Towards better fall prevention –

De Groot, Maartje

TOWARDS BETTER FALL PREVENTION

Examining the interplay between factors that influence gait in older patients

Maartje de Groot

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TOWARDS BETTER FALL PREVENTION

Examining the interplay between factors that influence gait in older patients

Op weg naar betere valpreventie – Een onderzoek naar de samenhang tussen factoren die het looppatroon van oudere patiënten beïnvloeden (met een samenvatting in het Nederlands)

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Contents

INTRODUCTION

CHAPTER 1

General Introduction

1

General introduction

Older patients visiting a geriatric outpatient clinic often suffer from multiple chronic conditions, e.g., physical, psychological and social problems, and use consequently multiple medications. These patients have a high risk of falling, hospitalization, institutionalization, and ultimately death [1, 2]. Falls are a major problem among older adults. About one third of the people aged 65 years and over fall annually, with approximately 5% of all fall incidents resulting in an injury that requires a visit to the emergency room or hospital admission, such as hip and wrist fractures or head injury [3]. The risk of falls and injuries increases when people become older and have more comorbidities [4]. Furthermore, recovery from a fall injury is often delayed in these old persons due to their decreased physical reserve, which consequently increases the risk of subsequent falls through deconditioning [5].

Most falls do not have a single cause, but are the result of the interaction between someone's physical functions (e.g., the ability to walk and maintain balance, muscle strength, visual and cognitive functioning), environmental hazards (e.g., wet floors and unsafe staircases), and medical factors (e.g., delirium, orthostasis, or medication-use) [6, 7]. In the past decades, numerous epidemiologic studies have investigated a wide variety of risk factors for falls [8–12], which can be classified as either intrinsic or environmental [7]. Intrinsic fall-related factors are physical and psychological characteristics that affect the ability of a person to maintain balance and prevent falling, such as gait and balance problems, muscle weakness, visual disability, or cognitive impairment [7]. Of these intrinsic risk factors, postural instability during daily activities, such as walking, is suggested to be the most consistent predictor for future falls [13], because it is related to many comorbidities, medication-use, muscle weakness, and cognitive impairment [14–20].

Walking is one of the cornerstones of independent living in the community, and an important factor for the quality of life in older adults [21, 22]. It is a multifactorial motor skill that requires a complex integration of, and cooperation between the sensory, neural, musculoskeletal, and cardiorespiratory systems in relation to the environment [23]. Due to advanced age a progressive loss of these systems occurs, which may cause impairments in postural control during walking. These problems can be induced by medical disorders, medication and alcohol-use [24].

Effects of age-related neurophysiological changes and medical conditions on the gait pattern can be quantified by a variety of measures, each characterizing a different aspect

of the gait pattern [25]. Walking speed can be easily measured and is therefore often used in clinical practice to reflect the functional status of older patients [26, 27]. However, it lacks specificity since gait speed is slower in many different pathologies, and does not reveal information about the quality of the walking pattern [28]. Analyzing stride-to-stride variability during walking provides additional information about gait performance, i.e., the ability of a person to adapt one's gait smoothly, and the variability and regularity of the gait pattern.

In the present thesis, gait parameters were used that assess time-dependent fluctuations throughout the gait cycle, such as detrended fluctuations analyses [29], sample entropy [30], and index of harmonicity [31]. Several studies among relatively young and healthy older adults have shown that gait characteristics, including gait speed, stride-to-stride variability, gait asymmetry, harmonic ratios, and sample entropy, can differentiate fallers from non-fallers [32, 33]. However, these results cannot be easily extrapolated to geriatric patients. In the geriatric population there are, besides the normal age-related neurophysiological changes, multiple other conditions present that might affect the walking pattern and consequently increase fall risk, such as comorbid diseases, the use of multiple medications, cognitive impairment and/or frailty [14–20].

Geriatric patients are different from other older adults due to their vulnerability and multi-morbidity (the presence of more than one chronic illness). They can be considered as frail, which is defined as "a geriatric syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse health outcomes including falls and fractures, disabilities, hospitalization, institutionalization and mortality" [34]. Frailty does not become evident in all elderly. It is estimated that about one third of the people aged 85 years and over are frail [1], because frailty may remain undetected, and only comes to clinical attention when illness occurs.

There are many tools to assess frailty in older adults [35], whereof the frailty criteria of Fried *et al*. [1] are widely used. According to Fried's described phenotype, an older person can be considered frail when three or more of the following criteria are present: unintentional weight loss, slow walking speed, exhaustion, low daily activity, or low muscle strength. Sarcopenia (i.e., the loss of muscle mass) and reduction of bone strength due to little physical activity seem to be the main cause of frailty [36, 37]. Besides the association with frailty, muscle strength is also an important factor in relation to walking [38], as muscle strength is necessary to maintain postural control,

which is the capacity to maintain the center of mass within the support base [39], in order to avoid falling.

Since falling is a complex problem, a multifactorial fall risk assessment followed by individualized interventions tailored to the identified intrinsic and extrinsic risk factors, seem to be the most attractive approach for preventing falls and functional decline in the older population. Because in the older patient population many comorbid factors are prevalent, fall risk assessments for geriatric patients should thus include multiple elements such as medication-use and the presence of fall-risk-influencing comorbidities, but should also include a gait and/or balance assessment, since gait and balance problems are the major risk factor for falls [13]. Indeed, a recent study [40] among older adults has shown that the ability to identify those at risk for falling based on questionnaires, grip strength, and a cognitive functioning test (sensitivity: 58%; specificity: 72%; area under the curve (AUC): 0.68) improved when accelerometer-derived parameters about the amount and quality of the gait pattern were added to the model (sensitivity: 70%; specificity: 81%; AUC: 0.82).

Because geriatric patients can be characterized by a unique set of variables that increases their risk of falling, it was aimed in this thesis to examine the association between characteristics that are common present in the geriatric population, including osteoporosis-related factors, medication-use, and frailty-related factors, with postural control during walking in older patients visiting a geriatric outpatient clinic. This multifactorial approach could provide insight in the interplay between all factors and gait performance, which can be used for future classification models of potential fallers, and subsequently could be used for the development of personalized intervention strategies to modify for example medication [41, 42], cognition [43], and physical activity levels [44] in order to reduce the number of falls and resultant injuries in older patients.

Outline of the thesis

In the first part of this thesis, it was investigated whether osteoporosis-related factors, e.g., vertebral fractures, increased thoracic kyphosis, and a flexed posture, are associated with postural control and fall incidence. Bone strength is an important factor in relation to falls and mobility [37], since deterioration of bone strength leads to bone fragility and increases the risk of fractures [45, 46]. The most prevalent type of fracture that is associated with osteoporosis, is the vertebral fracture [47]. In a population of patients who visited a geriatric outpatient clinic 51% were diagnosed with one or more

vertebral fractures [48]. Over time, thoracic vertebral fractures might increase the spinal thoracic kyphotic curvature, and might lead to a flexed posture [49]. These impairments could affect motor function and balance, and therefore increase the risk of falling and further fractures [50]. Since the exact cause and magnitude of balance problems in osteoporotic patients is not clear, chapter 2 provides a literature review describing impairments in postural control among patients with osteoporosis, vertebral fractures, increased thoracic kyphosis, and/or flexed posture. This chapter also includes an evaluation of instruments to measure postural control among osteoporotic patients in a clinical setting. In chapter 3, the association between a flexed posture and impairments in postural control during walking in older patients is studied. Additionally, geriatric phenomena that may cause a flexed posture, e.g., increased thoracic kyphosis, the presence of vertebral fractures, frailty, polypharmacy and cognitive impairments, are investigated. In the next chapter, chapter 4, the association of these clinical entities with fall incidents within the next year is described.

In the second part of this thesis, the focus is on the association between medication-use and postural control during walking. Because older patients often have multiple chronic diseases, they are copious medication users. Most drugs are used on a long-term basis to treat or prevent chronic disorders [51], such as anti-diabetic drugs, gastrointestinal drugs, diuretics, analgesics, sedatives and other psychotropic drugs. Some of these drugs are potential causes for unfavorable outcomes: meta-analyses have shown that medication affecting the central nervous system (e.g., antidepressants, neuroleptics, benzodiazepines, and antiepileptic drugs), and some cardiac drugs (digoxin, type IA anti-arrhythmics, and diuretics) are associated with an increased risk of falling [19, 52–55]. Falls due to these so-called fall-risk-increasing drugs (FRIDs) might be partly caused by impairments in postural control induced by these drugs due to their sedative side-effects [56]. Therefore, this hypothesis was investigated in chapter 5 describing a literature review that focuses on the effects of psychotropic and cardiac FRIDs on postural control. In addition, the effect of withdrawal of FRIDS on postural control is reviewed. In chapter 6, the association of medication-use and frailty-related factors with gait performance is described for a cohort of older patients with multiple comorbid diseases and polypharmacy.

In the last part of this thesis, in chapter 7, a model of the investigated factors in this thesis in relation to fall-status is presented. Since falling is a multifactorial problem, and walking is both influenced by factors that might be simultaneously present in the investigated population, e.g., the presence of frailty, comorbid diseases, cognitive impairment, and/or the use of different medications [14–16], a model was built

consisting of frailty-related parameters complemented with cognitive functioning and gait performance to discriminate fallers from non-fallers. This multifactorial approach could provide insight in the interplay between all factors and gait performance, which can be used for future classification models of potential fallers.

Finally, in chapter 8, the main results of the previous chapters are summarized and discussed, and recommendations for future research and clinical practice are presented.

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PART I

OSTEOPOROSIS-RELATED FACTORS

CHAPTER 2

Testing postural control among various osteoporotic patient groups: A literature review

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Abstract

Aim Osteoporosis can cause vertebral fractures, which may lead to a flexed posture, impaired postural control and consequently increased fall risk. Therefore, the aim of the present review, was to examine whether postural control of patients with osteoporosis, vertebral fractures, thoracic kyphosis and flexed posture is affected. Furthermore, instruments measuring postural control are evaluated and examined for sensitivity and easy clinical use.

Methods Until February 2011 electronic databases were systematically searched for cross-sectional studies. Methodological quality was assessed with a modified Downs & Black scale.

Results Of the 518 found studies, 18 studies were included. Postural control was generally affected for patients with vertebral fractures, thoracic kyphosis and flexed posture. Patients with osteoporosis had impaired postural control when assessed with computerized instruments. Easy performance based tests did not show any impairments.

Conclusions There is evidence for an impaired postural control in all included patient groups. Impaired postural control is an important risk factor for falls. Functional performance tests are not sensitive and specific enough to detect affected postural control in patients with osteoporosis. To detect impaired postural control among osteoporotic patients and to get more insight into the underlying mechanisms of postural control, computerized instruments are recommended, such as easy-to-use ambulant motion-sensing (accelerometry) technology.

Introduction

Osteoporosis is one of the major public health problems facing postmenopausal women and aging individuals of both sexes [1]. Currently, it is estimated that over 200 million people worldwide suffer from this disease [2]; approximately 30% of all postmenopausal women in Europe and the USA have osteoporosis. The risk of fractures in the osteoporotic population is higher as a result of an increased bone fragility [3]: the lifetime fracture risk for a 50-year-old woman is 40% [4]. Where peripheral osteoporotic fractures (e.g. wrist or hip) occur frequently after a fall, vertebral fractures result mostly from substantial loads during daily activity, such as bending forward, lifting objects and climbing stairs [5]. Peripheral osteoporotic fractures are easily diagnosed in a hospital because of pain and loss of function. In contrast, vertebral fractures do not immediately result in functional limitations or pain. Therefore, it might be assumed that only one-third of all vertebral fractures are coming to medical attention [5].

In a population of patients who visited a geriatric outpatient clinic, 51% were diagnosed with 31 vertebral fractures [6]. Vertebral fractures are associated with pain [7–9], impaired trunk muscle control, fear of falling [7] and poor physical function when compared with individuals without a history of vertebral fractures [3, 10, 11]. Over time, thoracic vertebral fractures and/or intervertebral disc deformities and/or muscle weakness might increase thoracic kyphotic curvature [12, 13]. In turn, a flexed posture is characterized by an increased thoracic kyphosis, protrusion of the head and, in severe cases, knee flexion [14]. These impairments can affect motor function and balance, and increase the risk of falling [7, 15], and therefore the risk for further fractures [16]. Where an increased thoracic kyphosis is an anatomical nonreversible phenomenon, a training program for patients with flexed posture can improve posture and musculoskeletal impairment [17].

Balance is a multidimensional concept, referring to the ability of a person not to fall. The ability to maintain, achieve or restore a state of balance during any posture or activity is called “postural control” [18]. Adequate postural control is essential for daily activities, and requires integration of visual, proprioceptive and vestibular information [19]. The degree to which individuals rely on this information depends on task difficulty, cognitive load [20], motor skills [21, 22], age [23, 24] and pathology [25, 26]. A wide variety of instruments and outcome variables has been used to examine postural control and assess its relationship with fall risk in different patient populations [27–29]. These instruments include both clinical tests, such as the Timed Up & Go test or the Berg Balance Scale, as well as computerized instruments; for example, force plates, balance

platforms and sway meter systems that measure postural control more objectively. Consequently, it is hard to derive from these studies what the exact cause and magnitude of the balance problems are in osteoporotic patients. Therefore, the aim of the present literature review was to examine whether postural control of patients with (i) osteoporosis; (ii) vertebral fractures; (iii) thoracic kyphosis; and (iv) flexed posture is affected. Furthermore, instruments measuring postural control were evaluated for clinical use, and which instruments are most sensitive in the osteoporotic population was examined.

Methods

Search strategy and selection criteria

Electronic databases (PubMed, Web of Science) were searched until February 2011 (see Appendix I for details of the search strategy for PubMed). Furthermore, reference lists from the included studies were checked and author's names were searched for additional studies.

Studies were included when written in English, and with an available abstract online. Only studies with a cross-sectional design or baseline characteristics of an intervention study were used. Patients in the included studies were diagnosed with osteoporosis, vertebral fractures thoracic kyphosis or flexed posture, and carried out one or more balance tests. Studies were excluded if patients had other physical problems not related to their osteoporosis (e.g. Parkinson's disease, obesity or stroke), or when the study did not have a control group.

Quality assessment and data abstraction

The methodological quality of the included studies was assessed with the Downs & Black instrument [30]. The original checklist was adapted, ruling out the criteria related exclusively to intervention and follow-up studies. A total of 17 items were evaluated, allowing a maximum score of 18 points (see Appendix II for the evaluated items). Each included study was evaluated separately by two authors of this literature review (MdG and HvdJ). In case of disagreement between the two investigators, the assessments were discussed to achieve consensus.

Descriptive data of the studies included study design, a description of the study subjects (mean age and characteristics of osteoporosis, vertebral fractures, thoracic kyphosis or flexed posture) and the results of the balance outcome variables. The

included studies are discussed by the various clinical entities: osteoporosis, vertebral fractures, thoracic kyphosis and flexed posture. In addition, the different balance outcome variables are discussed. These include clinical functional performance tests, measuring balance performance indirectly at a functional level (e.g. the Timed Up & Go test [TUG] and the Berg Balance Scale) [31, 32] and instrumental measurements of balance while standing and walking (e.g. force plates or an electronic walkway). The different balance outcome variables are discussed separately, because they all quantify different aspects of postural control.

Results

The search strategy resulted in 518 articles (Fig. 2.1). Based on the inclusion criteria, 16 studies were included. Two more studies were included after searching reference lists, author names and related articles. The median score for methodological quality among the reviewed studies was 14 points (range 9–17), where a maximum of 18 points was possible (Fig. 2.2). The scores for external validity were low, because just seven studies reported the population from which the research population was recruited. Study power was not described well in the reviewed studies. However, important effects were overall detected with a 5% significance level, although some studies had small sample sizes (Fig. 2.2). In the 18 reviewed studies, 27 different instruments with different balance outcome variables were used to assess balance performance among patients with osteoporosis, vertebral fractures, thoracic kyphosis and flexed posture. An overview of the used instruments and balance outcome variables is given in Table 2.1.

Influence of osteoporosis on various balance outcome variables

Ten studies compared various balance outcome variables among elderly with and without osteoporosis (Table 2.2) [33–42]. In eight studies, osteoporosis was diagnosed according to the patient's bone mineral density (BMD; t-score ≤2.5) [33, 34, 36–40, 42], two studies did not describe the BMD in their population [35, 41]. One study described the degree of thoracic kyphosis [40]. Whether the patients had vertebral fractures and/or flexed posture was not described in all 10 studies. Nine studies controlled for visual, vestibular and proprioceptive dysfunctions [33–36, 38–42].

Among these 10 studies, six studies investigated the influence of osteoporosis on functional performance tests among elderly [33–38]. In the study by Abreu *et al.* [34], elderly osteoporotic women scored significantly lower on the TUG that healthy elderly

women, although all women scored within the normal range. All other functional performance tests used in these studies did not show any significant differences between patients with and without osteoporosis [33–38].

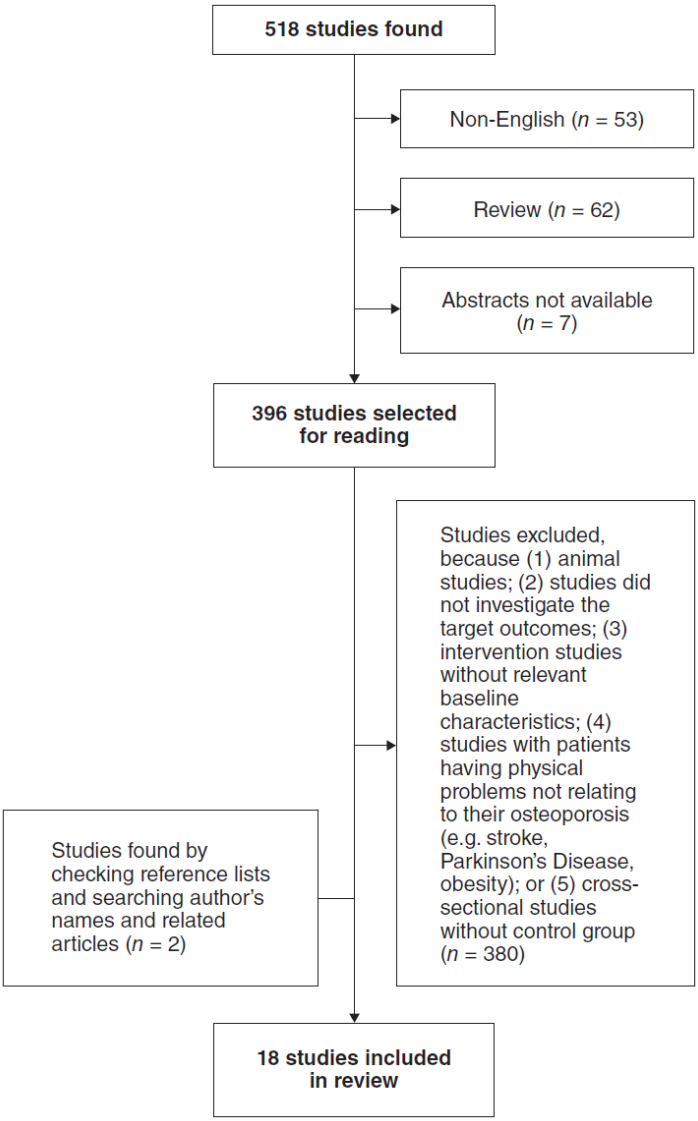

Fig. 2.1. Study selection: the flow chart shows the inclusion and exclusion of the studies used in this literature review.

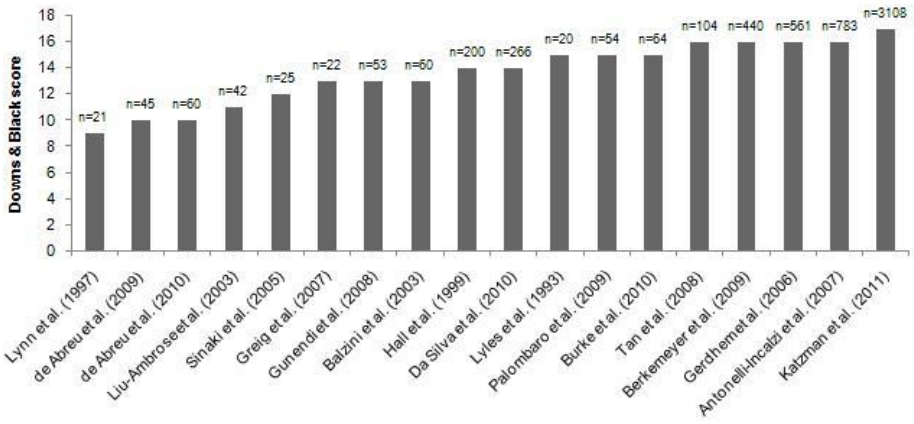

Fig. 2.2. Methodological scores and population size (n) of reviewed studies.

Seven of the reviewed studies examined balance while standing still using instrumental measurements [33, 36, 38–42]. All seven studies used a different test protocol and different terms for "standing balance." Among them were postural sway [38, 41], balance [36], postural control [40], and static balance [35, 39, 42]. No significant differences between patients with and without osteoporosis were found in the studies of Tan *et al.* [38] and Gunendi *et al.* [35] In contrast, other studies found a significant difference in standing balance in women with and without osteoporosis [38–42]. De Abreu *et al.* [39] showed that women with osteoporosis had significantly more body displacement in the medio-lateral and anterior-posterior direction than their healthy controls. Liu-Ambrose *et al.* [36] found that women with osteoporosis performed worse than healthy controls for all six subtests in which the Sensory Organization Test was examined. In contrast with the former studies [36, 39], in the study by Lynn *et al.* [41] women with osteoporosis had significantly less postural sway than healthy controls. In the study by Da Silva *et al.* [42], osteoporotic women had only greater mean sway amplitude in the anterior-posterior direction than non-osteoporotic women when they had their eyes open. Burke *et al.* [40] found that the osteoporotic group had only larger center of pressure (COP) velocity in normal conditions (standing with eyes open on a firm surface) than the healthy controls.

Table 2.1. Instruments and outcome variables used in the reviewed studies

Instrument	Outcome variable(s)	Used in reviewed studies
Functional performance tests		
Backward Tandem Walk test [43]	Time (s)	Palombaro *et al.* [33]
Berg Balance Scale [32]	Score: max. 45 points (= best performance)	De Abreu *et al.* [34]; Gunendi *et al.* [35]
Figure-of-8 test [44]	Speed (s^{-1})	Liu-Ambrose *et al.* [36]
Four Square Step test [45]	Time (s)	Gunendi *et al.* [35]
Functional Reach test [46]	Reached distance (cm)	Lyles *et al.* [47]
Mobility Skills protocol [47]	Score: max. 25 points (= best performance)	Lyles *et al.* [47]
Performance Oriented Mobility Assessment [48]	Score: max. unknown (higher score = better performance)	Balzini *et al.* [14]
Repeated Chair Stands [49]	Score: range 0-1 (1 = best performance)	Antonelli-Incalzi *et al.* [49]
Romberg test [50]	Score: max. 150 points (= best performance)	Gerdhem *et al.* [51]
Short Physical Performance Battery [52, 53]	Score: max. 12 points (= best performance)	Balzini *et al.* [14]; Antonelli-Incalzi *et al.* [49]
Standing Balance in 3 conditions (feet side-by-side, semi-tandem and tandem position for 10-seconds each) [49]	Score: range 0-1 (1 = best performance)	Antonelli-Incalzi *et al.* [49]
Timed Up & Go test [31]	Time (s)	Hall *et al.* [11]; De Abreu *et al.* [34]; Berkemeyer *et al.* [37]; Gunendi *et al.* [35]; Tan *et al.* [38]; Katzman *et al.* [54]
Standing balance		
Polhemus system – detection of magnetic fields [39]	Anterior-posterior and medio-lateral displacement (cm)	De Abreu *et al.* [39]
Force platform – modified Clinical Test of Sensory Interaction and Balance (CTSIBm) [40]	Mean COP sway velocity (°/s)	Burke *et al.* [40]
Force platform - 100% LOS test [40]	% of theoretical Limits of Stability of anterior-posterior and medio-lateral sway	Burke *et al.* [40]

Balance platform [35]	Static Balance Index indicating standing as motionless as possible on the balance platform for 30-seconds with visual feedback. Score: max. unknown (higher score = better performance)	Gunendi *et al.* [35]
Force plate - Sensory Organization Test (SOT) (existing of 6 subtests) [55]	Composite Balance Score (average of all six conditions of SOT) based on postural sway. Score: range 0-100 (0 = fall; 100 = no sway)	Liu-Ambrose *et al.* [36]; Sinaki *et al.* [56]
	Postural sway (score) on SOT subtests 5 (eyes closed and sway referencing on platform) and 6 (inaccurate vision and sway referencing on platform). Score: range 0-100 (0 = fall; 100 = no sway)	Lynn *et al.* [41]
	Balance Strategy Score = ratio of sway amplitude to horizontal forces. Quantifying the use of hip (= low score) or ankle strategy (= high score). Score: max. unknown	Lynn *et al.* [41]
Force platform - COP sway in anterior-posterior and medio-lateral direction [57]	Mean COP amplitude and mean COP velocity (cm/s)	Greig *et al.* [3]; Da Silva *et al.* [42]
Sway-meter system [58] – tracing the sway path on graph paper	Total sway (defined as the total number of 1-mm squares traversed by the pen over a 30-second period). Low score = better performance (less sway)	Tan *et al.* [38]
Outcome variables related to walking		
10-feet Walking test [47]	Time (s)	Lyles *et al.* [47]
4-meter Walking Speed test [49]	Score: range 0-1 (1 = best performance)	Antonelli-Incalzi *et al.* [49]
30-meter Gait Speed (including a turn after 15-m) [51]	Time (s)	Gerdhem *et al.* [51]
6-minute Walking test [59]	Distance (m)	Lyles *et al.* [47]

Table 2.1. *Continued*

Instrument	Outcome variable(s)	Used in reviewed studies
Gait analysis		
Gait Mat II (a 3.87-m walkway containing pressure-sensitive switches) [60]	Free Gait Speed (m/s) and Coefficient of Variation of Step Length, Step Width, Stride Length, Step Time, and Stance Time	Palombaro *et al.* [33]
Reflective markers on bony landmarks of the subject to collect three-dimensional marker trajectory data with a camera on a 10-meter walkway [61]	Right and left Step Length (cm), Stride Length (cm), Forward Velocity (m/s), Cadence (steps/minute), right and left Single Support Time (%), and Step Width (cm)	Sinaki *et al.* [56]
Electronic walkway GAITRite [62, 63]	Base-of-Support (cm), Cadence (steps/minute); Step Length (cm), Single Support Duration (% gait cycle), and Walking Speed (m/s)	Balzini *et al.* [14]

Table 2.2. Characteristics of controlled studies with osteoporotic (OP) patients, patients with vertebral fractures (VF), thoracic kyphosis (TK), and flexed posture (FP), included in this review. The abbreviations of the balance outcome variables are described in the footnote of the table.

Study	Study design	Subjects	n (mean age ± SD)	Patient characteristics	Balance outcome variables	Results
Studies with osteoporotic patients (OP)						
de Abreu *et al.* [34]	Cross-sectional study	1. Elderly women with normal BMD	15 (65 ± 4.11)	BMD: t-score > -1	BBS; TUG	BBS: Elderly women with and without osteoporosis had similar performance TUG: Elderly women with normal BMD performed significantly better than osteoporotic women. Both groups scored within the normal range.
		2. Elderly women with osteoporosis	15 (72 ± 5.54)	BMD: t-score ≤ -2.5		
De Abreu *et al.* [39]	Cross-sectional study	Women with…			BD in AP- & ML-dir (SS-OE, SS-CE, US-OE, US-CE)	Osteoporotic women had significantly more BD in AP-direction in all conditions than control group. Osteoporotic women had significantly more BD in ML-direction in all conditions than control group and osteopenic group.
		1. normal BMD	20 (66.2 ± 4.7)	BMD: t-score > -1		
		2. osteopenia	20 (67.5 ± 4.6)	BMD: t-score: < -1 & > -2.5		
		3. osteoporosis	20 (70.0 ± 5.4)	BMD: t-score ≤ -2.5		
Berkemeyer *et al.* [37]	Cross-sectional study	440 elderly (men/female: 243/197)			TUG	No significant differences between three groups:
		1. Healthy	196 (mean: 79,8)	BMD: t-score: 0.13		Mean: 9.8 (CI 95%: 91-10.4)
		2. Osteopenia	201 (mean: 79.9)	BMD: t-score: -1.64		Mean: 11.1 (CI 95%: 10.1-12.1)
		3. Osteoporosis	43 (mean: 81.6)	BMD: t-score: -3.06		Mean: 12.7 (CI 95%: 9.2-16.2)

Table 2.2. *Continued*

Study	Study design	Subjects	n (mean age ± SD)	Patient characteristics	Balance outcome variables	Results
Burke *et al.* [40]	Cross-sectional study	Women…			COP velocity (SS-OE, SS-CE, US-OE, US-CE); %LOS (AP, ML)	COP velocity: $p = 0.03$ for SS-OE condition between OP and NOP. For all other conditions, no significant differences between groups were found. %LOS: $p = 0.04$ for %LOS in AP-direction between groups. For ML-direction, no significant difference was found between OP and NOP.
		1. with osteoporosis (OP)	46 (73.0 ± 4.2)	BMD: t-score: -3.5 Kyphosis: 53.1° ± 13.8°		
		2. without osteoporosis (NOP)	20 (71.9 ± 3.2)	BMD: t-score: -1.0 Kyphosis: 45.9° ± 10.1°		
Gunendi *et al.* [35]	Intervention study	Postmenopausal women…			SBI; TUG; FSS; BBS	SBI: OP: 285.5 ± 113.4; NOP: 273.2 ± 111.6 ($p > 0.05$) TUG: OP: 7.1 ± 0.7; NOP: 6.9 ± 1.2 ($p > 0.05$) FSS: OP: 9.3 ± 1.0; NOP: 8.9 ± 1.1 ($p > 0.05$) BBS: OP: 53.8 ± 1.6; NOP: 54.1 ± 1.5 ($p > 0.05$)
		1. with osteoporosis (OP)	28 (56.3 ± 6.4)	t-score unknown		
		2. without osteoporosis (NOP)	25 (53.1 ± 7.6)	t-score unknown		
Lynn *et al.* [41]	Case-control study	Women with…			PS on SOT-5 and SOT-6; BSS	PS on SOT-5: $p = 0.044$ PS on SOT-6: $p = 0.002$ BSS: The osteoporosis group had greater reliance on hip strategies to maintain balance.
		1. "normal"	5 (69 yrs)	None		
		2. osteoporosis	10 (64 yrs)	Osteoporosis		
Liu-Ambrose *et al.* [36]	Cross-sectional study	Women…			CBS; Fo8	CBS: OP 70.9 ± 13.6; NOP: 79.4 ± 4.3 (p = 0.009) Fo8: OP: 2.34 ± 0.46; NOP: 2.41 ± 0.41 (p = 0.648)
		1. with osteoporosis (OP)	21 (68.3 ± 2.9)	BMD: t-score: < -2.5		
		2. without osteoporosis (NOP)	21 (68.6 ± 3.1)	BMD: t-score: > -1.0		

