated this association. Gait speed 5 years previously, and gait speed decline over 5 years were associated with dementia development in logistic regression analyses. During a two decade long follow-up, 175 (32.3%) developed dementia. Cox proportional-hazard models showed no association between physical activity around 65 years of age and subsequent dementia. In adjusted linear regression analyses, physical activity was not associated with cognitive function. Physical activity was associated with executive function in the unadjusted analysis but not after adjustments. Physical activity was associated with gait speed in unadjusted, but not analyses adjusted for traditional cardiovascular risk factors (hypertension, glucose intolerance, body mass index ≥ 30). IPAQ-E 80+ and accelerometer measures of total inactive time, night-time lying and sedentary times correlated fairly to substantially, according to Spearman's rho values. Bland-Altman plots showed that participants underreported total inactive and sedentary times. Correlations of

total active and walking time were moderate; sitting and moderate to vigorous walking and physical activity showed no correlation. The IPAQ-E 80+ showed low degrees of sensitivity and specificity for the accurate identification of participants (not) attaining the recommended physical activity level.

In conclusion, gait speed appears to be associated with cognitive function, and low or declining gait speed seems to be associated with increased odds of subsequent dementia development in very old people, among whom gait and cognitive impairments are common. Furthermore, declining gait speed seems to be associated with declining cognitive function among those who develop dementia. The present results support development of a gait speed screening index for predicting future cognitive decline, even among very old people. Walking aid use may influence the cognitive load and hence the association between gait speed and cognition. In this thesis, a low physical activity level in late middle to older age was not a risk factor for dementia development up to two decades later. The associations between physical activity and subsequent physical function seems to be mediated by traditional cardiovascular risk factors. The novel IPAQ-E 80+ may be a promising tool for studies of relationships between 24-hour physical activity patterns and health in this population.

Sammanfattning på svenska

Demens är en ledande orsak till funktionsnedsättning i hög ålder (60 år och över), och låg gånghastighet kan vara en tidig indikator på demenssjukdom som ibland uppträder före kliniska symtom på kognitiv nedsättning. Demens kan eventuellt fördröjas eller förhindras genom att minska antalet riskfaktorer, däribland fysisk aktivitet. Dock så har få av studierna av gånghastighet och fysisk aktivitet och dess samband med kognitiv funktion och demenssjukdom undersökt specifikt personer i väldigt hög ålder (80 år och över). Vidare så saknas det ett självskattningsformulär av fysisk aktivitet anpassat för personer i väldigt hög ålder. Målet med denna avhandling var att undersöka om gånghastighet och fysisk aktivitet är kopplade till demensutveckling och kognitiv funktion i väldigt hög ålder. Målet var också att studera hur väl ett nytt självskattningsformulär (IPAQ-E 80+) för fysisk aktivitet är anpassat för denna åldersgrupp.

Sambandet mellan gånghastighet och kognitiv funktion undersöktes i tvärsnitt bland 1317 deltagare, samt över fem års tid bland 296 deltagare, hos personer 85 år och över. Gånghastighet mättes över 2,4 meter och kognitiv funktion med Mini-Mental State Examination (MMSE). Sambandet mellan fysisk aktivitet och demens, kognitiv funktion, exekutiv funktion och gånghastighet upp till 20 år senare, undersöktes hos 541 personer 80 år och över. Fysisk aktivitet mättes med ett självskattningsformulär med sex svarsalternativ, som sedan grupperades i tre nivåer (låg, medel och hög). Kognitiv funktion och exekutiv funktion mättes med MMSE och Frontal Assessment Battery. Sjuttiosex deltagare 80 år och över deltog i studien som undersökte hur väl IPAQ-E 80+ var anpassat för personer i väldigt hög ålder. Deltagarna bar en aktivitetsmätare i en vecka varefter de fyllde i skattningsformuläret för samma tidsperiod.

Tvärsnittsanalyserna visade på ett samband mellan gånghastighet och kognition, både hos personer med och utan demens. Analyserna visade också att sambandet var svagare hos personer som använde gånghjälpmedel vid gångtestet. Både låg gånghastighet fem år tidigare, och sjunkande gånghastighet under fem år, uppvisade samband med demensutveckling. Under 20 års uppföljningstid utvecklade 175 (32.3%) av deltagarna demenssjukdom, men det fanns inget samband mellan demensutveckling och fysisk aktivitet runt 65 års ålder. Fysisk aktivitet visade ett samband med exekutiv funktion och gånghastighet i icke justerade analyser, men inte i analyser som justerade för störfaktorer. Sambandet mellan fysisk aktivitet och fysisk funktion, mätt via gånghastighet, påverkades av högt blodtryck, glukosintolerans och BMI ≥ 30. Deltagarnas självskattning via IPAQ-E 80+ visade en måttlig överensstämmelse med data från aktivitetsmätarna för total aktiv tid, inaktiv tid, tid i liggande under hela dygnet

och promenadtid. Självskattningsformuläret visade sig inte kunna identifiera huruvida deltagarna uppnådde rekommenderade nivåer av fysisk aktivitet.

Sammanfattningsvis uppvisar gånghastighet ett samband med kognitiv funktion hos personer i väldigt hög ålder i både ordinärt och särskilt boende. Låg och sjunkande gånghastighet över fem år verkar förknippat med högre risk att utveckla demens i väldigt hög ålder. Användande av gånghjälpmedel vid gångtest verkar försvaga sambandet mellan gånghastighet och kognition. Resultaten i denna avhandling fann inte stöd för låg fysisk aktivitet runt 65 års ålder som riskfaktor för demensutveckling upp till 20 år senare. Sambandet mellan fysisk aktivitet i och fysisk funktion mätt via gånghastighet i hög ålder verkar påverkas av traditionella kardiovaskulära riskfaktorer. Självskattningsformuläret IPAQ-E 80+ kan vara användbart när man studerar sambandet mellan fysisk aktivitet över hela dygnet och hälsa i väldigt hög ålder.

Abbreviations

AD, Alzheimer's disease

ADL, activities of daily living

BDNF, brain-derived neurotrophic factor

BMI, body mass index

CI, confidence interval

DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision

DSM-V, Diagnostic and Statistical Manual of Mental Disorders, fifth edition

FAB, Frontal Assessment Battery

GDS-15, 15-item Geriatric Depression Scale

GERDA, GErontological Regional Database

GS, gait speed

HR, hazard ratio

IPAQ, International Physical Activity Questionnaire

IPAQ-E, International Physical Activity Questionnaire-Elderly

IPAQ-E 80+, International Physical Activity Questionnaire adapted for adults aged ≥ 80 years

KM, Kaplan-Meier

MMSE, Mini-Mental State Examination

MNA, Mini Nutritional Assessment

MONICA, MONItoring of Trends and Determinants of CArdiovascular Disease

MV, moderate to vigorous

OR, odds ratio

PA, physical activity

PGCMS, Philadelphia Geriatric Centre Morale Scale

RCT, randomised controlled trial

SD, standard deviation

SPM, steps per minute

TUG, timed up-and-go

WHO, World Health Organization

Definitions

Physical activity: any voluntary action performed by the skeletal muscles that requires energy expenditure.

Physical inactivity: <30 min moderate-intensity physical activity/week.

Leisure-time physical activity: physical activity performed during one's free time.

Sedentary behaviour: waking behaviour characterised by <1.5 MET energy expenditure.

Preface

My parents told me that as a kid, I sometimes would lay down in the grass on our lawn and look for insects, proclaiming I would become a “bug scientist” when I grew up. Evidently, I did not become an entomologist, but I did find my way into academia. I completed my bachelor’s degree in cognitive science in 2011, and physiotherapy in 2015. Later I acquired a position as a project assistant at the unit of geriatric medicine at Umeå University, collecting data for several ongoing projects. This gave me valuable insights, stories, and life lessons by interviewing and listening to age-rich persons. After that I was lucky to get an opportunity to write a dissertation that combines my interest in cognitive and physical function. It has been a journey that have given me so much, it is difficult to put into words. I am so very thankful for these years. I’ve met hundreds of people in very high age that donated their time and patience to us. I also met so many talented and dedicated people in this field and beyond, from students to professors, that I feel share that curiosity I had as a kid gazing down at the fauna in our lawn. And I hope this curiosity never fades.

Original papers

This thesis is based on research reported in the papers listed, referred to using the roman numerals.

I. Öhlin J, Ahlgren A, Folkesson R, Gustafson Y, Littbrand H, Olofsson B, Toots A. The association between cognition and gait in a representative sample of very old people - the influence of dementia and walking aid use. BMC Geriatrics. 2020;20(1):34.

II. Öhlin J, Gustafson Y, Littbrand H, Olofsson B, Toots A. Low or Declining Gait Speed is Associated With Risk of Developing Dementia Over 5 Years Among People Aged 85 Years and Over. Journal of Aging and Physical Activity. 2021;29(4):678-685.

III. Öhlin J, Toots A, Littbrand H, Wennberg P, Olofsson B, Gustafson Y, Hörnsten C, Werneke U, Nordström P, Niklasson J, Söderberg S. Physical activity in late middle- to older aged people and dementia, cognitive and physical function two decades later. Manuscript.

IV. Öhlin J, Toots A, D Almevall A, Littbrand H, Conradsson M, Hörnsten C, Werneke U, Niklasson J, Olofsson B, Gustafson Y, Wennberg P, Söderberg S. Concurrent validity of the International Physical Activity Questionnaire adapted for adults aged ≥ 80 years (IPAQ-E 80+), tested with accelerometer data from the SilverMONICA study. Submitted.

Introduction

Ageing demographic

The global population is ageing; the number of very old (≥ 80 years) people tripled between 1990 and 2019, and is estimated to triple again by 2050, to total 426 million people.[1] The Swedish population will contain an estimated 1.1 million very old people by 2050.[2] As age is the primary risk factor for dementia, the number of people with dementia is estimated to triple worldwide with increasing life expectancy from 47 million in 2015 to 141 million people in 2050.[3] The prevalence of dementia has been reported to be 17.5–17.9 % among people aged ≥ 75 years in southern Sweden[4] and 37.2% in people ≥ 85 years in northern Sweden.[5]

Ageing and physical function

With ageing, there is typically a decline in physical function. The European Working Group on Sarcopenia in Older People defined sarcopenia, a hallmark of ageing, as low muscle strength, quantity, and quality.[6] They recommend evaluation of the severity of sarcopenia with physical performance measures such as gait speed (GS) and the Timed Up and Go (TUG) test.[6] In tandem with a decrease in muscle mass, the muscle fibre composition shifts with age to include a larger proportion of smaller, weaker, fatigue-resistant, aerobic, slow-twitch type 1 fibres than of stronger, more easily fatigued, anaerobic, fast-twitch type 2 fibres.[7] Central nervous system changes that affect balance[8] and the accumulating number of musculoskeletal disorders and non-communicable diseases also occur with age.[9] Physical activity (PA) play an important role combatting sarcopenia and balance disorders and in disease management as it may ameliorate the age-related decline in physical function.[10]

Cognitive function

Cognitive function refers to the mental processes that enables acquiring knowledge, information processing, problem solving and decision making. Significant interindividual differences in age-related cognitive decline have been observed[11] and can be described with several terms, notably brain reserve, cognitive reserve and brain maintenance. Differences in brain reserve, such as an increased number of neurons or synapses, buffer against cognitive decline. Cognitive reserve, instead, describes that compensatory approaches or strategies explain the improved performance in people resilient to cognitive decline.[12] Brain reserve has been described as a passive model, while cognitive reserve is an active model that proposes that brain function is more important than brain size.[12]

Regarding brain maintenance, differences in the manifestation of age-related brain changes and pathologies explains the occurrence of no or limited age-related cognitive decline in some individuals.[13]

Processing speed

Processing speed is a measure of the time taken to perform a cognitive task, and the speed of motor responses.[14] It is conceived of as part of higher cognitive function, and its alteration may cause other age-related changes in cognitive function. Cross-sectional data suggests that the processing speed begins to decline in early adulthood, but longitudinal studies suggests that this decline begins around the age of 60 years.[15]

Attention

Attention is defined as the focus on one or multiple tasks [14], referred to as selective and divided attention, respectively.[15] Age-related declines are steeper for more complex attention tasks than for simpler tasks, such as the repeating of a string of digits.[14]

Visuospatial ability

Visuospatial ability is the ability to understand spatial relationships between objects. Visuospatial recognition, e.g. remembering a face or familiar object, remains intact with normal ageing. Age-related declines in visual construction skills, involving the assembly of individual pieces to form a larger whole, have been observed.[14]

Executive function

Executive functions are higher-order cognitive functions that enables goal-oriented behavior, planning, problem solving, organising, reasoning and flexibility.[14,15] It comprises a set of abilities involving inhibition and the shifting and updating of representations in the working memory. With normal ageing, different aspects of executive function have shown stable performance (e.g. reasoning about familiar material), and declines (e.g. mental flexibility and abstraction).[14]

Memory

Memory can be divided into retrospective (e.g. remembering what happened yesterday) and prospective (e.g. paying bills, taking medications daily) forms. Retrospective memory, in turn, can be divided into short- and long-term memory. The latter consist of episodic memory (i.e. of lived experiences) and semantic memory (i.e. facts).[15] Semantic memory performance have shown minor increase

up to middle age, and a slower decline than observed for episodic memory in old age.[16] Working memory refers to the short term storage and manipulation of information [15] and appears to start declining at 60-65 years of age, according to longitudinal studies with control for practice effects.[13] The hippocampus is a part of the limbic system located deep in the medial temporal lobe that undergoes age-related decrease in volume in tandem with memory decline.[17]

Minor cognitive impairment

Minor Cognitive Impairment (MCI) is an intermediate state between normal cognitive function and dementia. It is characterised by mild cognitive deficits that does not affect functional capacities, but with potentially greater effort required than previously to perform those activities.[18] In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V)[19] MCI is replaced with Minor Neurocognitive impairment. Only 5-10 % of MCI cases progress to dementia annually.[20]

Dementia

This thesis uses the term dementia, reflecting use in the included papers. However, future work are recommended to use the term Major Neurocognitive Disorder as used in the DSM-V.[19] Dementia is comprised of a group of progressive age-related disorders that diminish cognitive functions from a previously higher level, causing significant impairment in social and/or occupational functioning. The DSM-V diagnosis entails specification of its cause as Alzheimer's disease (AD), frontotemporal lobar degeneration, Lewy Body disease, vascular disease, traumatic brain injury, substance or medication use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple aetiologies and unspecified. The most common cause of this disorder is AD, followed by vascular and Lewy Bodies. Dementia is a leading cause of disability in older people worldwide.[21] Although it has no cure, the improvement of early diagnosis is important, as it enables those affected, their relatives, and care givers to plan ahead[3] and implement preventive measures. Diagnoses are made on a clinical basis, as no sufficiently accurate biomarker or imaging technique is available. However, brain imaging is used routinely in the diagnostic process, in conjunction with cognitive tests and the interviewing of relatives and/or care providers. Six domains of cognitive function are considered in the diagnosis of dementia; complex attention, executive function, learning and memory, language, perceptual-motor function and social cognition.[22] Risk factors for dementia are non-modifiable (e.g. age, sex and genetic contribution) and modifiable (e.g. smoking, hypertension, cardiovascular disease, diabetes and low PA levels). Gait and balance deficits are common in affected individuals, and more pronounced in the later stages.[23,24]

Dementia due to Alzheimer's disease

AD is characterised by the progressive loss of synapses and neurons together with the accumulation of amyloid plaques and neurofibrillary tangles in the brain. Even in individuals with mild AD, the simultaneous performance of a cognitive task slows GS significantly.[25] People with AD perform worse on mobility tests than do people with MCI or normal cognition, but better than those with other forms of dementias.[26] AD causes gradually progressive cognitive decline, usually with memory and executive function impairment in its early stages, irritability and wandering in middle to later stages, sometimes dysphagia, incontinence and seizures in very late stages.[18,22]

Vascular dementia

Also known as arteriosclerotic dementia, multi-infarct dementia and vascular cognitive impairment/disorder, vascular dementia is caused by disease of large and small blood vessels of the brain. Depending on lesion location, its symptoms are heterogeneous and progression is rapid, fluctuating or gradual. In individuals with vascular dementia, cognitive decline is associated temporally with stroke or transient ischemic attack. Declines in complex attention and executive function, and gait disturbance with urinary and emotional symptoms, are common.[18] Although its manifestation are heterogeneous, vascular dementia often leads to the reduction of GS and step length and increased gait variability to a greater degree than AD.[22]

Dementia due to frontotemporal lobar degeneration

Dementia caused by frontotemporal lobar degeneration presents with prominent atrophy of the frontal and temporal lobes and gradual symptom progression. The location of brain atrophy influences the nature of symptoms and leads to behavioural and language variants. The behavioural variant, with distinct frontal lobe atrophy, entails primarily behavioural changes, such as disinterest, social withdrawal and persevering or compulsive motor behaviour. The language variant, with temporal atrophy, entails aphasia with intact syntax and prosody, and sometimes empathy loss and rigid behaviour.[18] People with the behavioural variant have shown increased stride time variability compared to AD and healthy controls.[27]

Dementia with Lewy bodies

This type of dementia, presenting with misfolded proteins that constitutes Lewy Bodies, is characterised mainly by the gradual decline of attention, visuospatial ability and executive function. It often involves fluctuating cognitive function, recurrent visual hallucinations and parkinsonism.[18] People with Lewy body dementia have shown decreased GS and impaired rhythm.[28]

Dementia due to multiple aetiologies

The clinical and pathological overlapping of dementia types increases with age. This dementia type is described as having multiple aetiologies, or as mixed dementia. AD and vascular dementia are common co-aetiologies.[22]

Physical activity

Caspersen et al. described PA as:

> ""…any bodily movement produced by skeletal muscles that results in energy expenditure. The energy expenditure can be measured in kilocalories. Physical activity in daily life can be categorized into occupational, sports, conditioning, household, or other activities."" [29(p126)]

Furthermore, they describe exercise and physical fitness:

> ""Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness. Physical fitness is a set of attributes that are either health- or skill-related. The degree to which people have these attributes can be measured with specific tests."" [29(p126)]

Physical activity and physical function

To improve aspects of physical function, such as endurance capacity and muscular strength, movements must be performed according to the overload principle, whereby the body is challenged near its maximum capacity.[10] The frequency, duration, intensity and mode of exercise determine the nature and magnitude of improvement, but in general, all PA has positive effects on health and wellbeing, at any age. The recently updated World Health Organization (WHO) recommendations[30] specify that older adults should perform at least 150–300 minutes moderate to vigorous physical activity (MVPA) / week with multicomponent functional balance and strength training on 3 or more days per week. This PA level and duration help to prevent falls and fall-related injuries,

and promote bone health and functional ability. The recent revision no longer includes a bout threshold of > 10 minutes, but rather emphasises that all movements matter, even in shorter bouts.[30]

Physical activity, cognition and dementia

A study conducted with 62 older adults who participated in a 24-week resistance exercise program showed improvements in short-term memory functions in the intervention group, which performed moderate to high-load resistance exercise training, compared with the control group which performed the same exercises but with minimum loading.[31] A one-year moderate intensity aerobic exercise intervention conducted with older adults (n=60, 67.6 years of age, and n=60, 65.5 years of age in intervention and control group, respectively) improved spatial memory, and led to increased hippocampus volume corresponding to 1 to 2 years of age-related change.[32] However, the Lifestyle Interventions and Independence for Elders trial, which included 1635 sedentary people with a mean age of 78.9 years, showed that a single domain PA intervention over 2 years did not improve the tertiary outcome of cognitive function.[33] Similarly, a systematic review of interventions ≥ 6 months found insufficient evidence to support that single domain PA interventions can prevent cognitive decline in persons without dementia.[34] Interventions may need to consist of multiple domains in addition to PA, to have a positive effect on cognitive decline. Indeed, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), randomly allocated 1260 participants, mean age 69.3 ± 4.7 SD years, to either a control group receiving regular health advice or a multi domain intervention consisting of nutritional advice, aerobic and resistance exercise, cognitive training, and management of metabolic and vascular risk factors over 2 years.[35] Their results showed improved cognitive function in the intervention group, supporting the notion that in order to prevent cognitive decline, a multicomponent intervention might be necessary. A meta-analysis including 25 RCTs of community living participants aged ≥ 50 years without known cognitive impairment reported that resistance training compared to stretching showed significant improvements in measures of reasoning, and Tai Chi compared to no exercise on measures of attention and processing speed, however there was no effect of PA on the remaining 26 comparisons.[36] An umbrella review reported beneficial effects of PA on attention, executive function and memory in people with MCI, with certainty of evidence ranging from low to moderate.[37] In the same review, very low certainty evidence supported that mixed PA or exercise improved global cognition in people with dementia, but PA had no effect on attention, executive function, memory, motor speed or language. Tentatively, the scarcity of evidence may be due to relatively short-term PA interventions may have limited potential to compensate for risk behaviour over a long lifetime. Also, as dementia development is a multifactorial, long-reaching process spanning decades,

randomized controlled trials over several decades may not be ethically or practically possible, hence we must also consider observational studies. A systematic review of 16 prospective studies with a total of 163 797 participants showed that exercise was associated inversely with dementia development over a period of up to 11 years.[38] However, issues have been raised that the association between PA and dementia seen over shorter time spans might be due to reverse causation, meaning reduced PA does not increase dementia risk, but is a preclinical symptom of dementia development.[39] As there are conflicting results regarding the association between PA and cognitive function and dementia over several decades,[39–43] more studies with decade long follow-ups are called for.