Palombaro *et al.* [33]	Observational cohort study	Women in early menopause with…			BTWL; FGS; CV of StL, SW, StrL, ST, StT	BTWL: low BMD: 10.04 ± 3.65; normal BMD: 8.76 ± 3.89 (p = 0.221) Coefficient of Variation of.. FGS: low BMD: 1.35 ± 0.17; normal BMD: 1.38 ± 0.20 (p = 0.260) StL: low BMD: 0.03 ± 0.016; normal BMD: 0.03 ± 0.012 (p = 0.537) SW: low BMD: 0.17 ± 0.224; normal BMD: 0.12 ± 0.084 (p = 0.293) StrL: low BMD: 0.02 ± 0.013; normal BMD: 0.02 ± 0.013 (p = 0.156) ST: low BMD: 0.09 ± 0.13; normal BMD: 0.03 ± 0.02 (p = 0.043) StT: low BMD: 0.07 ± 0.09; normal BMD: 0.03 ± 0.02 (p = 0.049)
		1. low BMD	31 (59.19 ± 3.30)	BMD: t-score < -2		
		2. normal BMD	23 (58.13 ± 3.33)	BMD: t-score > -1		
Da Silva *et al.* [42]	Cross-sectional study	Postmenopausal women…			COPamp & COPvel	OP group had increased sway (greater COPamp) in AP-direction than NOP group. No statistically differences were found in ML COPamp, COPvel, and ellipse area in the tests with eyes open and closed, and in COPamp in AP-direction with eyes closed.
		1. with osteoporosis (OP)	133 (66.0 ± 4.5)	BMD: 0.8 ± 0.1 g/cm^2		
		2. without osteoporosis (NOP)	133 (64.9 ± 4.4)	BMD: 1.2 ± 0.1 g/cm^2		
Tan *et al.* [38]	Cross-sectional study	Postmenopausal women…			TUG; TS (SS-OE, SS-CE, US-OE, US-CE)	TUG: OP: 8.4 ± 1.4; NOP: 7.8 ± 1.2 (p = 0.20) SB-EO: no significant difference between OP and NOP (p = 0.58) SB-EC: no significant difference between OP and NOP (p = 0.47) SB-FEO: no significant difference between OP and NOP (p = 0.43) SB-FEC: no significant difference between OP and NOP (p = 0.20)
		1. with osteoporosis (OP)	49 (72.8 ± 6.6)	BMD: t-score < -2.5		
		2. without osteoporosis (NOP)	55 (70.1 ± 4.8)	BMD: t-score unknown		

Table 2.2. *Continued*

Study	Study design	Subjects	n (mean age ± SD)	Patient characteristics	Balance outcome variables	Results
Patients with and without vertebral fractures (VF)						
Gerdhem *et al.* [51]	Population-based retrospective study	All 75 yrs old women with…			Romberg; 30m-GS	
		1. No fractures (NF)	505 for Romberg 487 for 30m-WS	No VF		Romberg: Median: 94 (range: 0-159) 30-m GS: Mean: 24 ± 9 s
		2. Vertebral fractures	56 for Romberg 49 for 30m-WS	≥1 VF		Romberg: Median: 81 (range: 0-135); $p = 0.012$ compared to NF 30-m GS: Mean: 29 ± 14 s; $p < 0.001$ compared to NF
Greig *et al.* [3]	Cross-sectional study	Women with osteoporosis and…			COPx; COPy; COPvx; COPvy	COPx: $p = 0.049$ COPy: $p = 0.421$ COPvx: $p = 0.531$ COPvy: $p = 0.163$
		1. with vertebral fracture(s) (VF)	10 (68.3 ± 7.1)	t-score < -2 and ≥1 VF		
		2. without vertebral fractures (NVF)	12 (63.5 ± 9.4)	t-score < -2 and no VF		
Hall *et al.* [11]	Cross-sectional study	Women…			TUG	TUG: VF: 13.8 ± 7.3; NVF: 10.1 ± 4.1 ($p < 0.001$)
		1. with vertebral fractures (VF)	100 (74.4 ± 7.2)	VF per patient: 2.9 ± 1.6		
		2. without vertebral fractures (NVF)	100 (74.3 ± 7.2)	No VFs		

Lyles *et al.* [47]	Cross-sectional study	Women… 1. without VF (NVF) 2. with ≥2 VF (VF)	 10 (79.6 ± 6.5) 10 (81.9 ± 5.9)	 No VF Average VF: 4.2 ± 2.6 Range VF: 2 - 10	FR, MS, 10ftW, 6mW	FR: VF: 26.9 ± 5.8; NVF: 34.5 ± 5.3 (p = 0.007) MS: VF: 21.2 ± 2.6; NVF: 24.9 ± 1.7 (p = 0.002) 10ftW: VF: 4.0 ± 1.5; NVF: 3.0 ± 0.5 (p = 0.068) 6mW: VF: 353.5 ± 91; NVF: 453.6 ± 113 (p = 0.042)
Patients with and without increased thoracic kyphosis						
Greig *et al.* [3]	Cross-sectional study	Women with osteoporosis and… 1. with low kyphosis 2. with high kyphosis	 11 (64.4 ± 7.3) 12 (66.6 ± 10.4)	 TK (centroid): 26.6° ± 4.9° TK (Cobb): 35.3° ± 6.0° TK (centroid): 39.7° ± 4.5° TK (Cobb): 46.6° ± 7.9°	COPx; COPy; COPvx; COPvy	COPx: p = 0.361 COPy: p = 0.981 COPvx: p = 0.973 COPvy: p = 0.790
Katzman *et al.* [54]	Prospective cohort study	Women with kyphosis	3.108 (68.2 ± 6.1)	Thoracic kyphosis (mean ± SD angle = 47.6° ± 11.9°)	TUG	For each SD (11.9°) increase in kyphosis angle, there was an increase in average performance on TUG time of 0.2 s (p < .001).

Table 2.2. *Continued*

Study	Study design	Subjects	n (mean age ± SD)	Patient characteristics	Balance outcome variables	Results
Lynn *et al.* [41]	Case-control study	Women with… 1. "normal" 2. osteoporosis 3. osteoporosis & kyphosis	 5 (69 yrs) 10 (64 yrs) 6 (69 yrs)	 None Osteoporosis Osteoporosis & kyphosis (Cobb angle > 54°)	PS on SOT-5 & SOT-6; BSS	SOT-5 – group comparisons - kyphosis/osteoporosis: p < 0.001 - kyphosis/"normal": p = 0.186 - osteoporosis/"normal": p = 0.044 SOT-6 – group comparisons - kyphosis/osteoporosis: p = 0.008 - kyphosis/"normal": p = 0.194 - osteoporosis/"normal": p = 0.002 BSS: Both osteoporosis groups had a significantly greater reliance on hip strategies to maintain balance. The kyphosis group showed the greatest reliance on hip strategies.
Sinaki *et al.* [56]	Cross-sectional study	1. Women with osteoporosis & hyperkyphosis (O-K) 2. Healthy women (control)	12 (76.5 ± 5) 13 (71 ± 5)	Osteoporosis (*t*-score < -2.5 SD) Hyperkyphosis (Cobb-angle T2-T12 is 50°-65°) None	Gait analysis (Cad; right & left StL; StrL; SW; WS; right & left SST); CBS	R StL: O-K: 57.4 ± 3.3; control: 61.83 ± 2.9 (p = 0.005) L StL: O-K: 58.0 ± 3.2; control: 60.87 ± 2.8 (p = 0.03) StrL: O-K: 115.4 ± 5.1; control: 122.70 ± 5.0 (p = 0.003) WS: O-K: 0.99 ± 0.15; control: 1.18 ± 0.09 (p = 0.004) Cad: O-K: 103.9 ± 13.6; control: 115.79 ± 7.2 (p = 0.03) R SST: O-K: 36.1 ± 1.4; control: 37.39 ± 2.2 (p = 0.15) L SST: O-K: 35.97 ± 1.8; control: 36.47 ± 1.7 (p = 0.37) SW: O-K: 8.62 ± 1.5; control: 7.85 ± 2.1 (p = 0.25)

Patients with and without flexed posture (FP)						
Antonelli-Incalzi *et al.* [49]	Cross-sectional study	Men with…	352 (73.8 ± 6.34)		SB; RCC; 4mWS; SPPB	SB: $p = 0.009$ between groups; men with long OWD performed worse
		1. Short OWD	87 (19.5% ≥ 75 yrs)	OWD < 2.39% of body height		RCS: $p = 0.790$ between groups; no differences between groups
		2. Medium OWD	175 (36.6% ≥ 75 yrs)	OWD ≥ 2.39% and ≤ 3.55% of body height		4mWS: $p < 0.001$ between groups; men with long OWD performed worse
		3. Long OWD	90 (54.4% ≥ 75 yrs)	OWD > 3.55% of body height		SPPB: p < 0.001 between groups, men with long OWD performed worse
		Women with…	431 (75.0 ± 6.85)			SB: $p < 0.001$ between groups; women with long OWD performed worse
		1. Short OWD	107 (22.4% ≥ 75 yrs)	OWD < 2.58% of body height		RCS: $p = 0.001$ between groups: women with long OWD performed worse
		2. Medium OWD	217 (44.7% ≥ 75 yrs)	OWD ≥ 2.58% and ≤ 3.90% of body height		4mWS: $p < 0.001$ between groups; women with long OWD performed worse
		3. Long OWD	107 (64.5% ≥ 75 yrs)	OWD > 3.90% of body height		SPPB: p < 0.001 between groups; women with long OWD performed worse
Balzini *et al.* [14]	Cross-sectional study	Elderly women with…			SPPB; POMA; Gait analysis (BoS; Cad; SL; SSD; WS)	SPPB: $p > 0.05$ between groups
		1. Mild FP	11 (74.8 ± 1.6)	OWD ≤ 5.0 cm		POMA: $p < 0.05$ for severe FP group versus mild FP
		2. Moderate FP	28 (77.0 ± 1.1)	OWD 5.1-8.0 cm		Gait analysis: $p < 0.05$ for moderate and severe group versus control group for all variables; $p <$ 0.05 for severe versus mild group for WS and BoS
		3. Severe FP	21 (78.0 ± 1.2)	OWD > 8.0 cm		

Table 2.2. *Footnote*

10ftW = 10-ft walk (s); **30m-GS** = Gait Speed over 30 meters (s); **4mWS** = Walking Speed over 4-m distance (m/s calculated as best performance score); **6mW** = 6-minute walk (m); **BBS** = Berg Balance Scale (score); **BD** = Body Displacement (cm); **BSS** = Balance Strategy Score; **BTWL** = Backward Tandem Walk Line (seconds); **CBS** = Composite Balance Score; **COPamp & COPvel** = mean amplitude (COPamp) of COP-movements (cm) in anterior-posterior and medio-lateral directions and mean velocity (COPvel) (cm/s), with eyes opened and closed; **COP velocity (SS-OE, SS-CE, US-OE, US-CE)** = Sway velocity of Centre of Pressure (degrees/second) on a Stable Surface with Eyes Open (SS-OE), Eyes Closed (SS-CE) and on an Unstable Surface with Eyes Open (US-OE) and Eyes Closed (US-CE); **COPx, COPy, COPvx & COPvy** = COP displacement in the anterior-posterior (COPx) and medio-lateral direction (COPy) and COP velocity in anterior-posterior (COPvx) and medio-lateral direction (COPvy); **CV of StL, SW, StrL, ST, StT** = Coefficient of Variation of Step Length (StL), Step Width (SW), Stride Length (StrL), Step Time (ST), and Stance Time (StT); **FGS** = Free Gait Speed (m/s); **Fo8** = Figure-of-8 test, speed adjusted for leg length (s^{-1}); **FR** = Functional Reach (cm); **FSS** = Four Square Step test (seconds); **Gait analysis (BoS; Cad; SL; SSD; WS)** = Gait analysis, measuring Base-of-Support (cm), Cadence (steps/minute); Step Length (cm), Single Support Duration (% gait cycle), and Walking Speed (m/s); **Gait analysis (Cad; right & left StL; StrL; SW; WS; right & left SST)** = Gait analysis, measuring Cadence (Cad); right and left Step (StL) and Stride Length (StrL); Step Width (SW); right and left Single Support Time (SST); and Walking Speed (WS); **%LOS (AP, ML)** = Percentage of theoretical Limits of Stability in anterior-posterior and medio-lateral direction; **MS** = Mobility Skills (tasks completed); **POMA** = Performance Oriented Mobility Assessment (score); **PS on SOT-5 & SOT-6** = Postural Sway (score) on Sensory Organization Test, Subtests 5 (eyes closed and sway referencing on platform) and 6 (inaccurate vision and sway referencing on platform); **RCS** = Repeated Chair Stands (score); **SB** = Standing Balance in 3 conditions (feet stand side-by-side, semi-tandem and tandem position for 10-second each); **SBI** = Static Balance Index (score); **TS (SS-OE, SS-CE, US-OE, US-CE)** = Total sway (defined as the total number of 1-mm squares traversed by the pen over a 30-second period) for standing on a Stable Surface with Eyes Opened (SS-OE) and Eyes Closed (SS-CE), and on a Unstable Surface with Eyes Opened (US-OE) and Eyes Closed (US-CE); **SPPB** = Short Physical Performance Battery (score); **TUG** = Timed Up & Go test (seconds)

Only one study examined walking characteristics of women with and without osteoporosis. Palombaro *et al.* [33] found significant increased step and stance time variability for women with osteoporosis compared with healthy women. Furthermore, they found a tendency toward increased variability in step width in the osteoporotic group.

Influence of vertebral fractures on various balance outcome measures

In four studies, balance was examined among patients with and without vertebral fractures (Table 2.2) [3, 11, 47, 51]. One study also assessed thoracic kyphosis and scored t-score for BMD [3]. Two studies controlled for visual, vestibular and proprioceptive dysfunctions [3, 47].

Three studies investigated the performance of these patients on clinically used functional performance tests [11, 47, 51]. Walking speed, measured by the 10-ft walk test, did not significantly differ between women with and without vertebral fractures in the study of Lyles *et al.* [47], but did significantly differ between these groups when measured with the 30-m walking speed test in a study by Gerdhem *et al.* [51]. Other tests measuring functional mobility were all carried out significantly worse by women with vertebral fractures: the Functional Reach test, the Mobility Scale protocol [47], and the TUG test [11].

Two studies investigated balance while standing still. Gerdhem *et al.* [51] measured balance during the Romberg test, finding a significantly worse performance of women with vertebral fractures. Greig *et al.* [3] found a significant difference between women with and without vertebral fractures in the mean anterior-posterior COP-displacement.

Walking characteristics are not yet evaluated between elderly with and without vertebral fractures.

Influence of thoracic kyphosis on various balance outcome measures

Table 2.2 shows furthermore the results of four studies that investigated the influence of thoracic kyphosis on various balance performance tests [3, 41, 54, 56]. Two studies registered the BMD [3, 56], and one study the amount of vertebral fractures as well [3]. Three studies controlled for visual, vestibular and proprioceptive dysfunctions [3, 41, 56].

Katzman *et al.* [54] concluded in their study that for each SD (11.9°) increase in thoracic kyphosis angle, there is an increase in average performance on the TUG time of 0.2 seconds.

Balance when standing still was recorded in three studies, with different results. Greig *et al.* [3] did not find any difference between patients with thoracic kyphosis and with normal posture for the mean COP displacement and velocity in anterior-posterior and medio-lateral direction. Likewise, Lynn *et al.* [41] did not find a significant difference between women with normal posture and with thoracic kyphosis for postural sway score. Contrary results were found by Sinaki *et al.* [56], who concluded that women with hyperkyphosis had significantly more postural sway than healthy women.

Furthermore, Sinaki *et al.* [56] carried out a gait analysis on a 10-meter walkway with 3-D marker trajectory data and a camera [61]. They found that women with hyperkyphosis had significant smaller step and stride lengths, a significantly lower walking speed and they performed significantly fewer steps per minute (cadence).

Influence of a flexed posture on various balance outcome measures

Two studies measured a variety of balance measurement among patients with flexed posture (Table 2.2) [14, 49]. Both studies measured the amount of flexed posture with the Occiput-to-Wall-Distance (OWD), and both studies were subdivided into three categories. Antonelli-Incalzi *et al.* [49] categorized men and women with short, medium and long OWD according to their body height. Balzini *et al.* [14] subdivided OWD into mild (≤5.0 cm), moderate (5.1–8.0 cm), and severe (>8.0 cm) flexed posture among women. Balzini *et al.* [14] mentioned the amount of vertebral fractures in their study; Antonelli-Incalzi *et al.* [49] did not assess the presence of osteoporosis, vertebral fractures or the degree of thoracic kyphosis. One study controlled for visual, vestibular and proprioceptive dysfunctions [14].

Balzini *et al.* [14] found significant differences between women with severe and mild flexed posture on the Performance Oriented Mobility Assessment [64]. However, they did not find a significant difference between the three groups for the Short Physical Performance Battery (SPPB). Contrary results were found by Antonelli-Incalzi *et al.* [49], where both men and women with increased OWD scored significantly lower on the SPPB than their healthy controls.

In the study of Antonelli-Incalzi *et al.* [49], standing balance was measured by asking patients to attempt to maintain their feet in a side-by-side, semi-tandem and tandem position for 10 s each. Both men and women with long OWD performed significantly worse than the other groups. Walking speed was evaluated over a 4-m distance. For both men and women, the long OWD groups performed significantly worse than the medium and short OWD groups.

Balzini *et al.* [14] analyzed gait, measuring cadence, step length, walking speed, base of support width and single support duration. For all variables, women with moderate or severe flexed posture performed significantly worse than women with mild flexed posture. Women with severe flexed posture had significantly lower walking speed and significantly wider base-of-support than women with moderate flexed posture.

Discussion

The aim of the present literature review was to examine whether postural control of patients with osteoporosis, vertebral fractures, thoracic kyphosis and flexed posture is affected, and which instruments measuring postural control are most sensitive in this population. A total of 18 eligible studies were included, assessing postural control with 27 different instruments. Postural control was generally affected for patients with vertebral fractures, thoracic kyphosis and flexed posture. For patients with osteoporosis alone, the results were more nuanced. These patients showed affected postural control when tested with instrumental tests under various conditions. In contrast, functional performance tests did not show significant differences in postural control for osteoporotic patients compared with their healthy controls. Apparently, functional performance tests are less sensitive than computerized tests in the osteoporotic population.

These functional performance tests are easy to assess, but measure more than postural control alone. The TUG test is a good example: this is a commonly-used test to examine functional mobility in older frail adults, and is validated to detect patients at risk of falling [31, 65]. The term “functional mobility” reflects the balance and gait maneuvers used in everyday life; for example, getting out of a chair, walking, turning and sitting down. In fact, the TUG measures postural control indirectly by timing a set of different actions, but provide no direct quantification of impaired postural control. In the present review article, three studies were included assessing only the TUG in their patient population [11, 37, 54]. All three studies had large sample sizes, and two of them showed an affected functional mobility for patients with vertebral fractures and thoracic kyphosis [11, 54], but not for osteoporotic patients [37]. An explanation might be that women with vertebral fractures, thoracic kyphosis or flexed posture have more functional loss than women with only osteoporosis. However, when a TUG performance is within the normal range, there still might be an impaired postural control, resulting in an increased risk of falling. This means that the performance on the TUG is not specific for (impaired) postural control in the osteoporotic population.

For the osteoporotic group, we therefore recommend instrumental tests to detect whether these patients have impaired postural control and to obtain more insight into the underlying mechanisms of (impaired) postural control. Eight studies carried out more refined analyses under various conditions (e.g. eyes open or closed, standing on a stable or unstable surface) using objective outcome measures derived from computerized instruments; for example, detection of magnetic fields [39], force plate [36, 40, 41], balance platform [35, 42], sway meter system [38] and electronic walkway [33]. Significant different outcome variables for standing balance were the body displacement [39], velocity and amplitude of center of pressure [40, 42], percentage of theoretical limits of stability of sway [40], postural sway score [41], composite balance score of the sensory organization test [36], and for gait analysis: step and stance time [33]. However, not all instruments are very useful in clinical practice, because not all are easily and quickly assessable during consultation with a patient, as a result of large instrument sizes and advanced technical aspects. Other drawbacks of these computerized instruments could be the need to carry out off-line data-analysis, pre-process the data, and the translation to clinically applicable outcome measures. However, these processes are being automated and simplified more and more for clinical use.

A relatively new instrument that is useful in clinical practice is ambulant motion-sensing (accelerometry) technology. This is an ambulatory instrument attached over the clothes on the body of the patient close to the center of body mass. These devices are light, compact and easy-to-use, with minimal awareness of the measuring process by the subject. The acceleration device records trunk acceleration in three dimensions, which can be used to assess postural control during walking and standing under various conditions, and for various patient groups [19, 27, 66–69]. From the accelerometer data, a variety of outcome variables can be calculated; for instance, to quantify amplitude of postural sway, stability and variability measures during standing and walking tasks [19, 22, 27, 66, 68, 69]. However, none of the included studies in the present review used an accelerometer to assess balance. Therefore, further research is required to investigate which outcome variables of accelerometry detect best the effect of postural changes on postural control and predict future falls in the osteoporotic population.

A limitation of the present literature review was the small amount of studies carried out to assess postural control in this population of elderly with osteoporosis, vertebral fractures, thoracic kyphosis or flexed posture. Also, the definition of osteoporosis was not clear in all studies [33, 35–42], particularly whether there were vertebral fractures and/or thoracic kyphosis and/or flexed posture in the osteoporotic group was not

mentioned, which could interfere with the results. Furthermore, as a result of small sample sizes and low scores for external validity, the results of the included studies cannot be easily extrapolated to larger groups. Nevertheless, despite the small groups, significant differences in postural control were found between patients with vertebral fractures, thoracic kyphosis and flexed posture, and their healthy controls in all nine studies. In four studies, there were some non-significant test-results [3, 14, 41, 47]. This was probably caused by methodological choices in the studies. For example, Lyles *et al.* [47] used a test that was probably not sensitive enough, Greig *et al.* [3] determined high and low kyphosis arbitrarily, Lynn *et al.* [41] assessed postural control under very challenging conditions, possibly causing a ceiling effect, and Balzini *et al.* [14] used a much smaller patient population compared with Antonelli-Incalzi *et al.* [49]

In conclusion, based on the reviewed studies, there is evidence for impaired postural control in patients with osteoporosis, vertebral fractures, thoracic kyphosis and flexed posture. An impaired postural control is a risk factor for falls and further fractures among the elderly [16, 70]. An early diagnosis of balance disorders is of great importance to prevent osteoporotic patients from falling by offering them an early intervention, for instance Tai Chi or vitamin D supplementation [71, 72]. Therefore, we recommend that physicians assess postural control in osteoporotic patients. Because functional performance tests are not sensitive and specific enough for all patients, we recommend easily clinically usable ambulant technology, for instance the accelerometer, to detect impairments in postural control during various standing and walking tasks.

Appendix I

Search strategy for PubMed

((“osteoporosis” [mesh] OR “osteoporosis” [tiab]) OR (“osteoporosis postmenopausal” [mesh] OR “osteoporosis postmenopausal” [tiab]) OR (“bone mass” [mesh] OR “bone mass” [tiab]) OR (“bone density” [mesh] OR “bone density” [tiab]) OR (“bone mineral density” [mesh] OR “bone mineral density” [tiab]) OR (“BMD” [mesh] OR “BMD” [tiab]) OR (“osteopenia” [mesh] OR “osteopenia” [tiab]) OR (“vertebral fractur*” [mesh] OR “vertebral fractur*” [tiab]) OR (“osteoporotic fractur*” [mesh] OR “osteoporotic fractur*” [tiab]) OR (“compression fractur*” [mesh] OR “compression fractur*” [tiab]) OR (“spinal fractur*” [mesh] OR “spinal fractur*” [tiab]) OR (“kyphosis” [mesh] OR “kyphosis” [tiab]) OR (“thoracic kyphosis” [mesh] OR “thoracic kyphosis” [tiab]) OR (“cobb angle” [mesh] OR “cobb angle” [tiab]) OR (“flexed posture” [mesh] OR “flexed posture” [tiab]) OR (“occiput-to-wall distance” [mesh] OR “occiput-to-wall distance” [tiab])) AND ((“gait” [mesh] OR “gait” [tiab]) OR (“gait analysis” [mesh] OR “gait analysis” [tiab]) OR (“gait speed” [mesh] OR “gait speed” [tiab]) OR (“walking speed” [mesh] OR “walking speed” [tiab]) OR (“balance measuremen*” [mesh] OR “balance measuremen*” [tiab]) OR (“balance tests” [mesh] OR “balance tests” [tiab]) OR (“balance testing” [mesh] OR “balance testing” [tiab]) OR (“balance test” [mesh] OR “balance test” [tiab]) OR (“dynamic balance” [mesh] OR “dynamic balance” [tiab]) OR (“static balance” [mesh] OR “static balance” [tiab]) OR (“functional mobility” [mesh] OR “functional mobility” [tiab]) OR (“motor skills” [mesh] OR “motor skills” [tiab]) OR (“gait disorders” [mesh] OR “gait disorders” [tiab]) OR (“force platform” [mesh] OR “force platform” [tiab]) OR (“timed up and go” [mesh] OR “timed up and go” [tiab]) OR (“TUG” [mesh] OR “TUG” [tiab]) OR (“berg balance scale” [mesh] OR “berg balance scale” [tiab]) OR (“BBS” [mesh] OR “BBS” [tiab]) OR (“center of pressure” [mesh] OR “center of pressure” [tiab]) OR (“COP” [mesh] OR “COP” [tiab]))

Appendix II

Downs & Black criteria used for methodological quality evaluation

Downs & Black [30] criteria used for the methodological quality evaluation of the reviewed studies. All items are scored 1 or 0 (yes or no), except item 4, which is scored 2, 1 or 0 (yes, partially or no).

Item	Score
Reporting	
Clear description of study's hypothesis, aim(s) or objective(s).	Yes(1)/No(0)
Definition of the main outcomes in the introduction or methods section.	Yes(1)/No(0)
Clear description of the individuals included in the study.	Yes(1)/No(0)
Description of the principal confounders.	Yes(2)/Partially (1)/No(0)
Clear description of the study's main findings.	Yes(1)/No(0)
Information on random data variability for the main outcomes.	Yes(1)/No(0)
Information on the real probability values for the main outcomes.	Yes(1)/No(0)
External validity	
Representativeness of the planned sample.	Yes(1)/No(0)
Representativeness of the individuals actually included in the final sample.	Yes(1)/No(0)
Internal validity – bias	
Blinding of those measuring the main outcomes.	Yes(1)/No(0)
Clear description of results not based on a priori hypothesis ('data dredging').	Yes(1)/No(0)
Adequacy of the statistical tests used to evaluate the main outcomes.	Yes(1)/No(0)
Accuracy of the main outcome measures.	Yes(1)/No(0)
Internal validity – confounding	
Comparability of the individuals included in all comparison groups in relation to the population they were recruited from.	Yes(1)/No(0)
Comparability of the individuals included in all comparison groups in relation to the period of time when they were recruited.	Yes(1)/No(0)
Adequate adjustment for principal confounders in the analysis from which the main findings were drawn.	Yes(1)/No(0)
Power	
Sufficient study power to detect an important effect, with a 5% significance level.	Yes(1)/No(0)

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CHAPTER 3

A flexed posture in elderly patients is associated with impairments in postural control during walking

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Abstract

A flexed posture (FP) is characterized by protrusion of the head and an increased thoracic kyphosis (TK), which may be caused by osteoporotic vertebral fractures (VFs). These impairments may affect motor function, and consequently increase the risk of falling and fractures. The aim of the current study was therefore to examine postural control during walking in elderly patients with FP, and to investigate the relationship with geriatric phenomena that may cause FP, such as increased TK, VFs, frailty, polypharmacy and cognitive impairments. Fifty-six elderly patients (aged 80 ± 5.2 years; 70% female) walked 160 m at self-selected speed while trunk accelerations were recorded. Walking speed, mean stride time and coefficient of variation (CV) of stride time were recorded. In addition, postural control during walking was quantified by time-dependent variability measures derived from the theory of stochastic dynamics, indicating smoothness, degree of predictability, and local stability of trunk acceleration patterns. Twenty-five patients (45%) had FP and demonstrated a more variable and less structured gait pattern, and a more irregular trunk acceleration pattern than patients with normal posture. FP was significantly associated with an increased TK, but not with other geriatric phenomena. An increased TK may bring the body's center of mass forward, which requires correcting responses, and reduces the ability to respond on perturbation, which was reflected by higher variation in the gait pattern in FP-patients. Impairments in postural control during walking are a major risk factor for falling: the results indicate that patients with FP have impaired postural control during walking and might therefore be at increased risk of falling.

Introduction

A flexed posture (FP) is characterized by an increased thoracic kyphosis (TK), protrusion of the head and, in severe cases, knee flexion [1], which is a postural correction to the increased TK [2]. In the elderly, TK is likely to increase over time [3] because of intervertebral disc deformities and/or spinal extensor muscle weakness [4, 5]. Vertebral fractures (VFs) are characteristic of osteoporosis: VFs in the thoracic vertebral column may also increase TK. These impairments may affect motor function, thus increasing the risk of falling [6] and fractures.

A recent review showed significant differences in postural control during standing and walking between patients with osteoporosis and healthy controls, particularly when variables indicating postural stability were calculated from objective measurements using instrumented devices like force plates and accelerometers [7]. In the majority of studies reviewed, however, the presence and severity of FP, TK and/or VFs in the osteoporotic group were not specified, and the relationship between these clinical entities is not yet clear.

Impaired postural control during walking is a major risk factor for falls and new fractures in the elderly [8]; therefore, early recognition and quantification of balance disorders is important in osteoporotic patients. Analyses of time-dependent variability, using measures derived from the theory of stochastic dynamics [9], enable differences in postural control during walking to be detected between young and old patients, fallers and non-fallers, and those with and without cognitive impairments [9–11]. Measures to quantify time-dependent variations of postural control during walking, such as the detrended fluctuations analyses [12], sample entropy [13] and maximal Lyapunov exponents [11], were used in the current study as well as more conventional gait parameters (e.g. average gait speed, and stride times). In conventional measures, each gait cycle is treated as an independent event unrelated to previous or subsequent strides, whereas the methods used in the current study assess fluctuations throughout the gait cycle, thereby providing greater insight into movement behavior.

The primary aim of the present study was to examine postural control during walking in elderly patients with FP, and the secondary aim was to examine the relationship with TK, VFs and grip strength (as an indicator for overall limb strength) as possible causes of FP [1, 4, 5]. Comorbid diseases, frailty, polypharmacy and cognitive impairments are often present in the elderly, so the association of these geriatric phenomena with FP was also examined. Patients with FP are hypothesized to have increased variability of gait parameters compared with patients with normal posture. Also, the presence of

increased TK, VFs, muscle weakness and other geriatric phenomena might further worsen FP, and consequently worsen postural control during walking.

Methods

Participants

Patients were recruited among the elderly who visited the Diagnostic Geriatric Day Clinic at the Slotervaart Hospital in Amsterdam. Patients aged at least 70 years who could walk safely for 3 minutes without assistance were included in the study. Patients who had any asymmetric mobility problems and/or did not understand the researcher's instructions were excluded from the study.

The study was approved by the Medical Ethical Committee of the Slotervaart Hospital. All included patients gave their informed consent.

Gait analysis

Patients walked about 160 m at a self-selected speed in a well-lit, 80-m-long hallway. Walking time was recorded to determine gait speed. Trunk accelerations were measured with a tri-axial accelerometer (DynaPort Minimod Hybrid, McRoberts BV, The Hague, the Netherlands; sample frequency 100 Hz) attached with a band at the level of the lumbar vertebral column.

Stride-related parameters

Medio-lateral (ML) and anterior-posterior (AP) trunk acceleration signals were analyzed using custom-made software in MATLAB (The MathWorks, Inc., Natick, MA, USA). Signals were corrected for horizontal tilt, and high-pass filtered using a Butterworth filter (4^{th} order; cut-off frequency 0.25 Hz). Foot contacts were determined from the peaks of the AP-acceleration time-series. A median filter was used to exclude outliers in the data due to turning points in the gait assessment. Foot contact data were used to calculate stride times, which were defined as the time interval between two ipsilateral foot contacts. Mean stride time, coefficient of variation (CV) of stride time, and stride frequency were calculated for each patient.

Further parameters were calculated to assess variations throughout the gait cycle. Temporal variability was quantified by the variance of the relative timing between sequential ipsilateral foot contacts using the point estimate of the relative phase: $\varphi_i = (FCR_{t(i)} - FCL_{t(i)}) / (FCL_{t(i+1)} - FCL_{t(i)}) \times 360°$ [14], where FCL and FCR are the left and right

foot contacts at time *t(i)*, respectively. The relative phase is a circular measure; therefore, circular statistics were applied to calculate the mean and variance of the relative phase over strides [15]. A temporally symmetrical gait pattern is denoted by φ_i = 180°; a higher variance indicates a more variable gait pattern.