There is an exponential increase in dementia risk with age and low PA is a potentially modifiable risk factor for dementia.[3] However, few studies have investigated PA and its association to dementia in the fastest growing age group, very old people. There is therefore a need for more studies investigating the long term association between PA and dementia in very old people. The follow-up has to be long enough to reach the higher risk age and begin before there is a risk of low PA being indicative of preclinical dementia.[43]

One suggested mechanism for the effects of PA on cognition involves the availability of neurotransmitters such as brain-derived neurotrophic factor (BDNF), a protein required for neuron growth and survival. A meta-analysis of 55 studies showed that longer durations of single exercise sessions (mostly cycling and running) were associated with greater increases in peripheral BDNF concentrations in healthy adults.[44] The hippocampus is involved in episodic[45] and declarative[46] memory, and hippocampal volume seems to decrease with age and is associated with memory decline.[17] A review including eight studies of participants around 70 years of age, reported inconsistent effect of exercise interventions between 6 weeks to 2 years on hippocampal volume in both healthy participants and people with AD.[47] The authors reported that the heterogeneous intervention duration and intensity in included studies precluded a meta-analysis, and this heterogeneity may also explain why some studies found an exercise effect of PA on hippocampal volume, while others did not. An indirect mechanism that can explain the beneficial effect of PA might be by lowering cardiovascular risk factors such as obesity, hypertension, and diabetes, and thereby lowering risk of cerebral hypoperfusion, hypoxia or stroke, preserving cognitive function.[48]

Measures of physical activity

PA can be measured by direct observation, devices, and questionnaires, in decreasing order of resource requirements and precision. Direct observation is

very precise but intrusive, as it requires participants to be monitored continually for the entire observation period. Actigraphy tools, formerly specialized, expensive and reserved for research and development purposes, have been incorporated into smart phones and wearable sensors available in the open market. Step counters, for example, use the reaction force generated by each step to determine the daily or weekly number of steps, and are typically worn on waist bands. Daily step counts of ≥ 4400 have been associated with less mortality among older women[49], and 7000-10000 correspond to WHO's previous recommendation of 150 minutes of MVPA per week for older adults.[50] Accelerometers measures acceleration in one to three axes of movement, and are often worn on the anterior part of the thigh, lower back or waist band. These devices also estimate step counts, and some detect the body position (e.g. sitting, lying, or standing).

Although PA questionnaires are prone to social desirability[51] and recall biases, they have long been used as a low-cost, quick and efficient, albeit not very precise, PA measure. Saltin and Grimby[52] developed an early questionnaire that distinguished four levels of PA. This scale was later expanded to six levels to better conform to an older population with lower PA levels and lesser physical function.[53] The International Physical Activity Questionnaire (IPAQ) developed in 1998, is suitable for PA measurement in different countries.[54] This scale was later adapted to apply to older people and translated to Swedish [as the International Physical Activity Questionnaire modified for the elderly (IPAQ-E)].[55] The IPAQ-E was further adapted for use with very old people aged ≥ 80 years (IPAQ-E 80+), by including time spent lying down during the day and at night, and including intensity of walking, one of the most common forms of exercise which older people may experience as requiring more exertion than do younger adults.[56] The scale also include proxy confirmation if cognitive deficit is suspected. When investigating the PA levels of very old people, the consideration of the 24-hour activity patterns is pertinent, as ageing is accompanied by increased nocturnal awakening and napping[57] leading to variable daytime activity patterns.

Gait and cognition

The relationship between gait and cognition has garnered increased research interest in recent decades. The formerly pervasive idea that gait is an automated task[58] has been replaced by the perspective that gait requires cognitive control.[59] Lundin-Olsson et al.[60] discovered that ambulant individuals in nursing homes who stopped walking when talking were at greater risk of future falls, which suggest that these individuals lacked the relevant cognitive resources to simultaneously walk and talk. In the Timed Up and Go dual task (TUG-dt) test,

the words-per-time measure seem a good predictor of conversion from subjective or mild cognitive impairment, to dementia.[61] A dual decline of GS and memory lead to higher risk of dementia than decline in only GS or memory.[62] A combination of self-reported cognitive decline and slow gait, termed motoric cognitive risk, have shown to predict dementia onset.[63] Motor slowing seem to precede cognitive impairment by approximately 2.5 years[64] and systematic reviews have shown that GS declines before cognition,[65] and precede dementia by up to nine years.[66] These results suggest a low or declining GS may be indicative of future cognitive function, though there is limited evidence among very old people including people with dementia and people living in nursing homes as studies are small and few.[65] This is despite that gait and cognitive dysfunction are more common[67] and severe[68,69] in these groups. In addition, walking aid use is more common among people of higher age.[70] Walking aids may improve gait by alleviating pain or compensating for balance deficits,[71] and may lower the cognitive challenge of a motor task and increase GS.[72] Conversely, more challenging motor tasks requiring more maneuvering of the walking aid may increase the cognitive load, thus lowering GS.[73] In addition, morbidity increases with age[74] and many diseases are associated with both gait and cognitive function. Therefore, it seems important to investigate if the association is robust when adjusting for potential confounders. Finally, many older people have impaired mobility[75] and difficulty performing GS tests according to protocol, which may lead to missing values and compromising generalizability.

Rationale

The global population is ageing, and the number of very old people is increasing rapidly. The severity of cognitive impairment appears to be associated with an increase in gait abnormalities. Gait and balance deficits are common among people with dementia, and more pronounced in the later stages. Although GS has been linked to cognition, this association in very old people, among whom the proportion of dementia is greatest, needs to be investigated further.

A decrease in GS has been shown to predict incident dementia up to 9 years before diagnosis. However, research of whether a decrease in GS is associated with incident dementia for people aged ≥ 80 years, among whom dementia is common, is limited. The examination of whether GS is associated independently with incident dementia requires adjustment for potentially confounding medical conditions.

Longitudinal studies have investigated the association of PA with incident dementia and cognitive function in older people. However, many had a relatively short follow-up time rendering them prone to biases attributable to subclinical dementia as physical inactivity may be a prodromal symptom of cognitive impairment and dementia. Despite dementia risk increasing exponentially with age, few studies have investigated the association between PA and subsequent dementia in the fastest growing age group, people aged ≥ 80 years. Therefore, there is a need for studies spanning several decades investigating the association between PA and dementia in very old people.

No Swedish questionnaire adapted for the measurement of PA and physical inactivity in people ≥ 80 is available. The validation of such a measure is important, as PA patterns in this age group differ from those of younger age groups due to age-related declines in cognitive and physical function. The 24-hour measurement of (in)activity in this population is likely important, as ageing is accompanied by increased nocturnal awakening and napping leading to variable daytime activity patterns.

Aims

The overall aims of this thesis were to explore the relationships of GS and PA to cognitive function and dementia in very old people, and to determine the validity of a novel self-reported PA questionnaire developed for use with very old people. Specific aims of this thesis were to investigate:

1. the association of GS with global cognitive function, and the effects of walking aid use on this association, in a representative sample of people aged ≥ 85 years, including people with dementia, and people living in nursing homes;
2. whether GS five years previously and the five-year change therein are independent predictors of indicent dementia, and whether changes in GS are associated with changes in cognitive function over five years, among people ≥ 85 years of age;
3. whether LTPA levels in late middle to old age are associated with incident dementia, cognitive function or GS in people ≥ 80 years of age; and
4. the validity of the IPAQ-E 80+ for assessment of PA in people aged ≥ 80 years using activPAL accelerometry.

Materials and Methods

This thesis was conducted with data from the Umeå 85+/GErontological Regional DAtabase (Umeå85+/GERDA) study (papers I and II), and the SilverMONICA study (papers III and IV). The characteristics of these studies and participants therein are summarised in Table 1.

Table 1. Overview of thesis data sources

Paper	I	II	III	IV
Study	Umeå85+/GERDA		SilverMONICA	
Design	Crossectional	Longitudinal	Longitudinal	Validity study
Participants, n	1317	296	541	76
Age baseline, years	89 (84–103)	87 (84–99)	65 (59–78)	84 (79–96)
Age follow-up, years		92 (89–104)	85 (79–96)	
Follow-up, years		5	17-20	
Women	893 (67.8)	190 (64.2)	304 (56.2)	42 (55.3)
Dementia	464 (35.2)	98 (33.1)	176 (32.5)	17 (22.4)
Outcome	GS	Dementia incidence, CF	Dementia incidence, CF, EF, GS	Validity of IPAQ-E 80+ PA questionnaire
Exposure / criterion	Cognitive function	GS, ΔGS	Self-rated LTPA	Accelero-metry
Cognitive measure	MMSE	MMSE, ΔMMSE	MMSE, FAB	MMSE, FAB
Physical function measure	GS over 2.4 meter	GS over 2.4 meter	A six item PA scale	IPAQ-E 80+, activPAL accelerometry
Data collected, years	2000–2012	2000–2017	1999–2019	2017–2019
Data analysis, outcome	Linear regression	Linear and logistic regression	Linear regression ,Cox PH regression	Spearman's ρ, Bland Altman plots, Cohen's κ.

Data presented as mean (range) or n (%). GERDA, GErontological Regional DAtabase; MONICA, MONItoring of Trends and Determinants of CArdiovascular Disease; GS, self-paced gait speed; CF, Cognitive function; EF, Executive function; IPAQ-E 80+: International Physical Activity Questionnaire adapted for people aged ≥ 80 years; PA, physical activity; LTPA, leisure time physical activity; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; PH, proportional hazard.

Setting

Umeå 85+/GERDA study

The population-based Umeå85+/GERDA study examined the health and living situations of community and nursing home-dwelling very old people and was conducted by Umeå University, Sweden, Åbo Academy University/University of Vaasa, and Novia University of Applied Sciences, Finland. Data were collected recurrently (at 5-year intervals) in selected urban and rural municipalities in Västerbotten County, northern Sweden (2000/2002, 2005/2007, 2010/2012, and 2015/2017) and in Österbotten County, western Finland (2006 and 2011). Individuals were invited to participate based on the systematic sampling of individuals from national tax– and population registers according to date of birth. From a randomised starting point, every other person turning 85 years old, every person turning 90 years old, and every person turning 95 years old or over that year were invited to participate. Previous participants were invited to participate in subsequent data collections. All eligible individuals were sent a letter detailing the Umeå85+/GERDA study and then invited by telephone to participate. A home visit was scheduled for each individual who provided informed consent to participate in the study. If cognitive impairment was suspected, a relative was consulted and were provided with study information. Data collection for each cohort lasted approximately 1 year. Visits were conducted in order of decreasing participant age and in participants' homes to accommodate for impaired mobility or living far from participating universities. Medical professionals (physicians, nurses and physiotherapists) trained in the study protocol conducted structured interviews and assessments, including the collecting of data on participants' medical histories and prescribed medications, medical record review, and interviews with relatives or caregivers when required.

SilverMONICA

The WHO's MONItoring of trends and determinants of CArdiovascular disease (MONICA) project was initiated in the early 1980s to follow cardiovascular risk factors and cardiovascular events in a large number of populations worldwide.[76] Centres in 26 countries, including a centre in northern Sweden covering 510,000 inhabitants of Västerbotten and Norrbotten conties participated. Most centres ceased data collection in the mid-1990s, but the MONICA centre in Northern Sweden has continued to monitor risk factors and events, taking advantage of the rapid accumulation of information with longer follow–up periods. The SilverMONICA project was initiated by researchers from the Umeå85+/GERDA and the northern Sweden MONICA project. SilverMONICA aims to investigate midlife risk factors of physical and cognitive disease in very old age. Individuals who had participated in the northern Sweden MONICA study at least twice through 1999, were still living in the study area, and were aged ≥ 80 years in

2016–2019 were eligible for the SilverMONICA study. Using methodology from the Umeå85+/GERDA study, data collection was performed in participants home by medical professionals (nurses, physiotherapists and physicians) trained in the study protocol. All eligible participants were informed about the SilverMONICA study by letter and later by telephone; home visits were conducted with those who consented to participate and if consenting, a home visit was scheduled. If cognitive impairment was suspected, a relative was consulted and were provided with study information. More detailed information was given, and a signed consent was collected from all participants at the home visit.

Participants and study designs

Paper I and II

Paper I describes a crossectional study conducted with data from 1317 participants (65% participation rate) who completed the Mini–Mental State Examination (MMSE) test from the 2000/2002, 2005/2007, and 2010/2012 cohorts (Figure 1). Paper II describes a longitudinal study conducted with data from participants without dementia who completed GS and MMSE assessments during baseline home visits 2000-2012 and follow–up cognitive function assessment during home visits 5 years later (n = 296 participants, 16% participation rate, Figure 2).

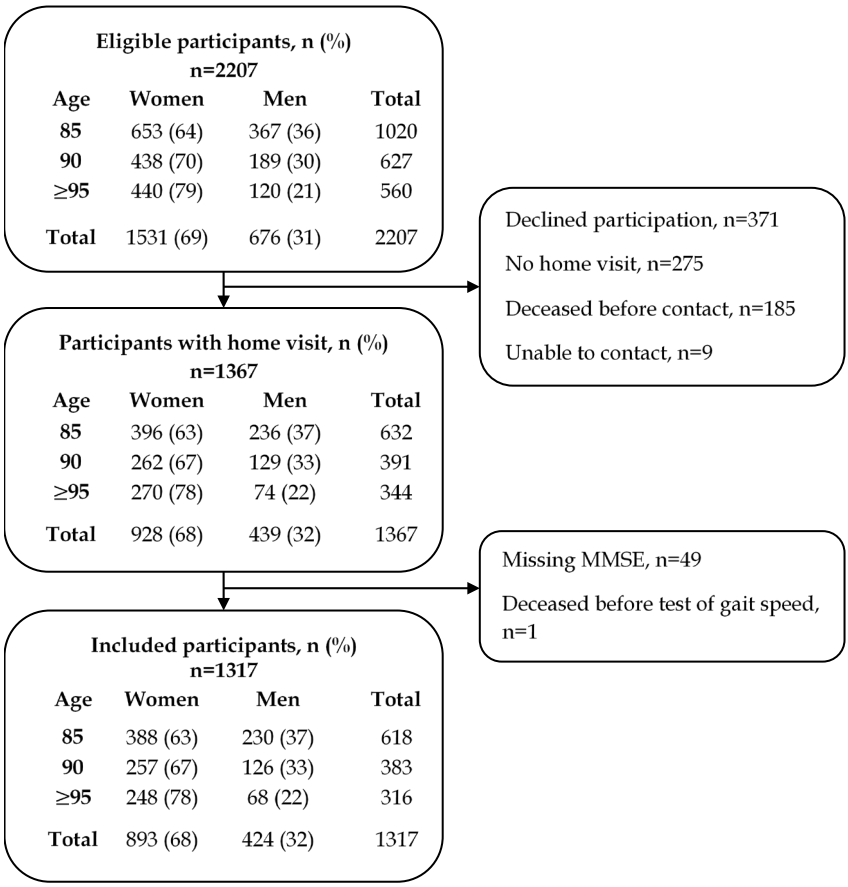

Figure 1 Flow of participants in the paper I study. MMSE, Mini-Mental State Examination.

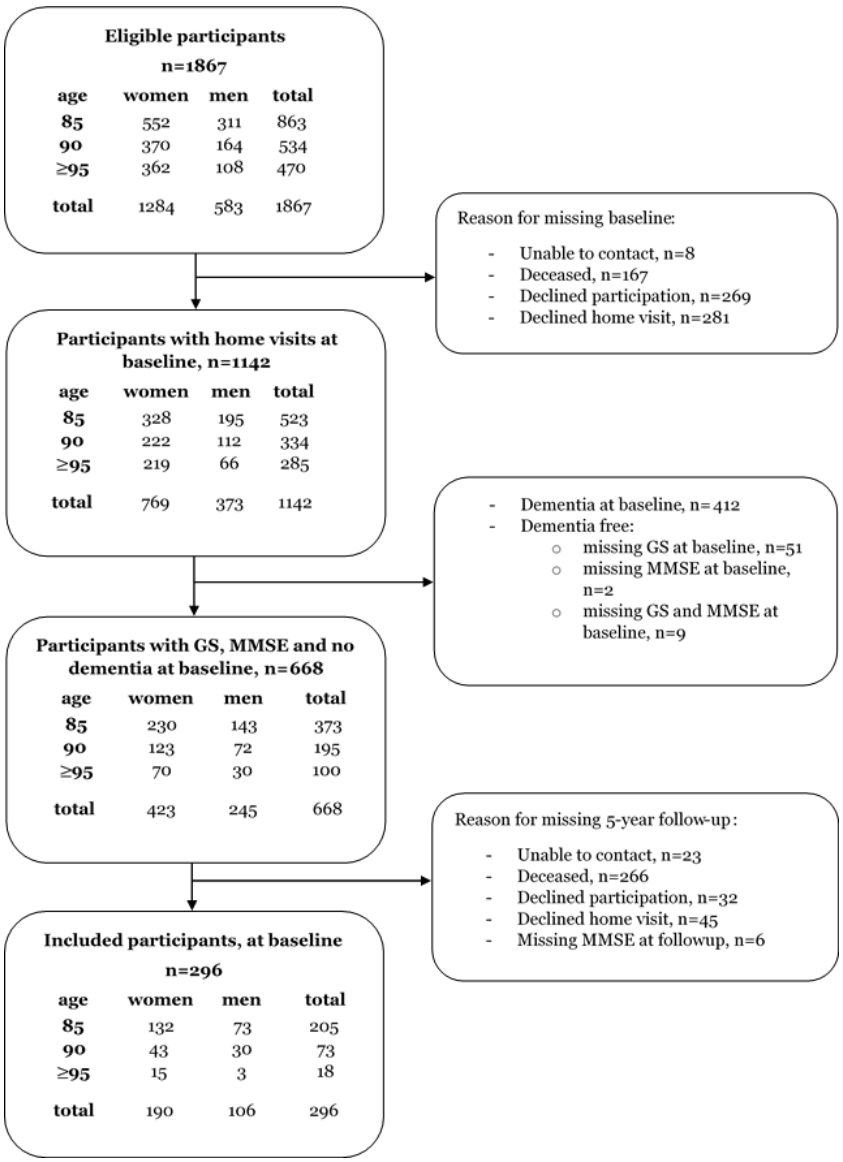

Figure 2 Flow of participants in the paper II study. GS, gait speed. MMSE, Mini-Mental State Examination.

Paper III and IV

Paper III describes a longitudinal study conducted with data from 541 SilverMONICA participants (participation rate 67%) with baseline values from the MONICA study in 1999 (Figure 3). Paper IV was a validity study that included 76 of 128 eligible SilverMONICA participants (participation rate 59%, Figure 4). Eligible for this study was those residing in Luleå or Boden municipalities from May 2017 to October 2019. Included participants fulfilled the inclusion criteria of ≥ 5 valid days of accelerometry, and completed at least parts of the IPAQ-E 80+ either by themselves, by proxy, or a combination.

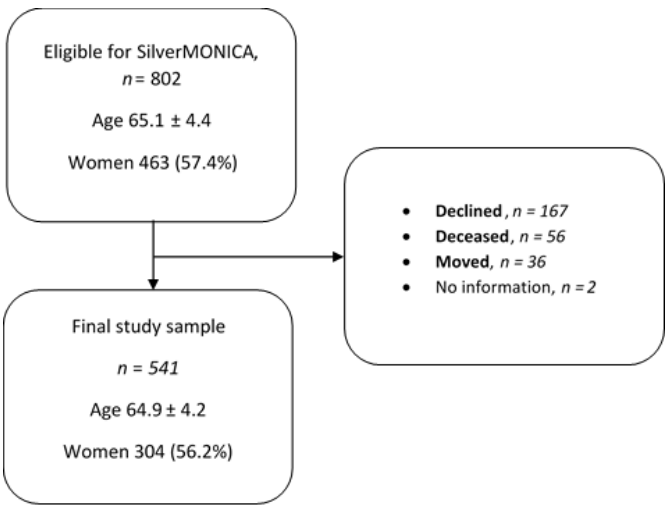

Figure 3 Flow of participants in the paper III study.

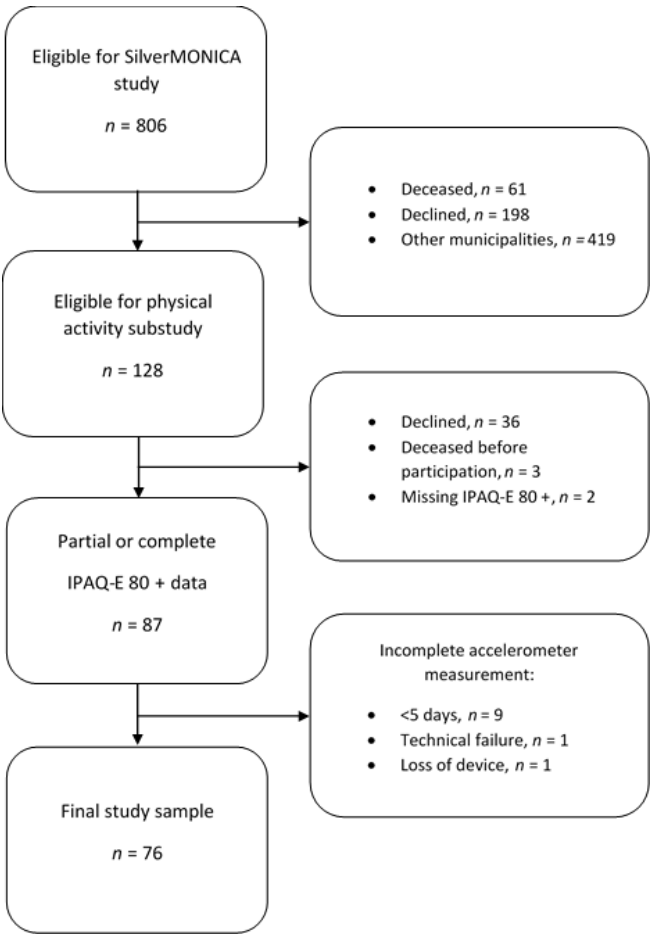

Figure 4 Flow of participants in the paper IV study. IPAQ-E 80 +, International Physical Activity Questionnaire adapted for people aged ≥ 80 years.

Ethics

Data collection for the Umeå85+/GERDA and SilverMONICA studies was performed in accordance with the Declaration of Helsinki. All participants were informed that they could withdraw from the studies at any time without explanation. All included participants gave informed consent, which was documented. If cognitive impairment was suspected, a relative was consulted and were provided with study information. The Umeå85+/GERDA study was approved by the regional ethics review board in Umeå (registration numbers: 99–326, 05-063M, 09-178 M) and the ethics committee of Vaasa Central Hospital (registration numbers: 05–87 and 10–54). The SilverMONICA study was approved by the regional and national ethical review boards (Dnr 0 29–2015 and Dnr 2017–322–32M).

Study variables and outcomes

Cognitive function

In the Umeå85+/GERDA study, cognitive function was measured using the swedish version of the MMSE. In the SilverMONICA study, it was also measured using the Frontal Assessment Battery (FAB). The MMSE is a commonly used dementia screening instrument that measures attention, temporal and spatial orientation, calculation, short–term memory and visuospatial function with 11 items; scores range from 0 to 30.[77] It has shown good reliability and validity.[78] The FAB measures frontal lobe function, i.e abstract reasoning, mental flexibility and motor programming, with six items; scores range from 0 to 18. It has shown good reliability and validity.[79]

Dementia

In the Umeå85+/GERDA study, dementia diagnoses were verified according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR)[80] criteria using information from participants' medical records, prescriptions and assessments, including the MMSE,[81] 15–item Geriatric Depression Scale,[82] Philadelphia Geriatric Center Morale Scale,[83] Life Orientation Scale,[84] Barthel Activities of Daily Living (ADL) Index,[85] Organic Brain Syndrome Scale,[86] and vision and hearing tests. One experienced specialist in geriatric medicine reviewed all medical records in Sweden and Finland. The procedure in the SilverMONICA study was similar except that dementia diagnoses were verified according to both the DSM-IV-TR[80] and DSM-V.[19]

Gait speed

GS was measured in the same way in the Umeå 85+/GERDA and SilverMONICA studies, over 2.4 m (8 feet), as part of the original Short Physical Performance Battery.[87] Participants were instructed to start from standing still behind a marking on the floor and walk at a self-paced speed past a second marking. The time taken to travel the distance, from the initiation of walking to the passing of a foot across the second marking, was measured using a stopwatch. The test was conducted twice and the mean GS was calculated in metres/second. When a participant could not perform the GS test, the reason for non-performance was recorded as related to cognition, physical impairment, motivation, or other (pain, unknown).

Physical activity questionnaires

In the paper III study, PA was measured using a 6-level scale, extended from the original 4-level version by Grimby,[88] and intended for older populations with

reduced physical function leading to relatively low physical activity levels.[53] The scale measures leisure time physical activity during the previous year. The six levels translated from swedish are; 1) "hardly any physical activity", 2) “mostly sitting, sometimes a walk or similar”, 3) “light physical exercise at least 2 hours a week, such as walks or biking (also to and from work or school), fishing, dancing etc.”, 4) “moderate exercise 1-2 hours a week, such as jogging, tennis, swimming, badminton, gymnastics.”, 5) “moderate exercise at least 3 hours a week, such as jogging, tennis, swimming, badminton, gymnastics.”, 6) "hard or very hard physical exercise regularly and several times per week with great physical effort, such as running, soccer, swimming." To attain the most even dispersion of participants as possible, PA was categorized into three groups, low if rated 1-2, medium if rated 3, and high if rated 4-6.

The IPAQ-E comprises four questions related to levels of PA reported as time (in hours and minutes per day) spent sitting, walking (≥10 min bouts), and conducting moderate-, and vigorous PA, based on the last seven days.[89] The IPAQ-E 80+ has an additional four questions related to time spent 1) lying down (for example, on a couch or in bed) in connection with sleep at night, 2) lying down (for example, on a couch or in bed) in connection with rest during the day, 3) walking (moderate effort), and 4) walking (vigorous effort). In cases of cognitive impairment (MMSE score < 20), responses are verified with relatives or caregivers.

Accelerometer measures

In the paper IV study, a threshold of ≥5 days valid accelerometer data, representative of a week of measurement in adults,[90] was used. The total inactive time was measured as the sum of sitting and night–time and daytime lying, the sedentary time was measured as the sum of sitting and daytime lying, and the total active time was measured as the total stepping time. The moderate to vigorous intensive (MV) walking time was measured as the time spent walking with a cadence > 100 steps per minute (SPM), excluding bouts of < 10 steps. The same measure, suggested as a threshold for MV activity in older adults [56], was used for MVPA. According to the accelerometer software’s standard validation algorithm, >4 hours continuous stillness was classified as non-wear.

Potential confounders

Education was dichotomized into < 8 or ≥ 8 years in paper I-III. Smoking status was defined as smoker or non-smoker (including previous smokers). Body mass index (weight in kilograms / height in meters squared, BMI) was calculated, and treated as continuous in paper I,II and IV, and coded as high if >30 in paper III. Systolic and diastolic blood pressure were measured with a calibrated sphygmomanometer and stethoscope after 5 min rest in a supine position in

paper I and II, and with a OMRON M7 blood pressure monitor (OMRON corporation, Kyoto, Japan) in paper III and IV. Hypertension diagnosis for paper I, II and IV used information from medical records. In paper III, hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or using antihypertensive medication. In paper III, glucose tolerance was defined as diabetes, impaired fasting glucose, impaired gluose tolerance, or normal glucose tolerance according to WHO 2006 guidelines[91] and the first three were merged into the category glucose intolerance. Depressive symptoms were measured with the 15-item Geriatric Depression Scale, with higher scores indicating more depressive symptoms[82] in paper I-IV. ADL was measured with the Barthel ADL Index in paper I and II (score range, 0–20), with lower scores indicating more dependence[85] and Katz ADL staircase[92] coded as independent in I-ADL and P-ADL in paper III and IV. In paper I, hearing and vision impairment were defined as the inability to hear a conversation at usual speaking volume within 1 m, with or without hearing aids, and to read a word in 5-mm capital letters at reading distance, with or without glasses, respectively. In paper II-IV, hearing or vision was coded as impaired if unable to hear or read without hearing or vision aid. Use of walking aid was dichotomized into using or not using a walking aid in paper I-IV.

Statistical analysis

All analyses were performed with IBM SPSS version 23 and 24 (IBM corporation, Armonk, NY, USA) except Fisher's *r–z* transformation in paper IV, which was performed using VassarStats.[93] Tests were two-tailed and p-values < 0.05 were considered statistically significant.

In papers I and II, data are reported as means with standard deviations (SDs) and frequencies with percentages of the total sample and according to dementia development. The association between GS and cognitive function, and decline in GS and decline in cognitive function over 5 years, was investigated with linear regression, and the association between GS, GS decline and dementia development with logistic regression. Potential confounders for adjusted analyses in paper I and II were chosen from preselected baseline variables that were believed to influence both GS and cognitive function. Variables that associated with both GS and cognitive function ($p < 0.15$) in univariate logistic or linear regression analyses were inspected for multicollinearity and excluded if Pearson's R or Spearman's Rho > 0.5. Linear regression analyses in paper I was adjusted for age, sex, lives alone, education < 8 years, current smoker, depression, cerebrovascular disease, heart failure, history of hip fracture, malignancy previous 5 years, benzodiazepine use, beta-blocker use, analgesic use, neuroleptic use, number of prescribed medications, systolic blood pressure, vision impairment, hearing impairment and use of walking aid during GS test. Linear

regressions in paper II were adjusted for age, sex, BMI, history of malignancy, use of walking aid during GS test. Logistic regression with dementia as outcome and change in GS as exposure was adjusted for age, sex, BMI, history of malignancy, nursing home resident, and Barthel ADL index score, and logistic regression with baseline GS as exposure adjusted for the same as change in GS, and also adding history of hip fracture and MMSE score.

In the paper III study, Student's *t* test and the chi-squared test were used to assess differences between participants and non-participants in age, sex, and education level in 1999. Cox proportional hazard regression analyses were performed with the self-rated PA level serving as the exposure and age at the time of dementia diagnosis or censoring serving as the outcome. Exact dates of dementia diagnosis were available for 114 participants; for 61 participants, only the year of diagnosis was available and July 1 was used as the estimated date. Survival curves were created using the Kaplan Meier (KM) method.[94] Schoenfeld residuals, KM curves and the time x age covariate did not indicate violation of the proportional hazard assumption. Log-rank test indicated no difference between survival curves of the three physical activity categories. Cox analyses were unadjusted, adjusted for age, sex, < 8 years of education, and smoking status (model A) and additionally adjusted for hypertension, BMI ≥ 30, and glucose intolerance (model B). Linear regression models were used to estimate the associations of PA with cognitive function, executive function, and GS. Dummy variables were constructed for covariates with more than two alternatives. The covariates were within reasonable limits regarding multicollinearity, distribution and outliers. The three linear regressions were performed unadjusted, and adjusted as desribed for the Cox analyses. To examine the influence of retirement status, education, and categorisation of the PA scale, stratified unadjusted Cox and linear regression analyses were performed.

In the paper IV study, the distribution of the differences (between IPAQ-E 80+ scores and accelerometry) of all inactivity and activity measures was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests of normality, QQ plots, and histograms. Only the total inactive time was distributed normally. Thus, Spearman's coefficients were used to measure the correlation between IPAQ-E 80+ and accelerometer measures. The chi-squared test was used to assess the difference in the proportions of males and females, and the Mann-Whitney *U* test was used to assess differences in age and years of education, between substudy participants and individuals who participated only in the Norrbotten SilverMONICA study. Correlations of, and systematic and random errors in, IPAQ-E 80+ scores and accelerometer measures of total inactive, nighttime and daytime lying, sitting, sedentary, total active time, walking and MV walking, MVPA, and total MVPA (MVPA + MV walking) times were investigated with Spearman's rho and Bland-Altman plots [y axis, difference between measures; x

axis, mean; 95% limit of agreement i.e., ± 1.96 (SDs)].[95] The strength of correlations was rated as poor (0–0.2), fair (0.21–0.4) moderate (0.41–0.6), substantial (0.61–0.8) or near perfect (0.81–1.0).[96] The sensitivity and specificity of the IPAQ-E 80+ for the identification of participants achieving the recommended PA level (150 min moderate or 75 min vigorous PA/week)[30] was tested using total MVPA time and two accelerometer conditions: >100 and >75 SPM. Agreement beyond chance with Cohen's kappa was also measured in the two SPM conditions. The impact of the exclusion of the two most sedentary participants (>20 h/day inactivity) was investigated with a sensitivity analysis. Differences in correlations among subgroups defined by sex, proxy rating, a GS < 0.5 m/s, dementia, and depression were investigated with Fisher's r-z transformation test. Using normative data on step length from a previous study of gait parameters in older people [97] estimated daily distance walked, in km, were calculated.

Missing values

In all studies, total scores on the 15-item geriatric depression scale (GDS-15) were imputed for participants with ≤5 missing answers by multiplying the mean score from existing responses by 15. Multiple imputation was conducted to estimate missing GS values [n = 287 (22%) in the paper I study, n = 51 (17%) at follow-up in the paper II study]. Multiple imputation uses a linear regression with adjustments called predictors, that estimate missing values in multiple data sets. The number of imputed data sets generated were set to the approximate percentage of missing values, 20 and 17 for the paper I and paper II studies, respectively. A pre-defined strategy for predictor selection was used in both of these studies, with the selection of target variables (GS, MMSE score, dementia), background characteristics associated with the target variables, and recorded reasons for missing GS values. The following two restrictions were implemented using the same predictors. For participants who did not perform the GS test for physical reasons, the maximum imputed value was restricted to the lowest observed value (0.08 and 0.1 m/s for paper I and II, respectively), assuming that the GS of these participants would be slow if they had been able to perform the test. For participants with other reasons, the maximum imputed values were restricted to the fastest observed value (1.5 and 1.2 m/s in the paper I and II studies, respectively) due to the greater uncertainty about these participants' GSs.

Results

Participant characteristics

Participant characteristics are presented according to dementia status (paper 1 study), and dementia status at follow-up (paper II study), in Table 2. In the paper I and II studies, 464 (35%) 98 (33%) participants, respectively, had dementia. Relative to participants without dementia, participants with dementia in both studies were older and had higher frequency of nursing home residence, depressive disorders, history of hip fracture and walking aid use during GS test. They also had lower BMIs, Barthel ADL index score and MMSE scores. The GS was lower among participants in the paper I study with dementia than among those without dementia (0.30 ± 0.23 vs 0.54 ± 0.24, respectively, $p < 0.001$); no such difference was observed in the paper II study (0.36 ± 0.25 dementia, 0.51 ± 0.20 without dementia). Mean baseline and 5-year follow-up GSs and MMSE scores, and mean differences therein, from the paper II study are presented in Table 3.