In addition, long-range correlations in stride time intervals were quantified by calculating scaling exponent a using the detrended fluctuation analysis (DFA) [12]. When $0.5 \geq \alpha \geq 1$, this indicates the presence of long-term correlations in the signal, which means future fluctuations are better predicted by past fluctuations. Therefore, α values closer to 1 represent a more structured pattern.

Trunk movement patterns

The magnitude of ML and AP trunk acceleration patterns was quantified by calculating the root mean square (RMS). The harmonic ratio (Hratio), sample entropy (SEn) [13], and maximal Lyapunov exponent (λ_{max}) [16] were calculated using open source software (UPMOVE version 0.2a; http://www.upmove.org), indexing the smoothness, degree of predictability, and local stability of the trunk acceleration patterns, respectively.

The Hratio was calculated using spectral dynamics to quantify the smoothness of the ML and AP trunk movements, with a higher Hratio representing a smoother trunk acceleration pattern. A discrete Fourier transform was used to estimate the power spectral density of the fundamental oscillatory frequency and of the six consecutive harmonics. The Hratio was defined by dividing the power spectral density of the fundamental oscillatory frequency by that of the first seven harmonics (the first seven harmonics were chosen because no additional information was obtained from spectral analysis of higher frequencies after low-pass filtering the data at 10 Hz).

The degree of predictability in ML and AP acceleration time-series was assessed by calculating the SEn, which is defined as the negative natural logarithm of an estimate of the conditional probability of epochs of length *m* (*m* = 3 in this study) that match point-wise within a tolerance *r* and repeats itself for *m* + 1 points. An optimization approach [17] was used to determine the tolerance parameter *r* and *m*, since the choice of *r* for given *m* is decisive. Smaller SEn values indicate greater regularity; larger SEn values are associated with a small chance of similar data being repeated. The ML and AP acceleration data were normalized to unit variance, so the outcome was scale-independent.

Local stability of the ML and AP trunk acceleration patterns was expressed by the λ_{max}, which was calculated by applying the Wolf algorithm [16]: this algorithm is most

appropriate to evaluate local dynamic stability from relatively small data sets. The time-series was first low-pass filtered using a least squares finite impulse response filter (6th order; cut-off frequency 10 Hz) [11]. All stride-cycles were then resampled to 100 samples to enable comparison of trials between patients with FP and those with normal posture on the same time scale. The estimated time interval was 10% of the stride cycle for all reconstructed state spaces. An embedded dimension of 5 was chosen, following previous studies [9]. Larger λ_{max} indicates greater sensitivity to local perturbations.

Additional measurements

Age, gender, body mass index (BMI) and number of prescriptions were recorded for each patient. FP was defined as an occiput-to-wall distance (OWD) of 5.0 cm or more [1]; OWD was measured while subjects stood with their head in a natural position with heels and back touching the wall and knees extended.

Lateral X-rays of the thoracic and lumbar spine were assessed to determine the degree of TK and the presence of VFs. TK was measured by the Cobb angle between the superior endplate of the second thoracic vertebra and the inferior endplate of the twelfth thoracic vertebra. The Cobb angle was measured independently by two observers and the mean value was used. An abnormal increased TK was defined as a Cobb angle of ≥50° [18], and a TK of <50° was considered normal. VFs were independently scored by two observers using Genant's semi-quantitative method [19]. When conclusions differed, final consensus was reached by discussion.

Grip strength (in kg) of the dominant hand was assessed with a Jamar hand-held dynamometer (average of three measurements; corrected for body height) and this was used as an indicator for overall limb strength [20]. Other geriatric phenomena were also recorded, including the presence of co-morbid diseases, using the Charlson comorbidity index (CCI) [21], cognitive functioning, using the mini mental state examination (MMSE) [22], risk of falling, using Pluijm's assessment [23] and the presence of frailty, according to the presence of three or more criteria of Fried *et al.* [24].

Statistical analyses

PASW Statistics 18 (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses (level of significance $p < 0.05$). Non-parametric tests (Mann–Whitney U and χ^2) were used to test group differences between patients with normal posture and those with FP.

Table 3.1. Characteristics of patients with normal (NP; OWD <5.0 cm) and flexed posture (FP; OWD ≥5.0 cm).

Patient characteristics	NP (n = 31)	FP (n = 25)	*p*-value
Age (years), mean (SD)	79.7 (5.50)	79.6 (4.92)	0.85
Female, n (%)	22 (71%)	17 (68%)	0.81
BMI (kg/m2), mean (SD)	26.8 (4.40)	27.1 (3.47)	0.70
Vertebral fractures			
Presence of VFs, n (%)	11 (36%)	11 (44%)	0.52
Thoracic VFs (T2-T8), n (%)	9 (29%)	8 (32%)	0.81
Thoracolumbar VFs (T9-L1), n (%)	4 (13%)	5 (20%)	0.47
Lumbar VFs, n (%)	2 (7%)	1 (4%)	0.69
Thoracic kyphosis			
Cobb angle T2-T12 (°), mean (SD)	44.5 (12.1)	58.6 (11.9)	<0.01
Increased thoracic kyphosis (Cobb angle ≥50°), n (%)	9 (29%)	20 (80%)	<0.01
Grip strength			
Grip strength (kg), mean (SD)	24.2 (8.76)	26.0 (8.45)	0.50
Comorbidities			
CCI score, median (range)	1 (0-4)	1 (0-5)	0.74
≥2 co-morbid diseases, n (%)	12 (39%)	11 (44%)	0.70
Dementia, n (%)	8 (26%)	7 (28%)	0.85
Myocardial infarct, n (%)	7 (23%)	7 (28%)	0.64
Chronic pulmonary disease, n (%)	2 (6%)	6 (24%)	0.06
Peripheral vascular disease, n (%)	5 (16%)	1 (4%)	0.15
Diabetes type II, n (%)	5 (16%)	2 (8%)	0.36
Cerebrovascular disease, n (%)	2 (6%)	3 (12%)	0.47
Prescriptions			
Number of prescriptions, median (range)	5 (0-15)	5 (0-15)	0.82
Polypharmacy (≥4 prescriptions), n (%)	21 (68%)	16 (64%)	0.77
Frailty			
Fried's frailty score, median (range)	1 (0-4)	1 (0-5)	0.30
Frail, n (%)	5 (16%)	3 (12%)	0.66
Cognitive functioning			
MMSE score, median (range)	24 (13-30)	25 (15-30)	0.24
Fall risk			
Pluijm score, median (range)	4 (0-19)	4 (0-20)	0.73
Increased fall risk (Pluijm score ≥7), n (%)	7 (23%)	4 (16%)	0.54

BMI Body Mass Index; **CCI** Charlson Comorbidity Index; **MMSE** Mini-Mental State Examination; **OWD** Occiput-to-Wall Distance; **VF** vertebral fracture; **SD** standard deviation

To test factors associated with FP, simple linear regressions were first calculated with the OWD as dependent variable, and patient characteristics, such as extent of TK, VFs and frailty, as independent variables. Three multiple linear regression models were then calculated: (A) a model based on the literature [1, 4, 5] (the independent variables included were the Cobb angle, presence of VFs, and grip strength corrected for body height); (B) a model with geriatric phenomena (CCI, number of prescriptions, Fried's frailty score, Pluijm's fall risk assessment score, and MMSE); and (C) a model based on the simple regression analyses (independent variables were included when $p < 0.30$).

Results

Fifty-six patients (aged 80 ± 5.2 years; 70% female) were included in the present study. Twenty-five patients (45%) were classified as having FP (OWD ≥5.0 cm). The characteristics of patients with normal posture and FP are presented in Table 3.1. Patients with FP had a significantly higher Cobb angle than patients with normal posture. Consequently, significantly more patients in the FP-group were classified as having an increased TK (Cobb angle ≥50°) compared with patients with normal posture (80% vs. 29%; $p < 0.01$). There were no differences between groups in the presence of VFs, an indicator for severe osteoporosis, or in other characteristics.

Effects of flexed posture on gait

Walking speed did not differ significantly between the two patient groups ($p = 0.26$). Variability (CV) of stride time was significantly higher ($p = 0.03$) and the scaling exponent α was significantly lower ($p < 0.01$) in patients with FP compared with those with normal posture, which implies less correlated stride time intervals (Table 3.2). In addition, patients with FP had a significantly less symmetrical gait pattern than patients with normal posture, i.e. there was greater variability of the relative phase between foot contacts ($p = 0.02$). There were no statistically significant differences in other gait parameters between the two groups.

Variables quantifying trunk acceleration patterns for both groups are presented in Fig. 3.1. Patients with FP had significantly lower ML RMS ($z = -2.18$; $p = 0.03$) and AP RMS ($z = -3.12$; $p < 0.01$), and significantly higher AP SEn values ($z = 1.99$; $p < 0.05$) compared with patients with normal posture. ML SEn values and ML and AP Hratio and λ_{max} did not differ significantly between groups.

Table 3.2. Group differences of patients with normal (NP) and flexed posture (FP) for gait variables. Values are presented as mean (SD). Statistical differences between patient groups are indicated by *z*- and *p*-values (based on Mann-Whitney U tests).

Gait parameters	NP (n=31)	FP (n=25)	*z*-value (*p*-value)
Walking speed (m/s)	0.90 (0.22)	0.81 (0.29)	-1.13 (0.26)
Mean stride time (s)	1.16 (0.15)	1.17 (0.12)	0.95 (0.34)
CV of stride time (%)	3.56 (1.68)	4.27 (1.53)	2.22 (0.03)
Stride frequency (strides/s)	0.88 (0.10)	0.85 (0.09)	-1.39 (0.16)
SD of relative phase (°)	4.11 (1.22)	4.98 (1.38)	2.37 (0.02)
α stride times	0.81 (0.16)	0.67 (0.19)	-2.65 (0.01)

CV Coefficient of Variation; **SD** Standard Deviation

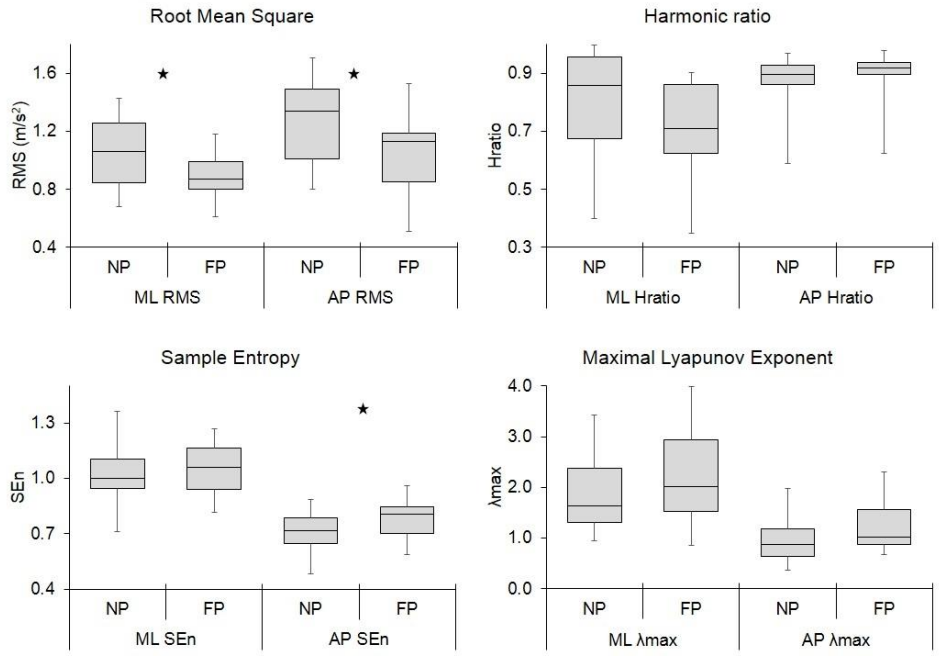

Fig. 3.1. Effects of normal (NP; *n* = 31) and flexed posture (FP; *n* = 25) on medio-lateral (ML) and anterior-posterior (AP) trunk movement pattern parameters, namely Root Mean Square (RMS), Harmonic Ratio (Hratio), Sample Entropy (SEn), and maximal Lyapunov exponent (λ_{max}), presented as boxplots. A significant difference between the patient groups is marked as ★ ($p < 0.05$, based on Mann-Whitney *U* tests).

Table 3.3. Results of simple and multiple linear regression analyses, examining the relationship between the Occiput-to-Wall Distance and (A) osteoporosis-related parameters, (B) comorbidities present in the population, and (C) a model based on the results of the simple linear regression analyses.

	Simple linear regression analyses			Multiple linear regression analyses					
				Model A		Model B		Model C	
Patient characteristics	**B (SE)**	***p*-value**	**R^2**	**B (SE)**	***p*-value**	**B (SE)**	***p*-value**	**B (SE)**	***p*-value**
Age (years)	0.03 (0.12)	0.82	<0.01						
Female	-1.76 (1.27)	0.17	0.04					-0.54 (1.74)	0.76
BMI (kg/m^2)	-0.03 (0.12)	0.83	<0.01						
Osteoporosis-related parameters									
Presence of VFs	0.55 (1.21)	0.65	<0.01	-0.83 (1.09)	0.45				
Cobb angle T2-T12 (°)	0.17 (0.04)	<0.01	0.27	0.18 (0.04)	<0.01			0.17 (0.04)	<0.01
Grip strength (kg)[a]	0.04 (0.04)	0.28	0.02	0.07 (0.03)	0.04			0.07 (0.05)	0.20
Co-morbidities									
CCI score	0.04 (0.46)	0.93	<0.01			0.23 (0.45)	0.64		
Number of prescriptions	-0.02 (0.15)	0.90	<0.01			-0.19 (0.18)	0.30		
Fried's frailty score	0.69 (0.50)	0.17	0.04			1.26 (0.59)	0.04	0.50 (0.47)	0.30
MMSE score	0.11 (0.14)	0.42	0.01			0.15 (0.15)	0.30		
Pluijm score	-0.08 (0.12)	0.47	0.01			-0.16 (0.13)	0.30		
R^2:				0.34		0.10		0.35	

B regression coefficient; **BMI** Body Mass Index; **CCI** Charlson Comorbidity Index; **MMSE** Mini-Mental State Examination; **R^2** Coefficient of Determination; **SD** Standard deviation; **SE** Standard Error; **VF** Vertebral Fracture.

[a] Grip strength was corrected for body height

Factors associated with flexed posture

The results of simple linear regression analyses to examine the relationship between each variable independently with OWD are shown in the first column of Table 3.3. Only the degree of TK was significantly associated with OWD ($p < 0.01$). Fig. 3.2 illustrates the relationship between the Cobb angle and OWD. The other well-known risk factors for FP, namely VFs and grip strength, were not associated with FP in this cohort. The other characteristics examined in this study were not significantly associated with OWD in the simple linear regression analyses.

Multiple linear regression analyses were also performed (see the second column of Table 3.3). In model A, which was a model based on the literature [1, 4, 5], the relationship between osteoporosis-related parameters and OWD was examined: the Cobb angle and grip strength (corrected for body height) were both associated with OWD (R^2 = 34%). In model B, which included independent variables related to geriatric phenomena, frailty was the only variable significantly associated with the OWD (R^2 = 10%). Finally, in model C, which was based on the results of the simple linear regression analyses, Cobb angle was significantly associated with OWD, whereas the other included variables were not (R^2 = 35%).

Discussion

The objective of the present study was to examine postural control during walking in elderly patients with FP, and to investigate factors that may influence this. The results of this study show that FP in elderly patients was associated with impairments in postural control during walking. Although walking speed did not differ significantly between the two patient groups, patients with FP showed a more variable and less structured gait pattern (higher CV of stride time), a less consistent gait pattern (greater variability of the relative phase), and less correlated stride times (lower α) than patients with normal posture. In addition, FP-patients exhibited a significantly decreased magnitude of trunk accelerations (lower values for ML RMS and AP RMS) compared with patients with normal posture. Trunk acceleration patterns were also significantly more irregular (higher AP SEn values), borderline significantly less smooth (lower Hratio values), and more unstable (higher AP λ_{max}) in patients with FP compared with patients with normal posture.

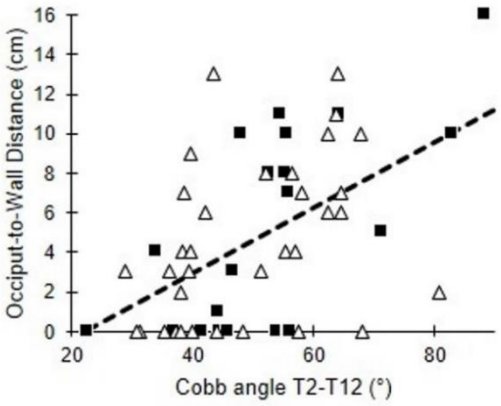

Fig. 3.2. Relation between the Cobb angle T2-T12, the presence of vertebral fractures and the Occiput-to-Wall Distance. The black squares (■) represent patients without VFs and the white triangles (Δ) patients with prevalent VFs. The dotted line is the fit-line of the model based on the linear regression analysis.

FP, as defined by the OWD, was also associated with an increased TK. This forward curvature of the trunk shifts the body's center of mass forward from the center of rotation (the spine), causing an increased forward bending moment [2, 25]. As postural control can be defined as the capacity to maintain the center of mass within the support base [26], it can be argued that patients with FP need adaptations to maintain balance. Therefore, an increased posterior counterbalancing force is required from dorsal musculature and ligaments. This can be obtained by flexing the knees and contracting the dorsal musculature to tilt hips [27], which brings the head and shoulders back up, but also tightens the hamstrings [2]. In addition, trunk movements and rotation, and arm sway may be reduced due to the changed trunk alignment and altered functioning of muscles and ligaments. Since dynamics of head, arms, and trunk are important mechanisms to maintain balance during walking [28], it is likely that the ability to react on (small) perturbations during walking is diminished in FP-patients. This was expressed in our results by a more robust effect on variability of the stride-related parameters than effect on the trunk acceleration patterns.

Factors present in the elderly patient population that were potentially associated with FP were also investigated. According to the results of multiple linear regression analyses, FP, expressed by the OWD, was associated with an increased TK and increased grip strength, but was not associated with the presence of VFs. Other common phenomena in the geriatric population, such as frailty, cognitive impairments, increased

fall risk, number of medications, and the presence of comorbid diseases, were weakly associated with the OWD (R^2 = 10%).

The hypothesis that the presence of VFs worsens the degree of TK and thus FP, was not confirmed in this study. Other known causes for an increased TK, and consequently FP, are degenerative disc diseases, or spinal extensor muscle weakness [1, 4, 5]; however, only grip strength was included in the present study. Grip strength is not a direct measure of spinal extensor muscle strength, but it was associated with the OWD in model A of the multiple linear regression analyses. Grip strength was higher in patients with FP compared with patients with normal posture; this may be explained by the increased posterior counterbalancing forces needed in FP-patients to maintain balance. However, this finding in the multiple regression analyses might be a coincidence since grip strength was not associated with OWD in the single linear regressions or in model C of the multiple linear regression.

The results of several outcome measures in the present study were borderline significant and the goodness-of-fit of the regression analyses was low-to-moderate (10–35%), which was probably caused by the large variation in patient data (see Figs. 3.1 and 3.2 presenting, respectively, boxplots of trunk movement pattern parameters, and the relationship between FP and TK). However, the heterogeneity in the present cohort is illustrative for the older population visiting a geriatric outpatient clinic. These patients are typically characterized by a combination of physiological, psychological and social problems, and comorbidities are often present [29]. In the present cohort, geriatric phenomena like frailty, cognitive impairment and polypharmacy were also present, and were equally distributed in patients with normal posture and FP; therefore, it can be concluded that these factors were not directly associated with the presence of FP. The patients of both groups were elderly with health issues: the comorbidities present in the included population might have impaired postural control during walking in both groups.

In summary, FP is characterized by an increased TK, which brings the body's center of mass forward and requires correcting responses of the body, such as counterbalancing force from posterior musculature to tilt the hips and flex the knees. These correcting responses may reduce the ability to respond on perturbations, which is reflected by the impaired postural control during walking in this study. Patients with FP demonstrated a more variable and less structured gait pattern, and a more irregular trunk acceleration pattern than patients with a normal posture. This may imply that patients with FP are at increased risk of falling compared with patients with normal posture, as impairments in postural control during walking are a major risk factor for falling.

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CHAPTER 4

Associations between vertebral fractures, increased thoracic kyphosis, a flexed posture and falls in older adults: a prospective cohort study

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Abstract

Background Vertebral fractures, an increased thoracic kyphosis and a flexed posture are associated with falls. However, this was not confirmed in prospective studies. We performed a prospective cohort study to investigate the association between vertebral fractures, increased thoracic kyphosis and/or flexed posture with future fall incidents in older adults within the next year.

Methods Patients were recruited at a geriatric outpatient clinic. Vertebral fractures were evaluated on lateral radiographs of the spine with the semi-quantitative method of Genant; the degree of thoracic kyphosis was assessed with the Cobb angle. The occiput-to-wall distance was used to determine a flexed posture. Self-reported falls were prospectively registered by monthly phone contact for the duration of 12 months.

Results Fifty-one older adults were included; mean age was 79 years (SD = 4.8). An increased thoracic kyphosis was independently associated with future falls (OR 2.13; 95% CI 1.10-4.51). Prevalent vertebral fractures had a trend towards significancy (OR 3.67; 95% CI 0.85-15.9). A flexed posture was not significantly associated with future falls.

Conclusion Older adults with an increased thoracic kyphosis are more likely to fall within the next year. We suggest clinical attention for underlying causes. Because patients with increased thoracic curvature of the spine might have underlying osteoporotic vertebral fractures, clinicians should be aware of the risk of a new fracture.

Background

Among older adults the prevalence of falls is high: at least 30-40% of patients aged over 65 experience one or more fall accidents annually [1]. Falls in the older population are generally caused by a combination of risk factors, such as balance and gait disorders, poor vision, polypharmacy and environmental factors, and could lead to serious injuries such as fractures [2]. In addition, diminished bone quality due to osteoporosis increases the risk of fall-related fractures, especially in women [3, 4]. However, typical osteoporotic fractures of the vertebrae are commonly not the result of a fall incident, but occur usually during normal activities of daily living, such as climbing stairs, lifting groceries, or bending forward [5]. The prevalence of vertebral fractures increases with age, and is up to 50% among geriatric outpatients [6]. Vertebral fractures could cause pain and may lead to postural changes, restrictive respiratory disease, poor physical condition, and loss of quality of life [7], and are independently associated with increased mortality [8, 9]. Furthermore, it was recently found that a prevalent vertebral fracture on a chest computed tomography (CT) was associated with a threefold increased risk of a future hip fracture [10].

Over time, thoracic vertebral fractures could increase the kyphotic curvature of the thoracic spine [11], and may therefore cause a flexed posture [12]. A flexed posture is characterized by an increased thoracic kyphosis, protrusion of the head, and in more severe cases also hip and knee flexion. A flexed posture is the more extreme expression of an increased thoracic kyphosis, when the compensatory mechanisms to correct the kyphosis fail [12].

Previous studies showed that the presence of both vertebral fractures and an increased thoracic kyphosis are related with increased fall risk [13–15]. Recently, we showed that vertebral fractures, increased thoracic kyphosis and a flexed posture are associated with an impaired postural control [16, 17]. Patients that have one or more of these entities present might fall more often, since impairments in balance and gait are the primary cause of falls [18]. Until now, this association has not been prospectively investigated. Therefore, we performed a prospective cohort study to investigate the association between prevalent vertebral fractures, increased thoracic kyphosis and a flexed posture with future fall incidents in older adults.

Methods

Patient characteristics

The study population comprised visitors of the geriatric outpatient clinic of the Slotervaart Hospital in Amsterdam between October 2010 and April 2012. They were referred to the clinic for various reasons, including memory complaints, mobility problems, or reducing polypharmacy. Eligible patients should be 70 years or older; should be able to walk safely for 3 minutes without using any assistive device (e.g. walking stick or wheeler); and should be able to understand and speak Dutch or English. Patients were excluded if they had any mobility problems due to (lateral) neurological or orthopedic disorders with function limitations of one or both legs; or if they were unable to understand the instructions of the researcher due to severe cognitive or hearing impairments.

All patients received a comprehensive geriatric assessment [19], being standard procedure at the geriatric outpatient clinic. Depending on the conclusions of the geriatrician, work up treatment was started. If the patient was referred to this clinic for fall-related problems, or reported falls in the last year, the Dutch national guidelines for the prevention of falls were followed [20]. The present study was approved by the Medical Ethical Committee of the Slotervaart Hospital and Reade. All patients (or their legal representatives) gave their informed consent.

Data collection

Gender, age, Body Mass Index (BMI), number of prescriptions, hip replacement in history, and self-reported falls in the last year were recorded. The presence of comorbid diseases was scored using the Charlson Comorbidity Index (CCI) [21]. Cognitive functioning was examined by the Mini Mental State Examination (MMSE) [22].

The prevalence of vertebral fractures was assessed on standing upright lateral X-rays of the thoracic and lumbar vertebral spine. Vertebral fractures were scored by the semi-quantitative technique of Genant [23, 24]. All radiographs were scored by two observers (MG and HJ). Their conclusions were compared, and if they differed, final consensus was reached by discussion.

The kyphosis of the thoracic vertebral column was determined by the Cobb angle, the angle between the superior endplate of the second, and the inferior endplate of the twelfth thoracic vertebra, as measured on the same lateral X-ray of the thoracic spine as was used for the judgment of vertebral fractures. In the present study, hyperkyphosis was defined as a Cobb angle of ≥50° [25], a Cobb angle <50° was considered normal. Two

observers (MG and HJ) measured the Cobb angle twice, and the mean value of the four measurements was used.

The severity of flexed posture was evaluated by measuring the occiput-to-wall distance (OWD), see Fig. 4.1. While subjects stood with their head in a natural position, their heels and back touching the wall and their knees as extended as possible, the distance between their occiput and the wall was measured [12]. A flexed posture was defined as an OWD >5.0 cm.

Fall incidents were prospectively registered for six months using a monthly calendar. A fall was defined as "an unexpected event where a person comes to rest on the ground from an upper level or the same level" [26]. During follow-up, patients (or their caregivers) were contacted by phone every month to report any fall incidents and/or injuries. When patients had a MMSE-score <24 points, caregivers who lived with the patient were asked to fill in the falls-and-fracture calendar. Since very few fall incidents were reported in the six-month follow-up period, we extended the falls-and fracture calendar with another six months. Main outcome of the study was the first fall during follow-up.

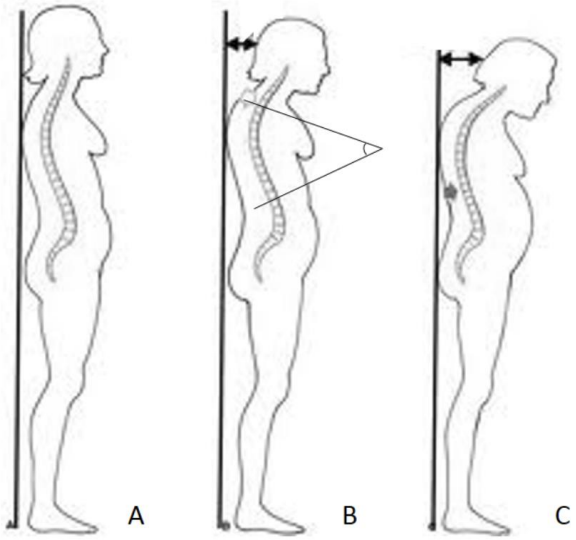

Fig. 4.1. Various postures among geriatric patients: (A) Normal posture; (B) Hyperkyphosis, defined as a Cobb angle ≥50 ° between T2 and T12 as measured on the X-ray of the vertebral column; (C) Flexed posture, defined as an occiput-to-wall distance >5.0 cm.

Statistical analysis

The associations among vertebral fractures, hyperkyphosis (Cobb angle ≥50°) and flexed posture (OWD >5.0 cm) were estimated using Chi-square tests. Then, to test which variables were associated with prospective falls, first univariate binary logistic analyses were performed for all patient characteristics. Secondly, a multivariate binary logistic regression analysis was computed (method: backward conditional), including all characteristics with P values < .20 in univariate analyses. Odds Ratio's (OR) with 95% Confidence Intervals (CI) and P values were calculated. In order to better compare the ORs of the variables, we standardized all continuous variables to unit variance, i.e., means were set to zero, and standard deviations to one (z-transformation). In addition, to test for multicollineartiy, we calculated the variance inflation factor (VIF) for the multivariate model. Since all VIF-values were around 1, we can assume that multicollinearity was not present in the model. For all statistical analyses, the level of significance was set on P < .05. SPSS Statistics version 21 was used.

Results

During the inclusion period, 139 possibly eligible patients visited the geriatric, whereof 60 persons gave their consent to participate in the present study. In nine cases, the falls-and-fracture calendar was not completed, due to lost to follow-up within the first month. Finally, 51 patients were included in the present study. The mean age of the included patients was 79 years, and 77% were female (Table 4.1). Seventeen patients (33%) reported ≥2 falls in the year previous to the baseline measurements. The mean follow-up for falls registration was 10.6 months. Thirty-eight patients (75%) had follow-up of twelve months with phone contact every month; the other thirteen patients had a mean follow-up of 6.2 months. After the first six months, eight patients refused further follow-up. Other reasons for lost to follow-up were: moving to a nursing home (*n* = 3); and being tired of registering high fall incidence (*n* = 2). Thirteen patients (25%) had at least one fall during follow-up; of these, eight patients were recurrent fallers (≥2 falls). Four patients had serious injury after the fall and had to visit a doctor, of whom one had a new non-vertebral fracture.

Table 4.1. Population characteristics (*n* = 51)

Population Characteristics	
Patient characteristics	
Age (years), mean (SD)	79.3 (4.8)
Female, *n* (%)	39 (77%)
BMI (kg/m^2), mean (SD)	27.4 (4.0)
CCI score, mean (SD)	1.4 (1.3)
Number of prescriptions, mean (SD)	5.8 (3.9)
MMSE score, median (range)	24 (13-30)
Hip replacement in history, *n* (%)	7 (14%)
Osteoporosis-related factors	
Presence of vertebral fractures, *n* (%)	20 (39%)
Thoracic kyphosis, Cobb angle (°), mean (SD)	51.2 (14.5)
OWD (cm), median (range)	4.0 (0-16)
Falls during follow-up	
- no falls, *n* (%)	38 (74%)
- 1 fall, *n* (%)	5 (10%)
- ≥2 falls during follow-up (range 2-9), *n* (%)	8 (16%)

CCI = Charlson Comorbidity Index; **MMSE** = Mini-Mental State Examination;
OWD = Occiput-to-Wall Distance

Relation between vertebral fractures, hyperkyphosis and flexed posture

Fig. 4.2 shows the distribution of vertebral fractures, hyperkyphosis (Cobb angle ≥50°), and flexed posture (OWD >5.0 cm) in the study population. Twelve patients (24%) had none of the three entities. Nine patients (18%) were diagnosed with all three entities. The remaining thirty patients (59%) had one, or a combination of the entities.

Of the twenty patients with one or more vertebral fractures, thirteen (65%) had also a hyperkyphosis (χ^2 = 1.36; P = .24). Hyperkyphosis was significantly associated with the presence of a flexed posture (χ^2 = 11.32; P < .01). The association between flexed posture and vertebral fractures was not significant (χ^2 = 0.47; P = .83).

Association of vertebral fractures, thoracic kyphosis and occiput-to-wall distance with future falls

In the univariate analyses (see Table 4.2), a significant association was found between the Cobb angle and future falls (OR 2.07; 95% CI 1.03-4.16). The presence of one or more vertebral fractures had a trend toward a significant association with future falls (OR 3.47; 95% CI 0.94- 12.8). The OWD was not significantly related with prospective fall incidents (OR 1.54; 95% CI 0.82-2.91).