Table 2. Characteristics of participants in the paper I and II studies according to dementia

	Paper I		Paper II at follow-up	
Characteristic	No dementia n=853	Dementia n=464	No Dementia n=198	Dementia n=98
Age, years	88.4 ± 4.2	91.1 ± 4.9**	91.4 ± 3.0	92.3 ± 3.7*
	[84–103]	[84–103]	[89–103]	[89–104]
Women	548 (64.2)	345 (74.4)**	128 (64.6)	62 (63.3)
Nursing home resident	155 (18.2)	307 (66.2)**	28 (14.5)	57 (59.4)**
Lives alone	632 (74.1)	382 (83.4)**	153 (78.5)	76 (82.6)
Education < 8 years	561 (66.3)	336 (77.8)**	125 (63.1)	66 (68.0)
Currently smoking	33 (3.9)	6 (1.3)*	7 (3.6)	3 (3.1)
Parkinson's disease	14 (1.6)	8 (1.7)	1 (0.5)	3 (3.1)
Depressive disorders	225 (26.4)	221 (47.6)**	47 (23.7)	41 (41.8)**
Cerebrovascular disease	159 (18.6)	101 (21.8)	44 (22.2)	29 (29.6)
Myocardial infarction prev. year	22 (2.6)	11 (2.4)	5 (2.5)	1 (1.0)
Heart failure	226 (26.5)	171 (36.9)**	27 (13.6)	15 (15.3)
History of hip fracture	111 (13.0)	108 (23.3)**	20 (10.5)	23 (25.0)*
Diabetes	147 (17.2)	74 (15.9)	32 (16.2)	12 (12.2)
Osteoarthritis	414 (48.5)	194 (41.8)*	105 (53.0)	45 (45.9)
Malignancy previous 5 years	124 (14.5)	41 (8.8)*	59 (29.8)	23 (23.5)
Number of prescribed medications	6.2 ± 4.0	7.4 ± 3.8**	6.4 ± 3.6	7.1 ± 3.8
Systolic blood pressure	150.9 ± 22.6	138.8 ± 22.5**	142.6 ± 20.1	139.1 ± 21.3
Diastolic blood pressure	75.5 ± 11.8	72.3 ± 12.4**	72.9 ± 12.6	72.4 ± 13.2
Body Mass Index	25.9 ± 4.2	25.0 ± 4.7*	25.4 ± 4.3	24.0 ± 4.4*
Barthel ADL Index (0-20)	18.7 ± 2.6	12.2 ± 6.6**	18.5 ± 2.7	13.8 ± 6.0**
Geriatric Depression Scale (0-15)	3.3 ± 2.5	4.2 ± 3.0**	3.2 ± 2.3	3.9 ± 3.1
Mini-Mental State Examination (0-30)	25.4 ± 3.3	13.2 ± 7.4**	25.1 ± 3.4	15.8 ± 6.3**
Vision impairment	89 (10.5)	114 (27.1)**	112 (56.9)	54 (56.3)
Hearing impairment	93 (11.0)	142 (31.3)**	86 (44.3)	47 (48.0)
Walking aid in gait speed test	185 (24.0)	136 (53.5)**	55 (27.8)	36 (55.4)**
Gait speed‡, m/s	0.54 ± 0.24	0.30 ± 0.23**	0.51 ± 0.20	0.36 ± 0.25
Missing gait speed values	79 (9.3)	208 (44.8)	19 (9.6)	33 (33.7)

Data are presented as mean ± standard deviation (SD), [range], or n (%). Barthel ADL: Activities of Daily Living, higher score indicate higher independence. Geriatric Depression Scale: higher score indicate more depressive symptoms. Mini-Mental State Examination: higher score indicate higher cognitive function. ‡ Measured and imputed values. * $p < 0.05$, ** $p < 0.001$ (t or $\chi 2$ test), dementia vs no dementia

Table 3. Mini-Mental State Examination scores, gait speed and changes in gait speed over 5 years and walking aid use in gait speed testing, in the total sample at baseline and according to dementia development at baseline and follow-up in the paper II study

	Developed dementia *n* = 98			Did not develop dementia *n* = 198		
	Baseline	Follow-up	Change	Baseline	Follow-up	Change
MMSE	25.2 ± 3.0	15.8 ± 6.3	-9.4 ± 6.4	26.7 ± 2.3	25.1 ± 3.4	-1.6 ± 1.5
GS, observed	0.57 ± 0.24	0.47 ± 0.19	-0.10 ± 0.20	0.68 ± 0.22	0.53 ± 0.18	-0.15 ± 0.20
GS observed+ imputed	0.57 ± 0.24	0.36 ± 0.25	-0.21 ± 0.25	0.68 ± 0.22	0.51 ± 0.20	-0.17 ± 0.21
Used walking aid in GS test	23 (23.5)	36 (55.4)[a]		17 (8.6)	55 (27.8)[b]	

Data are presented as mean ± standard deviation, or n (%). MMSE: Mini-Mental State Examination Score (0-30). Gait speed (GS) in meters / second. [a, b] 33 (33.7%) and 19 (9.6%), respectively, missing gait speed data, and hence no data on walking aid use

In paper III in 1999, compared to nonparticipants, participants were younger (64.9 ± 4.2 vs 66.1 ± 4.6, p = 0.03) and had more years of education (9.2 ± 3.6 vs 8.0 ± 2.7, p < 0.001), but there were no difference in sex distribution (p = 0.3). Table 4 shows baseline characteristics at 1999 in total sample according to dementia development in 2016-2019. Over a mean follow-up time of 19 ± 1.1 years, 175 (32%) developed dementia. Participants that developed dementia were on average 65.6 years of age at baseline and 58% had less than 8 years of education, while those that did not develop dementia were 64.6 years of age at baseline and 42% had less than 8 years of education. Table 5 shows participant characteristics in 1999 according to PA categories (low, medium, high). In the low PA group, 62% had < 8 years of education, 69% had hypertension, and 39% were classified as obese, whereas 40% had < 8 years of education, 60% had hypertension and 7% were classified as obese in the high PA group. Table 6 shows characteristics of participants in paper III and in paper IV. The mean ± SD age of participants at follow-up in paper III was 84.7 ± 3.6 years (range 79.3 - 96.3 years) and 304 (56%) were women. Fifty-two (10 %) lived in nursing homes, and 264 (49%) lived alone. Most frequent diagnoses at follow-up were hypertension

Table 4. Participants characteristics in paper III in the 1999 survey for the total sample and according to dementia in 2016-2019

	N=541	No Dementia n=366	Dementia n=175
Age 1999, years	64.9 ± 4.2 64 [59-78]	64.6 ± 4.1 64 [59-77]	65.6 ± 4.3 65 [59-78]
Follow-up, years	19.0 ± 1.1 19 [17-20]	19.0 ± 1.1 19 [17-20]	18.9 ± 1.1 19 [17-20]
Women	304 (56.2)	206 (56.3)	98 (56.0)
Lives alone, n=539	98 (18.2)	66 (18.1)	32 (18.4)
< 8 years education	257 (47.5)	155 (42.3)	102 (58.3)
Smoking, n=539	40 (7.4)	25 (6.8)	15 (8.6)
Myocardial infarction, n=536	26 (4.9)	20 (5.5)	6 (3.5)
Hypertension	361 (66.7)	239 (65.3)	122 (69.7)
Glucose intolerance, n=266	89 (33.5)	52 (28.4)	37 (44.6)
BMI, n=540	27.1 ± 4.1	27.0 ± 4.0	27.4 ± 4.3
Obese (BMI ≥ 30)	115 (21.3)	77 (21.1)	38 (21.7)
Systolic BP, mmHg	146.1 ± 21.3	145.0 ± 21.1	148.4 ± 21.4
Diastolic BP, mmHg	82.9 ± 10.9	82.8 ± 10.9	83.0 ± 10.9
Low PA[a]	80 (15.1)	47 (13.0)	33 (19.5)
Medium PA[a]	357 (67.2)	248 (68.5)	109 (64.5)
High PA[a]	94 (17.7)	67 (18.5)	27 (16.0)

Data are presented as n (%), mean ± standard deviations or median [range]. BMI: Body Mass Index. BP: Blood Pressure. PA: Physical Activity. [a] n=531

(80%), osteoarthritis (51%), hip fracture (38%), dementia (32%) and depressive disorders (29%). Thirty-eight and 83 percent were

independent in I-ADL and P-ADL, respectively. Their mean GS was 0.7 ± 0.22 m/s, and 71 (16%) used a walking aid during the GS test. The sex distribution, age, and years of education did not differ between participants in paper IV and individuals who participated only in the Norrbotten SilverMONICA study. The mean ± SD age of participants in paper IV was 84.4 ± 3.8 (range 79–96) years, and 42 (55%) were women. Two (3%) participants lived in nursing homes and 32 (42%) lived alone. The most frequent diagnoses included hypertension (74%), osteoarthritis (54%), dementia (22%), and depression (18%). The mean number of prescribed medications was 6.3 ± 3.7. Forty-seven percent of participants were independent in I-ADL and 90% were independent in P-ADL. The mean GS was 0.74 ± 0.19 m/s; eight participants had GS < 0.5 m/s, and 10 (14%) used walking aids during the GS test (Table 6).

Table 5. Participant characteristics in the 1999 survey according to level of physical activity

	Low, n=80	Medium, n=357	High, n=94
Age 1999, years	64.8 ± 4.5 64 [59-77]	64.9 ± 4.2 64 [59-78]	64.8 ± 4.2 64 [59-77]
Follow-up, years	19.0 ± 1.1 19 [17-20]	18.9 ± 1.1 19 [17-20]	19.0 ± 1.0 19 [17-20]
Women	51 (63.8)	204 (57.1)	45 (47.9)
Lives alone, n=539	18 (22.5)	61 (17.1)	16 (17.0)
< 8 years education	50 (62.5)	162 (45.4)	38 (40.4)
Smoking, n=539	13 (16.3)	22 (6.2)	5 (5.3)
Myocardial infarction, n=536	4 (5.0)	16 (4.5)	6 (6.4)
Hypertension	55 (68.8)	245 (68.6)	56 (59.6)
Glucose intolerance, n=266	20 (55.6)	60 (31.7)	6 (16.7)
BMI, n=540	28.5 ± 4.6	27.2 ± 4.0	25.7 ± 3.3
Obese (BMI => 30)	31 (38.8)	74 (20.7)	7 (7.4)
Systolic BP, mmHg	148.2 ± 22.6	147.1 ± 21.9	141.5 ± 17.5
Diastolic BP, mmHg	84.1 ± 12.3	83.1 ± 10.9	81.0 ± 9.6

Data presented as n (%), mean ± standard deviations, or median [range]. BMI: Body Mass Index. BP: Blood Pressure.

Table 6. Participant characteristics at follow-up in 2016-2019, paper III and paper IV studies

		Paper III		Paper IV
	Total, n=541	No dementia n=366	Dementia n=175	Actigraphy, n=76
Age, y (range)	84.7 ± 3.6 (79.3 - 96.3)	84.4 ± 3.5* 84 (79-96)	85.4 ± 3.8 85 (80-96)	84.4 ± 3.8 (79-96)
Women	304 (56.2)	206 (56.3)	98 (56.0)	42 (55.3)
Nursing home resident	52 (10.2)	6 (1.7)*	46 (27.9)	2 (2.6)
Lives alone	264 (48.8)	181 (53.2)	83 (55.0)	32 (42.1)
Education < 8 years	257 (47.5)	155 (42.3)*	102 (58.3)	28 (37.3)
Smoking	16 (3.3)	10 (3.0)	6 (3.9)	1 (1.3)
Alzheimer's dementia	70 (12.9)	-	70 (40.0)	11 (14.5)
Vascular dementia	68 (12.6)	-	68 (38.9)	3 (3.9)
Other / mixed dementia	38 (7.0)	-	37 (21.1)	3 (3.9)
Depressive disorder	156 (28.8)	75 (20.7)*	67 (39.2)	14 (18.4)
Cerebrovascular disease	98 (18.1)	44 (12.0)*	54 (30.9)	2 (2.6)
Myocardial infarction	99 (18.3)	68 (18.6)	31 (17.7)	4 (5.3)
Hypertension	435 (80.4)	289 (79.0)	146 (83.4)	56 (73.7)
Heart failure	83 (15.3)	47 (12.8)*	36 (20.6)	9 (11.8)
Hip fracture	208 (38.4)	151 (41.3)	57 (32.6)	4 (5.3)
Diabetes	119 (22.0)	73 (19.9)	46 (26.3)	8 (10.5)
Osteoarthritis	275 (50.8)	199 (54.4)*	76 (43.4)	41 (53.9)
No. of medications	7.1 ± 4.1	6.8 ± 4.0*	7.8 ± 4.3	6.3 ± 3.7
Hearing impairment	167 (35.2)	109 (33.1)	57 (39.7)	25 (33.3)
Vision impairment	270 (57.6)	184 (56.1)	86 (61.0)	24 (32.0)
MNA (0-30)	25.0 ± 3.9	26.0 ± 2.8*	22.8 ± 5.0	25.9 ± 2.2
BMI (weight/length^2)	26.5 ± 4.4	26.7 ± 4.4	26.1 ± 4.2	25.1 ± 4.1
Systolic BP mmHg	139 ± 20.3	139.8 ± 19.5	136.7 ± 21.7	144 ± 21
Diastolic BP mmHg	77± 10.5	77.2 ± 10.6	76.4 ± 10.5	77 ± 10
Independent in I-ADL	184 (37.6)	164 (49.2)*	20 (12.7)	36 (47.4)
Independent in P-ADL	404 (82.6)	310 (93.1)*	94 (60.3)	68 (89.5)
GDS-15 (0-15)	2.3 ± 2.0	2.0 ± 1.8*	2.8 ± 2.3	2.0 ± 1.7
MMSE (0-30)	24.6 ± 5.7	27.2 ± 2.1*	18.7 ± 6.9	26.1 ± 3.1
FAB (0-18)	12.4 ± 3.8	13.8 ± 2.5*	8.9 ± 4.1	13.4 ± 3.2
Gait speed	0.7 ± 0.22	0.7 ± 0.2*	0.6 ± 0.2	0.7 ± 0.19
Walking aid use GS test	71 (16.1)	45 (14.0)*	26 (21.8)	10 (14.3)

Data presented as mean ± standard deviation, or n (%). MNA: Mini Nutritional Assessment. BMI: Body Mass Index, weight / height^2. BP: Blood Pressure. I-ADL: Instrumental Activities of Daily Living. P-ADL: Personal Activities of Daily Living. GDS-15: Geriatric Depression Scale. GS: Gait speed. MMSE: Mini-Mental State Examination. FAB: Frontal Assessment Battery. * Statistically significant difference ($p<0.05$) between group that did and did not develop dementia.

Paper I outcomes

The univariate and multivariate associations between the MMSE score and GS in the total sample and in subgroups defined by dementia and walking aid use are shown in Table 7. Multivariate analysis revealed an association between MMSE and GS in the total sample (β = 0.006, 95% confidence intervals [CI] = 0.004, 0.008, p < 0.001; Table 7). This remained significant after the addition of imputed GS values (β = 0.011, 95%CI = 0.009, 0.013, p < 0.001). Multivariate analysis revealed no significant association of the MMSE score with GS in participants with dementia and available GS values (β = 0.003 m/s, 95%CI = 0.000, 0.006, p = 0.058), but this association was significant when imputed values for GS were added (β = 0.007 m/s, 95%CI = 0.002, 0.011, p = 0.002; Table 7). In participants without dementia, the MMSE score was associated with GS (with and without imputed values).

Table 7. Association between Mini-Mental State Examination score and gait speed in paper I

	n	Univariate β (95% CI)	p-value	Multivariate β (95% CI)	p-value
Total sample					
GS measured	1030	0.015 (0.013, 0.017)	<0.001	0.006 (0.004, 0.008)	<0.001
GS measured+imputed	1317	0.018 (0.016, 0.020)	<0.001	0.011 (0.009, 0.013)	<0.001
Dementia					
GS measured	256	0.008 (0.005, 0.012)	<0.001	0.003 (0.000, 0.006)	0.058
GS measured+imputed	464	0.013 (0.010, 0.016)	<0.001	0.007 (0.002, 0.011)	0.002
No dementia					
GS measured	774	0.020 (0.015, 0.025)	<0.001	0.010 (0.006, 0.015)	<0.001
GS measured+imputed	853	0.024 (0.019, 0.029)	<0.001	0.015 (0.010, 0.020)	<0.001
No walking aid [a]					
GS measured	703	0.012 (0.009, 0.016)	<0.001	0.010 (0.06, 0.014)	<0.001
Walking aid [a]					
GS measured	321	0.007 (0.005, 0.009)	<0.001	0.005 (0.002, 0.008)	<0.001

Multivariate linear regression analyses were adjusted for age, sex and baseline characteristics associated (p ≤ 0.15) with Gait Speed (GS) (measured and imputed) and Mini-Mental State Examination score: living alone, < 8 years education, smoking, depression, cerebrovascular disease, heart failure, history of hip fracture, malignancy previous 5 years, benzodiazepine use, beta-blocker use, analgesic use, neuroleptic use, number of prescribed medications, systolic blood pressure, vision impairment, hearing impairment and use of walking aid during GS test. In subgroup analyses performed according to walking aid use, this variable was omitted from the adjustment. [a] Participants who were unable to perform the GS test, and subsequently had a GS value imputed (n=287), had no reported walking aid and could therefore not be included in subgroup analyses of walking aid use. β, unstandardized beta. CI, confidence interval.

The MMSE score also was associated with GS regardless of walking aid use. Interaction analysis performed with measured GS values revealed that this association differed between groups (β -0.005, 95%CI = -0.009, 0.000, p=0.032) and was attenuated in participants who used a walking aids; when imputed GS values were added, the difference between groups remained significant (β -0.019, 95%CI = -0.024, -0.013, p<0.001). The univariate association between the MMSE score and GS according to walking aid use is shown in figure 5.

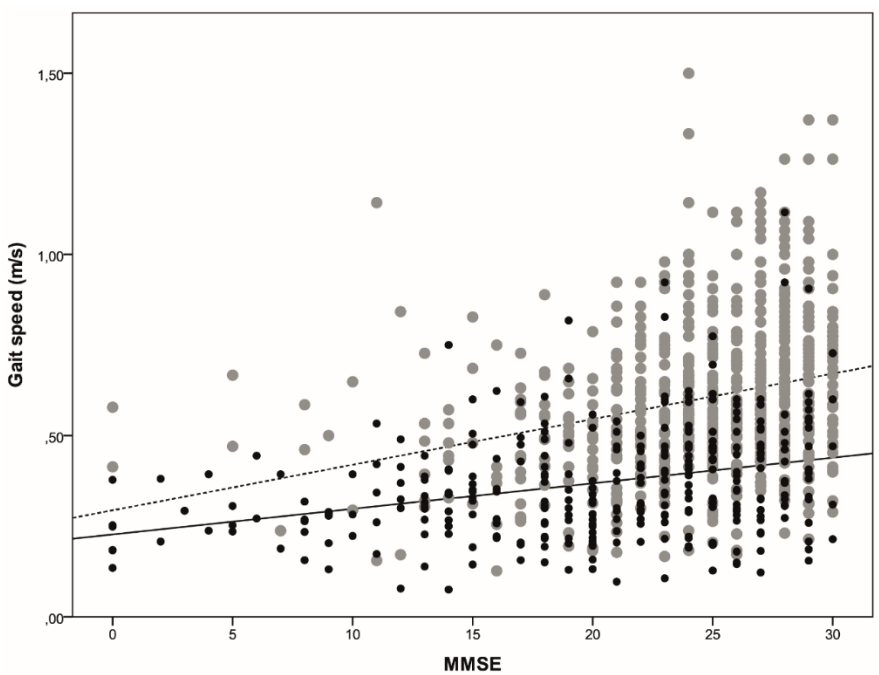

Figure 5 Univariate association between the Mini-Mental State Examination (MMSE) score and gait speed in paper I. The gray dots and dotted line represent participants who did not use a walking aid during the gait speed test (n = 703, r^2 = 0.073), and the black dots and solid line represent participants who used a walking aid during the test, (n = 321, r^2 = 0.098).

Paper II outcomes

Decline in GS was associated with dementia development in the adjusted, but not unadjusted, logistic regression analysis (Table 8). The baseline GS was associated with dementia development in unadjusted and adjusted analyses (Table 8). In unadjusted and adjusted linear regression models, ΔGS was associated significantly with ΔMMSE in the total sample and in participants that developed dementia, but not those that did not develop dementia (Table 9).

Table 8. Odds ratios (ORs) for incident dementia according to gait speed at baseline and change in gait speed

Measure	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Change in gait speed, m/s [a]	2.37 (0.79, 7.11)	0.124	4.38 (1.33, 14.43)	0.015
Gait speed at baseline, m/s [b]	8.04 (2.51, 25.77)	<0.001	4.33 (1.03, 18.14)	0.045

[a] Adjusted for age, sex, body mass index (BMI), history of malignancy, nursing home resident, and Barthel Activities of Daily Living (ADL) Index score. n = 51 with missing gait speed values at follow-up. [b] adjusted for age, sex, BMI, history of malignancy, nursing home resident, Barthel ADL Index score, history of hip fracture, and Mini-Mental State Examination (MMSE) score. CI, confidence interval.

Table 9. Linear association between decline in gait speed and decline in MMSE scores (dependent variable) in total sample and according to dementia development

Group	Unadjusted β (95% CI)	*P*	Adjusted β (95% CI)	*P*
Total [a]	6.41 (3.40, 9.41)	< 0.001	7.17 (4.17, 10.18)	<0.001
Developed dementia [a]	11.74 (7.01, 16.39)	< 0.001	13.01 (8.32, 17.83)	<0.001
Did not develop dementia [a]	-0.12 (-2.54, 2.30)	0.921	-0.062 (-2.59, 2.46)	0.961

[a] Adjusted for age, sex, body mass index, history of malignancy, and use of walking aid during the gait speed test. β, unstandardized beta. CI, confidence interval.

The omission of imputed GS values altered some results. The association between baseline GS and dementia was unchanged because there were no missing baseline GS values. After this omission, ΔGS was not associated with the subsequent development of dementia in the unadjusted [odds ratio (OR) = 0.45, 95%CI = 0.11, 1.89, p = 0.273] or adjusted (OR = 0.85, 95%CI = 0.18, 4.01, p = 0.838) analyses. In the total sample, ΔGS was not associated significantly with ΔMMSE in the unadjusted or adjusted analyses (β = 0.30, 95%CI -4.02, 3.42, p = 0.875 and β 1.21, 95%CI -2.61, 5.04, p = 0.533, respectively). Among participants that developed dementia, ΔGS was associated significantly with ΔMMSE in the adjusted analysis (β = 8.89, 95%CI 0.09, 17.69, p = 0.048), but not in unadjusted analyses (β = 6.10, 95%CI -2.01, 14.22, p = 0.138). Among participants without dementia development, ΔGS was not associated with ΔMMSE (unadjusted β = -0.75, 95%CI -3.26, 1.75, p = 0.553 and adjusted β = -0.69, 95%CI -3.34, 1.96, p = 0.607).

Paper III outcomes

Hazard ratios with 95% CIs for dementia development in very high age according to self-reported PA are presented in Table 10. No significant associations between PA and dementia were found in unadjusted or adjusted models. Survival curves according to PA categories are shown in Figure 6. Associations of PA with cognitive function, executive function and GS in very high age are shown in Table 11. PA was not associated with cognitive function in either model. PA was associated with executive function in the unadjusted model (unstandardized beta [95% CI]) (0.67 [0.07, 1.27]), but not after full adjustment (0.49 [-0.11, 1.09]). PA associated with GS in unadjusted model and model adjusted for age, sex, smoking status and < 8 years education (0.06 [0.02, 0.09], and 0.04 [0.01, 0.08], respectively) but not in the fully adjusted model (0.02 [-0.01, 0.06]). The stratified analyses with subgroups according to retired status and education < 8 years showed similar results as for the total group (data not shown). Using the original 6-level PA scale showed similar results as the 3-category variable (data not shown).

Table 10. Hazard ratios (HR) for dementia in very high age according to physical activity level two decades earlier

		Unadjusted		Model A		Model B	
Physical Activity	n	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
High	94	1		1		1	
Medium	357	1.36 (0.81, 2.26)	0.2	1.16 (0.68, 1.97)	0.6	1.10 (0.63, 1.92)	0.7
Low	80	1.04 (0.68, 1.59)	0.9	1.02 (0.67, 1.57)	0.9	1.00 (0.65, 1.56)	0.97
p trend	531	0.85 (0.65, 1.10)	0.2	0.93 (0.71, 1.21)	0.6	0.95 (0.72, 1.26)	0.7

Model A adjusted for age, sex, <8 years education, smoking. Model B additionally adjusted for glucose intolerance, hypertension and BMI>30 kg/meter squared. P trend: Physical activity was treated as a continuous variable. CI, confidence interval

Table 11. Linear associations of physical activity with cognitive function, executive function, and gait speed in very high age

		Unadjusted		Model A		Model B	
	n	**β (95% CI)**	**r^2 (p)**	**β (95% CI)**	**r^2 (p)**	**β (95% CI)**	**r^2 (p)**
Cognitive function	462	0.52 (-0.36, 1.41)	0.001 (0.2)	0.25 (-0.63, 1.13)	0.060 (0.6)	0.15 (-0.75, 1.06)	0.072 (0.7)
Executive function	458	0.67 (0.07, 1.27)	0.008 (0.03)	0.47 (-0.11, 1.04)	0.109 (0.1)	0.49 (-0.11, 1.09)	0.105 (0.1)
Gait speed	437	0.06 (0.02, 0.09)	0.019 (0.002)	0.04 (0.01, 0.08)	0.144 (0.02)	0.02 (-0.01, 0.06)	0.186 (0.2)

β, unstandardized beta. r^2, Adjusted. Model A adjusted for age, sex, <8 years education, smoking. Model B added glucose intolerance, hypertension, Body Mass Index > 30 kg/meter squared. CI, confidence interval

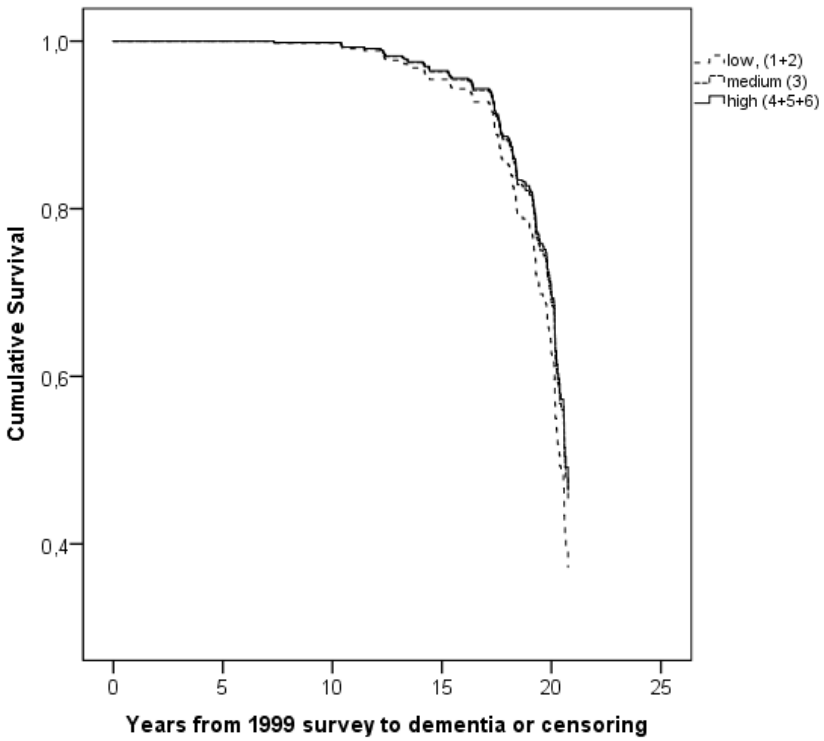

Figure 6 Kaplan-Meier Survival curves for dementia stratified by low, medium, and high physical activity. Log-rank test p = 0.5.

Paper IV outcomes

Correlations between IPAQ-E 80+ scores and accelerometer measures were significant for the total inactive (moderate, r = 0.55 $p < 0.001$), nighttime lying (substantial, r = 0.65 p < 0.001), daytime lying (fair, r = 0.26, $p = 0.025$) and sedentary (fair, r = 0.28, p = 0.015) times, but not for sitting time (r = 0.09, $p = 0.42$) (Table 12). The total inactive time was underestimated by a mean of -18.56 hours/week, and the night-time lying and daytime lying times were overestimated by means of 1.28 hours/week and 2.04 hours/week, respectively, the latter with heteroscedasticity (Figure 7).

Plots for sitting and sedentary times showed similar underestimation by means of -22.74 and -20.86 hours/week, respectively, Figure 7. Correlations with IPAQ-E 80+ scores were also significant for the total active (moderate, r = 0.60 p < 0.001) and walking (moderate, r = 0.54, p <0.001) times, but not for the MV walking, MVPA, or total MVPA times (Table 12, Figure 8).

Table 12. Self-reported and accelerometer-measured (in) activity (hours/week) of participants in the paper IV study (n = 76), and correlation between measures

Measure	IPAQ-E 80+	Accelerometry	Spearman's r, p
Total inactive time[a] (n = 69)	109.0 ± 23.8 [101.5 (73.5–167.4)]	127.9 ± 15.4 [126.9 (96.3–166.8)]	0.55, <0.001
Nighttime lying down[a] (n = 70)	59.7 ± 10.2 [59.5 (42.0–85.7)]	58.5 ± 15.4 [57.7 (26.3–139.4)]	0.65, <0.001
Daytime lying down[a]	6.9 ± 8.1 [3.5 (0–35.0)]	4.8 ± 6.9 [2.0 (0–30.5)]	0.26, 0.025
Sitting (n = 75)	41.3 ± 15.5 [41.3 (14.0–84.0)]	64.5 ± 15.5 [65.9 (20.9–100.9)	0.09, 0.42
Sedentary time (daytime lying down + sitting; n = 75)	48.1 ± 17.2 [45.5 (19.2–92.2)]	69.4 ± 14.4 [69.6 (20.9–100.9)]	0.28, 0.015
Total active time[a] (n = 75)	9.19 ± 9.3 [6.1 (0–45.5)]	9.9 ± 5.5 [9.3 (0.01–25.7)]	0.60, <0.001
Walking	5.7 ± 6.2 [3.9 (0–35.0)]	9.7 ± 5.6 [9.3 (0–25.7)]	0.54, <0.001
MV walking[a]	0.3 ± 0.7 [0.0 (0–3.7)]	1.4 ± 1.9 [0.5 (0–7.1)]	0.06, 0.58
MVPA (n = 75)	3.5 ± 6.1 [0.6 (0–35.0)]	1.4 ± 1.9 [0.5 (0–7.1)]	0.17, 0.13
Total MVPA (MVPA + MV walking[a]; n = 75)	3.8 ± 6.2 [1.0 (0–35.0)]	1.4 ± 1.9 [0.5 (0–7.1)]	0.17, 0.16
Daily steps	–	6200 ± 3763 [5743 (4–16.947)]	
Estimated daily distance walked, km	–	3.79 ± 2.34 [3.56 (0.002–11.19)]	

Values are presented as mean ± standard deviation [median (range)].
[a] Addition to the original IPAQ-E.
IPAQ-E 80+, International Physical Activity Questionnaire adapted for adults aged ≥ 80 years. MV, moderate to vigorous. PA, physical activity.

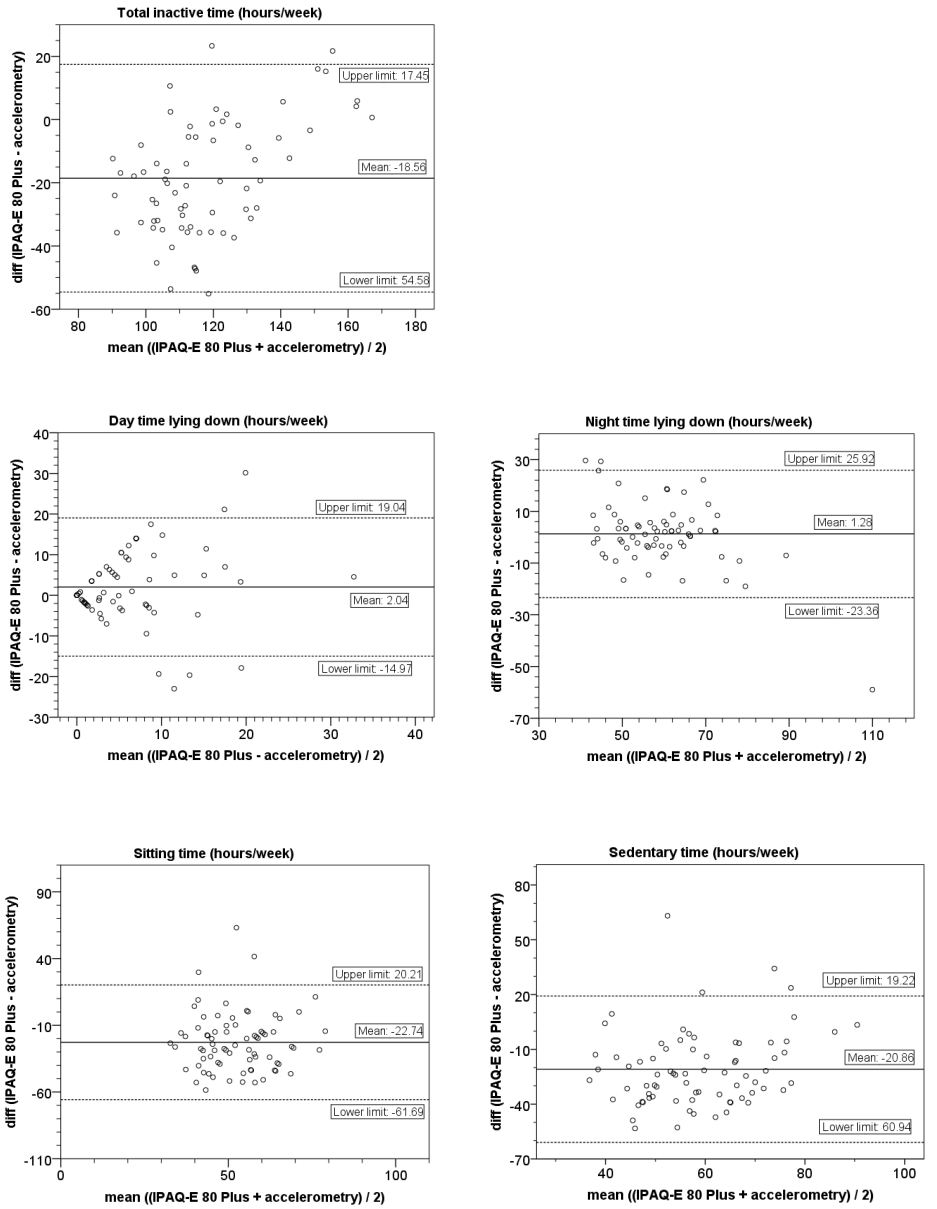

Figure 7 Bland-Altman plots of differences (in hours per week) in inactive time between IPAQ-E 80+ and accelerometer measures. IPAQ-E 80+, International Physical Activity Questionnaire adapted for adults aged ≥ 80 years.

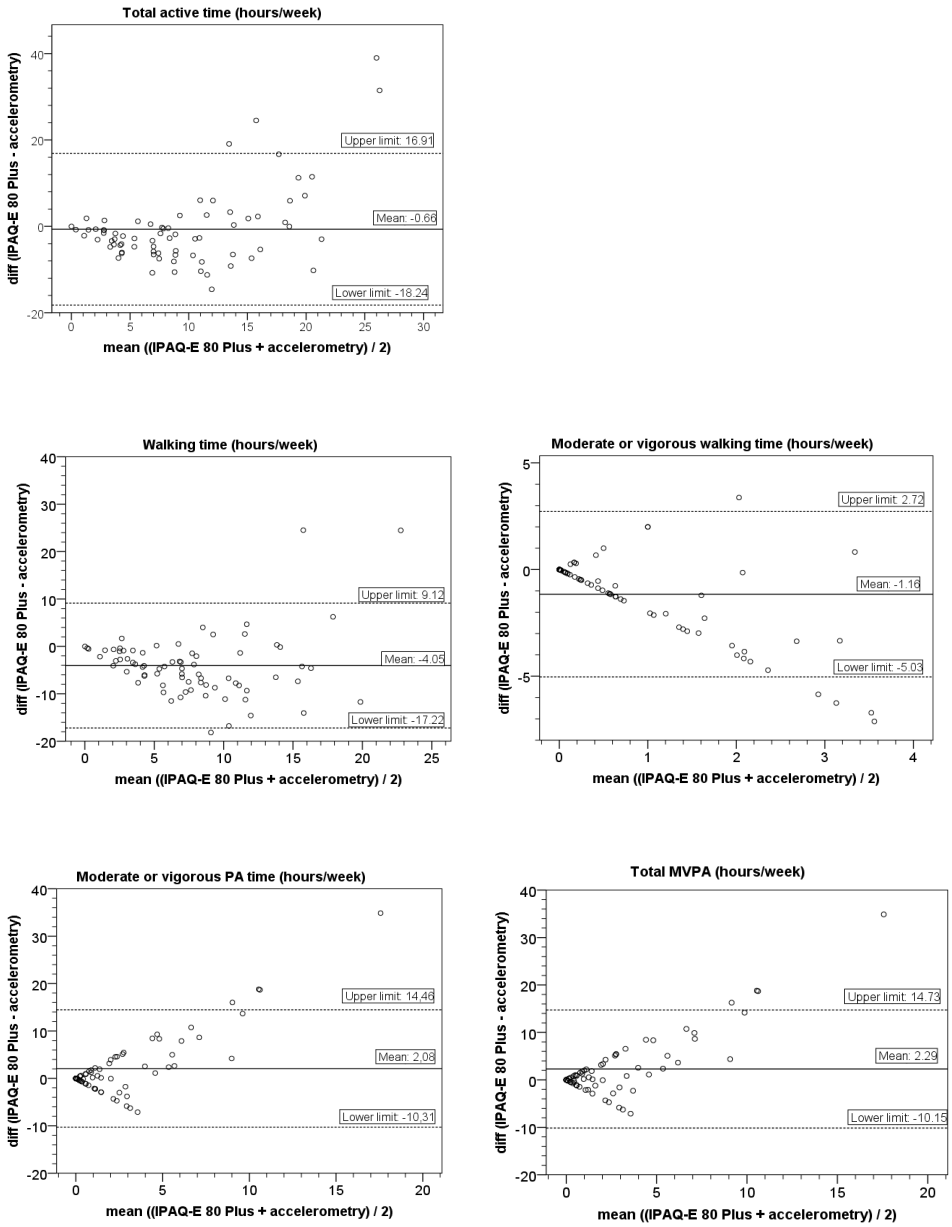

Figure 8 Bland-Altman plots of differences (in hours per week) in active time between IPAQ-E 80+ and accelerometer measures. IPAQ-E 80+, International Physical Activity Questionnaire adapted for adults aged ≥ 80 years.

The total active and walking times were underestimated by -0.66 and -4.05 hours/week, respectively (Figure 8). The MV walking time was also underestimated (by 1.16 hours/week), but this result was characterised by heteroscedasticity. MVPA and total MVPA times were overestimated (by 2.08 and 2.29 hours/week, respectively), both with heteroscedasticity. Of the 76 participants, 41 reported any time spent performing MVPA and 48 reported any time spent performing MVPA including MV walking.

Sensitivity and specificity values reflecting the ability of the IPAQ-E 80+ to correctly identify participants achieving, and not achieving, the recommended PA level were 61% and 59%, respectively, for 100 SPM, and 55% and 70%, respectively, for 75 SPM (Table 13). The measure of agreement beyond chance was significant only for 75 SPM (Cohen's $\kappa = 0.228$, $p = 0.033$). The results of the sensitivity analysis performed with the exclusion of the two most sedentary participants were similar to those of the main analysis. In subgroup analyses, the correlation coefficient for total inactive time was larger in the proxy than in the no-proxy subgroup ($z = -2.9$, $p = 0.004$), and the coefficient for walking time was larger in the depression than in the no-depression subgroup ($z = -2.67$, $p = 0.0076$). No difference in the degree of correlation related to sex, GS threshold, or dementia disorders was observed.

Table 13 Proportions of participants achieving the recommended physical activity levels, and IPAQ-E 80+ sensitivity and specificity

SPM threshold	Achieved recommended physical activity levels [*n* (%)]		Sensitivity	Specificity	*κ*	*p*
	Accelerometry	IPAQ-E 80+[a]				
≥100	18 (23.7)	35 (46.1)	61.1%	58.6%	0.149	0.142
≥75	49 (64.5)	35 (46.1)	55.1%	70.4%	0.228	0.033

[a]Moderate or vigorous walking + moderate or vigorous physical activity. IPAQ-E 80+, International Physical Activity Questionnaire adapted for adults aged ≥ 80 years. SPM: steps/minute. K: Cohens Kappa

Discussion

Gait speed was associated with cognition both cross-sectionally and longitudinally, and low and declining GSs were associated with greater odds of dementia development, in very old people. Use of walking aids seem to attenuate the association between GS and cognition. PA in late middle to old age was not associated with dementia development nor cognitive function up to two decades later, irrespective of adjustments. PA was associated with subsequent executive function in unadjusted, but not adjusted analyses. PA was associated with GS in an unadjusted analysis and an analysis adjusted for age, sex, education and smoking, but not in an analysis additionally adjusting for hypertension, glucose intolerance and obesity. The novel IPAQ-E 80+ showed fair to substantial correlation to total inactive time, total active time and walking time, but low sensitivity and specificity for the identification of individuals attaining recommended PA levels.