In the multivariate analysis (Table 4.2), including all characteristics with P < .20 in the univariate analysis, only the Cobb angle was independently associated with falls during follow-up (OR 2.13; 95% CI: 1.10- 4.51). This indicates that for every standard deviation increase in the Cobb angle, the probability of a future fall doubles. Furthermore, the presence of vertebral fractures, and the number of prescriptions showed a trend towards significance for future falls in our study population.

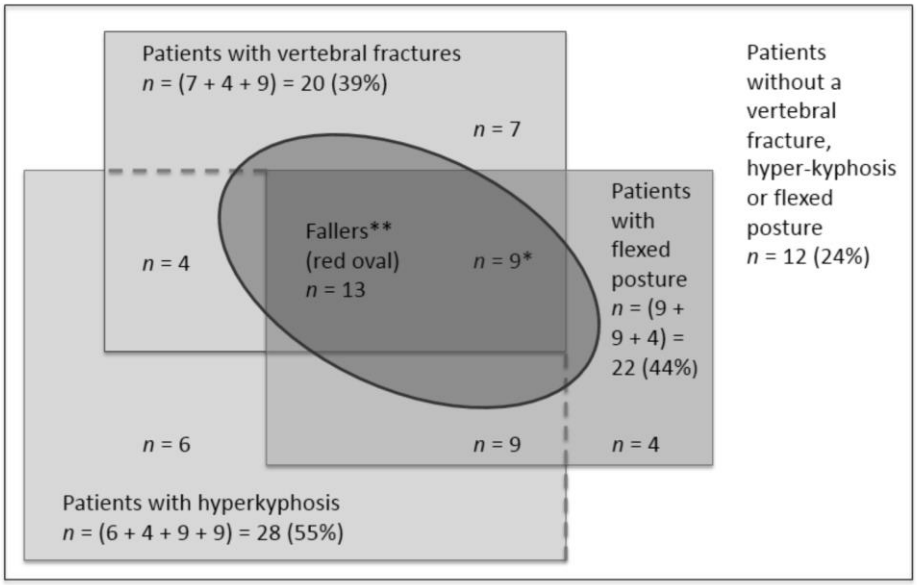

Fig. 4.2. Illustration of the distribution of patients in the study according to the presence of vertebral fractures, hyperkyphosis and flexed posture in relation to future falls. The large white rectangle represents all patients in the study (*n* = 51), whereof in the blue rectangle patients with vertebral fractures (*n* = 20; 39%); in the grey rectangle patients with a hyperkyphosis (Cobb angle ≥50 °; *n* = 28; 55%); and in the pink rectangle patients with a flexed posture (OWD >5.0 cm; *n* = 22; 44%). Patients with combinations of these entities are represented by the overlapping areas of the colored rectangles, with *n* noted in each box. Twelve patients (24%) had none of the entities present (white rectangle).

* 9 patients had all entities present.

** The red oval represents all fallers (*n* = 13); all fallers had at least one of the three entities present. In nine fallers all entities were present.

Table 4.2. Univariate and multivariate associations of the patient characteristics with future falls. All continuous variables were first *z*-transformed.

Patient characteristics	Non-fallers (n=38)	Fallers (n=13)	Univariate analyses		Multivariate analysis[a]	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years), mean (SD)	79.7 (4.7)	78.0 (5.0)	0.70 (0.37-1.32)	0.27		
Female, n (%)	28 (74%)	11 (85%)	1.96 (0.37-10.4)	0.43		
BMI (kg/m^2), mean (SD)	27.3 (3.9)	27.7 (4.3)	1.12 (0.58-2.16)	0.73		
CCI (score), median (SD)	1 (0-4)	1 (0-5)	1.26 (0.68-2.34)	0.47		
Number of prescriptions, median (range)	4.5 (0-15)	7 (0-13)	1.51 (0.81-2.80)	0.19	1.86 (0.91-3.79)	0.09
MMSE (score), median (range)	24 (15-30)	23 (13-28)	0.82 (0.44-1.52)	0.53		
Hip replacement in history, n (%)	5 (13%)	2 (15%)	1.20 (0.20-1.09)	0.84		
Vertebral fractures, n (%)	12 (32%)	8 (62%)	3.47 (0.94-12.8)	0.06	3.67 (0.85-15.9)	0.08
Cobb angle (°), mean (SD)	49 (13)	59 (16)	2.07 (1.03-4.16)	0.04	2.13 (1.10-4.51)	0.04
OWD (cm), mean (SD)	4.2 (4.5)	6.2 (4.1)	1.54 (0.82-2.91)	0.18		

BMI = Body Mass Index; **CCI** = Charlson Comorbidity Index; **CI** = Confidence Interval; **MMSE** = Mini-Mental State Examination; **OR** = Odds Ratio; **OWD** = Occiput-to-Wall Distance

[a] Adjusted for vertebral fractures, the Cobb angle, the OWD, and the number of prescriptions. After step 1, the OWD was excluded.

Discussion

We showed that in this population an increased thoracic kyphosis, as measured by the Cobb angle, was independently associated with future fall incidents (standardized OR: 2.13; 95% CI: 1.10-4.51). We did not find a significant association between a flexed posture, as indicated by the OWD, and falls. In the multivariate analysis, the presence of one or more vertebral fractures and future falls had a trend towards a significant association (P = .08).

It is remarkable that the presence of an increased thoracic kyphosis had such a clear association with future falls, even in this small study sample. This is in coincidence with previous retrospective studies [13–15]. The Rancho-Bernardo study (*n* = 1883) [14, 15], for instance, showed that men with hyperkyphotic posture had an independent age-adjusted association with self-reported falls in the past year. In women, this association appeared to be age-dependent. In addition, a smaller study (*n* = 92) showed that kyphosis of the total spine was independently associated with self-reported falls [13].

An increased thoracic kyphosis can originate from many causes, such as vertebral fractures, degenerative disc diseases, muscle weakness, and genetic disorders such as Scheuermanns disease [12, 27]. The prevalence of vertebral fractures in patients with hyperkyphosis (39%) in our study was equal compared to other studies [28–30]. In these studies also no relation was found between vertebral fractures and hyperkyphosis [28–30]. However, the consequences of hyperkyphosis in the long term may be severe, even without vertebral fractures. One study showed that older women with greater degrees of kyphosis are at increased risk of non-spinal fractures, independent of bone mineral density and vertebral fractures [11]. In addition, patients with more severe kyphosis experienced more decline in functioning occurs during a long-term follow-up [31]. Therefore, clinicians should be alert of the presence of vertebral fractures in patients with hyperkyphosis and provide adequate treatment to prevent subsequent fractures. In addition, several studies have shown promising improvements in kyphosis with, amongst others, 6-month spinal bracing intervention [32], 12-week yoga intervention [33], and 12 weeks of multidimensional group exercise [34].

In the present study, fall incidence was lower than expected, namely 26% where at least 30% was expected based on the literature [2]. This low fall rate was remarkable, because our participants were relatively old (mean age: 79 years) and had many fall risk factors such as a history of falls in the past year, substantial co–morbidity. The low fall incidence in our cohort might be the result of a successful visit to our geriatric outpatient clinic, where fall risk was analyzed, and various advices were given to minimize the

chance of a fall accident according to the Dutch guidelines [20]. Otherwise, although we gave a calendar and called patients every month, there might be underreporting: it is known that falls, even in healthy older adults, are easily forgotten [35].

Some limitations of this study should be addressed. Because of the small sample size and the low fall incidence during follow-up, we might have overestimated the independent association between the Cobb angle and future falls. Our standardized OR of 2.13 is larger than reported OR's in studies with more participants [14, 15]. Moreover, the association between vertebral fractures and prospective falls was quite strong, but not significant (P = .08). This might be a type II error, namely the failure to reject the false null hypothesis, caused by the low sample size, and therefore the large confidence interval. The relatively high OR of 3.67 shows the importance of vertebral fractures in relation to future falls. Future larger studies between older adults should investigate the association between vertebral fractures and falls, since this was not investigated before.

However, despite these limitations, we can conclude that there is a clear independent association between an increased thoracic curvature of the spine and future falls. An explanation might be that due to the forward curvature of the upper body, the center of mass shifts forward and requires correcting responses of the body. These correcting responses may reduce the patient's ability to respond on perturbations, which is reflected by an impaired postural control during walking as found in previous studies [16, 17].

Conclusions

Since older adults with a hyperkyphosis may thus have an increased fall risk, as we show in this study, we suggest clinical attention for these patients to search for underlying causes. In almost 40% of the patients with hyperkyphosis in our cohort, one or more vertebral fractures were present. For these patients, we therefore should not forget to prescribe anti-osteoporosis medication. Future research should further evaluate whether hyperkyphosis is an important risk factor for falls and which therapies may prevent, improve or delay its progression.

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PART II

MEDICATION-USE

CHAPTER 5A

The effects of fall-risk-increasing drugs on postural control: A literature review

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Abstract

Meta-analyses showed that psychotropic drugs (antidepressants, neuroleptics, benzodiazepines, antiepileptic drugs) and some cardiac drugs (digoxin, type IA antiarrhythmics, diuretics) are associated with increased fall risk. Because balance and gait disorders are the most consistent predictors of future falls, falls due to use of these so-called fall-risk-increasing drugs (FRIDs) might be partly caused by impairments of postural control that these drugs can induce. Therefore, the effects of FRIDs on postural control were examined by reviewing literature. Electronic databases and reference lists of identified papers were searched until June 2013. Only controlled research papers examining the effects of FRIDs on postural control were included. FRIDs were defined according to meta-analyses as antidepressants, neuroleptics, benzodiazepines, antiepileptic drugs, digoxin, type IA antiarrhythmics, and diuretics. Ninety-four papers were included, of which study methods for quantifying postural control, and the effects of FRIDs on postural control were abstracted. Postural control was assessed with a variety of instruments, mainly evaluating aspects of body sway during quiet standing. In general, postural control was impaired, indicated by an increase in parameters quantifying body sway, when using psychotropic FRIDs. The effects were more pronounced when people were of a higher age, used psychotropics at higher daily doses, with longer half-lives, and administered for a longer period. From the present literature review, it can be concluded that psychotropic drugs cause impairments in postural control, which is probably one of the mediating factors for the increased fall risk these FRIDs are associated with. The sedative effects of these drugs on postural control are reversible, as was proven in intervention studies where FRIDs were withdrawn. The findings of the present literature review highlight the importance of using psychotropic drugs in the older population only at the lowest effective dose and for a limited period of time.

Introduction

Drugs play a fundamental role in treating and preventing disorders that frequently occur in elderly patients. Appropriate use of drugs may reduce mortality and morbidity and improve quality of life. As a result of multi-morbidity, older people are extensive drug users: in a population-based cohort of community-dwelling older people, almost 72% used one or more prescribed drugs, of whom 20% used four or more drugs [1]. In contrast to younger adults, who mainly use medications for a short duration to treat acute illness, older people tend to use drugs on a long-term basis for chronic diseases [2], e.g., analgesics, diuretics, other cardiovascular drugs, sedatives, gastrointestinal drugs, and anti-diabetic drugs. Psychotropic drugs are also extensively used by older people [3]. In Finland, for example, more than one-third of the community-dwelling people aged 75 years or over use at least one psychotropic drug [4]. In nursing homes, this rate is even higher: 66% of the Dutch nursing home inhabitants use psychoactive medication [5]. These frequently used drugs in the older population are potential causes of unfavorable outcomes: meta-analyses showed that medication affecting the central nervous system (CNS; antidepressants, neuroleptics, benzodiazepines, antiepileptic drugs (AEDs)) and some cardiac drugs (digoxin, type IA antiarrhythmics, diuretics) are associated with an increased risk of falling (odds ratios of 1.1-6.0) [6–10]. These so-called fall-risk-increasing drugs (FRIDs) are often used among older people: about one third of the older patients taking prescribed medicine use FRIDs [1].

The relationship between FRIDs and the risk of falling has been established in a number of studies [6–10], while withdrawal of FRIDs has been shown to decrease the incidence of falls in the older population [11–14]. However, less is known about the underlying mechanisms of fall accidents. Because a primary cause of falling is postural instability during daily activities, such as walking [15], falls due to the use of FRIDs might be partly caused by impairments of postural control induced by these drugs [16]. Therefore, the present review discusses studies examining the effects of both psychotropic and cardiac FRIDs on postural control. Furthermore, the effects of withdrawal of FRIDs on postural control are reviewed.

Search methods

To examine the effects of FRIDs on postural control, the electronic databases of PubMed, Web of Science, CINAHL, EMBASE, and Cochrane were searched until June 2013. The search terms included (“postural control” OR “gait” OR “walking” OR “body sway”) AND

("fall risk increasing drug" OR "psychotropic" OR "antidepressant" OR "neuroleptic" OR "benzodiazepine" OR "antiepileptic" OR "cardiac drug" OR "digoxin" OR "type IA antiarrhythmic" OR "diuretic"). Synonyms of these terms, and generic medication names of the various medication groups, were also used in the search. Furthermore, reference lists of relevant included and excluded research papers and literature reviews were reviewed for additional papers.

Studies were included for the present literature review if they (1) examined the effects of FRIDs (selected based on the results of meta-analyses [6–10], namely antidepressants, neuroleptics, benzodiazepines, AEDs, digoxin, type IA antiarrhythmics, diuretics) on postural control, and (2) were placebo controlled, had a control group, or a before-and-after design. Review articles and papers not written in English were excluded. There were no restrictions for inclusion regarding the instruments used for assessing postural control. Because postural control can be assessed with many different test protocols, we provide an overview of the various instruments used in the included studies.

The methodological quality of the included studies was assessed using the Downs and Black instrument [17]. A total of 27 items was evaluated, distributed between five subscales: reporting (10 items), external validity (3 items), internal validity–bias (7 items), internal validity–selection bias (6 items), and power (1 item). A maximum score of 28 points was allowed. Higher scores indicate better methodological quality.

Testing postural control

Postural control can be defined as the act of maintaining, achieving, or restoring a state of balance during any posture or activity [18]. Adequate postural control is essential for daily activities, and requires the integration of visual, proprioceptive, and vestibular information [19]. The degree to which individuals rely on this information depends on task difficulty, cognitive load [20], motor skill [21, 22], age [23, 24], and pathology [25, 26]. Due to a more general age-related deterioration of sensory and neuromuscular control mechanisms, aging has a detrimental effect on postural control [27].

A large variety of test protocols, both in the motor laboratory and in clinical practice, exist to quantify postural control during different standing and walking tasks. Performance based tests, e.g., the Timed Up and Go (TUG) test [28], the Berg Balance Scale (BBS) [29], or Tinetti's Performance Oriented Mobility Assessment (POMA) [30], are frequently used in a clinical setting. These tests assess postural control indirectly by

scoring and/or timing different sets of actions, e.g., standing still, walking, turning, going from sit to stand, or standing on one leg.

More refined analyses of postural control can be obtained by using objective measures derived from computerized instruments, such as a force platform, an electronic walkway, or body-worn sensors like gyroscopes and accelerometers [31]. These instruments record data over time, e.g., force platforms and electronic walkways register ground reaction forces, and accelerometers record accelerations of the body segment it is fixed on. From these data, a wide variety of outcome parameters can be calculated that all quantify different aspects of postural control, for instance, linear spatial (e.g., step length, or length of displacement of the center of pressure [CoP]) or time-dependent (e.g., walking speed, stride times, or cadence) parameters may be computed [32–34].

For the present review, 94 studies were included [35–128]. Among these studies, only one study used a typical performance based test [114], the Romberg test: observing body sway while standing quiet with eyes opened and closed. More body sway during the Romberg test is associated with an increased chance of falling [129].

All other included studies used instruments to assess postural control during standing or walking. One of the instruments that was frequently used for assessing standing balance was an ataxia meter [35–54]. This instrument integrates the amplitude of bidirectional body movements in the anterior-posterior plane only, transferred through a string attached to the subject's waist. Body sway is measured in units of sway recorded as ⅓° of angle of arc [130]. The ataxia meter gives only a single reading at the end of the test of the total amount of sway in the forward-backward direction during the duration of the test.

For assessing standing balance in a more quantitative way, a force platform was the instrument used in the majority of the included studies [61–110]. The platform identifies the position on the base of support of the instantaneous center of feet pressure during quiet stance [131]. Under quiet stance, the CoP broadly reflects the position on the support base of the projection of the body's center of mass [132]. Measuring changes in CoP, e.g., the length or the area included within the path of the CoP, is mostly used as an indicator of the amount of body sway during quiet standing. A force platform gives time-series data of the CoP in both the anterior-posterior and lateral directions, which can be processed at a later time. Among older people, greater CoP displacement measured with a force platform is typically used to indicate impaired postural control [133].

Other studies included in the present literature review used comparable methods, based on the same principles as an ataxia meter and/or force platform, to assess body sway, such as a stabilometer [116–120], a sway table [122–124], and a body sway meter [57–59]. Two of the included studies analyzed gait [112, 113]. Draganich *et al*. [112] used a three-dimensional optical system to analyze the effects of FRIDs on obstructed and unobstructed gait over a 9.5-m distance in healthy older people. Of the motion data, temporal-distance measures were calculated, consisting of stride length, walking velocity, and cadence (strides/minute). Paleacu *et al*. [113] used force-sensitive insoles placed in the subject's shoe to measure gait rhythm and timing of the gait cycle during a 2-min walk. Walking speed, stride length, stride time, stride time variability (i.e., the magnitude of the stride-to-stride variations) [134–136], swing time, and gait asymmetry (defined as 100 times the absolute value of the natural logarithm of the ratio between the left foot and right foot swing times) [137] were determined.

Effects of FRIDs on postural control

Psychotropic drugs

Generally, psychotropic medication can be defined as drugs that cross the blood-brain barrier and act directly on the CNS. Psychotropic drugs can be categorized into a number of groups. In the present review, only groups of psychotropic drugs associated with an increased fall risk, according to meta-analyses [6–9], are discussed: (1) antidepressant medications; (2) neuroleptic medications; (3) benzodiazepines; and (4) AEDs. These groups of medications are somewhat arbitrary [14], because many of these drugs are used in multiple conditions. For example, benzodiazepines are used as hypnotics, anxiolytics, muscle relaxants, and to treat or abort epileptic seizures. However, classifying drugs into different groups provides a framework for reviewing the effects of these drugs on postural control.

Antidepressant medications

The main indication for prescribing antidepressants is moderate to severe depression, although a number of other indications exist. Mainly, there are three classes of antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase A (MAO-A) inhibitors. TCAs and SSRIs (although SSRIs to a less extent than TCAs) have been associated with autonomic adverse effects, such as orthostatic hypotension [138, 139], and psychomotor impairment [140]. Their use has

also been related to an increased incidence of falls [6–9], and hip fractures in older patients [141, 142].

Twelve studies examined the effects of antidepressants on postural control among healthy young subjects [35, 42, 67, 68, 106, 109], healthy older people [35, 42, 90, 93, 112], and older patients with (major) depression [91–93, 113] (Table 5.1). The methodological quality score of these studies was in the range of 17-23 points. One study performed a power analysis to estimate the sample size [35].

Among healthy subjects, amitriptyline was the only antidepressant that impaired postural control during standing and walking: body sway was significantly increased in young subjects [42, 67, 106], and older people [42, 90], and gait velocity and cadence were significantly reduced [112]. This effect was only present when the daily dose was 50 mg or higher. Other antidepressants, such as the TCA desipramine [67, 112], the SSRIs femoxetine [68], paroxetine [112], and zimelidine [42, 67], and the MAO-A inhibitors befloxatone [90], and minaprine [35], did not affect postural control significantly among healthy young subjects and old people.

Antidepressants are generally prescribed in patients with a (major) depression, and it is known that depression itself is associated with alterations in locomotion and increased fall risk [143, 144]. However, the link between depression, falls, and postural control is not fully clear [145], because depression itself is among the most common risk factors for falls [144], and medication may cause confounding effects. Therefore, it was questioned what the isolated effects of antidepressants are on postural control among depressed older people.

Four studies examined the effects of antidepressants on postural control among older patients suffering a (major) depression [91–93, 113]. Both the TCA nortriptyline and the SSRI paroxetine did not have significant influence on postural control while standing with eyes opened and closed after 2 [93], or 6 weeks of treatment [91, 92]. On the other hand, sertraline, another SSRI, caused a significant increase in body sway in older depressed patients after 1 week of treatment, when standing with eyes opened and closed [93]. Opposite results were found by Paleacu *et al*. [113] They demonstrated in older people diagnosed with clinical depression that antidepressant pharmacological therapy with SSRIs or SNRIs (serotonin norepinephrine reuptake inhibitors) for 10 weeks brings significant improvements in gait (increased gait speed and stride length, and reduced stride time variability and gait asymmetry). Furthermore, significantly better cognitive functioning (higher scores on the Mini Mental State Examination (MMSE) and Instrumented Activities of Daily Living (IADL)), and an improved affective state (lower.

Table 5.1. The effects of various antidepressants on postural control.

Drug	Daily dose (mg)	Subjects	Method	Outcome variables	Effect	Study (quality score)[a]
Tricyclic antidepressants (TCA)						
Amitriptyline	75	12 HYS	Force platform	L, Ao, PSD	↑	Patat *et al.* [106] (21)
	50	12 HOS	Gait analysis with 3D optical system	SL, WS, Cad	↓	Draganich *et al.* [112] (23)
		12 HOS	Force platform	L, Ao	↑	Rosenzweig *et al.* [90] (23)
		12 HYS	Force platform	Body sway	↑	Linnoila *et al.* [67] (19)
		4 HYS & 4 HOS	Ataxia meter	Body sway	↑	Swift *et al.* [42] (17)
		12 HYS	Force platform	Body sway	=	Strömberg & Mattila [68] (19)
	25	9 HYS & 9 HOS[b]	Ataxia meter	°AS in AP plane	=	Kinirons *et al.* [35] (22)
		5 HYS	Force platform	Sway index	=	Dorian *et al.* [109] (18)
Desipramine	100	12 HYS	Force platform	Body sway	=	Linnoila *et al.* [67] (19)
	50	12 HOS	Gait analysis with 3D optical system	SL, WS, Cad	=	Draganich *et al.* [112] (23)
Nortriptyline	60	10 DOP	Force platform	L, Ao	=	Laghrissi-Thode *et al.* [91] (20)
	51 (mean)	17 DOP	Force platform	L, Ao	=	Mamo *et al.* [92] (21)
	52 (mean)	11 DOP	Force platform	L, Ao	=	Laghrissi-Thode *et al.* [93] (18)
Selective serotonin reuptake inhibitors (SSRI)						
Femoxetine	200	12 HYS	Force platform	Body sway	=	Strömberg & Mattila [68] (19)
Paroxetine	23 (mean)	25 DOP	Force platform	L, Ao	=	Mamo *et al.* [92] (21)
	20	12 HOS	Gait analysis with 3D optical system	SL, WS, Cad	=	Draganich *et al.* [112] (23)
		10 DOP	Force platform	L, Ao	=	Laghrissi-Thode *et al.* [91] (20)
Sertraline	67 (mean)	10 DOP	Force platform	L, Ao	↑	Laghrissi-Thode *et al.* [93] (18)
Zimelidine	200	12 HYS	Force platform	Body sway	=	Linnoila *et al.* [67] (19)
	100	4 HYS & 4 HOS	Ataxia meter	Body sway	=	Swift *et al.* [42] (17)
Various SSRIs and SNRIs	100	19 DOP	Gait analysis with force-sensitive insoles	WS, SL Stvar, Gait asymmetry ST, SwT	↑ ↓ =	Paleacu *et al.* [113] (20)

Monoamine oxidase A inhibitors						
Befloxatone	10	12 HOS	Force platform	L, Ao	=	Rosenzweig *et al.* [90] (23)
Minaprine	100	9 HYS & 9 HOS[b]	Ataxia meter	°AS in AP plane	=	Kinirons *et al.* [35] (22)

°AS degree of angle of sway (°); **Ao** area included within the path of the center of pressure (cm^2); **Cad** cadence (strides/minute); **DOP** depressed older patients; **HOS** healthy older subjects; **HYS** healthy young subjects; **L** total length of displacement of the center of pressure (cm); **PSD** power spectral density (total energy, energy less than 0.5 Hz, corresponding to the constant displacement of the center of gravity, and energies between 0.5 and 2 Hz, corresponding to postural readjustment mechanisms of an essentially muscular origin); **SL** stride length (m); **ST** stride time (ms); **Stvar** stride time variability (ms); **SwT** swing time (%); **WS** walking speed (m/s); ↑ significant increase in outcome variable; **=** no significant change in outcome variable; ↓ significant decrease in outcome variable

[a] Downs and Black score (maximum 28 points)

[b] A power analysis was performed to estimate the sample size

scores on the Hamilton Depression Rating Scale (HDS)) were found after the 10-week intervention

In summary, amitriptyline ≥50 mg was the only antidepressant that impaired postural control in healthy subjects. In depressed older patients, sertraline was the only antidepressant that increased body sway significantly. However, this result was only found in one study where the methodological quality was moderate. One study found improvements in gait in this patient population after therapy with SSRIs or SNRIs. Thus, it seems that amitriptyline is the only antidepressant to cause impairments in postural control in the reviewed studies.

Neuroleptic medications

Neuroleptic, or antipsychotic, medication is primarily used for the treatment of psychotic disorders. However, these drugs have a number of other indications, including the treatment of behavioral and psychiatric symptoms of dementia (BPSD). However, the use of neuroleptics other than risperidone to treat BPSD is off-label, and associated with various boxed warnings, e.g., metabolic syndrome and cardiovascular disorders such as stroke. Neuroleptics can be categorized into two groups: conventional (or first-generation) neuroleptics (CNLs) and atypical (second-generation) antipsychotics (AAPs). AAPs differ from CNLs with respect to their adverse effects profile (lower incidence of extra-pyramidal adverse effects and tardive dyskinesia) and their therapeutic properties [95].

Thirteen studies examined the effects of neuroleptics on postural control among healthy young subjects [37, 57–59, 69, 87, 94, 110, 125], and older subjects [36, 95, 96, 126] (Table 5.2). The methodological quality score of these studies was in the range of 18-24 points. Two studies performed a power analysis to estimate the sample size [57, 95].

Haloperidol 3 mg was found to be the only CNL causing deterioration in postural control, indicated by significantly more body sway in young subjects [57], and older subjects [126]. However, this effect was only found in two studies [57, 126], whereas two other, comparable studies did not find a significant effect with the same dose of haloperidol in young subjects [58, 125]. Lower daily doses of haloperidol and the use of chlorpromazine (another CNL) did not influence body sway significantly [36, 69, 125].

Table 5.2. The effect of various neuroleptics on postural control.

Drug	Daily dose (mg)	Subjects	Method	Outcome variables	Effect	Study (quality score)[a]
Conventional neuroleptics (CNL)						
Chlorpromazine	50	12 HYS	Ultrasound ranging device	Body sway	=	McClelland *et al*. [125] (19)
		12 HYS	Force platform	Body sway	=	Mattila *et al*. [69] (21)
Haloperidol	3	14 HOS	Unknown	Body sway	↑	Beuzen *et al*. [126] (22)
		35 HYS[b]	Body Sway meter	Body sway	↑	Liem-Moolenaar *et al*. [57] (24)
		12 HYS	Body Sway meter	Body sway	=	Liem-Moolenaar *et al*. [58] (22)
		12 HYS	Ultrasound ranging device	Body sway	=	McClelland *et al*. [125] (19)
	2	16 HOS	Ataxia meter	⅓°AS	=	Legangneux *et al*. [36] (22)
Atypical antipsychotics (AAP)						
Amisulpride	200	16 HOS	Ataxia meter	⅓°AS	=	Legangneux *et al*. [36] (22)
		18 HYS	Force platform	L	=	Mattila *et al*. [87] (18)
		18 HYS	Force platform	L, Ao	=	Perault *et al*. [94] (21)
	50	16 HOS	Ataxia meter	⅓°AS	=	Legangneux *et al*. [36] (22)
		18 HYS	Force platform	L, Ao	=	Perault *et al*. [94] (21)
Olanzapine	3	14 HOS	Unknown	Body sway	↑	Beuzen *et al*. [126] (22)
Remoxipride	120	11 HYS	Ataxia meter	⅓°AS	=	Fagan *et al*. [37] (19)
	60	11 HYS	Ataxia meter	⅓°AS	=	Fagan *et al*. [37] (19)
	30	11 HYS	Ataxia meter	⅓°AS	=	Fagan *et al*. [37] (19)
Risperidone	3	12 HYS	Force platform	Vel	↑	Corbeil *et al*. [110] (23)
	2	18 HYS	Body Sway meter	Body sway	↑	Liem-Moolenaar *et al*. [59] (23)
	1	12 HYS	Force platform	Vel	↑	Corbeil *et al*. [110] (23)
	0.5	12 HOS[b]	Force platform	L, Ao	=	Allain *et al*. [95] (24)
	0.25	12 HOS[b]	Force platform	L, Ao	=	Allain *et al*. [95] (24)
Sulpiride	400	12 HYS	Ultrasound ranging device	Body sway	=	McClelland *et al*. [125] (19)
Tiapride	100	12 HOS	Force platform	L, Ao	=	Patat *et al*. [96] (22)

⅓°AS ⅓ degree of angle of sway; **Ao** area included within the path of the center of pressure (in cm^2); **HOS** healthy older subjects; **HYS** healthy young subjects; **L** total length of displacement of the center of pressure (in cm); **Vel** mean velocity (cm/s); ↑ significant increase in outcome variable; **=** no significant change in outcome variable; ↓ significant decrease in outcome variable; [a] Downs and Black score; [b] A power analysis was performed to estimate the sample size

Among the AAPs, olanzapine 3 mg [126], and risperidone ≥1 mg increased body sway significantly [59, 110], whereas other AAPs, such as amisulpride [36, 87, 94], remoxipride [37], sulpiride [125], tiapride [102], and daily doses smaller than 1 mg of risperidone [95], did not affect postural control significantly in healthy young and older subjects.

To summarize these results, we can conclude that olanzapine 3 mg and risperidone ≥1 mg impair postural control in quiet standing, whereas other neuroleptics did not show any significant effect on body sway. For haloperidol 3 mg, the results were not consistent: two studies found an effect on postural control in healthy young subjects and older adults, whereas two other studies did not. Because the two studies finding an effect had higher methodological quality and performed a power analysis, we tentatively conclude that haloperidol 3 mg has serious effects on postural control in both young and older subjects.

Benzodiazepines

There is a number of indications for the use of benzodiazepines, and the appropriateness of their use depends on the actual indication and consideration of the risks and benefits for individual patients [14]. Indications include insomnia, anxiety, panic disorders, seizures/epilepsy, and acute alcohol withdrawal. Benzodiazepines are frequently used in the elderly community: between 16.6% [146] and 25.4% [147] of community-dwelling older people use one or more benzodiazepines. In nursing homes, this rate is even higher: 50-80% of the residents take one or more benzodiazepines [148]. The use of benzodiazepines has been associated with falls [6–9], hip fractures [149], and impaired cognitive function [150]. Therefore, benzodiazepine use in older people has been questioned, especially for benzodiazepines with long half-lives , because these are more likely to accumulate, remain longer in the body, and cause prolonged sedation [151].

Benzodiazepines have sedative effects, and may impair psychomotor function, which potentially causes falls. Especially among older adults who use benzodiazepines as a hypnotic, walking to the toilet in the night because of nocturia might increase the risk of falling. Another problem, associated with the use of benzodiazepines as a hypnotic, is the risk of 'hangover' effects, e.g. residual daytime sleepiness and impairment of psychomotor and cognitive functioning the day after bedtime administration [152]. These effects of benzodiazepines on postural control appear to be stronger with increasing half-lives, higher daily dosage, and longer duration of use of these drugs [152]. Enhanced receptor sensitivity to benzodiazepines with increasing age has also been

documented, which together with pharmacokinetic change probably contributes to an accentuated and prolonged sedative effect [39, 40, 49].