Gait and cognition

The cross-sectional association identified between cognitive function and GS with adjustment for potential confounders in the paper I study is in line with the association between gait and cognitive function in healthy older adults revealed by a recent systematic review.[98] Relative to the review sample, participants in the paper 1 study were older, and included people living in nursing homes, people with dementia and those unable to perform the GS test. Older populations have been described as heterogeneous, with large degrees of variations in physical and cognitive functions and number of diseases and disorders, and prescribed medications; this description applies to the paper I study group. Despite such heterogeneity, and the presence of many potential confounders, GS was associated positively and independently with cognitive function.

The association between cognitive function and GS among people with dementia in an unadjusted analysis in the paper I study is in line with age-adjusted analyses among older people with dementia.[99] Potential confounding factors that could influence the association between cognitive function and GS include medical conditions and medication use, which are prevalent among people with dementia.[100] Adjustment for such confounders is especially important when investigating this association in very old people due to the age-related increase of clinical diagnoses that may affect gait and/or cognition. Indeed, adjusted analyses in the paper I study revealed no association between GS and cognitive function until participants with missing GS values were accounted for. Likewise, in a cross-sectional study including 161 people with dementia in nursing homes,

cognitive function was not associated with GS in comprehensively adjusted analyses that excluded those unable to perform a GS test.[72]

The paper II study results extend previous findings of an association between GS decline and dementia development, primarily among younger old people[101–103] to also include very old people. The influence of potential confounders may help to explain the identification of an association between change in GS and dementia development only after analysis adjustment in the paper II study. Another potential explanation is the relatively low power of the analysis, given the limited number of participants retained throughout the entire study period. The paper II study found that a decline in GS and a low baseline GS were independently associated with higher odds of dementia development within 5 years, after adjusting for potential confounders. In addition, declining GS was associated with declining cognitive function among those that developed dementia, but not among people that remained dementia free. No association was found between cognitive function and GS in participants with dementia until compensating for missing values.

The paper II study showed that low baseline GSs were associated with increased odds of dementia development in very old people after adjustments for baseline cognitive performance. Low GS has been found to precede dementia in younger old people[66,101]; few such studies have included only very old people. Notably, Bullain et al.[104] found that baseline GS was associated with dementia development in people aged ≥ 90 years in analyses adjusted thoroughly for potential confounders. They also included baseline cognitive status determined by in-person neurological examination and cognitive measures of the MMSE, Modified MMSE, or Clinical Dementia Rating scale[104]; the analyses reported on in paper II were adjusted for baseline MMSE scores. Thus, GS seems to be associated independently with dementia development, and may provide unique and clinically useful information regarding the risk of dementia that is not evident from direct assessments of very old people's cognitive function.

The association between GS decline and dementia development was strengthened further by the observation in the paper II study that GS decline was associated with cognitive function decline among people who developed dementia. A recent meta-analysis showed that participants with declines in GS and memory task performance were at greater risk of dementia development than were those with a decline in only one of these dimensions.[62] Conversely, a large study provided no support for a synergistic effect between GS and cognition, treated as an aggregate measure involving memory, time orientation, verbal fluency and processing speed.[105] The lack of a significant association between declines in GS and cognitive function in the group without dementia is consistent with the findings

from Welmer et al.[103] that cognitive function remained relatively stable while GS declined over a 6 year period in older (mean age, 72 years) people who did not develop dementia.

Among participants of the paper I study who used walking aids, the association between cognitive function and GS was attenuated. The use of an aid when walking straight may decrease the cognitive processing burden, possibly by compensating for poor balance, muscle strength, or lower limb motor control, or by alleviating pain. This finding is in line with a study of the association between backwards walking speed and cognitive function in older people with dementia living in nursing homes.[72] In addition, in a small study of healthy adults, walking aid use reduced reaction times while beam-walking, indicating reduced cognitive load.[106] Conversely, the use of a walking aid during more complex walking tasks (e.g. turning), which requires greater manoeuvring of the walking aid, may increase cognitive load.[73] The impact of walking aid use on cognitive load needs to be investigated further, but in light of the present result, physical exercise may be indicated to augment gait, thereby alleviating the cognitive load and increasing the availability of cognitive resources for complex walking task and fall avoidance.

Mobility limitations, which may impact the ability to perform a GS test, become more prevalent with age, and their prevalence has been reported to approach 90% in some nursing home settings.[98,107] One previous study conducted with very old people showed that the ability to perform the GS test declined with age in women, with GS values missing for more than half of the female participants aged ≥ 95 years.[108] Studies investigating GS in older populations, in clinical[109] and nursing home[75] settings, have highlighted the exclusion of persons who cannot walk from most studies. The same exclusion criterion is used in most studies investigating the association between gait and cognition,[98] which may restrict the interpretation of results. In the paper I study, GS values were missing for about one-fifth of participants, who were older, had more prescribed medications, diagnoses and medical conditions, and had worse scores on most assessments, than did participants with measured GS. Notably, the majority of participants with missing GS values had dementia and severe cognitive impairment.

Models of gait and cognition

Many physiological explanations for, and models describing, the association between gait and cognition have been proposed. GS may be a more sensitive measure of cognitive decline than are traditional cognitive tests because gait dependends on the majority of the bodys organ systems (circulatory, nervous, musculoskeletal and sensory) all of which exhibit age-related declines.

Montero-Odasso et al.[110] integrated the study of falls and dementia into a single model, postulating that cognition predicts mobility decline and falls, and that mobility decline and slow gait concurrently predict cognitive decline. Amboni et al.[111] added to this model by developing integrated tools for risk assessments and highlighting possible lines of intervention (i.e. cognitive therapy for falls prevention and walking programs for reducing dementia risk).

Grande et al[112] proposed body- and brain-driven hypotheses to explain the relationship between gait and cognition. The brain-driven hypothesis postulates that neurodegenerative or vascular damage causes cognitive and motor dysfunction. However, contradicting evidence from post-mortem studies show that impairment is not proportional to this damage. The body-driven hypothesis states that diseases and disorders outside the central nervous system can have concurrent, detrimental impacts on cognitive and motor functions. This hypothesis has good face validity, as many modifiable risk factors for cognitive decline, such as smoking, hypertension, and diabetes, are shared with cardiovascular disease.[48] In the paper I study, smoking, low educational level, malignancy, and systolic and diastolic blood pressure were associated with GS (a measure of physical function) and MMSE (a measure of cognitive function). Although cross-sectional, these data provide some support for the body-driven hypothesis.

Physical activity and cognition

The lack of an association between PA and dementia development in the paper III study is similar to the findings of Sabia et al.,[43] that PA had no neuroprotective effect in people aged 35-55 years at baseline over a 27-year follow-up period, but that the PA level began to decline up to 9 years before the diagnosis of dementia. Sabia et al.[43] proposed that this finding reflects reverse causation, i.e. that reduced PA is a preclinical symptom of dementia. However, several other large studies have shown that PA is associated with dementia development more than two decades later, in the seventh decade of life at follow-up.[40–42] As participants in the paper III study were about 10 years older at follow-up than were participants those three studies, these result raise the interesting question of whether PA have a successive diminishing impact on future dementia with increasing age.

In addition to the follow-up period, the intensity of PA may also affect the association with subsequent dementia development. Tan et al.[113] reported that PA was associated with dementia in people ≥ 70 years of age only when comparing the lowest with the higher quintiles (Q1 vs. Q2-Q5), which indicates the existance of a threshold effect of PA's protection against dementia. This may explain the

lack of an association between PA and dementia development in the paper III study, as only 17% (n=94) of participants had high PA levels (levels 4-6).

Discrepancies among study findings may also be due to differences in PA assessment. The questionnaire used in the paper III study combined PA intensity and duration. The separate assessment of PA intensity, frequency, and duration may be needed to more clearly understand the potential effect of PA on dementia development.

A meta-analysis of prospective studies showed consistent protection of all PA levels against cognitive decline in participants without dementia.[114] Ten of the 15 studies included showed a protective effect of PA; participants where generally younger at baseline, and were followed for a shorter period than were participants in the paper III study. Thus, the protective effect on cognition may be limited to high PA levels at an earlier point in life, perhaps in middle age. In addition, participants with better executive function may be able to maintain higher PA levels throughout life.

Regarding intervention studies of PA and cognitive function, tertiary outcomes from a randomized controlled trial of 1476 sedentary adults over 70 years of age, found no effect of a 24 month moderate-intensity PA program (walking, resistance training, flexibility) over a health education program on incident MCI or dementia.[33] A systematic review of RCTs[34] produced insufficient evidence for the ability of single-component PA interventions to prevent cognitive decline over a 6-month follow-up period. The authors stated that short-term interventions may not be able to reverse the effects of high-risk behaviour over a long lifetime. As the aetiology of dementia is multifactorial, succesful interventions may need to be multidomain in nature. The 2 year multidomain FINGER intervention, consisting of diet modification, cognitive training, physical exercise and vascular risk factor management, improved cognitive function in a group of older people at risk of cognitive decline,[35] but data on dementia from this trial have not yet been published.

Physical activity and gait speed

A small but meaningful change in GS has been suggested to be 0.04 m/s,[115] in line with the difference separating low, medium, and high PA categories in the paper III study. In unadjusted analyses, higher PA levels associated with subsequently higher GS; participants with higher PA levels in middle to old age had better physical function and overall health in very high age than did those with lower PA levels. The association between PA and GS was robust when adjusting for age, sex, smoking, and education, but not when also adjusting for cardiovascular risk factors (hypertension, high BMI and diabetes status). This indicate that

cardiovascular risk factors may mediate the association between PA and GS, i.e. PA may lower cardiovascular risk factor burden, which in turn protects against decline in physical function as measured by GS. This finding is in agreement with the positive association of PA with GS 8 years later in an observational study conducted with 1655 participants with a mean age of 69 years at followup; the authors proposed that this association was mediated mainly by body composition (lean to fat mass ratio).[116] However, PA associated with the lowest quartile of GS over 5 years among 711 participants with a mean age of 74.1 years, irrespective of adjustments of factors such as diabetes, waist circumference, and hypertension.[117]

Measurement of physical activity

IPAQ-E 80+ and accelerometer measures of total active time, total inactive time, nighttime lying and sedentary time showed fair to substantial correlations. Total active time and total inactive time were underreported. An underestimation of self-reported sedentary time was indicated, primarily time in sitting, which also showed signs of systematic error. Correlations of total active and walking times were moderate, but not significant for sitting, MV walking, and MVPA. Systematic errors were observed in assessments of MV walking and MVPA. The sensitivity and specificity of the IPAQ-E 80+ for the accurate identification of participants (not) attaining the recommended PA level with the two SPM thresholds tested were low.

To my knowledge, Hurtig-Wennlöf et al.[55] have done the only IPAQ-E validation study. Thus, studies of IPAQ use with adult and older adult populations are also considered here. The IPAQ-E 80+ correlated substantially with accelerometer measures of night-time lying, with a slight overestimation. The correlation for daytime lying time was fair, with a systematic error of over- and underreporting. Similar systematic errors in MVPA times have been reported.[118,119] IPAQ-E 80+ scores showed moderate correlations to accelerometer measures and led to underestimation of total inactive and slight underestimation of total active time, indicating that the scale can be used to rank individuals PA levels, but with uncertainty about its accuracy in absolute values. As no other study to my knowledge has employed a similar methodology measuring very old people's 24-hour activity patterns, no direct comparison is possible.

The lack of correlation of IPAQ-E 80+ and accelerometer-derived sitting times in the paper IV study is in line with the results of a study conducted with adults using the long-form IPAQ.[120] For both questionnaires, item order (with the sitting item following lying items in IPAQ-E 80+ and appearing last in the IPAQ long form) may lead participants to underestimate their sitting times. In contrast, fair to substantial correlations of IPAQ/IPAQ-E– and accelerometer-measured sitting

times in older adults have been reported (Spearman's r = 0.26 – 0.70).[55,118,119] Thus, the questionnaire-based measurement of sitting time appears to be possible, but challenging with increasing respondent age; all adults may be prone to the underestimation of sitting time, and this tendency may increase with age. The lack of correlation of sitting times in the paper IV study does not appear to be attributable to the proportion of people with dementia, as demonstrated by the results of the subgroup analysis.

The moderate correlation of the walking time (but not the MV walking or MVPA time) between measures in the paper IV study stands in contrast to the correlation of accelerometer and IPAQ-derived MVPA measures reported by Cleland et al. (Spearman's r = 0.43 – 0.56).[118] However, Ryan et al.[119] reported a correlation (Spearman's r = 0.19) between self-reported and accelerometer-measured MVPA with no accelerometer bout threshold, and no correlation with a 10-min bout threshold. Participants in both of those studies were 10 years younger on average than the paper IV study participants. As MVPA decreases with age and was reported by only 41 of paper IV study participants (48 with the inclusion of MV walking), power issues may be responsible for the lack of correlation in this sample. Furthermore, evidence regarding the step cadence required to attain moderate intensity in older people is contradictory; this cadence may be greater[121] or lesser[122] than that required in younger adults, and has to my knowledge been investigated only in the two cited studies. A threshold of >100 SPM has been proposed for adults,[56] and was tentatively used in the paper IV study given the lack of a recommendation for very old people.

The findings in the paper IV study regarding the sensitivity and specificity of the IPAQ-E 80+ are inconclusive, given the methodological limitations of accelerometers pertaining to PA intensity measurement. MVPAs mentioned in the questionnaire (gardening, window cleaning, biking, swimming, wood chopping, construction work, aerobics and running) can be strenuous, but most of them likely do not generate step cadences >100 or >75 SPM.

The findings of stronger correlations for the total inactive time in the proxy than in the no-proxy subgroup, and walking time in participants with than in those without depression, suggest that the IPAQ-E 80+ enables more precise total inactive time measurement with proxy consultation, and that people with depression more accurately recall walking time than do those without depression. As the subgroups were small, however, these results should be interpreted with caution. The sensitivity analyses conducted with the exclusion of the two most sedentary participants yielded essentially the same results as the main analyses. Thus, the subgroup and sensitivity analyses suggest that the IPAQ-E 80+ is valid for use with these common subgroups of very old people.

The paper IV study showed that the IPAQ-E 80+ seems to be able to rank individuals aged 80 years and over into PA levels. This tool appears to hold promise for use in studies of relationships between 24-hour activity patterns and health in this population. Given the proxy confirmation option for respondents with impaired cognition, the scale may also be suitable for use with people with dementia. The low degrees of sensitivity and specificity may reflect the methodological issue of the use of step cadence as a measure of very old people's PA intensity.

Methodological considerations

The representativeness of participants in the Umeå85+/GERDA age groups (85, 90 and ≥ 95 years), which included individuals with dementia and nursing home residents, is a strength of this thesis. The MONICA cohort is well-defined and has been thoroughly tested; the following of this cohort to high age with the SilverMONICA project provides a great opportunity for the investigation of long-term risk factors in high age. Furthermore, assessment in participants' homes in both Umeå85+/GERDA and SilverMONICA enabled the inclusion of individuals with mobility impairments and those residing far from the research institution. Another strength of this thesis is that it includes a longitudinal study of the association between GS and cognition over 5 years among very old people. Because comorbidities that can influence gait and cognition are common in the target population, the analyses were adjusted thoroughly for potential confounders. A strength of all papers included in this thesis is the verification of diagnoses by experienced geriatricians which reduced the risk of misclassification. The MMSE is a common measure of cognition but it has been criticised due to its considerable ceiling and training effects[123] and the lack of assessment of executive functions that are often affected in dementia. Thus, the FAB was also administered in the SilverMONICA project, to more broadly cover cognitive function. Another strength is the heterogeneous sample in the paper IV study, which reflects the heterogeneity of very old people's activity patterns. Another strength is the concurrent accelerometer measurement and self-reporting of PA, which drastically reduces the potential that PA fluctuation will affect self-reporting precision.

However, this thesis is not without limitations. Inferences based on the paper I and II studies are limited to individuals in the age groups 85, 90, and ≥ 95 years, due to the inclusion criteria of the Umeå85+/GERDA project. Five-year follow-up data were available for 296 individuals without dementia at baseline, among almost 2000 study participants. The sample size in Paper II, with 98 participants with all-cause dementia over five years, prevented further subgroup analysis of potential relationships of GS with particular dementia subtypes. As the paper III study included participants aged ≥ 80 years in 2016-2019, participants who

where truncated due to death before 2016 may have been high, considering the high mortality rate of people with dementia, contributing to risk of type 2 error. In addition, the six item PA questionnaire used in the paper III study may not have been sufficiently sensitive to enable the detection of meaningful differences in PA; together with the majority rating of 3 on the initial scale, this may have increased the risk of type 2 errors. A limitation of the paper IV study is that the 10-minute bout threshold was used for the IPAQ-E 80+ items but not the accelerometer measures. In addition the paper IV sample, and especially the subgroups, were small; in combination with the reporting of MVPA by only 41 participants, this factor may have led to type 2 errors in the MV walking and MVPA measures. Furthermore, few participants in the paper IV sample had severe cognitive impairment, which limits the generalisability of findings to other samples of very old people. Although the test-retest reliability of the IPAQ has been shown to be adequate,[54] the reliability of the IPAQ-E 80+, and IPAQ-E, has not been examined. The measurement of PA intensity using accelerometer step counts could have resulted in misclassification inaccuracy for participants with habitual walking speeds < 0.5 m/s. In addition, the analyses could not be adjusted for the apolipoprotein E (APO-E) ε4 allele or other genetic factors conferring predisposition to dementia development. The comparatively short distance of 2.4 meters was chosen due to concerns about limited space in participants' homes; since the acceleration phase constitutes a relatively large proportion of this distance, which may have influenced the results. In the paper I and II studies, the MMSE was used to measure global cognitive function; this measure covers some aspects of cognitive function but not all, e.g. executive function, which is associated with gait.[65] Furthermore, the MMSE score may be influenced by many factors, including respondents' education levels, hearing, vision and motor deficits. This issue constitutes a limitation of cognitive function screening among very old people, and may have affected the estimation.

Missing values

As ageing entails successive declines in bodily and cognitive functions, missing values are common in studies including older adults. The exclusion of participants with missing values may result in biased estimates as it increases risk of selection bias. The use of the Last Observation Carried Forward (LOCF) and mean imputation methods for the analysis of data from very old people is not advised as a lack of decline may actually be the result of a successful intervention, or indicate the existence of a protective factor, in this population. Of course, complete data are always preferable, but attrition is sometimes unavoidable, especially among very old people with high proportion of frailty and disability. The handling of missing values continues to be a matter of debate. Multiple imputation has been proposed as a way to somewhat compensate for missing data. In the paper I and paper II studies, a pre-planned strategy, that accounted

for known causes for missingness according to recommendations was used.[124] Multiple imputation reduces the risk of type 1 errors by building in variation (noise) through the creation of multiple datasets with statistically likely values for the entire sample based on available information for each individual.[125] In the paper I study, the sample of participants with dementia was comparatively large (n = 464), but more than half of GS values were missing, and different results were obtained when imputed GS values were included in the analysis. This difference may be due to the low MMSE scores of participants with dementia and missing GS values. These findings suggest that the exclusion of people with dementia who are unable to perform GS tests from study samples increases the risk of selection bias; at minimum, the numbers of such excluded individuals should be reported to aid the interpretation of findings. In the paper II study, almost two-thirds of participants with missing follow-up GS values developed dementia, which may reflect age-related increases in gait and cognitive deficits as well as the putative association between these two parameters. The weakening of statistical power due to a large proportion of missing follow-up GS values can reasonably be inferred to explain, at least to some extent, the significance of the association between GS and dementia development only after compensation for missing GS values.

Ethical considerations

All studies included in this thesis were performed in accordance with the Declaration of Helsinki and obtained approval from appropriate ethics review boards. Given the need for special consideration when conducting research involving people in high age due to disease burden and cognitive decline in this population, data collection in the UMEÅ85+/GERDA and Silver-MONICA studies was performed by assessors with medical backgrounds (physicians, nurses and physiotherapists) who were trained in the studies' methods, procedures and ethical considerations. All assessors had the opportunity to discuss any ethical considerations with the project staffs. If cognitive impairment was suspected, a relative was consulted and were provided with study information. Data collection was sometimes performed over the course of several home visits, and was not completed if the participants showed any sign of not wanting to participate further.

Clinical implications

GS seem useful in screening for mortality risk and declining physical and cognitive health in older people, including very old people.[101,126–128] GS can be used as a screening instrument, relating performance to normative values and help guide clinical decisions, where a threshold of < 1.0 m/s has been suggested to reflect an increased risk of dementia.[101] However, that cut-off may be too high,

and resulting in low discriminative ability for very old people, given that few participant in the studies included in this thesis had GS ≥ 1 m/s. Changes in GS have also been associated with dementia. The GS of participants in the paper II study with and without dementia declined over 5 years (0.21 and 0.17 m/s, respectively). Small and moderate changes (at 0.04 and 0.10 m/s, respectively), have been reported for people aged > 70 years.[115] GS threshold could be better adapted on an individual basis, as the same absolute increase in GS can reflect different degrees of improvement in slower and faster walkers. Thus, the use of relative GS values, or age-stratified cut-offs should be explored in future research. Furthermore, as walking depends on many body functions, the cause of a deviation in GS can be challenging to discern. This issue should be examined further with more specific tests.

The unadjusted association between PA and subsequent GS implies that GS may be a suitable measure of response to exercise interventions targeting walking ability, balance and lower limb strength. The IPAQ-E 80+, with items capturing 24-hour activity patterns and intensity of walking, seems able to rank individuals aged 80 years and over into PA levels. Therefore, it presents as a promising questionnaire for use in studies of relationships between 24-hour activity patterns of PA and health in very old people. Given the proxy confirmation option for respondents with impaired cognition, it may also be suitable for people with dementia.

Implications for future research

Optimal GS cut-off scores and combination with cognitive parameters to best predict dementia development is an interesting field of future research. Further evaluation of the influence of walking aid use during walking is also warranted, as walking aid use appear to attentuate the association between gait and cognition when walking straight ahead. Furthermore, compensation for missing values is important in analyses of this type, especially when examining data from very old people, as attrition from longitudinal studies becomes more prevalent with increasing participant age. The protective effects of physical activity on cognitive function and dementia development, and the temporal nature of these effects, needs further investigation. In addition, the accuracy of the IPAQ-E 80+ regarding PA intensity needs to be determined.

Conclusion

Low and declining GS seems associated with lower cognitive function and higher odds of dementia development in very old people, living in both community and nursing homes. Furthermore, declining GS seems associated with declining cognitive function among those who develop dementia. The present results support development of a GS screening index for predicting future cognitive decline among very old people. However, walking aid use may influence the cognitive load and hence the association between GS and cognition. In this thesis, low physical activity levels in middle to older aged people did not constitute a risk factor for dementia development up to two decades later. The novel IPAQ-E 80+, with items capturing 24-hour activity patterns and intensity of walking, seems able to rank individuals aged 80 years and over into PA levels. Therefore, it shows promise for use in studies of relationships between 24-hour activity patterns of PA and health in very old people.

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List of dissertations

DISSERTATIONS FROM THE UNIT OF GERIATRIC MEDICINE, UMEÅ UNIVERSITY 1983-2021

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8. Birgitta Bernspång. Consequences of stroke. Aspects of impairments, disabilities and life satisfaction. With special emphasis on perception and on occupational therapy. Umeå University Medical Dissertations, New Series No.

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12. Matti Viitanen. Long-term effects of stroke. Umeå University Medical Dissertations, New Series No. 201, 1987. (Departments of Geriatric Medicine, Medicine and Medical Rehabilitation)

13. Elsy Athlin. Nursing based on an interaction model applied to patients with eating problems and suffering from Parkinson´s disease and dementia. Umeå University Medical Dissertations, New Series No. 230, 1988. (Departments of Geriatric Medicine and Advanced Nursing, Umeå University and Geriatric Medicine, Karolinska Institute)

14. Sture Åström. Attitudes, empathy and burnout among staff in geriatric and psychogeriatric care. Umeå University Medical Dissertations New Series No. 267, 1990. (Departments of Geriatric Medicine and Advanced Nursing, Umeå University and Geriatric Medicine, Karolinska Institute)

15. Britt Mari Åkerlund. Dementia care in an ethical perspective. An exploratory study of caregivers´ experiences of ethical conflicts when feeding severely demented patients. Umeå University Medical Dissertations, New Series No. 299, 1990. (Departments of Geriatric Medicine and Advanced Nursing)

16. Yngve Gustafson. Acute confusional state (delirium). Clinical studies in hip-fracture and stroke patients. Umeå University Medical Dissertations, New Series No. 309, 1991. (Departments of Geriatric Medicine, Medicine, Umeå University and Geriatric Medicine, Karolinska Institute)

17. Benny Brännström. Care of the acutely confused elderly hip-fracture patient. Empirical studies and an ethical model of care. Umeå University Medical Dissertations, New Series No. 324, 1991. (Departments of Advanced Nursing, Geriatric Medicine, Umeå University and Geriatric Medicine, Karolinska Institute)

18. Per Allard. Dopamine uptake sites in rat- and human brain. Pharmacological characterization and applied studies in ageing, dementia of the Alzheimer type and Parkinson's disease, including some aspects on the cytochrome P 450-system in the human brain. Umeå University Medical Dissertations, New Series No. 355, 1992. (Departments of Psychiatry and Geriatric Medicine)

19. Ann-Christine Löfgren. Health status of a representative sample of elderly patients/people living in Umeå and of married long term care patients – why are some married patients cared for in home care and others in nursing homes? How do social conditions and physical status influence care decisions? Licentiate thesis in medical science, 1992. (Department of Geriatric Medicine)

20. Per Olov Österlind. Medical and social conditions in the elderly gender and age differences. Umeå University Medical Dissertations, New Series No. 369, 1993. (Department of Geriatric Medicine)

21. Christina Sällström. Spouses' experiences of living with a partner with Alzheimer's disease. Umeå University Medical Dissertations, New Series No. 391, 1994. (Departments of Advanced Nursing, Geriatric Medicine and Psychiatry)

22. Birgitta Näsman. The limbic-hypothalamic-pituitary-adrenal axis in Alzheimer's disease. Umeå University Medical Dissertations, New Series No. 408, 1994. (Departments of Geriatric Medicine and Medicine)

23. Göran Nordström. Oral health and dietary habits in an elderly city population. A report from the Umeå longitudinal study. Umeå University odontological dissertations, 1995. Abstract No. 57 ISSN 0345-7532. (Departments of Prosthetic Dentistry and Geriatric Medicine)

24. Lars Nyberg. Falls in the frail elderly. Incidence, characteristics and prediction, with special reference to patients with stroke and hip fractures. Umeå University Medical Dissertations, New Series No. 483, 1996. (Department of Geriatric Medicine)

25. Sigbritt Rasmuson. Glucocorticoid – serotonin interactions in the brain with focus on Alzheimer's disease. Umeå University Medical Dissertations, New Series No. 563, 1998. (Departments of Geriatric Medicine and Medicine)

26. Lennart Norberg. A comparative investigation of the interaction between different binary combinations of CNS depressant drugs in male rats evaluated with an EEGthreshold method. Umeå University Medical Dissertations, New Series No. 582, 1999. (Departments of Pharmacology and Community Medicine and Rehabilitation, Geriatric Medicine)

27. Birgit Rasmussen. In pursuit of a meaningful living amidst dying: Nursing practice in a hospice. Umeå University Medical Dissertations, New Series No. 592, 1999. (Departments of Advanced Nursing and Community Medicine and Rehabilitation, Geriatric Medicine)

28. Britta Löfgren. Rehabilitation of old people with stroke. Outcome prediction and long-term follow-up. Umeå University Medical Dissertations, New series No. 584, 1999. (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

29. Anna Ramnemark. Osteoporosis and fractures after stroke. Umeå University Medical Dissertations, New Series No. 600, 1999. (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

30. Stig Karlsson. Physical restraint use in the care of elderly patients. Umeå University Medical Dissertations, New Series No. 613, 1999. (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Department of Nursing)

31. Ove Hellzén. The meaning of being a carer for people with mental illness and provoking actions: Carers´ exposure in problematic care situations. Umeå University Medical Dissertations, New Series No. 650, 2000. (Department of Nursing and the Department of Community Medicine and Rehabilitation, Geriatric Medicine)

32. Lillemor Lundin-Olsson. Prediction and prevention of falls among elderly people in residential care. Umeå University Medical Dissertations, New Series No. 671, 2000 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

33. Olov Sandberg. Delirium, psychiatric symptoms and treatment of sleep apnea in older patients. Clinical studies in institutional care and in stroke rehabilitation. Umeå University Medical Dissertations, New Series No. 687, 2000 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

34. Imogene Nilsson. Grappling with life after stroke. Some perspectives. Umeå University Licentiate Thesis, 2000. (Department of Nursing and Department of Community Medicine and Rehabilitation, Geriatric Medicine)

35. Karl Gustaf Norberg. Institutional care of people with dementia. Functional ability and daily life in different care settings. Umeå University Licentiate Thesis, 2001. (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Department of Nursing)

36. Jane Jensen. Fall and injury prevention in older people living in residential care facilities. Umeå University Medical Dissertations, New Series No. 812, 2003 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

37. Anna Nordström. Bone mass and physical activity. Umeå University Medical Dissertations, New Series No. 881, 2004 (Department of Public Health and Clinical Medicine, Medicine; Department of Surgical and Perioperative Sciences, Sports Medicine; Department of Community Medicine and Rehabilitation, Geriatric Medicine)

38. Eva Elinge. Life after hip fracture. Association with dependency in old age and the effects of a group learning programme. Umeå University Licentiate Thesis, 2004. (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

39. Eva Elgh. Neuropsychological function in relation to structural and functional brain changes in Alzheimer´s disease. Umeå University Medical Dissertations, New Series No. 903, 2004 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

40. Maria Lundström. Delirium in old patients with femoral neck fracture. Risk factors, outcome, prevention and treatment. Umeå University Medical Dissertations, New Series No. 909, 2004 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

41. Erik Rosendahl. Fall prediction and a high-intensity functional exercise programme to improve physical functions and to prevent falls among older people living in residential care facilities. Umeå University Medical Dissertations, New Series No. 1024, 2006 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

42. Kristina Kallin. Falls in older people in geriatric care settings. Predisposing and precipitating factors. Umeå University Medical Dissertations, New Series No.

902, 2004 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

43. Michael Stenvall. Hip fractures among old people. Their prevalence, consequences and complications, and the evaluation of a multi-factorial intervention program designed to prevent falls and injuries and enhance performance of activities of daily living. Umeå University Medical Dissertations, New Series No. 1040, 2006 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

44. Petra von Heideken Wågert. Health, physical ability, falls and morale in very old people: the Umeå 85+ Study. Umeå University Medical Dissertations, New Series No. 1038, 2006, (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

45. Birgitta Olofsson. Old people with femoral neck fracture. Delirium, malnutrition and surgical methods – an intervention program. Umeå University Medical Dissertations, New Series No. 1093, 2007, (Department of Surgical and Perioperative Sciences, Orthopaedics and Department of Community Medicine and Rehabilitation, Geriatric Medicine)

46. Annika Bylund. Phytoestrogens and prostate cancer. Experimental, clinical, and epidemiological studies. Umeå University Medical Dissertations, New Series No. 1127, 2007, (Department of Community Medicine and Rehabilitation, Geriatric Medicine; Medical Biosciences, Pathology; Public Health and Clinical Medicine, Nutritional Research, and Surgical and Perioperative Sciences, Urology and Andrology)

47. Ellinor Bergdahl. Depression among the very old. Umeå University Medical Dissertations, New Series No. 1132, 2007 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Clinical Sciences, Division of Psychiatry)

48. Staffan Eriksson. Falls in people with dementia. Umeå University Medical Dissertations, New series no 1135, 2007 (Department of Community Medicine and Rehabilitation, Physiotheraphy and Geriatric Medicine)

49. Nina Lindelöf. Effects and experiences of high-intensity functional exercise programmes among older people with physical or cognitive impairment. Luleå University of technology, 2008. (Departments of Health science, Health and rehabilitation, Luleå University of Technology, and Community Medicine and Rehabilitation, Geriatric Medicine, Umeå University)

50. Hugo Lövheim. Psychotropic and analgesic drug use among old people. With special focus on people living in institutional geriatric care. Umeå University Medical Dissertations, New Series No. 1157, 2008 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

51. Taru Tervo. Physical activity, bone gain and sustainment of peak bone mass. Umeå University Medical Dissertations, New Series No. 1282, 2009 (Department of Surgical and Perioperative Sciences, Sports Medicine, Department of Community Medicine and Rehabilitation, Geriatric Medicine, Department of Community Medicine and Rehabilitation, Rehabilitation Medicine)

52. Undis Englund. Physical activity, bone density, and fragility fractures in women. Umeå University Medical Dissertations, New Series No. 1298, 2009 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

53. Tony Pellfolk. Physical restraint use and falls in institutional care of old people - Effects of a restraint minimization program. Umeå University Medical Dissertations, New Series No. 1336, 2010 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

54. Lena Molander. Blood pressure in advanced age: with focus on epidemiology, cognitive impairment and mortality. Umeå University Medical Dissertations, New Series No. 1372, 2010. (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

55. Pia Hedberg. Purpose in life among very old people. Umeå University Medical Dissertations, New Series No. 1384, 2010. (Department of Nursing, Department of Community Medicine and Rehabilitation, Geriatric Medicine)

56. Håkan Littbrand. Physical exercise for older people – focusing on people living in residential care facilities and people with dementia. Umeå University Medical Dissertations, New series No. 1396, 2011. (Departments of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

57. Peder Wiklund. Adipose tissue, the skeleton and cardiovascular disease. Umeå University Medical Dissertations, New Series No. 1417, 2011. (Departments of Community Medicine and Rehabilitation, Geriatric Medicine and Department of Surgical and Perioperative Sciences, Sports Medicine)

58. Irene Eriksson. Urinary tract infection – a serious health problem in old women. Umeå University Medical Dissertations, New Series No. 1410, 2011. (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

59. Maine Carlsson. Nutritional status, body composition and physical activity among older people living in residential care facilities. Umeå University Medical Dissertations, New Series No. 1428, 2011. (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

60. Fredrik Toss. Body fat distribution, inflammation and cardiovascular disease. Umeå University Medical Dissertations, New Series No. 1451, 2011 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

61. Mia Conradsson. Physical exercise and mental health among older people - measurement methods and exercise effects focusing on people living in residential care facilities. Umeå University Medical Dissertations, New Series No. 1537, 2012 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

62. Johan Mathillas. Dementia, depression and delirium in the very old. Prevalences and associated factors. Umeå University Medical Dissertations, New Series No. 1595, 2013 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

63. Magdalena Eriksson Domellöf. Cognitive and motor dysfunction in the early phase of Parkinson's disease. Umeå University Medical Dissertations, New Series No. 1615, 2013 (Department of Pharmacology and Clinical Neuroscience; Department of Community Medicine and Rehabilitation, Geriatric Medicine)

64. Johan Niklasson. Morale in very old people with focus on stroke, depression and survival. Umeå University Medical Dissertations, New Series No. 1750, 2015 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

65. Maria Gustafsson. Optimizing drug therapy among old people with dementia - the role of clinical pharmacists. Umeå University Medical Dissertations, New Series No. 1789, 2016 (Department of Community Medicine and Rehabilitation, Geriatric Medicine, Department of Pharmacology and Clinical Neuroscience, Clinical Pharmacology and Department of nursing)

66. Helena Claesson Lingehall. Delirium in older people after cardiac surgery-risk factors, dementia, patients' experiences and assessments. Umeå University Medical Dissertations, New Series No. 1783, 2016 (Department of Nursing, Department of Surgical and Preoperative Sciences, Department of Community Medicine and Rehabilitation, Geriatric Medicine)

67. Gustaf Boström. Depression in older people with and without dementia – non-pharmacological interventions and associations between psychotropic drugs

and mortality. Umeå University Medical Dissertations, New Series No. 1797, 2016 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

68. Carl Hörnsten. Stroke and Depression in very old age. Umeå University Medical Dissertations, New Series No. 1800, 2016 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)

69. Helena Nyström. Parkinson's disease: the prodromal phase and consequences with respect to working life. Umeå University Medical Dissertations, New Series No. 1810, 2016 (Department of Community Medicine and Rehabilitation, Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine)

70. Annika Toots. Gait speed and physical exercise in people with dementia. Umeå University Medical Dissertations, New series No 1866, 2016 (Department of Community Medicine and Rehabilitation, Geriatric medicine and Physiotherapy)

71. Bodil Weidung. Blood pressure in very old age: determinants, adverse outcomes, and heterogeneity. Umeå University Medical Dissertations, New series No 1868, 2016 (Department of Community Medicine and Rehabilitation, Geriatric medicine)

72. Gabriel Högström. Cardiovascular disease and all-cause mortality: influence of fitness, fatness and genetic factors. Umeå University Medical Dissertations, New series No 1865, 2016 (Department of Community Medicine and Rehabilitation, Geriatric medicine)

73. Monica Långström Berggren. Consequences of a hip fracture among old people. Umeå University Medical Dissertations, New series No 1923, 2017 (Department of Community Medicine and Rehabilitation, Geriatric medicine)

74. Jon Albin Brännström. Adverse Effects of Psychotropic Drugs in Old Age. Umeå University Medical Dissertations, New series No 2098, 2020 (Department of Community Medicine and Rehabilitation, Geriatric medicine)

75. Åsa Karlsson. Team-based home rehabilitation after hip fracture in older adults – effects, experiences and impact of dementia. Umeå University Medical Dissertations, New Series No 2112, 2021 (Department of Community Medicine and Rehabilitation, Geriatric medicine and Physiotherapy)

76. Maria Burman. Malnutrition and obesity among older adults, assessed by Mini Nutritional Assessment and the body mass index, respectively: prevalence and associations with mortality and urinary tract infection. Umeå University Medical Dissertations, New Series No 2121, 2021 (Department of Community Medicine and Rehabilitation, Geriatric medicine)