Therefore, in the present review, the effects of benzodiazepines were categorized into drugs with (a) long half-life (>24 h), (b) intermediate half-life (8-24 h), and (c) short half-life (<8 h). Furthermore, (d) benzodiazepine receptor agonists, e.g., zolpidem and zopiclone, are discussed. Then, the various benzodiazepines were categorized into (a) short effects (within 8 h after administration, the so-called "nightly effects"), (b) some longer effects (past 8 h after administration, the so-called "day after" or "hangover" effects), and (c) long-term effects, when using benzodiazepines for a longer period (at least 7 days). Among the psychotropics, the effects of benzodiazepines on postural control are the most extensively studied: 68 studies (Table 5.3) examined effects of benzodiazepines on postural control among healthy young subjects [38, 39, 41, 43–51, 54, 55, 62, 64–66, 69–82, 85, 86, 88, 89, 94, 96, 99–101, 103, 106–108, 111, 114, 116–118, 120–124, 127, 128], and older people [39, 41, 49, 54, 61, 63, 64, 83, 95, 98, 102, 104, 115, 124], and older subjects with chronic insomnia [56]. All studies assessed postural control during quiet standing, none analyzed gait. The methodological quality score of these studies ranged between 13 and 25 points. Nine studies performed a power analysis to estimate the sample size [46, 48, 63, 66, 74, 95, 97, 98, 105].

Benzodiazepines with a long half-life (>24 h)

Diazepam has been the most extensively studied individual benzodiazepine in 14 studies among young subjects [38, 39, 43–45, 70, 71, 73, 82, 108, 121, 122, 127], and older subjects [39, 61]. Generally, significant more body sway was found as nightly effect for daily doses of diazepam ≥0.2 mg/kg or ≥10 mg [38, 39, 43, 82, 106, 108, 121, 122, 127], except for two studies [70, 71]. For lower daily doses of diazepam, the results were more nuanced [44, 45, 61, 73, 108, 122, 127]. Three studies examined hangover effects of diazepam [38, 39, 106], of which one study found significant effects after >8 h for diazepam 10 mg [38]. The other two studies did not find any significant effects for body sway for the same daily dose of diazepam [42, 106]. Only one study examined the long-term effects of diazepam; Aranko *et al*. [73] did not find any significant effect for postural control during standing after 2 weeks of daily diazepam 15 mg administration.

Nightly, hangover, and long-term effects were also examined for other benzodiazepines with a long half-life, namely flurazepam [55, 56, 98, 114], nitrazepam [54, 72, 115–118, 120], and quazepam [123]. These effects were examined in 12 studies for healthy young subjects [54, 55, 72, 114, 116–118, 120, 123], and older persons [54, 98, 115], and for older subjects with chronic insomnia [56]. Increased postural sway

Table 5.3. The effects of various benzodiazepines on postural control.

Benzodiazepines were categorized according to their half-life: long (>24 h), intermediate (8-24 h) and short half-life (<8 h). Effects of benzodiazepines on postural control were subdivided in nightly (NE; <8 h post-dose), hangover (HE; >8 h post-dose), and long-term effects (LTE; >7 days of usage).

Drug ($t_{1/2}$, in h)	Daily dose	Subjects	Method	Outcome variables	NE	HE	LTE	Study (quality score)[a]
Benzodiazepine derivatives								
Long half-life (>24 h)								
Diazepam	0.3 mg/kg	120 HYS	Force platform	SF	↑			Ghoneim *et al.* [108] (14)
(43 ± 13)	0.21 mg/kg	16 HYS	Sway table	TPS	↑			Nikaido *et al.* [122] (19)
	0.2 mg/kg	120 HYS	Force platform	SF	↑			Ghoneim *et al.* [108] (14)
		21 HYS	Force platform	CSV	↑			Jansen *et al.* [82] (17)
		48 HYS	Unknown electronic device	Body sway	↑			Schuckit *et al.* [127] (23)
	0.14 mg/kg	16 HYS	Sway table	TPS	=			Nikaido *et al.* [122] (19)
		12 HOS	Force platform	Ao	=			Cutson *et al.* [61] (21)
	0.12 mg/kg	48 HYS	Unknown electronic device	Body sway	↑			Schuckit *et al.* [127] (23)
	0.1 mg/kg	120 HYS	Force platform	SF	=			Ghoneim *et al.* [108] (14)
	0.07 mg/kg	16 HYS	Sway table	TPS	=			Nikaido *et al.* [122] (19)
	20 mg	5 HYS	Statometer IV	Amp	↑			Orr *et al.* [121] (18)
	15 mg	12 HYS	Force platform	Body sway	=			Mattila *et al.* [70] (19)
		24 HYS	Force platform	Body sway			=	Aranko *et al.* [73] (19)
	10 mg	12 HYS	Ataxia meter	⅓°AS	↑	↑		Cohen *et al.* [38] (19)
		12 HYS	Force platform	L, Ao, PSD	↑	=		Patat *et al.* [106] (21)
		11 HYS & 12 HOS	Ataxia meter	⅓°AS	↑	=		Swift *et al.* [39] (19)
		12 HYS	Ataxia meter	Body sway	↑			van Steveninck *et al.* [43] (21)
		5 HYS	Statometer IV	Amp	↑			Orr *et al.* [121] (18)
		156 HYS	Force platform	Body sway	=			Palva [71] (16)

	5 mg	12 HYS	Ataxia meter	Body sway	=			Gerrard *et al.* [44] (18)
		12 HYS	Ataxia meter	Body sway	=			Gerrard *et al.* [45] (18)
		24 HYS	Force platform	Body sway	=			Aranko *et al.* [73] (19)
Flurazepam	30 mg	25 HOS[b]	Force platform	L, Ao		↑		Boyle *et al.* [98] (25)
(74 ± 24)		48 HYS	Romberg test	Score	=	=		Hill *et al.* [114] (19)
		14 HYS	Balance platform	Time	↑	=		Roth *et al.* [55] (20)
	15 mg	14 HYS	Balance platform	Time	↑	=		Roth *et al.* [55] (20)
		36 OCI	Balance platform	Time			↑	Mamelak *et al.* [56] (19)
Nitrazepam	10 mg	14 HYS	Force platform	Body sway		=	↑	Mattila *et al.* [72] (20)
(26 ± 3)	5 mg	8 HYS	Stabilometer	Ao	↑	=		Tazaki *et al.* [116] (17)
		20 HYS	Stabilometer	Time		↑		Hindmarch [120] (15)
		24 HOS	Self-designed sway meter	0.1° body sway			↑	Campbell & Somerton [115] (18)
		8 HYS	Stabilometer	L, Ao, Vel, Acc	=			Tada *et al.* [117] (20)
		12 HYS & 12 HOS	Ataxia meter	Cumulative sway	=			Castleden *et al.* [54] (18)
		8 HYS	Stabilometer	L, Ao, Vel, Acc		=	=	Muraoka *et al.* [118] (18)
Quazepam	30 mg	21 HYS	Sway table	TPS	↑			Nikaido & Ellinwood [123] (19)
(±39)	15 mg	21 HYS	Sway table	TPS	=			Nikaido & Ellinwood [123] (19)
Intermediate half-life (8-24 h)								
Alprazolam	1.5 mg	19 HYS & 17 HOS	Sway table	TPS	↑			Nikaido *et al.* [124] (17)
(12-15)	0.75 mg	19 HYS & 17 HOS	Sway table	TPS	↑			Nikaido *et al.* [124] (17)
		24 HYS	Force platform	Body sway			=	Aranko *et al.* [73] (19)
	0.25 mg	24 HYS	Force platform	Body sway	=			Aranko *et al.* [73] (19)
Bromazepam	6 mg	16 HYS	Force platform	SE	↑		=	Patat & Foulhoux [107] (20)
(16-24)								
Clobazam	20 mg	16 HYS	Force platform	SE	=		=	Patat & Foulhoux [107] (20)
(18-32)		20 HYS	Stabilometer	Time		↑		Hindmarch [120] (15)
Flunitrazepam	2 mg	20 HYS	Force platform	L		↑		Seppälä *et al.* [88] (21)
(18-26)	1 mg	16 HYS	Force platform	L, Ao	↑			Allain *et al.* [99] (22)

Table 5.3. *Continued*

Drug ($t_{1/2}$, in h)	Daily dose	Subjects	Method	Outcome variables	NE	HE	LTE	Study (quality score)[a]
Lorazepam (14 ± 5)	2.5 mg	12 HYS	Unknown electronic device	Body sway	↑			Seppälä *et al.* [128] (21)
	2 mg	16 HYS	Force platform	L, Ao	↑	↑		Patat *et al.* [100] (22)
		12 HYS	Force platform	L, Ao	↑	↑		Norris *et al.* [101] (22)
		16 HYS	Force platform	Ao	↑	=		Patat *et al.* [96] (22)
		20 HYS[b]	Ataxia meter	Body sway	↑	=		de Haas *et al.* [46] (22)
		12 HYS	Ataxia meter	Body sway	↑	=		de Haas *et al.* [47] (21)
		12 HYS[b]	Ataxia meter	Body sway	↑	=		de Haas *et al.* [48] (22)
		16 HYS	Force platform	SE	↑		=	Patat & Foulhoux [107] (20)
		12 HYS[b]	Force platform	Body sway	↑		=	Vanakoski *et al.* [74] (23)
		27 HYS	Force platform	Body sway	↑			Hege *et al.* [75] (22)
		18 HYS	Force platform	L, Ao	↑			Perault *et al.* [94] (21)
	1 mg	12 HOS[b]	Force platform	L, Ao	↑			Allain *et al.* [95] (24)
		12 HOS	Force platform	L, Ao	↑			Patat *et al.* [102] (20)
	0.057 mg/kg	6 HYS	Force platform	FPS	↑			Gupta *et al.* [85] (16)
Lormetazepam (10 ± 2.5)	1 mg	48 HOS[b]	Force platform	L, Ao	↑	=		Allain *et al.* [97] (24)
Loprazolam (8-12)	1 mg	10 HYS & 9 HOS	Ataxia meter	⅓°AS	↑	↑		Swift *et al.* [40] (21)
	0.5 mg	10 HYS & 9 HOS	Ataxia meter	⅓°AS	↑	=		Swift *et al.* [40] (21)
Oxazepam (8 ± 2.4)	30 mg	12 HYS	Force platform	Body sway	=			Mattila *et al.* [70] (19)
	15 mg	14 HYS	Force platform	Body sway	↑			McDevitt *et al.* [76] (19)
		12 HYS	Force platform	Body sway	↑			McDevitt *et al.*[77] (18)
		12 HYS	Force platform	Body sway	↑			Nicholson *et al.* [78] (13)
		14 HYS	Force platform	Body sway	=			Nicholson *et al.* [79] (14)
Temazepam (11 ± 6)	30 mg	14 HYS	Balance platform	Time	↑	=		Roth *et al.* [55] (20)

	20 mg	9 HYS & 9 HOS	Ataxia meter	Body sway	↑			Swift *et al*. [49] (13)
		16 HYS	Ataxia meter	Body sway	↑			van der Post *et al*. [50] (22)
		10 HYS & 10 HOS	Ataxia meter	⅓°AS	=	=		Briggs *et al*. [41] (20)
		14 HYS	Force platform	Body sway		=	=	Mattila *et al*. [72] (20)
	15 mg	14 HYS	Balance platform	Time	=	=		Roth *et al*. [55] (20)
Short half-life (<8 h)								
Brotizolam (4.4)	0.25 mg	36 OCI	Balance platform	Time			↑	Mamelak *et al*. [56] (19)
Midazolam (1.9 ± 0.6)	0.080 mg/kg	12 HYS	Force platform	L	↑			Mattila *et al*. [89] (20)
	15 mg	11 HYS	Force platform	L, Ao	↑			Patat *et al*. [103] (21)
		12 HYS & 12 HOS	Ataxia meter	Cumulative sway	=			Castleden *et al*. [54] (18)
	5 mg	8 HOS	Force platform	L, Ao	=			Krupka *et al*. [104] (19)
Triazolam (2.9 ± 1.0)	1 mg	21 HYS	Sway table	TPS	↑			Nikaido & Ellinwood [123] (19)
		10 HYS	Force platform	FPS	↑			Gupta *et al*. [86] (16)
	0.5 mg	19 HYS & 17 HOS	Sway table	TPS	↑			Nikaido *et al*. [124] (17)
		21 HYS	Sway table	TPS	↑			Nikaido & Ellinwood [123] (19)
	0.375 mg	6 HYS	Force platform	Ao	↑	=		Robin *et al*. [62] (20)
		16 HOS[b]	Force platform	Ao	↑			Kinirons *et al*. [63] (22)
		9 HYS & 9 HOS	Force platform	Ao	↑			Robin *et al*. [64] (21)
	0.25 mg	18 HYS	Force platform	Ao	↑	=		Berlin *et al*. [65] (22)
		19 HYS & 17 HOS	Sway table	TPS	↑			Nikaido *et al*. [124] (17)
		8 HYS	Stabilometer	L, Ao, Vel, Acc	↑			Tada *et al*. [117] (20)
		8 HYS	Force-sensitive insoles	L, Ao	↑			Nakamura *et al*. [111] (19)
		12 HYS	Force platform	Body sway	=			Kuitunen *et al*. [80] (20)
		8 HYS	Stabilometer	L, Ao, Vel, Acc		=	=	Muraoka *et al*. [118] (18)

Table 5.3. *Continued*

Drug ($t_{1/2}$, in h)	Daily dose	Subjects	Method	Outcome variables	NE	HE	LTE	Study (quality score)[a]
		24 HOS	Self-designed sway meter	0.1° body sway			↑	Campbell & Somerton [115] (18)
		6 HYS	Force platform	Ao	↑	=		Robin *et al.* [62] (20)
		48 HYS	Romberg test	Score	↑	=		Hill *et al.* [114] (19)
	0.125 mg	6 HYS	Force platform	Ao	=	=		Robin *et al.* [62] (20)
Benzodiazepine receptor agonists								
Alpidem (18-20)	50 mg	16 HYS	Force platform	L, Ao	=	=		Patat *et al.* [96] (22)
Zaleplon (1-2)	10 mg	16 HYS[b]	Force platform	Ao	↑			Whitmore *et al.* [66] (23)
Zolpidem	15 mg	12 HYS	Force platform	Body sway	↑			Mattila *et al.* [70] (19)
(1.9 ± 0.2)	10 mg	18 HYS	Force platform	Ao	↑	=		Berlin *et al.* [65] (22)
		14 HYS	Ataxia meter	Body sway	↑	=		de Haas *et al.* [51] (21)
		16 HYS	Force platform	L, Ao	↑			Allain *et al.* [99] (22)
		12 HOS	Force platform	ES	↓			Zammit *et al.* [83] (22)
		8 HYS	Force-sensitive insoles	L, Ao	↑			Nakamura *et al.* [111] (19)
	5 mg	48 HOS[b]	Force platform	L, Ao	↑	=		Allain *et al.* [97] (24)
		24 HOS[b]	Force platform	L, Ao	↑	↑		Boyle *et al.* [105] (25)
Zopiclone	7.5 mg	8 HYS	Stabilometer	L, Ao, Vel, Acc	↑			Tada *et al.* [117] (20)
(3.5-6.5)		12 HYS	Force platform	Body sway	↑			Mattila *et al.* [70] (19)
		12 HYS	Force platform	Body sway	↑			Mattila *et al.* [69] (21)
		16 HYS	Force platform	L, Ao	↑			Allain *et al.* [99] (22)
		12 HYS	Force platform	Body sway	↑			Kuitunen *et al.* [81] (20)
		12 HYS	Force platform	Body sway	=			Kuitunen *et al.* [80] (20)
		20 HYS	Force platform	L		=		Seppälä *et al.* [88] (21)
	3.75 mg	48 HOS[b]	Force platform	L, Ao	↑	=		Allain *et al.* [97] (24)

⅓°AS ⅓ degree of angle of sway; **Acc** mean acceleration (m/s2); **Amp** amplitude; **Ao** area included within the path of the center of pressure (in cm2); **Cad** cadence (steps/min); **CSV** common sway vector (the areas between the mean positions of the center of pressure integrated and divided by the sampling time; in cm x 0.01); **ES** equilibrium scores of the sensory organization test (higher score indicates better balance); **FPS** summarized frequency power scales below 2.5 Hz obtained from four directions; **HE** Hangover effects; **L** total length of displacement of the center of pressure (in cm); **HOS** healthy older subjects; **HYS** healthy young subjects; **LTE** Long-term effects; **NE** Nightly effects; **OCI** older subjects with chronic insomnia; **TPS** total power score; **SE** spectral energies (total energy, (0-0.5 HZ) energy band, (0.5-2 Hz) energy band; **SL** step length (cm); **SF** sway frequency (sway units per centimeter of displacement of the center of gravity); **Stab** length and amplitude of stabilogram; **Vel** mean velocity (cm/s); **WS** walking speed (m/s); ↑ significant increase in outcome variable; **=** no significant change in outcome variable; ↓ significant decrease in outcome variable

[a] Downs and Black score (max. 28 points)

[b] A power analysis was performed to estimate the sample size

during quiet standing was found as a nightly effect among healthy young subjects for flurazepam 15 and 30 mg [55], nitrazepam 5 mg [116], and quazepam 30 mg [123]; as a hangover effect for flurazepam 30 mg [98], and nitrazepam 5 mg [120]; and as a long-term effect for flurazepam 15 mg [56], and nitrazepam 10 and 5 mg [72, 115]. Other studies did not find any significant effects on standing steadiness for benzodiazepines with a long half-life [54, 114, 117, 118].

Benzodiazepines with an intermediate half-life (8-24 h)

The effects of benzodiazepines with an intermediate half-life were examined in 31 studies for healthy young subjects [40, 41, 46–50, 55, 70, 72–79, 85, 88, 94, 96, 99–101, 107, 120, 124, 128], and older people [40, 41, 49, 95, 97, 102, 124]. Significant nightly effects on postural control, quantified by increased parameters indicating body sway, were found for alprazolam ≥0.75 mg [124], bromazepam 6 mg [107], flunitrazepam 1 mg [99], lorazepam ≥1 mg [46–48, 74, 75, 85, 94, 96, 100, 101, 107, 128], lormetazepam 1 mg [97], loprazolam ≥0.5 mg [40], oxazepam 15 mg [76–78], and temazepam 20 mg [49, 50, 55]. Hangover effects were found for clobazam 20 mg [120], flunitrazepam 2 mg [88], lorazepam 2 mg [100, 101], and loprazolam 1 mg [40]. Other studies did not find any hangover effects on parameters indicating quiet standing abilities [40, 41, 46–48, 55, 72, 96, 97]. Long-term effects on postural control when using benzodiazepines with an intermediate half-life were not found [72–74, 107].

Benzodiazepines with a short half-life (<8 h)

The effects of benzodiazepines with a short half-life on body sway were examined for 18 studies in healthy young subjects [54, 62, 64, 65, 80, 86, 89, 103, 111, 114, 117, 118, 123, 124], and older subjects [54, 63, 64, 104, 115, 124], and older persons with chronic insomnia [56]. Midazolam 15 mg [103], and 0.080 mg/kg [89], and triazolam ≥0.25 mg [62–65, 86, 111, 114, 117, 123, 124] had significant nightly effects on postural control during standing, indicated by increased parameters of body sway. There were no hangover effects found for the benzodiazepines with a short half-life [62, 65, 114, 118]. Long-term effects were only investigated in two studies, whereof one study found that body sway was significantly greater after using 0.25 mg triazolam for one week [115]. The other study did not find any long-term effects for this drug on body sway [118].

Benzodiazepine receptor agonists

Body sway has been investigated in 15 studies among healthy young subjects [51, 65, 66, 69, 70, 80, 81, 88, 96, 99, 111, 117], and older subjects [83, 97, 105] for four

benzodiazepine receptor agonists: alpidem [96], zopiclone (both intermediate half-life) [69, 70, 80, 81, 88, 97, 99, 117], zaleplon [66], and zolpidem (both short half-life) [51, 65, 70, 83, 97, 99, 105, 111]. Alpidem 50 mg did not have significant nightly or hangover effects among healthy young subjects [96]. Six studies found significant nightly impairments in standing steadiness for zopiclone 7.5 mg [69, 70, 81, 99, 117], and 3.75 mg [97]. There were no hangover effects found for benzodiazepine receptor agonists with an intermediate half-life on postural control [88, 97].

Nine studies found nightly effects, indicated by increased body sway parameters, for zaleplon 10 mg [66], and zolpidem ≥5 mg [51, 65, 70, 83, 97, 99, 105, 111]. One study found a hangover effect for zolpidem 5 mg [105], whereas other studies did not [51, 65, 97].

Summary

It can be concluded that benzodiazepines and benzodiazepine receptor agonists have effects on postural control within 8 h after administration (the so-called nightly effects). These effects are more pronounced when the dosage is higher, and when people are older. Hangover effects on postural control (more than 8 h after administration) are, as expected, more present in benzodiazepines with an intermediate or long half-life (half-life >8 h) than in drugs with a short half-life (<8 h). The long-term effects of these drugs on postural control are not fully clear, because results differed strongly between studies and the methodological quality of these studies was moderate. Therefore, we suggest that more research of higher quality is needed to investigate the long-term effects of benzodiazepines on postural control.

Antiepileptic drugs

AEDs are used in older patients, not only to treat epilepsy, but also as mood stabilizers and to treat a variety of other conditions, e.g., post-herpetic neuralgia, and other neuropathic pain. The frequency of AED use in nursing homes is in the range of 10-12% [153, 154]. In people with epilepsy, falls and skeletal fractures are significantly more frequent than in the general population, and less than half are directly related to seizures [155]. Therefore, it is suggested that some falls may be caused by medication effects [156], because dizziness, ataxia, and unsteady gait are known adverse effects of AEDs [157]. Furthermore, using AEDs is associated with a reduced bone mineral density and lower levels of vitamin D, and therefore increases the risk of fractures [158].

Table 5.4. The effects of various antiepileptics on postural control

Drug	Daily dose (mg)	Subjects	Method	Outcome variables	Effect	Study (quality score)[a]
Carbamazepine	600	22 PTN	Force platform	ES	↓	Delcker *et al*. [84] (15)
		12 HYS	Ataxia meter	Body sway	↑	Hamilton *et al*. [52] (19)
		12 HYS	Force platform	Body sway	↑	Kuitunen *et al*. [81] (20)
	400	6 HYS	Ataxia meter	Body sway	↑	Hockings *et al*. [53] (19)
		5 HOS	Ataxia meter	Body sway	↑	Hockings *et al*. [53] (19)
		12 HYS	Stabilometer	RMS sway	↑	Noachtar *et al*. [119] (19)
		22 PTN	Force platform	ES	↓	Delcker *et al*. [84] (15)
		12 HYS	Ataxia meter	Body sway	=	Hamilton *et al*. [52] (19)
		12 HYS	Electronic sway meter	Amp	=	Wildin *et al*. [60] (22)
	200	22 PTN	Force platform	ES	=	Delcker *et al*. [84] (15)
		12 HYS	Ataxia meter	Body sway	=	Hamilton *et al*. [52] (19)
Gabapentin	600	12 HYS	Stabilometer	RMS sway	↑	Noachtar *et al*. [119] (19)
Lamotrigine	300	12 HYS	Ataxia meter	Body sway	=	Hamilton *et al*. [52] (19)
	240	12 HYS	Ataxia meter	⅓°AS	↑	Cohen *et al*. [38] (19)
	150	12 HYS	Ataxia meter	Body sway	=	Hamilton *et al*. [52] (19)
	120	12 HYS	Ataxia meter	Body sway	=	Cohen *et al*. [38] (19)
Phenytoin	1000	12 HYS	Ataxia meter	Body sway	↑	Cohen *et al*. [38] (19)
	500	12 HYS	Ataxia meter	Body sway	=	Cohen *et al*. [38] (19)

Amp mean amplitude of sway; **ES** equilibrium score of the sensory organization test (higher score indicates better balance); **HOS** healthy older subjects; **HYS** healthy young subjects; **L** total length of displacement of the center of pressure (in cm); **PTN** patients with trigeminal neuralgia; **RMS sway** root mean square of anterior-posterior and medio-lateral sway; ↑ significant increase in outcome variable; **=** no significant change in outcome variable; ↓ significant decrease in outcome variable;

[a] Downs and Black score (max. 28 points)

The effects of AEDs on postural control have been investigated in seven studies among healthy young subjects [38, 52, 53, 60, 81, 119], and older subjects [53], and patients with trigeminal neuralgia [84] (Table 5.4). The methodological quality score of these studies was in the range of 15-22 points. None of these studies performed a power analysis to estimate the sample size.

Among healthy subjects, postural control was impaired, as quantified by more body sway, when using carbamazepine 600 mg [52, 81], and 400 mg [53, 119], although two studies did not find significantly increased body sway for carbamazepine 400 mg among healthy young subjects [52, 60]. Postural control was not significantly impaired by a lower dose of carbamazepine [52]. Body sway was significantly increased when using gabapentin 600 mg [119] and lamotrigine 240 mg [38]. Other dosages, including a higher dose of lamotrigine (300 mg), did not impair postural control [38, 52]. Furthermore, 1,000 mg of phenytoin increased body sway significantly, whereas a lower dosage of 500 mg did not [38].

Among patients with trigeminal neuralgia, postural stability was reduced when using ≥400 mg of carbamazepine [84]. A lower dose of carbamazepine did not impair postural control in this patient group [84].

AEDs seem to impair postural control when administered in relatively higher doses. It is therefore recommended, if appropriate, to administer AEDs only at the lowest effective dose.

Cardiac drugs

Other than the already discussed psychotropic FRIDs, there are some cardiac drugs associated with an increased risk of falling: digoxin, type IA antiarrhythmics and diuretics [10]. However, these associations were weak since pooled odds ratios for these drugs were in the range of 1.08-1.59 [10]. It was therefore questioned by Leipzig *et al.* [10] whether these cardiac medications substantially increase the risk of falls. Because there is a (weak) association between these cardiac FRIDs and falling, it has been examined whether there is also an association with impaired postural control, as this is one of the primary causes of falling [15]. The effects of the known cardiac FRIDs on postural control are discussed below.

Digoxin

Digoxin is a cardiac glycoside and is widely used in the treatment of heart conditions, namely rate control in atrial fibrillation and heart failure that cannot be controlled by other medication. As far as the authors know, the effects of digoxin use on postural control have not yet been investigated, although this drug may cause adverse effects that may impair postural control, for instance, dizziness, blurred vision, or cardiovascular adverse effects such as arrhythmias.

Type IA antiarrhythmics

Type IA antiarrhythmics are typically used for supraventricular tachycardia and arrhythmias. This class of anti-arrhythmic agents includes disopyramide, procainamide, and quinidine. There were no studies found examining the effects of type IA antiarrhythmics on postural control. However, these drugs may cause adverse effects that may be associated with impairments in postural control, such as hypotension, arrhythmias (bradycardia), or blurred vision.

Diuretics

Diuretics are used to treat hypertension, and as a therapy for heart failure, ascites in liver cirrhosis, and nephrotic syndrome. There are various types of diuretics, e.g., high-ceiling loop diuretics, thiazides, potassium-sparing diuretics, and osmotic diuretics. These drugs may cause adverse effects that may cause impairments in postural control, for example, orthostatic hypotension, arrhythmias, or hypokalemia, which may cause muscle weakness. Diuretics have been associated with an increased risk of falling [10]. However, thiazide diuretics appear to reduce the risk of hip fracture [159], perhaps because chronic ingestion of thiazides is associated with higher bone mineral density [160].

Two studies have examined the effects of a thiazide diuretic, bendroflumethiazide (formerly named bendrofluazide), on body sway among healthy young subjects [45, 77]. Gerrard *et al*. [45] did not find any significant effects of bendroflumethiazide 5 mg on the amount of body sway. On the other hand, McDevitt *et al*. [77] found increased amplitude of body sway for bendroflumethiazide 2.5 mg, where the increase in amplitude of body sway was not significantly affected in higher doses.

Table 5.5. Effect of FRID withdrawal on postural control

Study (quality score)[a]	Study design	Sample (n_{total}; age; gender; population)	CON and INT activities	Method	Outcome variables	Results
van der Velde *et al.* [161] (23)	Prospective cohort study	137[b]; 77.7±5.7 y; 72% F; patients visiting a geriatric outpatient clinic and using ≥1 FRIDs[c]	INT: fallers with FRID withdrawal in 1-month CON: non-fallers and fallers without FRID change	10m WT; TUG; FR; IQFMS; body sway with force platform	10m WT – time (s); TUG – time (s); FR – distance reaching forward (cm); IQFMS – strength (N); body sway – length of displacement of center of gravity (cm)	Fallers with FRID change: 10m WT -1.3 s (p = 0.021); TUG -3.0 s (p = 0.026); FR +0.5 cm (NS); IQFMS +7 N (NS); body sway -3.8 cm (NS) Fallers without FRID change: 10m WT +3.4 s (p = 0.004); TUG +3.8 s (p = 0.002); FR -3.0 cm (p = 0.023); IQFMS +4 N (NS); body sway -2.6 cm (NS) Non-fallers without FRID change: 10 m WT +1.2 s (p < 0.001); TUG +1.6 s (p = 0.003); FR -4.3 cm (p < 0.001); IQFMS -27 N (p = 0.008); body sway +6.1 cm (p = 0.004)
Tsunoda *et al.* [162] (23)	Open-label study	30; 79.1±8.9 y; 43% F; nursing home residents receiving BZD as hypnotic	INT: tapering off BZD over 3 weeks CON: NA	Clinical Stabilometric Platform	Range (cm^2) and total length (cm) of trunk motion during 30 s with eyes opened and closed	Change: total length of trunk motion, eyes open -0.5 cm (NS), eyes closed -1.5 cm (p = 0.002); range of trunk motion, eyes open -0.02 cm^2 (p = 0.046), eyes closed -1.51 cm^2 (p = 0.010)

BZD benzodiazepine; **CON** control group; **F** female; **FR** functional reach test (cm); **FRID** fall risk increasing drug; **INT** intervention group; **IQFMS** isometric quadriceps femoris muscle strength (N); **NA** not available; **NS** not significant; **TUG** timed up & go test (s); **WT** walking time (s);

[a] Downs and Black score (max. 28 points);

[b] A power analysis was performed to estimate the sample size;

[c] FRIDs in this study were defined as anxiolytics/hypnotics, antipsychotics, antidepressants, antihypertensives, antiarrhythmics, nitrates and other vasodilators, digoxin, β-adrenoceptor antagonist eye drops, analgesics (mainly opioids), anticholinergic drugs, antihistamines, antivertigo drugs and antihyperglycaemics

Effects of FRIDs withdrawal on postural control

Because psychotropic drugs have been associated with numerous deleterious effects, including impaired postural control and increased risk of falling, it could be argued that the use of psychotropic drugs in older people should be reduced to a minimum. Withdrawal of FRIDs, especially psychotropic drugs, reduces the risk of falling, as three intervention studies concluded [11–13]. It is questioned whether this effect is induced by an improved postural control.

We only found two studies examining the effects of discontinuation of FRIDs on postural control (see Table 5.5) [161, 162]. Van der Velde *et al*. [161] showed that among geriatric outpatients, withdrawal of FRIDs significantly improved walking time on the 10-m walking test and the TUG over a mean follow-up period of 6.7 months. The results of Tsunoda *et al*. [162] are in line with these results, that is, they found that discontinuation of benzodiazepine hypnotics was feasible in a majority of older persons. Benzodiazepine withdrawal resulted in a significant improvement in the stability of the body and a recovery of cognitive functions during the daytime.

Discussion

Psychotropics and some cardiac drugs are associated with an increased risk of falling in older adults [6–10]. The aim of the present literature review was to examine the effects of these so-called FRIDs on postural control. Of the 94 included studies, there were 71 that found impairments in postural control after using FRIDs, all using objective measures to assess postural control during standing or walking. In the reviewed studies, affected postural control during standing was indicated by an increase in parameters quantifying body sway (e.g., greater CoP displacement, larger postural sway), while impairments in postural control during walking were quantified by, amongst others, slower walking speed, smaller step length, and lower cadence.

The present review showed that of the known FRIDs, especially psychotropic drugs affected postural control. Among the antidepressant, neuroleptic, and antiepileptic medications, there were specific drugs with specific daily dosages significantly affecting postural control in healthy young subjects and older subjects. Of the antidepressants, administering the TCA amitriptyline ≥50 mg resulted in significantly impaired postural control. The CNL haloperidol ≥3 mg, and the AAPs olanzapine 3 mg, and risperidone ≥1 mg, were the drugs in the group of neuroleptics affecting postural control. In addition,

among the AEDs, carbamazepine ≥400 mg, gabapentin 600 mg, lamotrigine 240 mg, and phenytoin 1,000 mg caused significant more body sway.

In particular, the effects of using benzodiazepines on postural control have been studied in a large number of studies. These studies showed that benzodiazepines had an effect on postural control within 8 h after administration, the so-called nightly effects. These effects were larger when people were older, and when the daily dose was higher. Hangover effects on postural control (after 8 h of administration) were mainly found for benzodiazepines with an intermediate and a long half-life. The long-term effects of benzodiazepines on postural control are not fully clear yet. Importantly, the effects of these psychotropic FRIDs on postural control were reversible after discontinuation, as two intervention studies concluded [161, 162].

In contrast to psychotropic FRIDs, we only found two studies of the possible effects of a cardiac FRID, bendroflumethiazide, a thiazide diuretic, on postural control during standing or walking [45, 77]. Although cardiac drugs have been reported to increase fall risk [10], the present review, with only two studies, did only find a significant effect of bendroflumethiazide 2.5 mg on body sway in healthy young subjects [77], whereas higher doses did not show any effect [45, 77]. Presumably, the increased fall risk these cardiac FRIDs are associated with is not caused by impairments in postural control, but is more likely a direct result of the underlying cardiovascular disease, e.g., arrhythmias, or the adverse effects these drugs may induce, such as orthostatic hypotension.

On the other hand, the effects of psychotropic drugs on postural control, and consequently on fall risk, are likely to be induced by the adverse effects of these drugs. All psychotropic FRIDs have sedative effects, inducing muscle relaxation and decreased grip strength [163], therefore impairing postural control [164]. In addition, TCAs and neuroleptics can cause orthostatic hypotension [138]. It is likely that an acute orthostatic drop in blood pressure may lead to diminished blood flow to the brain, causing acute and temporal difficulties in maintaining postural control, which may subsequently lead to falls [165]. CNLs, SSRIs, and some AEDs may cause extrapyramidal adverse effects, such as parkinsonism (tremor, bradykinesia, muscle rigidity), causing postural instability, and consequently increase the risk of falling [166].

Furthermore, the effects of psychotropic FRIDs on cognitive functioning [150] might indirectly influence postural control. Current evidence suggests that postural control, during both quiet standing and walking, is closely related to cognition, especially with executive functions, e.g., attention, planning, and working memory [32, 34, 167]. Especially among older persons, the age-related loss of visual, proprioceptive, and vestibular sensitivity requires more conscious attention for maintaining postural stability

during standing and walking [168]. Consequently, as results of the present review showed, effects of psychotropic drugs on postural control are more pronounced in older than younger subjects.

The quality of the listed evidence was moderate to good, as Downs and Black methodological quality scores were in the range of 13-25 points. Only 11 of the 94 reviewed studies estimated sample size by a priori power analysis, all other studies should have done this because the sample size was quite low. None of the studies reported any information regarding external validity, so it was not clear from which population subjects were recruited. The examined older subjects were healthy and relatively young (around 65 years of age), therefore it can be questioned what impact FRIDs would have on postural control in frailer older people with multiple co-morbidities and taking multiple medications. Further research should investigate this.

To conclude, the review shows that it has been underestimated that FRIDs have negative effects on postural control in older people due to their sedative adverse effects, which may consequently contribute to fall risk. Therefore, it is important that physicians take into account the adverse effects of psychotropic drugs on postural control, and consequently fall risk, when prescribing these types of drugs to older patients. Preferably, psychotropic drugs should only be administered after consideration of other pharmacological (with potentially less effect on postural control) or non-pharmacological interventions, and when administered, only at the lowest effective dose, with a short half-life, and for a limited period of time. Interestingly, the adverse effects of FRIDs have been reported to be reversible, for postural control [161, 162], cognition [169], and for fall incidents [11–14]. For older patients who are using psychotropic drugs on a regular basis, withdrawing or reducing the use FRIDs appears to be effective [170]. Patients who need psychotropic drugs, even on a reduced dose, may consider reducing their risk of falling by physical exercise involving gait, standing balance, or muscle strengthening [24].

To monitor the effects of (withdrawing) FRIDs on postural control, and adjust the intervention accordingly, refined analyses of postural control are needed, which can be obtained from computerized instruments, e.g., force platforms, electronic walkways, or body-worn sensors. Monitoring postural control among older persons who start or stop using psychotropic drugs may give relevant information about the effects of these drugs on the ability to maintain, achieve, or restore a state of balance during any posture or activity, and may therefore detect patients at risk for falling. Then, (preventive) interventions can be offered, for instance, withdrawing or reducing psychotropic drug

use, and/or exercise training, to prevent falls and possible adverse injuries, for instance, hip fractures or head trauma.

Conclusion

Increased fall risk from the use of psychotropic drugs is associated with impairments in postural control these drugs can induce. The effects seem to be more pronounced in the older than the younger population, and when the daily dose is higher and the half-life and duration are longer. The effects on postural control, as well as the mediating sedative adverse effects such as impaired cognitive functioning and muscle relaxation, are reversible after withdrawing FRIDs as was proven in a small number of intervention studies. The findings of the present literature review highlight the importance of monitoring effects of psychotropic drugs on postural control, to detect patients at risk for falling, and offer them interventions, e.g., discontinuing or reducing the use of psychotropic drugs, or offering physical exercise training, to prevent them for possible adverse fall-related injuries, such as hip fractures.

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CHAPTER 5B

Authors' reply to Toda: "The effects of fall-risk-increasing drugs on postural control: A literature review"

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Letter to the Editor

We thank Dr. Toda [1] for his interesting question. Dr. Toda asked, in response to our literature review [2], whether psychotropic drugs with longer half-lives are more likely to increase fall risk than psychotropic drugs with shorter half-lives. In our paper [2], we concluded that psychotropic fall-risk-increasing drugs (FRIDs) cause impairments in postural control, which is probably one of the mediating factors for the increased fall risk with which these FRIDs are associated. The effects of psychotropic FRIDs on postural control are more pronounced when people are of higher age, use psychotropics at higher daily dosages, for a longer period of time, and when the half-life of the drug is longer. By the latter, we mean that the effects on postural control of benzodiazepines with intermediate to long half-lives (>8 h) sustain for a longer period of time after taking the drug (the so-called hangover effect).

Regrettably, since we only examined the effects of FRIDs on postural control [2]—not on fall risk—we cannot conclude whether psychotropic drugs with a longer half-life are more likely to increase the risk of falling than psychotropics with a shorter elimination time. However, an interesting study by De Vries *et al*. [3] has recently been published, examining prospectively whether long-acting benzodiazepines are associated with a higher fall risk than short-acting benzodiazepines. The findings of De Vries *et al*. [3] are in line with the meta-analysis of Leipzig *et al*. [4], namely that the use of short-acting benzodiazepines is not associated with a lower fall risk compared with long-acting benzodiazepines. Remarkably, it must be noted that the cut-off defining short and long half-life differs in studies: for instance, we defined short half-life as ≤8 h [2], De Vries *et al*. [3] defined it as ≤10 h, and Leipzig *et al*. [4] as ≤24 h.

Thus, it can be stated that both short- and long-acting psychotropics increase the risk of falling in older people, the former not more than the latter. However, we can speculate about the moment and location of fall incidents caused by psychotropic FRIDs. For example, it can be hypothesized that short-acting benzodiazepines (mainly hypnotics) increase the risk of falling during the night, for instance when walking to the toilet because of nocturia (the nightly effects); while long-acting benzodiazepines (mainly anxiolytics) may increase the risk of falling both during the night and daytime because of residual daytime sleepiness (the hangover effect).

Nevertheless, the use of psychotropic FRIDs, both with short and long half-lives, should be discouraged in the older population, and when administered, only at the lowest effective dose and for a limited period of time.

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CHAPTER 6

The association of medication-use and frailty-related factors with gait performance in older patients

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Abstract

The increased fall risk associated with the use of psychotropic drugs might be caused by underlying problems in postural control that are induced by sedative side-effects of these drugs. The current literature on the effects of psychotropics on postural control only examined acute single-drug effects, and included relatively healthy young elderly. Consequently, it is unclear what the impact of the long-term use of these drugs is on gait in frail older persons with polypharmacy. Therefore, it was aimed in the present study to explore the association between the use of psychotropics, multiple other medications, frailty-related parameters and gait performance in older patients. Eighty older persons (79±5.6 years) were recruited. Comorbid diseases, frailty-related parameters, and medication-use were registered. Trunk accelerations during a 3-minute-walking-task were recorded, whereof walking speed, mean stride times, coefficient of variation (CV) of stride times, and step consistency were determined. Multivariate Partial Least Squares (PLS) regression analysis was used to examine the association between population characteristics and medication-use, versus gait parameters. A PLS-model existing of four latent variables was built, explaining 45% of the variance in four gait parameters. Frailty-related factors, being female, and laxative-use were most strongly associated with lower walking speed, higher mean stride times, higher CV of stride times, and less consistent steps. In conclusion, frailty-related parameters were stronger associated with impaired gait performance than the use of psychotropic drugs. Possibly, at a certain frailty-level, the effect of the deterioration in physical functioning in frailty is so large, that the instability-provoking side-effects of psychotropic drugs have less impact on gait.

Introduction

Older persons visiting a geriatric outpatient clinic are characterized by a combination of physical, psychological and social problems. They often have multiple chronic conditions, and use therefore multiple medications (polypharmacy). These frail old people have a high risk of adverse events, such as falling, hospital admissions, and ultimately death [1, 2].

The past decades, many risk factors for falls in elderly people have been identified, which can be classified as either intrinsic (e.g., age-related changes in the sensor-motor system leading to gait and balance deficits), extrinsic (e.g., polypharmacy), or environmental factors [3]. In addition, meta-analyses showed that specific medication classes, including psychotropics and some cardiac drugs, have been associated with an increased risk of falling [4–7]. In a recent literature review [8], we suggested that the increased fall risk with which these psychotropic drug classes are associated, is caused by underlying problems in postural control these drugs can induce. That is because postural instability during daily activities, such as walking, is a primary cause of falling [9]. Walking can be characterized by a wide variety of gait parameters, each characterizing different aspects of the gait pattern. Walking speed is easily assessable and often used in clinical practice to reflect the functional status in older patients [10]. However, it lacks specificity (gait speed is slower in many different pathologies), and does not reveal information about the quality of the walking pattern, i.e., the ability of a person to adapt his/her gait smoothly, and the variability and regularity of the gait pattern. Stride-to-stride variability during walking provides additional information about gait performance, since high variability in stride times in frail elderly can be considered as a marker of abnormal regulation of gait [11, 12]. Both walking speed and characteristics indicating the variability in the walking pattern are suggested to be associated with increased fall risk [13, 14].

The current literature about the effects of psychotropic drugs on postural control assessed postural control during quiet standing, described only acute single-drug effects, and included relatively healthy young elderly [8]. Thus, the impact of long-term psychotropic drug-use on gait performance in frail older people with multiple comorbid diseases and polypharmacy remains still unclear.

In the present study, we therefore aimed to explore the association between the use of psychotropic drugs and gait performance in a cohort of older patients. Because in this frail older population many factors may be simultaneously present that could influence gait (e.g., the use of multiple medications, the presence of comorbid diseases, cognitive

impairment, and/or frailty [11, 12, 15, 16]), we included these factors in our analyses as well. The use of a cross-sectional study design, and a Partial Least Squares (PLS) regression analysis, enabled us to examine the association between the use of psychotropic drugs and gait parameters, in relation to other factors that might influence the walking pattern. We hypothesized that a deterioration in gait performance was not only explained by the use of psychotropics, but that in older patients frailty-related parameters, polypharmacy and comorbidity would also be associated.

Methods

Ethics statement

The study was approved by the local Medical Ethics Committee of the MC Slotervaart (registration number: NL33825.048.10). All participants or their legal representatives (when participants had cognitive impairment) gave their written informed consent.

Participants

Eighty patients were recruited consecutively among the elderly that visited the geriatric outpatient clinic of the MC Slotervaart in Amsterdam between October 2010 and April 2013. They were referred to the clinic by their general practitioner for various reasons, including memory complaints, mobility problems, or for evaluating polypharmacy. Patients were eligible to participate in the study if they were at least 65 years or older, and could walk safely for at least 3-minutes without any assistive device. They were excluded when they had any mobility problems due to neurological or orthopedic disorders, or were not able to understand the instructions of the researcher due to severe cognitive or hearing impairment.

During the study period, 619 older adults visited the geriatric outpatient clinic. Thereof, 392 patients (63%) did not meet the in- and exclusion criteria. In total, 227 (37%) patients were eligible, whereof 80 patients (13% of all visitors of the geriatric outpatient clinic) were willing to cooperate in the present study. The other 147 patients refused to cooperate because they felt too tired after the day in the hospital or did not want to cooperate (without giving reason).

Measurements

Population characteristics

All participants underwent extensive physical and cognitive examination, as part of a Comprehensive Geriatric Assessment (CGA) [17]. General information was obtained from their patient file. All population characteristics were binary coded for statistical analyses. Age was coded as being ≥80 or <80 years, because this was the mean age of the included participants). Cognitive functioning was assessed using the Mini Mental State Examination (MMSE) [18]. Participants scoring ≤23 points were categorized as being cognitive impaired [19]. Fall risk was examined using the LASA fall risk assessment [20]. When participants scored ≥8 points, they were identified as having an increased risk of recurrent falling. Four frailty criteria were registered [1], namely: unintentional weight loss, self-reported exhaustion, low physical activity, and low hand grip strength. Walking speed was a dependent variable in the statistical analyses. Comorbid diseases were registered using the Charlson's Comorbidity Index (CCI) [21]. Table 6.1 lists the registered comorbid diseases.

Medication-use

Medication-use was systematically reviewed by the participant's physician as part of the CGA. Prior to their visit to the Geriatric Outpatient Clinic, patients were requested to bring the packaging of their medications or a list of their pharmacist with the drugs they use. The physician went through the list with the patients and/or their caregivers to check if the patients used all medications appropriately and/or used other non-prescribed drugs or supplements. The actual medication-use was then registered in the patients' file, which was used in the present study.

All generic names of the drugs (trade names) were manually looked up and subsequently linked with the corresponding code of Anatomical Therapeutic Chemical (ATC) classification system [22] (see Appendix I for an overview of the prevalence of all drugs in the study population). The medications were clustered into ATC-drug classes (see Table 6.1 for an overview of the 37 included ATC-drug classes in the present study). For each participant it was binary scored whether the participant used a drug in a specific ATC-drug class or not. Furthermore, the total number of drugs used per participant was registered. Polypharmacy was present when the participant used ≥4 drugs.

Table 6.1. Prevalence of the independent variables (population characteristics, comorbid diseases, and medication-use per ATC-drug class) is presented in the left column as *n* (%) in the population (N=80). In the right column, the captured variance (%) in every independent variable per latent variable (LV) of the PLS-model, and the total variance is presented. Values with high modeling power (>6.90%)[a] are relevant to the LVs.

	Prevalence		Captured Variance (%)				
Independent variables	*n*	(%)	LV 1	LV 2	LV 3	LV 4	TOTAL
Population characteristics							
Female	50	(63%)	13.26	3.20	24.72	2.37	43.55
≥80 years	41	(51%)	9.65	0.75	1.94	3.41	15.76
≥2 comorbid diseases	29	(36%)	13.21	16.63	4.86	6.84	41.55
Cognitive impairment (MMSE ≤23 points)	35	(44%)	0.55	2.70	0.24	3.22	6.71
Increased fall risk (Pluijm score ≥8 points)	14	(18%)	15.90	1.09	21.45	0.82	39.26
Polypharmacy (≥4 medications)	52	(65%)	35.52	20.44	5.44	1.26	62.66
Frailty-criteria							
- Unintentional weight loss	13	(16%)	14.09	3.30	1.78	1.83	20.99
- Self-reported exhaustion	21	(26%)	24.77	0.00	0.44	1.67	26.87
- Low physical activity	12	(15%)	24.92	0.23	0.05	2.18	27.38
- Low hand grip strength	20	(25%)	10.85	1.33	24.00	5.71	41.89
Comorbid diseases (CCI)							
Myocardial infarct	21	(26%)	9.51	11.14	0.12	19.40	40.17
Peripheral vascular disease	8	(10%)	2.39	6.85	2.03	0.05	11.32
Cerebrovascular disease	5	(6%)	0.39	0.02	0.00	0.21	0.62
Dementia	22	(28%)	0.37	2.90	10.44	1.74	15.45
Chronic pulmonary disease	8	(10%)	7.45	0.45	19.96	2.32	30.17
Connective tissue disease	2	(3%)	0.00	0.65	1.28	0.06	1.99
Ulcer disease	4	(5%)	3.96	0.31	0.37	6.39	11.02
Diabetes	11	(14%)	2.92	4.67	0.69	0.36	8.65
Moderate or severe renal disease	6	(8%)	2.81	11.53	1.22	1.96	17.52
Diabetes with end organ damage	2	(3%)	3.35	0.48	0.50	3.51	7.84
Any tumor	10	(13%)	0.81	8.31	0.74	6.66	16.52

Leukemia		1	(1%)	0.49	0.22	1.11	0.01	1.83
Medication-use (per ATC-drug class)								
Agents for alimentary tract & metabolism (group A)								
A02A	Antacids	2	(3%)	2.01	0.55	4.25	0.13	6.93
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	31	(39%)	39.46	7.92	0.21	0.66	48.24
A03	Drugs for functional gastrointestinal disorders	3	(4%)	4.76	0.00	3.24	2.15	10.15
A06	Drugs for constipation	12	(15%)	11.13	4.29	6.06	0.65	22.13
A07	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	2	(3%)	4.33	0.08	1.79	0.04	6.24
A09	Digestives, incl. enzymes	1	(1%)	2.25	0.17	3.91	0.38	6.71
A10	Drugs used in diabetes	11	(14%)	5.63	8.89	1.40	0.01	15.92
A11 & A12	Vitamins & mineral supplements	25	(31%)	9.07	0.63	18.18	2.43	30.30
Drugs acting on the cardiovascular system (group C)								
C01AA05a	Digoxin	4	(5%)	0.03	1.26	0.13	0.98	2.41
C01B	Antiarrhythmics (class I and III), excl. type IA	2	(3%)	0.61	0.37	3.46	0.76	5.20
C01BA	Type IA antiarrhythmicsb	0	(0%)b					
C01D	Vasodilators used in cardiac diseases	10	(13%)	6.79	16.39	0.96	2.50	26.65
C01E	Other cardiac preparations	2	(3%)	1.03	3.91	0.84	1.59	7.37
C03	Diuretics	30	(38%)	2.01	27.48	6.21	1.61	37.31
C07	Beta blocking agents	25	(31%)	1.55	18.13	3.25	10.40	33.33
C08	Calcium channel blockers	13	(16%)	4.52	9.03	0.00	1.76	15.31
C09	Agents acting on the renin-angiotensin system	31	(39%)	0.56	35.73	4.91	13.54	54.74
C10	Lipid modifying agents	38	(48%)	3.98	20.24	7.59	4.82	36.64
Drugs acting on the nervous system (group N)								
N02	Analgesics (no paracetamol)	6	(8%)	12.15	0.26	7.85	2.06	22.33
N02BE	Paracetamol/acetaminophen	5	(6%)	9.95	0.10	15.57	2.74	28.37
N03A	Antiepileptics	6	(8%)	1.12	1.81	7.29	4.23	14.46
N05A	Antipsychotics	2	(3%)	1.61	0.68	0.01	0.21	2.52
N05BA	Anxiolytics (benzodiazepine-derivatives)	8	(10%)	0.47	0.11	0.00	0.83	1.41

Table 6.1. *Continued*

Independent variables		Prevalence *n*	(%)	Captured Variance (%) LV 1	LV 2	LV 3	LV 4	TOTAL
N05C	Hypnotics, excl. benzodiazepine-derivatives	7	(9%)	15.58	1.61	5.70	2.91	25.80
N05CD	Hypnotics & sedatives (benzodiazepine-derivatives)	5	(6%)	0.37	0.44	4.20	0.00	5.02
N06A	Antidepressants	12	(15%)	7.93	7.15	0.01	2.07	17.15
N07	Other nervous system drugs	2	(3%)	0.24	0.47	6.05	0.03	6.80
Other ATC-drug classes								
B01	Antithrombotic agents	34	(43%)	12.48	22.64	7.16	2.30	44.59
B03	Anti-anemic preparations	4	(5%)	3.67	1.56	0.41	6.58	12.22
D	Antifungals for dermatological use	1	(1%)	2.76	2.46	2.35	0.04	7.61
G	Genito-urinary system and sex hormones	11	(14%)	12.63	1.39	0.73	2.04	16.78
H	Systemic hormonal preparations, excl. sex hormones and insulins	5	(6%)	7.85	0.61	1.03	1.51	10.99
J	Anti-infectives for systemic use	4	(5%)	5.15	0.38	0.07	2.77	8.37
L	Antineoplastic and immunomodulating agents	1	(1%)	0.01	2.78	0.83	6.49	10.11
M	Musculo-skeletal system	10	(13%)	5.88	1.59	0.61	6.38	14.46
R	Respiratory system	13	(16%)	7.71	0.02	5.77	0.82	14.32
S	Sensory organs	8	(10%)	3.41	17.45	5.68	5.63	32.18

[a] Variables with low modeling power, i.e., around A/K, are of little relevance (A = number of LVs = 4; and K = number of independent variables = 58). Thus variables with less variance captured than 4/58=6.90% are not important to the LV [23].

[b] This item was excluded from further PLS-analyses, because n=0.

Gait parameters

Participants walked 3-minutes in a 80-meter long hallway at a self-selected speed while trunk accelerations were recorded using an accelerometer (DynaPort Minimod Hybrid; McRoberts BV; sample frequency 100 Hz), which was attached with a band at the level of the lumbar spine. Walking distance was recorded to determine gait speed. Trunk acceleration signals were analyzed using custom-made software in MATLAB (version 2011b; The MathWorks Inc.). Foot contact moments were determined from the peaks of the anterior-posterior-acceleration time-series. From the foot contact moments, stride times were calculated defined as the time interval between two ipsilateral foot contacts. For each participant, mean and CV of stride times were computed. The variability between left and right steps within the strides was quantified by the standard deviation (SD) of the relative timing between ipsilateral foot contact moments, with larger values indicating less consistent steps [24, 25]. See De Groot *et al*. [16] for a detailed description of the calculated gait parameters.

Statistical analyses

To test the association between the various drug classes, the population characteristics, and the comorbid diseases in relation to stride variability, a multivariate PLS regression analysis was computed using the PLS_toolbox for Matlab (version 3.7.1; Eigenvector Research Inc.). PLS-regression is a technique that combines features from principal component analysis and multiple regression, and is not impeded by collinearity among variables [26–28]. PLS has particularly been applied in studies in which a set of dependent variables is predicted from a relatively large set of independent variables with relatively few observations [29–31]. In these studies, similar to our study, continuous, ordinal and binary data were included. It is well known that their exists an interdependency among different gait variables, such as walking speed, mean stride times, and variability in stride times [32–34]. When using PLS, a model can be constructed wherein the dependency among these gait variables is taken into account. That makes the PLS-regression analysis more favorable over the more conventional multiple regression analysis.

In the PLS-regression analysis, 58 independent variables (the population characteristics, comorbid diseases, and medication-use) and four dependent gait parameters were included. In order to give the variables the same scale, i.e., the same importance in the analysis, all independent (binary coded) variables were mean-centered (i.e., means of each column were set to zero), and the dependent gait

parameters were scaled to unit variance by dividing each variable by their SD's and centering them by subtracting their averages [23, 35].

PLS-regression analysis searches for a set of latent variables (LVs) explaining as much as possible of the covariance between the independent (the population characteristics, comorbid diseases, and medication-use per ATC-class), and dependent variables (the four gait parameters). With numerous and correlated variables, there is a substantial risk for "over-fitting", i.e., getting a well-fitting model with little or no predictive power. Cross-validation is a practical and reliable way to test the predictive significance of the model [35]. Cross-validation was performed by dividing the data into eight groups (method: Venetian Blinds), and then developing eight parallel models from reduced data with one of the groups deleted. Then, differences between the actual and the predicted values for the gait parameters were calculated for the deleted data. The sums of squares of these differences were computed and collected from all the parallel models to form the predictive residual sum of squares (PRESS), which estimates the predictive ability of the model. The optimal number of LVs was determined by stop adding LVs as soon as the Predicted REsidual Sum of Squares (PRESS) decreased [36]. From the PRESS-values of the final model, the predictive ability of the model was indicted by the parameter Q^2, the predicted variation, or: *the goodness of prediction*. This value can be compared to R^2, the explained variation, which is the capacity of the population characteristics, comorbid diseases and medication-use to explain the variance among the gait variables, or: *the goodness of fit*.

From the PLS model, a set of model parameters was computed (see Table 6.2). A downside of using PLS is that it is relatively difficult to interpret model parameters, since these are biased and *p*-values and confidence intervals are lacking. By interpreting the model parameters simultaneously, the associations between the independent variables (the population characteristics, comorbid diseases, and medication-use) were examined in relation to the gait parameters. The relevance of each independent variable to the LVs was indicated by the percentage variance that was captured by the LV [23]. Variables with low modeling power, i.e., around A/K (in our study, A = number of LVs = 4; and K = number of independent variables = 58), were of little relevance. Thus variables with variance below 4/58=6.90% are not important to the LV [23, 29]. Therefore, variables with high captured variance for the same LV were clustered in the same LV.

Table 6.2. List of abbreviations and explanations of outcome variables of the PLS-analysis.

Abbreviation	Outcome variable	Indicator of	Interpretation
	Independent variables		Population characteristics, comorbid diseases, medication-use in various ATC-drug classes
	Dependent variables		Gait parameters: walking speed, mean stride times, CV of stride times, and step consistency
Q^2	Predicted variance	Goodness of prediction	Higher Q^2 means better predictive ability of the model. Q^2 >50% is regarded good [23].
R^2	Explained variance	Goodness of fit	Higher R^2 means better capacity of the independent variables to explain the variance among the gait parameters
RC	Regression Coefficient	Association between independent and dependent variable in the model	Higher positive or negative RC means that the independent variable is stronger related to gait parameter
	Variance Captured	Relevance of the independent variable to the LV	Variance>6.9% means that independent variable is relevant to the LV. Higher captured variance means more relevant
VIP	Variable Importance on Projection	Importance of each independent variable for the gait parameters	VIP>1.0 means that independent variable is influential to the gait parameters. Higher VIP means more influence

The association between each independent variable and the gait parameters was indicated by regression coefficients. A higher positive or negative regression coefficient means that the independent variable is stronger related to the gait parameter. The importance of each variable in explaining the variation among gait parameters was given by the variable importance in projection (VIP) value. A VIP-value higher than 1 means that the independent variable is influential to the gait parameters. At last, score and weight plots illustrate and summarize the relationship between observations (the participants) and independent variables (population characteristics, comorbid diseases and medication-use), respectively, with respect to the latent variables.

Since the model parameters are biased, the important variables in relation to the gait parameters have overall higher modeling power (high captured variance), have higher positive or lower negative regression coefficients, and have a VIP-value higher than one. Moreover, these important variables have higher positive or lower negative weight-values, and are therefore clustered in the upper right or lower left quadrant of the weight plot. Based on the scores and weights of the model, predicted values for the gait parameters were calculated to illustrate the fit of the model [23, 28, 36]. See for a more detailed mathematical description of the PLS regression analysis the Supplementary Information (Appendix II).

Results

Descriptive characteristics of the study population

Eighty older persons were included in the present study (aged 79±5.6 years). Cognitive impairment was present in 35 participants (44%); the median MMSE score was 24 points (range: 11-30). Fourteen participants (18%) scored ≥8 points on the LASA fall risk assessment, indicating an increased risk for recurrent falls. Considering the frailty-related indicators, 13 participants (16%) reported ≥5kg unintentional weight loss, 21 participants (26%) had self-reported exhaustion, 12 participants (15%) had low physical activity, and 20 participants (25%) had low grip strength. Twenty-nine participants (36%) had ≥2 comorbid diseases on the CCI. Dementia, myocardial infarct, and diabetes were most present in the included population (respectively 27%, 26%, and 14%). See Table 6.1 for the prevalence of other comorbid diseases.

The participants used 5.5±3.9 drugs; 52 participants (65%) were categorized as having polypharmacy, because they used ≥4 drugs. Twenty-nine participants (36%) used one or more psychotropic medications that are known to be associated with increased fall risk, e.g. antiepileptics (N03A), antipsychotics (N05A), anxiolytics (N05BA), hypnotics

(N05C), and antidepressants (N06A). Medication-use per ATC-class is presented in Table 6.1.

Mean walking speed was 0.90±0.24 m/s, mean stride time was 1.16±0.13 seconds, the variation (CV) of stride times was 3.81±1.61%, and step consistency was 4.67±1.68°.

Association between population characteristics, comorbid diseases, and medication-use in relation to gait parameters

The PLS-regression testing the association between population characteristics, comorbid diseases and medication-use in relation to gait parameters yielded a model of four LVs (see Table 6.3), explaining 27.6% of the variance between the population characteristics, comorbid diseases, and medication-use, and 45.4% of the variance in gait parameters (R^2). Adding more LVs to the model did not improve R^2, as indicated by the PRESS.

The variable most relevant to the model, i.e., with the most variance captured by the model, was the presence of polypharmacy (63%). The first LV captured most variance of the following variables: using drugs for ulcer and reflux disease (A02B; 39%), polypharmacy (36%), and two frailty criteria: low physical activity (25%), and self-reported exhaustion (25%). The second LV captured most variance in polypharmacy (20%), and in using drugs acting on the cardiovascular system (ATC-drug classes C09, C10, C03, C07, and C01D). Most variance by the third LV was captured in being female (25%), having low hand grip strength (24%), and increased fall risk (21%). By the fourth LV, most variance was captured in having myocardial infarction in medical history (19%), and using agents acting on the renin-angiotensin system (C09; 14%), and beta-blocking agents (C07; 10%). The variance captured by the model for all variables per LV are presented in Table 6.1.

Table 6.3. Explained variance (%) in the population characteristics, comorbid diseases and medication-use (independent variables) and gait parameters (dependent variables) by the PLS-model existing of four latent variables (LVs).