DISSERTATIONS BY PHYSIOTHERAPISTS, UMEÅ UNIVERSITY 1989-2021

1. *Birgitta Bergman*. Being a physiotherapist - Professional role, utilization of time and vocational strategies. Umeå University Medical Dissertations, New Series no 251, 1989 (Department of Physical Medicine and Rehabilitation)
2. *Inger Wadell*. Influences from peripheral sense organs on primary and secondary spindle afferents via gamma-motoneurones - A feedback mechanism for motor control and regulation of muscle stiffness. Umeå University Medical Dissertations, New Series no 307, 1991 (Department of Physiology)
3. *Jessica Elert*. The pattern of activation and relaxation during fatiguing isocinetic contractions in subjects with and without muscle pain. Arbete och hälsa 1991:47. Diss. 1992 (sammanfattning). (Departments of Clinical Physiology, National Institute of Occupational Health and Physical Medicine and Rehabilitation)
4. *Gunnevi Sundelin*. Electromyography of shoulder muscles - The effects of pauses, drafts and repetitive work cycles. Arbete och Hälsa, 1992:16. Diss. (sammanfattning). (Departments of Anatomy, National Institute of Occupational Health, Division of Work and Environmental Physiology, Divisions of Occupational Medicine and Applied Work Physiology and Occupational Medicine)
5. *Birgit Rösblad*. Visual and proprioceptive control of arm movement - Studies of development and dysfunction. Diss. (sammanfattning) 1994 (Department of Paediatrics)
6. Charlotte Häger-Ross. To grip and not to slip - Sensorimotor mechanisms during reactive control of grasp stability. Umeå University Medical Dissertations, New Series no 429, 1995 (Department of Physiology)
7. *Lars Nyberg*. Falls in the frail elderly – Incidence, characteristics and prediction with special reference to patients with stroke and hip fractures. Umeå Medical Dissertations, New Series no 483, 1996 (Department of Geriatric Medicine)
8. *Margareta Barnekow-Bergkvist*. Physical capacity, physical activity and health -A population based fitness study of adolescents with an 18-year follow-up. Umeå University Medical Dissertations, New Series no 494, 1997 (Departments of Physiology and Technology, National Institute for Working Life and Epidemiology and Public Health)
9. *Britta Lindström*. Knee muscle function in healthy persons and patients with upper motor neurone syndrome. Umeå University Medical Dissertations, New Series no 505, 1997 (Departments of Physical Medicine and Rehabilitation and Clinical Neuroscience)

10. *Monica Mattsson*. Body Awareness - applications in physiotherapy. Umeå University Medical Dissertations, New Series no 543, 1998 (Departments of Psychiatry and Family Medicine)
11. *Hildur Kalman*. The structure of knowing. Existential trust as an epistemological category. Umeå studies in the humanities. 145, 1999 (Department of Philosophy and Linguistics
12. *Hamayun Zafar*. Integrated jaw and neck function in man: studies of mandibular and head-neck movements during jaw opening-closing tasks. Umeå University Medical Dissertations, New series no 74, 2000 (Departments of Odontology, Clinical Oral Physiology and Centre for Musculoskeletal Research, National Institute for Working Life, Umeå)
13. *Lillemor Lundin-Olsson*. Prediction and prevention of falls among elderly people in residential care. Umeå University Medical Dissertations, New Series no 671, 2000 (Department of Community Medicine and Rehabilitation, Physiotherapy and Geriatric Medicine)
14. *Christina Ahlgren*. Aspects of rehabilitation – with focus on women with trapezius myalgia. Umeå University Medical Dissertations, New Series no 715, 2001 (Department of Public Health and Clinical Medicine, Occupational Medicine)
15. *Ann Öhman*. Profession on the move - changing conditions and gendered development in physiotherapy. Umeå University Medical Dissertations, New series No 730, 2001 (Departments of Community Medicine and Rehabilitation, Physiotherapy and Public Health and Clinical Medicine, Epidemiology)
16. *Kerstin Söderman*. The female soccer player – Injury pattern, risk factors and intervention. Umeå University Medical Dissertations, New series no 735, 2001 (Departments of Surgical and Perioperative Sciences, Sports Medicine, and Community Medicine and Rehabilitation, Physiotherapy)
17. *Lena Grönblom-Lundström*. Rehabilitation in light of different theories of health. Outcome for patients with low-back complaints – a theoretical discussion. Umeå University Medical Dissertations, New series no 760, 2001 (Departments of Public Health and Clinical Medicine, Epidemiology, and Community Medicine and Rehabilitation, Social Medicine)
18. *Kerstin Waling*. Pain in women with work-related trapezius myalgia. Intervention effects and variability. Umeå University Medical Dissertations, New series no 762, 2001 (Departments of Public Health and Clinical Medicine, Occupational Medicine, and Community Medicine and Rehabilitation, Physiotherapy)
19. *Eva-Britt Malmgren-Olsson*. Health problems and treatment effects in patients with non-specific musculoskeletal disorders. A comparison between Body Awareness Therapy, Feldenkrais and Individual Physiotherapy. Umeå University Medical Dissertations, New series no 774, 2002 (Department of

Community Medicine and Rehabilitation, Physiotherapy and Department of Psychology)

20. *Jane Jensen*. Fall and injury prevention in older people living in residential care facilities. Umeå University Medical Dissertations, New series no 812, 2003 (Department of Community Medicine and Rehabilitation, Physiotherapy and Geriatric Medicine)
21. *Anncristine Fjellman-Wiklund*. Musicianship and teaching. Aspects of musculoskeletal disorders, physical and psychosocial work factors in musicians with focus on music teachers. Umeå University Medical Dissertations, New series no 825, 2003 (Department of Community Medicine and Rehabilitation, Physiotherapy)
22. *Börje Rehn*. Musculoskeletal disorders and whole-body vibration exposure among professional drivers of all-terrain vehicles. Umeå University Medical Dissertations, New series no 852, 2004 (Department of Public Health and Clinical Medicine, Occupational Medicine)
23. *Martin Björklund*. Effects of repetitive work on proprioception and of stretching on sensory mechanisms. Implications for work-related neuromuscular disorders. Umeå University Medical Dissertations, New series no 877, 2004 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit, Umeå University, The Center for Musculoskeletal Reseach, University of Gävle, Umeå, and Alfta Forskningsstiftelse, Alfta)
24. *Karin Wadell*. Physical training in patients with chronic obstructive pulmonary disease – COPD. Umeå University Medical Dissertations, New series no 917, 2004 (Departments of Community Medicine and Rehabilitation, Physiotherapy; Public Health and Clinical Medicine, Respiratory Medicine and Allergy, Surgical and Perioperative Sciences, Sports Medicine)
25. *Peter Michaelson*. Sensorimotor characteristics in chronic neck pain. Possible pathophysiological mechanisms and implications for rehabilitation. Umeå University Medical Dissertations, New series no 924, 2004 (Departments of Surgical and Perioperative Sciences, Sports Medicine Unit, University of Umeå, Southern Lappland Research Department, Vilhelmina, Centre for Musculoskeletal Research, University of Gävle, Umeå)
26. *Ulrika Aasa*. Ambulance work. Relationships between occupational demands, individual characteristics and health related outcomes. Umeå University Medical Dissertations, New series no 943, 2005 (Department of Surgical and Perioperative Sciences, Sports Medicine and Surgery, University of Umeå and Centre for Musculoskeletal Research, University of Gävle)
27. *Ann-Katrin Stensdotter*. Motor Control of the knee. Kinematic and EMG studies of healthy individuals and people with patellofemoral pain. Umeå University Medical Dissertations, New series no 987, 2005 (Department of Community Medicine and Rehabilitation, Physiotherapy)

28. *Tania Janaudis Ferreira*. Aspects of muscle function and training with oxygen in patients with chronic obstructive pulmonary disease – COPD. Umeå University Licentiate Thesis, 2005 (Department of Community Medicine and Rehabilitation, Physiotherapy)
29. *Erik Rosendahl*. Fall prediction and a high-intensity functional exercise programme to improve physical functions and to prevent falls among older people living in residential care facilities. Umeå University Medical Dissertations, New Series no 1024, 2006 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)
30. *Michael Stenvall*. Hip fractures among old people. Their prevalence, consequences and complications and the evaluation of a multi-factorial intervention program designed to prevent falls and injuries and enhance performance of activities of daily living. Umeå University Medical Dissertations, New Series no 1040, 2006 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)
31. *Petra von Heideken Wågert*. Health, physical ability, falls and morale in very old people: the Umeå 85+ Study. Umeå University Medical Dissertations, New Series no 1038, 2006 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)
32. *Karl Gisslén*. The patellar tendon in junior elite volleyball players and an Olympic elite weightlifter. Umeå University Medical Dissertations, New Series no 1073, 2006 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit)
33. *Gerd Flodgren*. Effect of low–load repetitive work and mental load on sensitising substances and metabolism in the trapezius muscle. Umeå University Medical Dissertations, New series no 1130, 2007 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit, Centre of Musculoskeletal Research, University of Gävle, Umeå, and the Department of Community Medicine and Rehabilitation, Rehabilitation Medicine)
34. *Staffan Eriksson*. Falls in people with dementia. Umeå University Medical Dissertations, New series no 1135, 2007 (Department of Community Medicine and Rehabilitation, Physiotherapy and Geriatric Medicine)
35. *Jonas Sandlund*. Position-matching and goal-directed reaching acuity of the upper limb in chronic neck pain: Associations to self-rated characteristics. Umeå University Medical Dissertations, New series no 1182, 2008 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit, Umeå University, Centre of Musculoskeletal Research, University of Gävle, Umeå)
36. *Gunilla Larsson*. Motor function over time in Rett syndrome-loss, difficulties and possibilities. Umeå University Licentiate Thesis, 2008 (Department of Community Medicine and Rehabilitation, Physiotherapy)
37. *Charlotte Åström*. Effects of vibration on muscles in the neck and upper limbs. With focus on occupational terrain vehicle drivers. Umeå University

Medical Dissertations, New series no 1135, 2008 (Department of Community Medicine and Rehabilitation, Physiotherapy)

38. *Ellinor Nordin*. Assessment of balance control in relation to fall risk among older people. Umeå University Medical Dissertations, New series no 1198, 2008 (Department of Community Medicine and Rehabilitation, Physiotherapy)
39. *Bertil Jonsson*. Interaction between humans and car seat. Studies of occupant seat adjustment, posture, position and real world neck injuries in rear-end impacts. Umeå University Medical Dissertations, New Series no 1163, 2008 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit)
40. *Jenny Röding*. Stroke in the younger. Self- reported impact on work situation, cognitive function, physical function and life satisfaction. A national survey. Umeå University Medical Dissertations, New series no 1241, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy)
41. *Therese Stenlund*. Rehabilitation for patients with burn out. Umeå University Medical Dissertations, New series no 1237, 2009 (Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine)
42. *Elisabeth Svensson*. Hand function in children and persons with neurological disorders. Aspects of movement control and evaluation of measurements. Umeå University Medical Dissertations, New series no 1261, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy)
43. *Helena Nordvall*. Factors in secondary prevention subsequent to distal radius fracture. Focus on physical function, co-morbidity, bone mineral density and health-related quality of life. Umeå University Medical Dissertations, New series no 1252, 2009 (Department of Community Medicine and Rehabilitation Physiotherapy and Department of Surgical and Perioperative Sciences, Orthopaedics)
44. *Ingela Marklund*. Intensivträning av nedre extremitet för personer med stroke– effekter och upplevelser. Umeå University Licentiate Thesis, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy)
45. *Ulrik Röijezon*. Sensorimotor function in chronic neck pain. Objective assessments and a novel method for neck coordination exercise. Umeå University Medical Dissertations, New series no 1273, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy, Centre of Musculoskeletal Research, University of Gävle, Umeå)
46. *Birgit Enberg*. Work experiences among healthcare professionals in the beginning of their professional careers. A gender perspective. Umeå University Medical Dissertations, New series no 1276, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy and Department of Public Health and Clinical Medicine, Epidemiology and Public Health Sciences)

47. *Per Jonsson*. Eccentric training in the treatment of tendinopathy. Umeå University Medical Dissertations, New series no 1279, 2009 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit)
48. *Taru Tervo*. Physical activity, bone gain and sustainment of peak bone mass. Umeå University Medical Dissertations, New series no 1282, 2009 (Department of Surgical and Perioperative Sciences, Sports Medicine, Department of Community Medicine and Rehabilitation, Geriatric Medicine, Department of Community Medicine and Rehabilitation, Rehabilitation Medicine)
49. *Kajsa Gilenstam*. Gender and physiology in ice hockey: a multidimensional study. Umeå University Medical Dissertations, New series no 1309, 2010 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit)
50. *Margareta Eriksson*. A 3-year lifestyle intervention in primary health care. Effects on physical activity, cardiovascular risk factors, quality of life and costeffectiveness. Umeå University Medical Dissertations, New series no 1333, 2010 (Department of Community Medicine and Rehabilitation, Physiotherapy and Department of Public Health and Clinical Medicine, Epidemiology and Public Health Sciences)
51. *Eva Holmgren*. Getting up when falling down. Reducing fall risk factors after stroke through an exercise program. Umeå University Medical Dissertations, New series no 1357, 2010 (Department of Community Medicine and Rehabilitation, Physiotherapy and Department of Public Health and Clinical Medicine, Medicine)
52. *Tania Janaudis Ferreira*. Strategies for exercise assessment and training in patients with chronic obstructive pulmonary disease. Umeå University Medical Dissertations, New series no 1360, 2010 (Department of Community Medicine and Rehabilitation, Physiotherapy)
53. *Sólveig Ása Árnadóttir*. Physical activity, participation and self-rated health among older community-dwelling Icelanders. A population-based study. Umeå University Medical Dissertations, New series no 1361, 2010 (Department of Community Medicine and Rehabilitation, Physiotherapy)
54. *Maria Wiklund*. Close to the edge. Discursive, embodied and gendered stress in modern youth. Umeå University Medical Dissertations, New series no 1377, 2010 (Department of Public Health and Clinical Medicine, Epidemiology and Global Health and Department of Community Medicine and Rehabilitation, Physiotherapy)
55. *Catharina Bäcklund*. Promoting physical activity among overweight and obese children: Effects of a family-based lifestyle intervention on physical activity and metabolic markers. Umeå University 2010 (Department of Food and Nutrition)
56. *Helene Johansson*. En mer hälsofrämjande hälso- och sjukvård: hinder och möjligheter utifrån professionernas perspektiv. Umeå University Medical

Dissertations, New series no 1388, 2010 (Department of Public Health and Clinical Medicine, Epidemiology and Global Health)

57. *Håkan Littbrand*. Physical exercise for older people: focusing on people living in residential care facilities and people with dementia. Umeå University Medical Dissertations, New series no 1396, 2011 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)
58. *Marlene Sandlund*. Motion interactive games for children with motor disorders. Umeå University Medical Dissertations, New series no 1419, 2011 (Department of Community Medicine and Rehabilitation, Physiotherapy)
59. *Ann Sörlin*. Health and the Elusive Gender Equality. Can the impact of gender equality on health be measured? Umeå University Medical Dissertations, New series no 1420, 2011 (Department of Public Health and Clinical Medicine, Epidemiology and Global Health)
60. *Björn Sundström*. On diet in ankylosing spondylitis. Umeå University Medical Dissertations, New series no 1440, 2011 (Department of Public Health and Clinical Medicine, Rheumatology)
61. *Gunilla Stenberg*. Genusperspektiv på rehabilitering för patienter med rygg- och nackbesvär i primärvård. Umeå University Medical Dissertations, New series no 1482, 2012 (Department of Community Medicine and Rehabilitation, Physiotherapy and Umeå centre for Gender Studies)
62. *Mia Conradsson*. Physical exercise and mental health among older people - measurement methods and exercise effects with focus on people living in residential care facilities. Umeå University Medical Dissertations, New series 1537, 2012 (Department of Community Medicine and Rehabilitation, Geriatric Medicine)
63. *Mattias Hedlund*. Biomechanical and Neural Aspects of Eccentric and Concentric Muscle Performance in Stroke Subjects. Implications for resistance training. Umeå University Medical Dissertations, New series no 1510, 2012 (Department of Community Medicine and Rehabilitation, Physiotherapy)
64. *Joakim Bagge*. TNF-alfa och neurotrophins in achilles tendinosis. Umeå University Medical Dissertations, New series no 1538, 2013 (Department of Integrative Medical Biology, Anatomy and Department of Surgical and Perioperative Sciences, Sports Medicine)
65. *Gunilla Larsson*. Motor development, mobility and orthostatic reactions in Rett syndrome. Loss of function, difficulties and possibilities. Umeå University Medical Dissertations, New series no 1566, 2013 (Department of Community Medicine and Rehabilitation, Physiotherapy)
66. *Ludvig J Backman*. Neuropeptide and catecholamine effects on tenocytes in tendinosis development. Studies on two model systems with focus on proliferation and apoptosis. Umeå University Medical Dissertations, New series no 1572, 2013 (Department of Integrative Medical Biology, Anatomy and Department of Surgical and Perioperative Sciences, Sports Medicine)

67. *Sven Blomqvist*. Postural balance, physical activity and capacity among young people with intellectual disability. Umeå University Medical Dissertations, New series no 1579, 2013 (Department of Community Medicine and Rehabilitation, Physiotherapy)
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71. *Joakim Bjerke*. Gait and postural control after total knee arthroplasty. Umeå University Medical Dissertations, New series no 1664, 2014 (Department of Community Medicine and Rehabilitation, Physiotherapy)
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74. *Petra Pohl*. Falls in older community-dwelling women and men: risk factors and safety strategies. Fall risk awareness, fear of falling, and preferred exercise properties from a gender perspective. Umeå University Medical Dissertations, New series No 1692, 2015 (Department of Community Medicine and Rehabilitation, Physiotherapy)
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(Department of Public Health and Clinical Medicine, Medicine, Department of Community Medicine and Rehabilitation, Physiotherapy)

77. *Tobias Stenlund*. Seated postural reactions to mechanical shocks. Laboratory studies with relevance for risk assessment and prevention of musculoskeletal disorders among drivers. Umeå University Medical Dissertations, New series No 1780, 2016 (Department of Community Medicine and Rehabilitation, Physiotherapy)
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85. Umeå University Medical Dissertations, New series No 1917, 2017 (Department of Public Health and Clinical Medicine, Medicine, and Department of Community Medicine and Rehabilitation, Physiotherapy)
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University Dissertations, New series no 1949, 2018 (Department of Public Health and Clinical Medicine, Rheumatology)

87. *Elisabeth Pietilä-Holmner*. Multimodal Rehabilitation of Patients with Chronic Musculoskeletal Pain, focusing on Primary Care. Umeå University Medical Dissertations, New series No 1970, 2018 (Department of Community Medicine and Rehabilitation, Rehabilitation medicine)
88. *Sara Lundell*. COPD in primary care. Exploring conditions for implementation of evidence-based interventions and eHealth Care. Umeå University Medical Dissertations, New series No 1982, 2018 (Department of Community Medicine and Rehabilitation, Physiotherapy) and Department of Radiation Sciences, Radiation physics and Biomedical Engineering)
89. *Frida Bergman*. Active workstations – a NEAT way to prevent and treat overweight and obesity. Umeå University Medical Dissertations, New series No 1981, 2018 (Departments of Public Health and Clinical Medicine, Medicine and Community Medicine and Rehabilitation, Physiotherapy)
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93. *Anna Sondell*. Exercise and team rehabilitation in older people with dementia: applicability, motivation and experiences. Umeå University Medical Dissertations, New series No 2064, 2020 (Department of Community Medicine and Rehabilitation, Physiotherapy)
94. *Veronica Lundberg*. Children with Juvenile Idiopathic Arthritis, Health-related quality of life and participation in healthcare encounters. Umeå University Medical Dissertations, New series No 2088, 2020 (Department of Community Medicine and Rehabilitation, Physiotherapy)
95. *Åsa Karlsson*. Team-based home rehabilitation after hip fracture in older adults – effects, experiences and impact of dementia. Umeå University Medical Dissertations, New series No 2112, 2021 (Department of Community Medicine and Rehabilitation, Geriatric medicine and Physiotherapy)
96. *Linda Månsson*. Digital fall prevention for older adults – Feasibility of a self-managed exercise application and development of a smartphone self-test for balance and leg strength. Umeå University Medical Dissertations, New series No 2113, 2021 (Department of Community Medicine and Rehabilitation,

Section of Physiotherapy, and Department of Radiation Sciences, Radiation Physics and Biomedical Engineering)

97. *Beatrice Pettersson*. Fall prevention exercise for older adults – Self-management with support of digital technology. Umeå University Medical Dissertations, New series No 2122, 2021 (Department of Community Medicine and Rehabilitation, Section of Physiotherapy)

Papers I-IV