	LV 1	LV 2	LV 3	LV 4	TOTAL
Explained variance in the independent variables (%)	9.62	8.57	5.76	3.67	27.61
Explained variance in the dependent variables (%)	20.71	9.33	5.70	9.69	45.43

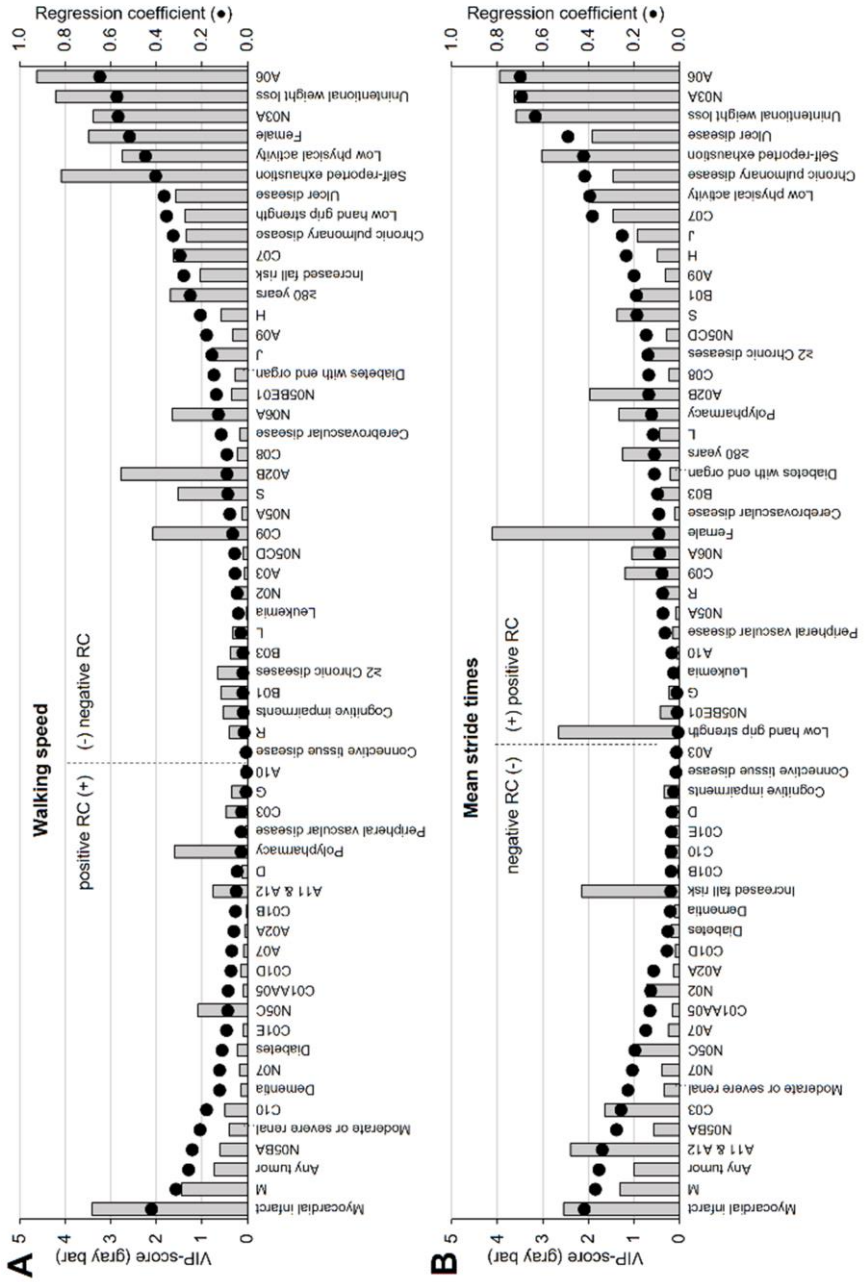

Fig. 6.1. VIP-values and regression coefficients.

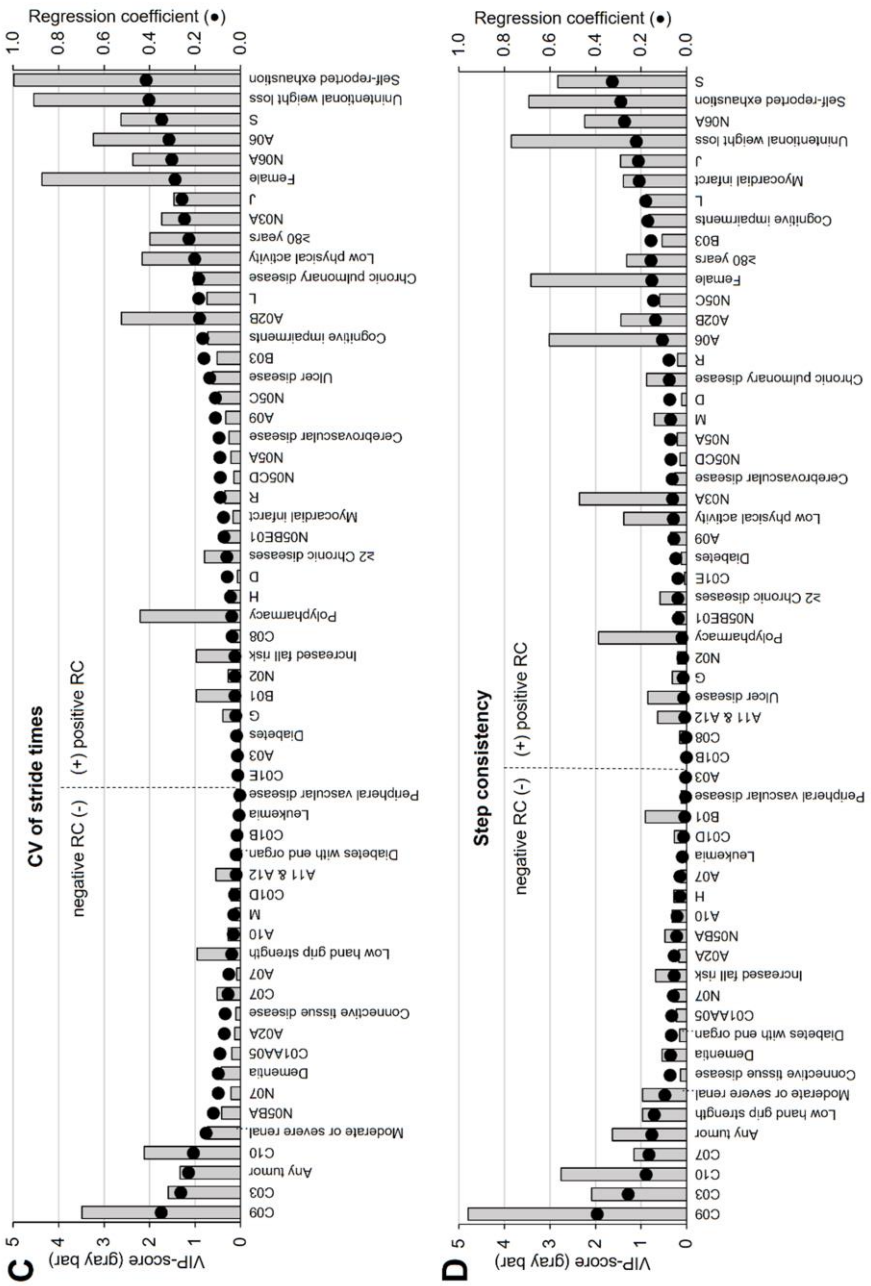

Fig. 6.1. VIP-values and regression coefficients.

Fig. 6.1. VIP-values and regression coefficients.
VIP-values (gray bars; left Y-axis) and regression coefficients (black dots (●); right Y-axis) of all population characteristics, comorbid diseases and medications used are presented for **(A)** walking speed, **(B)** mean stride times, **(C)** CV of stride times, and **(D)** step consistency. The variables are placed on the horizontal axis and sorted according to the height of the regression coefficient. Variables placed at the outer left and right side of the graph have a stronger association with the gait parameter than the variables in the middle of the graph. Variables with a VIP-value of >1 are important to the model. Note that right of the vertical dotted line the variables are presented that are associated with impaired gait ability, that is negative regression coefficients for walking speed, and positive regression coefficients for mean stride times, CV of stride times and step consistency. See Table 1 for a description of the ATC-drug classes.

In Fig. 6.1, the VIP-values and regression coefficients of all population characteristics, comorbid diseases and medication-use for the gait parameters are presented. The most important variables to the model (highest VIP-values) were unintentional weight loss, self-reported exhaustion, being female, and the use of drugs for constipation (A06). These variables were associated with lower walking speed (negative regression coefficients), and higher mean and CV of stride times and less consistent steps (positive regression coefficients).

The association between the participants and the independent variables (population characteristics, comorbid diseases, and medication-use) in relation to the gait parameters is revealed in Fig. 6.2. The position of the participants in a given direction in the score plot (Fig. 6.2A) is influenced by the independent variables lying in the same direction in the weight plot (Fig. 6.2B). Participants in the upper right quadrant of the score plot had overall higher stride variability, whereas persons clustered in the lower left quadrant had lower stride variability. Furthermore, in the weight plot, the relations between the independent variables are visualized. Variables with high regression coefficients and high VIP-scores, e.g., unintentional weight loss, self-reported exhaustion, and being female (see Fig. 6.1), are situated in the upper right quadrant of the weight plot, illustrating that they are associated with each other (as can be also seen by the captured variance of LV1 as presented in Table 6.1), and are associated with higher values for the gait parameters (higher regression coefficients; see Fig. 6.1).

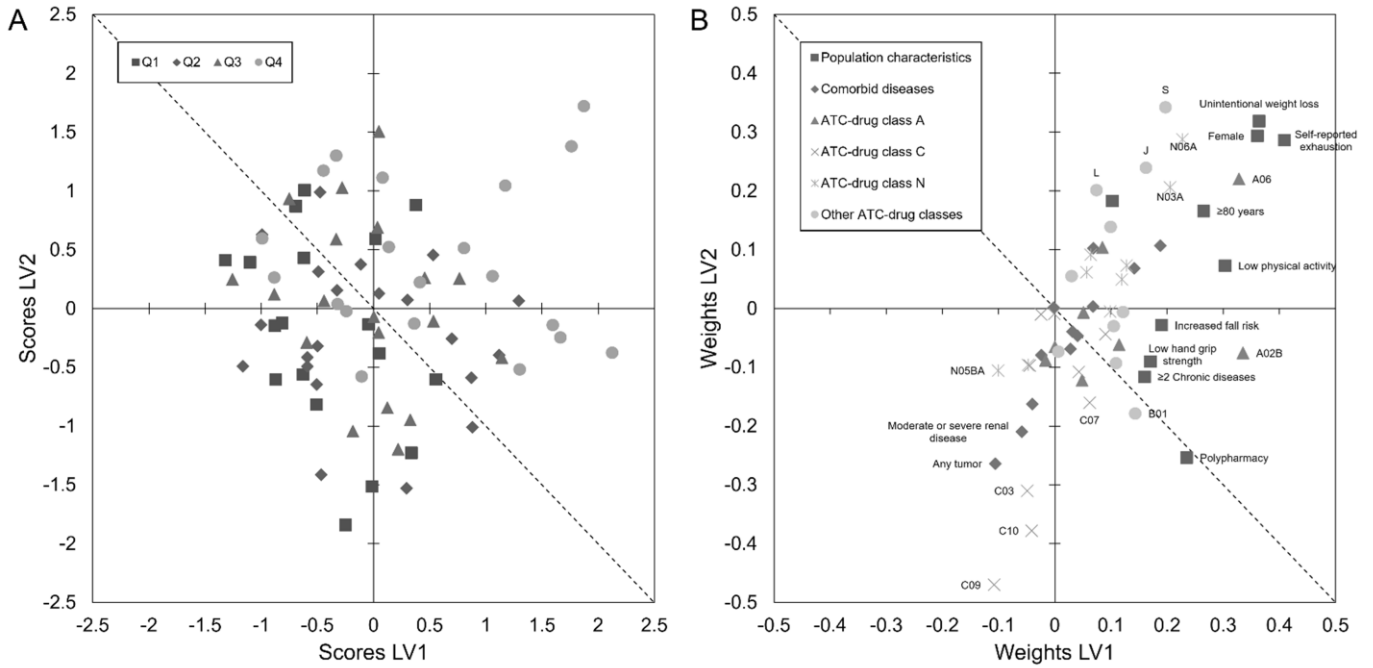

Fig. 6.2. Score and weight plot.

The score-plot **(A)** shows the relationship between the participants. The participants are categorized according to their CV of stride times: quartile 1 (Q1; lowest variability; < 2.6%), quartile 2 (Q2; 2.7-3.4%), quartile 3 (Q3; 3.4-4.4%), and quartile 4 (highest variability in stride times; >4.4%). Coupled to the weight plot **(B)**, the inter-relatedness among the patient characteristics and stride variability is revealed. The weight plot can be considered as a coordinate system, where the underlying structure between the variables in relation to stride variability is revealed. The most influential variables are situated far from origo, with the variables at upper right quadrant associated with higher stride variability, and those situated in the lower left quadrant are associated with lower variability.

The fit and predictive ability of the model are illustrated in Fig. 6.3. The observed versus predicted values of the PLS model for walking speed (R^2=60%; Q^2=92%), mean stride times (R^2=56%; Q^2=98%), CV of stride times (R^2=39%; Q^2=88%), and for step consistency (R^2=26%; Q^2=87%) are presented in this figure.

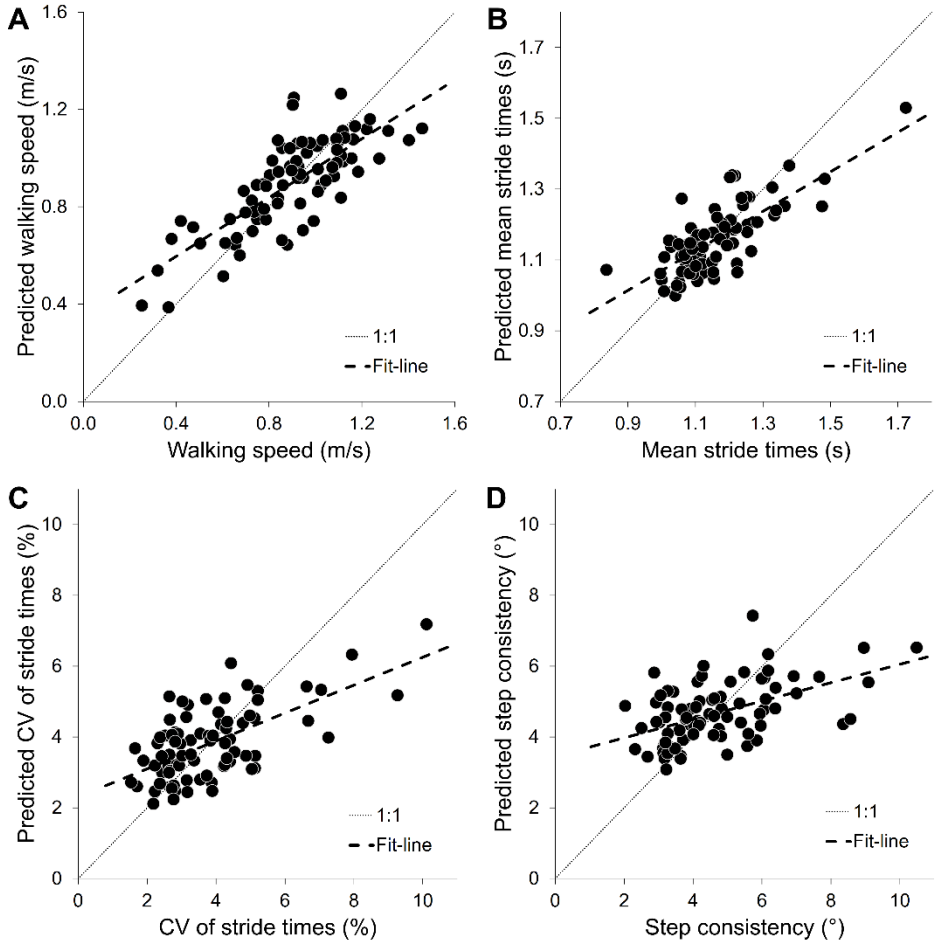

Fig. 6.3. Observed versus predicted values.
For **(A)** walking speed, **(B)** mean stride times, **(C)** CV of stride times, and **(D)** step consistency the observed and predicted values are presented. The striped line represents the fit-line, and the dotted line is the 1:1-line.

In summary, the results show that impairments in gait performance are strongest associated with unintentional weight loss, self-reported exhaustion, being female and the use of laxatives (A06). These variables had overall most variance captured by the model, and the highest VIP-values and regression coefficients.

Discussion

In the present cross-sectional study, we aimed to determine the association between population characteristics, comorbid diseases, medication-use and gait parameters in a population of older patients visiting a geriatric outpatient clinic. Therefore, a PLS-regression model was created testing the association between the use of medications in various ATC-drug classes, comorbid diseases, and common factors in a geriatric population, versus gait parameters. In total, 58 variables were included, explaining 45% of the total variance in four gait parameters, namely walking speed, mean stride times, variation in stride times, and step consistency. R^2- and Q^2-values showed that the model had an appropriate fit and a good predictive ability (see Fig. 6.3).

We created a statistical model including characteristics common in a population of older patients visiting a geriatric outpatient clinic. 45% of the variance in four gait parameters was explained by this model. Gait is a complex motor behavior requiring adequate integration of sensor-motor information. With aging, there is an age-related deterioration of postural control due to progressive loss of functioning of the neurophysiological system, resulting in, amongst others, visual problems, vestibular impairment, affected proprioception, changes in central processing mechanisms, reduced muscle strength, and slower reaction times [37, 38]. These factors are also present in our geriatric study population, but were not as such included in our model. Therefore, these not included aging-related factors presumably account for the unexplained variance in gait parameters in our model.

Nevertheless, most variance in the gait variables was explained by the first LV, and the clustered variables in this LV were therefore strongest related with the gait parameters. In particular, frailty-related criteria were clustered in this first LV, such as unintended weight loss, self-reported exhaustion, low physical activity, and low hand grip strength (see Table 6.1 and Fig. 6.2), and these were associated with lower walking speed, and higher mean stride times, increased variability of stride times, and less consistent steps. The identified association between these frailty-related indicators and gait parameters is in line with previous research [15, 39]. Montero-Odasso *et al*. [15] suggested that frailty reflects a general deterioration in the neurophysiological system.

At the same time, gait can be considered as a complex task that is highly regulated by neurophysiological systems. Consequently, the decreased walking speed, increased stride variability, and worse step consistency that was seen in frail elderly and was found to be related with frailty-related parameters as found in the present study, may reflect the multisystem reduction in neurophysiological capacity.

Based on a previous literature review [8], we anticipated a strong association between the use of psychotropic drugs and gait performance. However, the association of the use of antiepileptics (N03A) and antidepressants (N06A) with impaired gait ability was moderate, while hardly any association with other psychotropic drug classes was observed. We suggest that the effect of the deterioration in physical functioning in the frailest elderly is so large, that the added impact of the side-effects of psychotropics on gait regulation is relatively small. What also may have contributed to the weak associations between gait performance and psychotropic drugs is that the dosages of drugs that were taken by our study population (see Appendix I) was much lower than reported in the aforementioned literature review [8]. This underpins the recommendation of Lader *et al*. [40] that psychotropic drugs – when administered – should only be prescribed at the lowest effective dose and for a restricted period of time to limit the side-effects of these drugs.

Beside the strong association between frailty-related characteristics and gait parameters, and the moderate association of psychotropic drugs with gait, in the present study also other medication classes were found to be associated with impaired gait ability. The use of laxatives (A06), agents acting on sensory organs (ATC-class S), and drugs for peptic ulcer and reflux disease (A02B) were strongly associated with lower walking speed and higher stride variability as was indicated by high VIP-values and regression coefficients (Fig. 6.1), and illustrated in the score and weight plots (Fig. 6.2). These medication-classes are among the most prescribed medications, and are much more commonly used in individuals with indicators of frailty. For instance, laxatives are used for constipation that, in turn, may be caused by inactivity (one of the indicators of frailty) or the use of constipation-associated medications (e.g., opioid analgesics) [41]. Therefore, these kind of drugs may act as frailty markers [42, 43].

The results of the present study correspond with a study of Askari *et al*. [43] who reported that besides known “fall-risk-increasing drugs”, such as analgesics (N02), anti-Parkinson drugs (N04) and psychoanaleptics (N06), also relatively new classes showed significant association with recurrent falls in elderly, namely nasal preparations (R01), ophthalmologicals (S01), and drugs for acid-related disorders (A02). Especially the finding that drugs for acid-related disorders were associated with recurrent falling and

increased stride variability is interesting, because these drugs are commonly used in our study population (see Appendix I) and in the older population in general [44]. Proton-pump inhibitors (PPIs; A02BC), a subclass of drugs for acid-related disorders (A02), have been associated with an increased risk of fractures [45]. It is assumed that PPIs reduce calcium absorption, possibly leading to reduced bone mineral density that would lead to increased fracture risk [46]. Another explanation could be that PPI-use may lead to muscle weakness and gait disorders [46]. This might explain our finding that these drugs were associated with impaired gait ability, and with recurrent falling as Askari *et al*. [43] found. However, further longitudinal research is necessary to confirm this suggestion.

Conclusion

In the present study, we found an association between frailty-related parameters and impaired walking ability, as was expressed by lower walking speed and increased stride variability. The absence of a strong association between the use of psychotropic drugs and gait parameters is in accordance to our hypothesis that results from studies in healthy and relatively young elderly cannot be extrapolated to a frail population, because comorbid diseases and the use of many medications are complicating factors in this population leading to multisystem reduction in the neurophysiological system. Therefore, in future studies among frail elderly we recommend to develop models which include frailty-related parameters.

Appendix I

Prevalence of the medications used by the study's participants and the dosage range.

ATC-code	Description	*n*	(%)	Dosage range	
A02A	*Antacids*	2	(3%)		
A02AA02	magnesium oxide	2	(3%)	724-1448	*mg*
A02B	*Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)*	31	(39%)		
A02BA02	ranitidine	3	(4%)	150-300	*mg*
A02BC01	omeprazole	12	(15%)	20-80	*mg*
A02BC02	pantoprazole	11	(14%)	20-40	*mg*
A02BC03	lansoprazole	1	(1%)	15	*mg*
A02BC04	rabeprazole	1	(1%)	20	*mg*
A02BC05	esomeprazole	3	(4%)	40-80	*mg*
A03	*Drugs for functional gastrointestinal disorders*	3	(4%)		
A03AA04	mebeverine	1	(1%)	400	*mg*
A03FA01	metoclopramide	1	(1%)	10	*mg*
A03FA03	domperidone	1	(1%)	30	*mg*
A06	*Drugs for constipation*	12	(15%)		
A06AC01	ispaghula (psylla seeds)	3	(4%)	1-3	*dose/day*
A06AD65	macrogol, combinations	9	(11%)	1-2	*mg*
A06AD11	lactulose	2	(3%)	15	*ml*
A07	*Antidiarrheals, intestinal antiinflammatory/antiinfective agents*	2	(3%)		
A07DA03	loperamide	1	(1%)	2	*mg*
A07EC02	mesalazine	1	(1%)	1000	*mg*
A09	*Digestives, incl enzymes*	1	(1%)		
A09AA02	multienzymes (lipase, protease, etc.)	1	(1%)	3	*dose/day*

A10	*Drugs used in diabetes*	11	(14%)		
A10AD05	insulin aspar	1	(1%)	32	*units*
A10BB01	glibenclamide	1	(1%)	7.5	*mg*
A10BB03	tolbutamide	2	(3%)	1000	*mg*
A10BB12	glimepiride	3	(4%)	0.5-2	*mg*
A10BD02	metformin and sulfonylureas	6	(8%)	1000-2550	*mg*
A11&A12	*Vitamins & mineral supplements*	25	(31%)		
A11BA	multivitamins, plain	4	(5%)		
A11CC03	alfacalcidol	3	(4%)	0.25	*µg*
A11CC05	colecalciferol	16	(20%)	400-880	*IE*
A11DA01	thiamine (vit B1)	2	(3%)	100	*mg*
A12AA02	calcium glubionate	1	(1%)	500	*mg*
A12AA04	calcium carbonate	15	(19%)	500	*mg*
B01	*Antithrombotic agents*	34	(43%)		
B01AA07	acenocoumarol	9	(11%)	1	*g*
B01AC04	clopidogrel	4	(5%)	75	*mg*
B01AC06	acetylsalicylic acid	3	(4%)	80	*mg*
B01AC07	dipyridamole	4	(5%)	200-400	*mg*
B01AC08	carbasalate calcium	22	(28%)	38-100	*mg*
B03	*Antianemic preparations*	4	(5%)		
B03AA02	ferrous fumarate	1	(1%)	600	
B03AA07	ferrous sulfate	1	(1%)	325	*mg*
B03BA03	hydroxocobalamin	1	(1%)	1	*dose/day*
B03BB01	folic acid	3	(4%)	5	*mg*
*C01AA05**	*Digoxin*	4	(5%)		
C01AA05	digoxin	4	(5%)	0.0625-0.25	*mg*
C01B	*Antiarrhythmics (class I and III), excl. type IA*	2	(3%)		
C01BC04	flecainide	2	(3%)	100	*mg*

Appendix I. *Continued*

ATC-code	Description	*n*	(%)	Dosage range	
*C01BA**	*Type IA antiarrhythmics**	0	(0%)		
C01D	*Vasodilators used in cardiac diseases*	10	(13%)		
C01DA02	glyceryl trinitrate	2	(3%)		
C01DA08	isosorbide dinitrate	2	(3%)	2.5-5	*mg*
C01DA14	isosorbide mononitraat	8	(10%)	30-100	*mg*
C01DX16	nicorandil	1	(1%)	10	*mg*
C01E	*Other cardiac preparations*	2	(3%)		
C01EB17	ivabradine	2	(3%)	10-70	*mg*
*C03**	*Diuretics*	30	(38%)		
C03AA03	hydrochlorothiazide	17	(21%)	12.5-25	*mg*
C03BA04	chlortalidone	1	(1%)	12.5	*mg*
C03CA01	furosemide	8	(10%)	20-40	*mg*
C03CA02	bumetanide	2	(3%)	1	*mg*
C03DA01	spironolactone	4	(5%)	25-50	*mg*
C03DB02	triamterene	6	(8%)	50	*mg*
C03EA03	epitizide and potassium-sparing agents	2	(3%)	4	*mg*
C07	*Beta blocking agents*	25	(31%)		
C07AA07	sotalol	1	(1%)	240	*mg*
C07AB02	metoprolol	21	(26%)	25-200	*mg*
C07AB03	atenolol	2	(3%)	25-100	*mg*
C07AB04	acebutolol	1	(1%)	100	*mg*
C07AG02	carvedilol	1	(1%)	12.5	*mg*
C08	*Calcium channel blockers*	13	(16%)		
C08CA01	amlodipine	7	(9%)	5-10	*mg*
C08CA02	felodipine	1	(1%)	5	*mg*

C08CA05	nifedipine	4	(5%)	30-240	*mg*
C08DA01	verapamil	1	(1%)	120	*mg*
C09	*Agents acting on the renin-angiotensin system*	31	(39%)		
C09AA02	enalapril	5	(6%)	5-40	*mg*
C09AA03	lisinopril	5	(6%)	10-20	*mg*
C09AA04	perindopril	7	(9%)	2-8	*mg*
C09AA06	quinapril	1	(1%)	20	*mg*
C09CA01	losartan	4	(5%)	50-100	*mg*
C09CA03	valsartan	1	(1%)	80	*mg*
C09CA04	irbesartan	4	(5%)	150-300	*mg*
C09CA06	candesartan	4	(5%)	16-20	*mg*
C10	*Lipid modifying agents*	38	(48%)		
C10AA01	simvastatin	26	(33%)	10-40	*mg*
C10AA03	pravastatin	4	(5%)	20-40	*mg*
C10AA04	fluvastatin	1	(1%)	80	*mg*
C10AA05	atorvastatin	4	(5%)	20-40	*mg*
C10AA07	rosuvastatin	2	(3%)	5-40	*mg*
C10AB04	gemfibrozil	1	(1%)	1200	*mg*
C10AX09	ezetimibe	1	(1%)	10	*mg*
D	*Antifungals for dermatological use*	1	(1%)		
D02AB	zink products	1	(1%)	1	
G	*Genito urinary system and sex hormones*	11	(14%)		
G01AF04	miconazole	1	(1%)	1	*dose/day*
G01AF15	butoconazole	1	(1%)		
G03CA04	estriol	2	(3%)	0.5	*mg*
G03HA01	cyproterone	1	(1%)	50	*mg*
G04BD08	solifenacin	2	(3%)	5	*mg*
G04BD10	darifenacin	1	(1%)	7.5	*mg*
G04CA01	alfuzosin	1	(1%)	10	*mg*

Appendix I. *Continued*

ATC-code	Description	*n*	(%)	Dosage range	
G04CA02	tamsulosin	5	(6%)	0.4-0.5	*mg*
G04CB01	finasteride	1	(1%)	5	*mg*
G04CB02	dutasteride	2	(3%)	0.4-0.5	*mg*
H	*Systemic hormonal preprarations, excl. Sex hormones and insulins*	5	(6%)		
H03AA01	levothyroxine sodium	5	(6%)	50-150	*µg*
J	*Antiinfectives for systemic use*	4	(5%)		
J01XE01	nitrofurantoin	3	(4%)	50-100	*mg*
J04BA02	dapsone	1	(1%)	100	*mg*
L	*Antineoplastic and immunomodulating agents*	1	(1%)		
L01BC02	fluorouracil	1	(1%)		
M	*Musculo-skeletal system*	10	(13%)		
M04AA01	allopurinol	4	(5%)	100-200	*mg*
M01AB05	diclofenac	1	(1%)	100	*mg*
M05BA04	alendronic acid	4	(5%)	70	*mg/week*
M05BA06	ibandronic acid	1	(1%)	150	*mg/month*
M09AA01	hydroquinine	2	(3%)	200	*mg*
N02	*Analgesics (no paracetamol)*	5	(6%)		
N02AX02	tramadol	2	(3%)	37.5-50	*mg*
N02BA01	acetylsalicylic acid	3	(4%)	80	*mg*
N02BE	*Paracetamol/acetaminophen*	9	(11%)		
N02BE01	buspirone	5	(6%)	500-1500	*mg*
N02BE51	paracetamol, combinations excl. psycholeptics	1	(1%)	65	*mg*
N02BE71	paracetamol, combinations with psycholeptics	3	(4%)	10-30	*mg*

*N03A**	*Antiepileptics*	6	(8%)		
N03AE01	clonazepam	2	(3%)	0.5-1	*mg*
N03AF01	carbamazepine	1	(1%)	400	*mg*
N03AG01	valproic acid	2	(3%)	600-1600	*mg*
N03AX12	gabapentin	1	(1%)	600	*mg*
N03AX16	pregabalin	1	(1%)	150	*mg*
*N05A**	*Antipsychotics*	2	(3%)		
N05AD01	haloperidol	1	(1%)	1	*mg*
N05AX12	aripiprazole	1	(1%)	5	*mg*
*N05BA**	*Anxiolytics (benzodiazepine-derivatives)*	8	(10%)		
N05BA01	diazepam	1	(1%)	6	*mg*
N05BA04	oxazepam	5	(6%)	10-30	*mg*
N05BA12	alprazolam	1	(1%)	1.5	*mg*
N05BAXX	mexazolam	1	(1%)	0.5	*mg*
N05C	*Other hypnotics, excl. benzodiazepine-derivatives*	7	(9%)		
N05CH01	melatonin	3	(4%)	1-2	*mg*
N05CM09	valerianae radix	3	(4%)	45-350	*mg*
N05CX04	clomethiazole, combinations	1	(1%)	20	*mg*
*N05CD**	*Hypnotics & sedatives (benzodiazepine-derivatives)*	5	(6%)		
N05CD02	nitrazepam	1	(1%)	2.5	*mg*
N05CD07	temazepam	3	(4%)	5-10	*mg*
N05CF01	zopiclone	1	(1%)	7.5	*mg*
*N06A**	*Antidepressants*	12	(15%)		
N06AB04	citalopram	3	(4%)	20	*mg*
N06AB05	paroxetine	2	(3%)	20	*mg*
N06AB06	sertraline	2	(3%)	50-100	*mg*
N06AX11	mirtazapine	3	(4%)	30-45	*mg*
N06AX16	venlafaxine	2	(3%	75-450	*mg*

Appendix I. *Continued*

ATC-code	Description	*n*	(%)	Dosage range	
N07	*Other nervous system drugs*	2	(3%)		
N07CA01	betahistine	2	(3%)	8-16	*mg*
R	*Respiratory system*	13	(16%)		
R01AD08	fluticasone	2	(3%)	100	*µg*
R03AC13	formoterol	3	(4%)	200-400	*mg*
R03AK06	salmeterol and fluticason	4	(5%)	1-2	*dose/day*
R03AL01	fenoterol and ipratropium bromide	1	(1%)	4	*dose/day*
R03BA02	budesonide	4	(5%)	2-12	*mg*
R03BB04	tiotropium bromide	7	(9%)	1	*dose/day*
R05CB01	acetylcysteine	1	(1%)	1200	*mg*
R06AE09	levocetirizine	1	(1%)	5	*mg*
R06AX15	mebhydrolin	1	(1%)	1	*dose/day*
R06AX27	desloratadine	2	(3%)	5	*mg*
S	*Sensory organs*	8	(10%)		
S01ED02	betaxolol	1	(1%)	1	*dose/day*
S01ED51	timolol, combinations	1	(1%)	1	*dose/day*
S01EE04	travoprost	2	(3%)	1	*dose/day*
S01XA20	artificial tears and other indifferent preparations	4	(5%)	1	*dose/day*
S02CA03	hydrocortisone and antiinfectives	1	(1%)	1	*dose/day*

Appendix II

Detailed mathematical description of the PLS regression analysis

PLS – Analysis [23, 28, 36]

The *X* and *Y*-matrices represent respectively, the independent variables (population characteristics, co-morbidities and medication-use) and the dependent variables (gait parameters):

$$X = \begin{pmatrix} x_{11} & \cdots & x_{1j} \\ \vdots & \ddots & \vdots \\ x_{i1} & \cdots & x_{ij} \end{pmatrix} \qquad Y = \begin{pmatrix} y_{11} & \cdots & y_{1j} \\ \vdots & \ddots & \vdots \\ y_{i1} & \cdots & y_{ij} \end{pmatrix} \qquad (1)$$

with *i* is the i^{th} participant and *j* the j^{th} variable. The relationship between the *X* and *Y* is defined by the function *F*: $Y = F * X + e$, where *F* is modelled with the PLS analysis.

Number of latent variables (LVs) based the goodness of prediction (Q2)

$$Q2_k = 1 - \frac{PRESS_k}{RSS_{k-1}} \qquad (2)$$

$$PRESS = \sum\left(y_{k-1,m} - \hat{y}_{k-1,-m}\right)^2 \qquad (3)$$

where *PRESS* is the predictive sum of squares of the model containing *k* components and *RSS* is the residual sum of squares of the model. The *PRESS* depends on the $y_{k-1,m}$ the residual of observation *m* when *k*–1 components are fitted in the model and $\hat{y}_{k-1,-m}$ the predicted *y* when the latest observation of *m* is removed. When Q2 decreases after reaching a plateau, this is considered the optimal number of latent variables.

Goodness of fit

The R2 explains how well the model fits the data and is defined by te residual sum of squares (RSS) of the k^{th} LV and the total sum of squares (TSS):

$$R2_k = 1 - \frac{RSS_k}{TSS} \qquad (4)$$

The scores

Scores of the PLS reflect the individual participants contribution/position on the LVs as follows:

$$X = T * P' + xres \text{ and } Y = U * Q' + yres \qquad (5)$$

X represents the independent variables (population characteristics, co-morbidities and medication-use), with *T* are the *X*-scores, *P* the *X*-loadings, *U* the Y-scores, and *Q* as *Y*-loadings.

X-weights (W)

Weights describe the importance of the variables on the model for individual latent factors, if they are for all identified LVs near zero than they add little to the model.
Weights are defined by the *X*-loadings (*P*) and the matrix of weights from the model (see eq. 6). They represent the correlation between the *X*-variables and *U*, whereas *Q* represents the correlation between the *Y*-variables and *T* (see eq. 5). Note that the *X*-loadings *P* and the *X*-weights *W* are very similar.

$$W^* = (P * w)^{-1} \qquad (6)$$

The Variable Importance of Projection (VIP)

The VIP-values are based on the explained sum of squares and the weights as follow:

$$VIP_j = \sqrt{p \sum_{k=1}^{N} \left[SS_k \left(w_{kj}/\|w_k\|^2\right)\right] / \sum_{k=1}^{N} (SS)_k} \qquad (7)$$

with SS_k is the explained sum of squares of the k^{th} LV, *N* the number of LVs in the model. The VIP_j weights w_{kj} quantify the contribution of each variable *j* according to the variance explained by each k^{th} LV.

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PART III

CLASSIFICATION OF FALLERS

CHAPTER 7

Gait dynamics to optimize fall risk assessment in geriatric patients

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Abstract

The development of interventions that aim to decrease fall risk in old adults requires knowledge about modifiable fall risk factors. Fall prediction in geriatric patients remains challenging because the increased fall risk in this population involves multiple, interrelated factors caused by natural age and/or pathology. Therefore, we used a multi-factorial statistical approach to model categories of modifiable fall risk factors among geriatric patients to identify fallers with highest sensitivity and specificity. We particularly focused on gait performance. Sixty-one patients (mean age 79 ± 5.0; 41% fallers) underwent extensive screening in three categories: (1) patient characteristics (e.g., handgrip strength, medication use, osteoporosis-related factors), (2) cognitive function (global cognition, memory, executive function), and (3) gait performance (speed-related and dynamic outcomes assessed by tri-axial trunk accelerometry). Falls were registered prospectively (mean follow-up 8.6 months) and one year retrospectively. Principal Component Analysis (PCA) on 11 gait variables was performed to determine underlying gait properties. Three fall-classification models were then built using Partial Least Squares–Discriminant Analysis (PLS-DA), with separate and combined analyses of the fall risk factors. PCA identified 'pace', 'variability', and 'coordination' as key properties of gait. The best PLS-DA model produced a fall classification accuracy of AUC=0.93. The specificity of the model using patient characteristics was 60% but reached 80% when cognitive and gait outcomes were added. The inclusion of cognition and gait dynamics in fall classification models reduced misclassification. We therefore recommend assessing geriatric patients' fall risk using a multi-factorial approach that incorporates patient characteristics, cognition, and gait dynamics.

Introduction

Approximately 30% of all old adults aged 65 or older experience a fall at least once a year. Falls are associated with pain, functional impairments, morbidity, devastating psychological impacts, and even mortality [1]. Preventing falls therefore remains a health care priority and early identification of individuals at risk is the first step in fall prevention. Older compared with younger adults are more likely to fall due to age-related declines in sensory, cognitive, and neuromuscular function, leading to an impaired gait [2]. Consequently, impaired gait and balance, in addition to personal characteristics (e.g., gender, age, anthropometry, polypharmacy), are related to falls in community dwelling adults [3].

Age-related slowing of gait is the most documented gait outcome, with habitual gait speed slowing by 16% per decade after age 60 [4–6]. A gait speed below 1.0 m/s signifies potential clinical or sub-clinical impairment, such as mobility impairments, recurrent falling, loss of independence and institutionalization [4]. In addition to gait speed, a variety of measures can quantify the dynamic nature (time dependent variations in time) of gait, such as detrended fluctuation analysis [7], sample entropy [8], and index of harmonicity [9]. Each of these gait dynamics reflect a unique characteristic of gait (e.g. speed, coordination, variability) and can be considered as complementary to each other. However, some gait measures are not independent but inter-related [10]. For instance, the coefficient of variation of stride time increases when gait speed decreases [11]. Factor analysis takes these inter-relations into account and reduces the dimensionality of the gait data by identifying underlying clusters of gait characteristics [12–15].

With respect to falling, prediction models become more accurate when characteristics of gait are included [16, 17]. For example, gait smoothness prospectively discriminated fallers from non-fallers in community dwelling old adults with a sensitivity of 68.8 % and a specificity of 84.2% [17]. In addition, the accuracy of fall prediction models based on clinical tests commonly used in fall risk assessments such as questionnaires, handgrip strength, and neuropsychological tests, increased by 0.14 when comprehensive gait analysis was added (AUC from 0.68 to 0.82, sensitivity: 70%; specificity: 81% [16]).

The accuracy of fall prediction models may be population-dependent and may not be generalizable to patients admitted to geriatric outpatient clinics. Geriatric patients do not only walk slower than the clinical threshold of 1.0 m/s [4, 18], but pathological conditions also modify gait dynamics. For example, 50% of geriatric patients use polypharmacy, which increases the risk for falls [19, 20]. Also, nearly 50% of geriatric

patients suffer from osteoporotic vertebral fractures, a condition associated with an increase in thoracic kyphosis, decrease in gait stability, and increased fall risk [21, 22]. Moreover, up to 30% of geriatric patients above age 60 present with sarcopenia, which is also associated with gait slowing and an increased fall risk [23]. Finally, the prevalence of cognitive impairment ranges from 22-71% in old adults above age 65 [24] and contributes to slow gait, increased gait variability, decreased gait stability, and increased fall risk [25].

Geriatric patients can thus be characterized by a unique set of variables that increases their risk for a fall. Hence, one approach to identify fallers is by grouping fall risk factors into categories, e.g., personal characteristics typically assessed in clinical practice, cognitive function, as well as gait performance, and apply multi-factorial data analysis. Such an approach would allow us to examine the role of each factor in fall risk. Subsequently, it facilitates the development of personalized interventions strategies to modify for example medication [20], cognition [26], and physical activity levels [6]. The present study therefore aims to statistically model categories of fall risk factors that identify geriatric fallers with the highest sensitivity and specificity, with a focus on gait characteristics. To this aim, we pursued two complementary objectives: (1) to identify unique gait properties by extracting the underlying clusters of 11 gait measures and remove redundancies in these measures using factor analysis; and (2) to examine if the sensitivity and specificity of a fall risk model improves when adding first cognitive measures to personal characteristics, and adding thereafter the gait factors identified by factors analysis. We hypothesized that different gait measures sum into the key properties of gait, related to speed and dynamics. With respect to the second aim, we expected an increase in either sensitivity or specificity of fall classification when gait factors are added to the statistical model.

Materials and methods

Study population

The present study included 61 patients (41 women and 20 men) of a database of patients that visited the geriatric day clinic of the MC Slotervaart Hospital, Amsterdam between 2011 and 2013 [21, 27, 28]. Patients were admitted to the day clinic based on a medical referral by a general practitioner and underwent extensive screening for physical, psychological, and cognitive functions. Inclusion criteria were: age 70 or older. Exclusion criteria were: (1) Inability to walk for at least three minutes without a walking aid, (2) inability to speak fluently Dutch, and (3) having mobility disability caused by neurological

or orthopedic conditions, limiting function in one or both legs. The Medical Ethical Committee of the MC Slotervaart Hospital approved the study protocol. Written informed consent was obtained from all participants or their legal representatives.

Outcome measures

Determination of fall status

A fall was defined as unintentionally coming to rest on the ground, floor, or other lower level. Patients were interviewed retrospectively about the number of falls over the past year. Also, falls were prospectively registered with a 'fall calendar', for which patients were contacted monthly up to 12 months follow-up, with a minimum of 6 months. For patients with an MMSE-score below 24, fall history was obtained from a caregiver. A patient was classified as 'faller' when one or more falls occurred retrospectively or prospectively.

Patient characteristics

Demographic information including age, gender, and body mass index (BMI) were recorded. Maximal grip strength of the dominant hand [29], was quantified with a Jamar hand-held dynamometer (average of 3 trials). The amount of comorbidities was categorized with the Charlson Comorbidity Index (CCI) [30]. Medications were classified according to the Anatomical Therapeutic Chemical (ACT) codes [31] and quantified as the total number of 'Fall Risk Increasing Drugs' (FRIDs), including psychotropic and diuretic drugs [20]. Lateral X-rays of the thoracic spine were analyzed to determine the degree of thoracic kyphosis, indicated by the Cobb angle between the superior endplate of the second thoracic vertebra and the inferior endplate of the twelfth thoracic vertebra [21]. Finally, fall risk was assessed according to the Longitudinal Aging Study Amsterdam (LASA) fall risk profile [32].

Cognitive function

Global cognition was assessed with the Mini Mental State Examination (MMSE) with scores below 24 denoting cognitive impairment [33]. The 7-minute screen [34] was administered to assess memory and executive function using the Benton's Temporal Orientation (BTO), the Enhanced Cued Recall (ECR), the animal verbal fluency and the clock drawing test.

Gait performance

All patients walked 160 meters at habitual speed on an 80-meter long hallway. A tri-axial accelerometer (87x45x14 mm; sample frequency 100 Hz; Dynaport® MiniMod, McRoberts BV, The Hague, the Netherlands) was attached to the lower back at the level of the third lumbar spine segment to measure medio-lateral (ML) and anterior-posterior (AP) trunk accelerations. Acceleration signals were analyzed with custom-made software in MATLAB (version 2014b; The MathWorks, Inc). The signals were corrected for horizontal tilt and low-pass filtered with a 2nd order Butterworth filter with a cut-off frequency of 15 Hz. Outliers due to turns were removed from the data using a median filter. Walking speed was calculated by dividing distance walked by the time.

Peak accelerations from AP signals were used to detect time indices of left and right foot contacts. Mean and coefficient of variation (CV) of stride times were computed from the time interval between two consecutive ipsilateral foot contacts. Step consistency was quantified by the standard deviation (SD) of the relative phase between sequential ipsilateral indices of foot contact [35]. Higher SD of the relative phase implies a more inconsistent gait pattern. Long-range correlations between strides were quantified by the scaling exponent α using detrended fluctuation analysis [7]. A value of $0.5 \geq \alpha \geq 1$ suggests the presence of long-range correlations and signifies that future fluctuations in strides are more accurately predicted by previous fluctuations.

The Root Mean Square (RMS) of the AP and ML acceleration quantified the variability in the magnitude of the trunk accelerations. The Index of Harmonicity (IH) was computed to examine the smoothness (frequency content) of the signal, using spectral analysis. Perfect smooth trunk accelerations would reveal an IH of 1 [9]. To quantify the degree of predictability of trunk acceleration time series, the Sample Entropy (SEn) was calculated [36]. A complete predictable (periodic) signal will adopt a SEn of 0, with a larger SEn representing a less predictable gait.

Statistical analysis

Principal Component Analysis (PCA) with a Varimax rotation and Kaiser normalization was performed on the 11 gait variables to determine underlying gait properties, and to reduce the dimensionality of the data to unique factors. The number of extracted principal components (PC's) was determined by analyzing the scree plot which reveals the percentage explained variance by each component. PC's with eigenvalues larger than 1 were considered eligible for inclusion in the final model. The regression coefficients of the extracted PC's were then used for further analyses [13].

To examine the contribution of different fall risk factors, three Partial Least Squares Discriminant Analyses (PLS-DA) were performed using the PLS_toolbox for MatLab (version 3.7.1; Eigenvector Research Inc.). PLS-DA combines PCA and regression analysis and can handle data consisting of a large number of independent, highly collinear, inter-related variables with relatively few observations (subjects) [37]. In the PLS-DA analyses, patient characteristics, cognitive and gait measures represented the independent variables (X), and fall-status the categorical, dependent variable (Y). The analysis seeks to find underlying latent variables (LV's) to investigate fundamental relations between the matrices X and Y by modelling the covariance structures in these two spaces. All variables were normalized to unit variance. The optimal number of LV's was determined using the scree plot and defined at the level where a plateau phase in the goodness of prediction (Q^2) was reached [37].

Three models were developed based on: (1) only patient characteristics, (2) patient characteristics and cognitive function, and (3) patient characteristics, cognitive function, and the regression coefficients derived from the factor analysis; the gait factors. Outcome measures of the PLS-DA included scores (individual patients observations) and weights (contribution of fall risk factors to the model), quantifying the relationship between fall risk factors and fall status. The variance explained reflected how variables are clustered within each LV. Classification accuracy of the models was quantified as sensitivity, specificity, and area under the curve (AUC), and visualized with receiving operating characteristic (ROC) curves, with an AUC of 1 representing a perfect fit.

Results

Patient characteristics

Fallers (mean age 80.2 ± 4.7) compared to non-fallers (78.8 ± 5.1) presented with a lower handgrip strength (23.7 ± 8.0 versus 27.2 ± 8.8), the same number of FRIDS (1.3 ± 1.2 versus 1.3 ± 1.4), and a comparable CCI (1.6 ± 1.4 versus 1.3 ± 1.2), BMI (27.7 ± 4.2 versus 26.0 ± 3.5), and Cobb angle (52 ± 14 versus 50 ± 13). Fallers scored higher on the LASA risk profile (8.0 ± 1.2 versus 2.4 ± 0.4).

Falls

Retrospective fall data was registered from all 61 patients during the interview. From six patients, follow-up fall calendar data was obtained for less than 6 months, because patients changed address, or withdrawn from participation and did not want to be

contacted any longer. The mean follow-up duration was 8.6 months. Twenty-five patients were classified as fallers (41%); 18 retrospective fallers, 19 prospective fallers, and 12 patients fell during the last year as well as during follow-up.

Gait Analysis

Three PC's with eigenvalues >1 and absolute factor loadings >0.4 explained 67.50% of the total variance of the 11 gait measures. PC1 reflected measures related to gait speed, stride times, and the amplitude of trunk accelerations and was labeled 'pace'. PC2 and PC3 represented measures related to gait variability and coordination respectively, and were labeled 'variability' and 'coordination' (Table 7.1). These three identified gait components were then used for the PLS-DA analyses below.

Table 7.1. Loadings of the gait variables (eigenvalue >1 and absolute loadings > 0.4) as revealed by PCA with Varimax Rotation.

Gait measures	Pace	Variability	Coordination
Walking Speed	-.848		
Root Mean Square AP	-.844		
Root Mean Square ML	-.820		
Index of Harmonicity ML	.791		
Stride Time	.748		
CV Stride Time	.583	.435	
Step Consistency		.781	
Long range correlations		-.774	
Sample Entropy AP		.677	
Sample Entropy ML			.850
Index of Harmonicity AP			.512

CV = Coefficient of Variation; **AP** = Anterior-Posterior; **ML** = Medio-Lateral

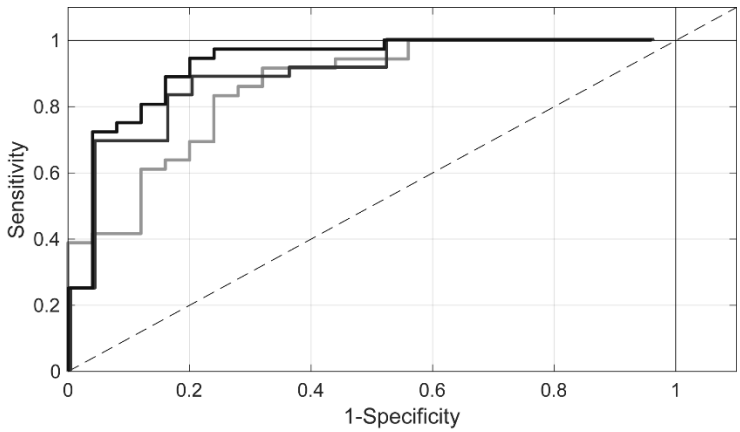
The PLS-DA models

Table 7.2 and Fig. 7.1 show the results of the three PLS-DA models. Model 1 and 2 included three LV's, and five LV's were extracted for model 3. Note that in all models, LV1 explains most of the variance in the independent variables (X) and falls (Y), followed by LV2 and by LV3, but based on the Q^2 criteria, five LV's were included. Classification accuracy of the first model with patient characteristics increased from 0.86 to 0.90 (AUC) when cognitive measures were added. Model accuracy further increased from 0.90 to 0.93 (AUC) when the principal gait components derived were subsequently added. In particular specificity increased in the second model from 60% to 72% and reached 80% when gait measures were included.

Table 7.2. Characteristics of the three PLS-DA models: Number of latent variables, variance explained in X (fall risk factors) and Y (fall-status), and classification accuracy of fallers and non-fallers

Model	Factors included	Number of LV's		X-block (%)	Y-block (%)	Sensitivity (%)	Specificity (%)	AUC
1	Patient characteristics	3	LV1	23.7	32.5	92	60	0.86
			LV2	15.0	6.5			
			LV3	15.9	0.7			
			Sum	**54.5**	**39.7**			
2	Patient characteristics + cognition	3	LV1	15.1	34.5	89	72	0.90
			LV2	13.1	9.5			
			LV3	20.5	2.1			
			Sum	**48.7**	**46.1**			
3	Patient characteristics + cognition + gait	5	LV1	31.8	33.6	92	80	0.93
			LV2	7.8	13.5			
			LV3	18.4	1.3			
			LV4	7.5	1.4			
			LV5	5.3	0.8			
			Sum	**52.4**	**50.7**			

LV = Latent Variable; **AUC** = Area Under the Curve



Model 1 (light gray) = Patient characteristics;
Model 2 (medium gray) = Patient characteristics + cognitive outcomes;
Model 3 (dark gray) = Patient characteristics + cognitive outcomes + gait outcomes.

Fig 7.1. Receiving Operating Characteristic - curves for the three fall classification models.

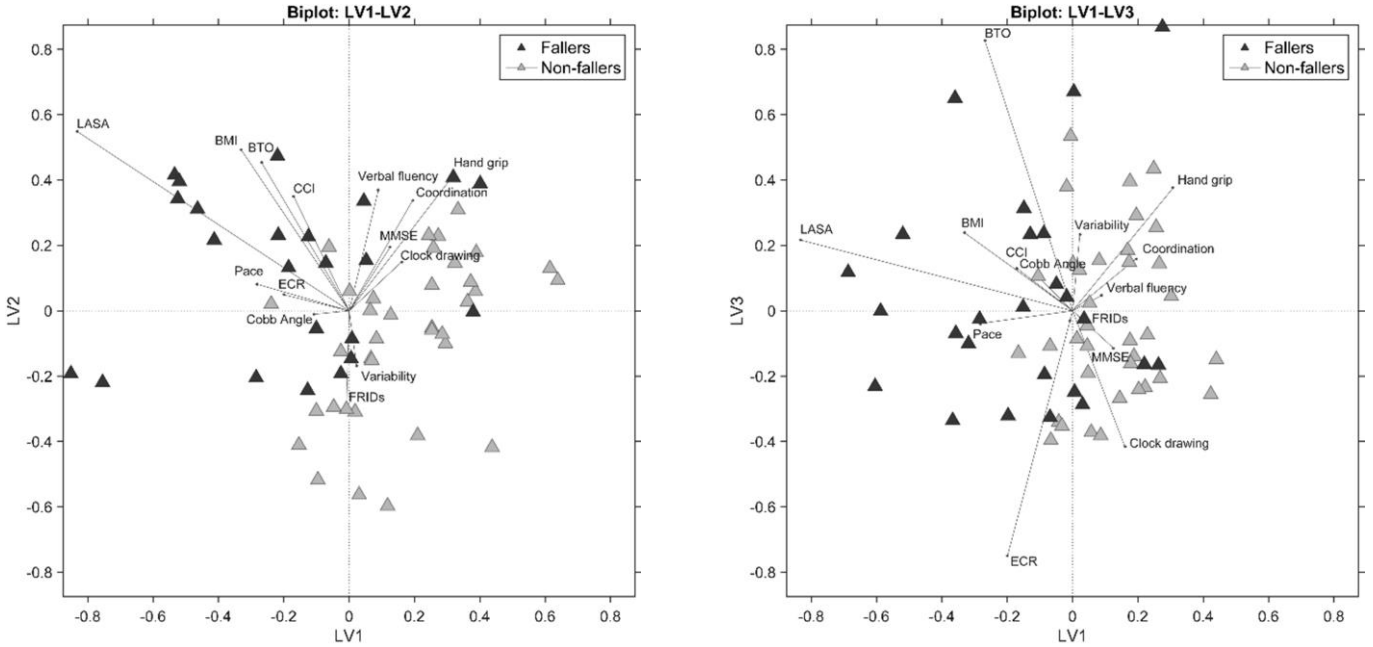
Table 7.3 presents the amount of explained variance per independent variable of each included LV of the final model (model 3). The results signify that X-variables are clustered within the LV's. Motor performance and the LASA were mainly presented in LV1, cognitive function in LV2 and LV3, and patient characteristics in LV4 and LV5.

Biplots of the final model provide a graphical representation of the Y-variable (falls) and weights of the X-variables (patient characteristics, cognitive outcomes, and gait outcomes) with respect to the LV's (Fig. 7.2). Fallers and non-fallers present in sharply separated clusters. The coordinates (size) of the weight vectors reflect the importance of the X-variable to the LV's. In this figure, the direction of the vectors reflects how these X-variables relate to fallers or non-fallers. The weights show that LASA, BTO, BMI and gait pace are particularly relevant in the identification of fallers, whereas handgrip, clock drawing, verbal fluency, gait variability, and gait coordination are relevant in the identification of non-fallers.

Table 7.3. Explained variance (%) per independent variable of the 5 extracted Latent Variables in model 3.

Independent variable	LV1	LV2	LV3	LV4	LV5	Sum
Gait						
Gait Pace	12.2	0.0	6.0	2.2	1.0	22.2
Gait Variability	0.3	5.9	5.5	7.2	2.1	21.0
Gait Coordination	20.4	13.3	1.3	0.4	3.6	39.0
Cognition						
Mini Mental State Examination (MMSE)	7.7	0.5	58.7	7.5	4.6	86.6
Benton's Temporal Orientation (BTO) test	1.7	0.5	58.7	0.5	1.3	62.7
Enhanced Cued Recall (ECR) test	6.3	5.5	53.4	0.1	4.8	70.0
Clock Drawing test	9.1	12.9	21.7	0.7	8.5	52.0
Verbal Fluency test	10.4	15.5	28.1	16.1	0.1	70.3
Patient characteristics						
Fall Risk Increasing Drugs (FRIDs)	2.8	8.2	2.3	18.4	4.5	36.2
Charlson Comorbidity Index (CCI)	0.2	6.0	9.0	21.1	0.0	36.4
Body Mass Index (BMI)	3.8	8.3	4.1	28.9	26.4	71.5
Longitudinal Aging Study Amsterdam (LASA)	74.4	2.4	0.7	1.4	5.6	84.5
Handgrip	40.9	15.6	8.9	0.2	0.6	66.2
Cobb Angle	2.5	0.8	0.0	0.0	10.6	13.9

LV = Latent Variable



BMI = Body Mass Index; **CCI** = Charlson Comorbidity Index; **LASA** = Longitudinal Aging Study Amsterdam; **FRIDs** = Fall Risk Increasing Drugs; **MMSE** = Mini Mental State Examination; **BTO** = Benton Temporal Orientation; **ECR** = Enhanced Cued Recall.

Fig 7.2. Biplots of Latent Variables (LV's) 1 vs. 2 (left) and LV's 1 vs. 3 (right) provide a graphical representation of the response variable (fall-status) and weights of the independent variables (patient characteristics, cognitive, and gait factors) with respect to the included LV's. As clearly shown, fallers and non-fallers (dark and light gray respectively) are clustered. Weight vector size reflects the importance of the variable to the model. The direction of the vector refers to whether variables mainly relate to classification of fallers (sensitivity) or non-fallers (specificity).

Discussion

We applied a factor analysis to speed-related and dynamic gait measures and we then statistically modeled combinations of factors that classified geriatric fallers with the highest sensitivity and specificity. The factor analysis identified pace, variability, and coordination as key properties of gait. A model that included patient characteristics, cognitive function, as well as gait performance produced high classification accuracy (AUC=0.93) and showed an increase in specificity from 60% to 80% compared to a model that only included patient characteristics. We discuss how successful fall risk assessment in the future will most likely include a large array of variables to optimize geriatric patients' fall prediction.

First, PCA applied to 11 gait variables revealed three unique gait properties: pace, variability, and coordination. 'Pace' comprised speed-related measures, namely gait speed, stride time, and the amplitude of AP and ML accelerations (RMS). 'Variability' and 'coordination' are considered as gait properties that reflect the dynamics of gait and were mainly derived from trunk accelerations. The loading structure was consistent, except for the IH in ML direction, which loaded on the pace component (absolute loading: 0.791) while it was expected to load on the coordination component. This might imply that IH ML is related to gait speed. In general, the extracted components were comparable with components identified by previous studies [12–15].

Second, three PLS-DA models were generated and compared (Table 7.2 and Fig 7.1). The first model based on patient characteristics already achieved high classification accuracy (AUC=0.86). LASA clearly outperformed the other variables, as indicated by the size of the weight vectors. LASA provides an extensive screening tool consisting of nine fall-related factors such as dizziness, fear of falling, alcohol intake, fall history, and education level [32]. Although sensitivity of this first model was quite high (80%), specificity remained relatively low (60%). A low specificity (i.e., true negative rate) hampers clinical application because non-fallers will be erroneously identified as fallers and such misclassifications may induce fear of falling and unnecessary interventions.

Adding cognitive measures to the model increased specificity by 12%, reaching a value of 72% (Table 7.2). Age-related decline in gait and cognition co-occurs because brain areas that control gait partly overlap with brain areas that control cognitive function [2]. Gait dysfunction can thus be expected in the presence of cognitive impairment [25, 38] and an impaired gait control in turn increases fall risk. On the other hand, old adults rely on executive functions in daily activities that require divided

attention (e.g., in traffic and walking while talking). Impairment in executive functions may thus cause dangerous situations and increase fall risk.

Adding gait outcomes to the model further increased the models' specificity by 8%, reaching a value of 80% (Table 7.2). Progressive age-related deterioration in neuromuscular and neurophysiological function engenders decline in sensory systems, sarcopenia, slower movement time and central processing, all linked to deficits in gait and balance [39]. In particular gait components 'variability' and 'coordination' accounted for the increase in specificity, as indicated by the size and direction of the corresponding vectors towards non-fallers (high specificity). These results support the idea that speed-related measures (captured by the pace domain) may be sufficient for classifying fallers. They do, however, lack specificity that could result in misclassification of non-fallers. Gait speed is widely recognized as an important variable associated with many clinical conditions later in life [4]. The results of the present study show that combining gait speed and speed-related measures with dynamic gait measures will increase specificity and thus classification accuracy. Hence, gait dynamics could easily be added to measures usually addressed in clinical practice. Such gait dynamics can be obtained by clinicians in about 10 minutes. Nowadays, extensive gait analysis is more easily accessible for clinical practice due to the rapid development of off-the-shelf smartphones, iPods and similar smart devices. Equipped with built-in accelerometers and gyroscopes, the devices are light, inexpensive, easy to handle, and thus suitable to analyze gait in a clinic [40].

In conclusion, geriatric patients represent a vulnerable population with an increased risk for falling. Fall risk assessment including modifiable fall risk factors revealed high classification accuracy (AUC = 0.93). Although patient characteristics can accurately identify fallers, the evaluation of executive function and gait dynamics reduced misclassification with an increase in specificity from 60% to 80%. Therefore, we underscore the need for a multifactorial approach in fall risk assessment in geriatric patients, including a comprehensive evaluation of patient characteristics, cognitive function, and gait performance. These fall risk factors should ultimately be targeted by individualized interventions to reduce fall risk.

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DISCUSSION

CHAPTER 8

Conclusions & Future Perspectives

Conclusions and perspectives

The studies described in this thesis investigated the association between common geriatric phenomena (e.g., osteoporosis, medication-use, frailty and cognitive impairment) with postural control during walking in older patients visiting a geriatric outpatient clinic. This provided insight into the interplay between these geriatric phenomena and different properties of the gait pattern. This chapter will discuss the main results and conclusions from this thesis and suggests future perspectives for clinical practice and subsequent research.

Part I: Osteoporosis-related factors

Osteoporosis is frequently present in older patients [1], and might in time cause vertebral fractures, which could lead to a flexed posture, and consequently to impaired postural control and an increased risk of falling. In the first part of this thesis, this assumption was studied by investigating (1) the relationship between osteoporosis, vertebral fractures, increased thoracic kyphosis and a flexed posture, then (2) the association between these osteoporosis-related factors and postural control, and finally (3) the risk of falling in osteoporotic patients.

Relationship between osteoporosis, vertebral fractures, increased thoracic kyphosis and flexed posture

Osteoporosis is characterized a by low bone mass leading to enhanced bone fragility and an increased risk of fractures [2, 3]. Fractures of the vertebrae are typical osteoporotic fractures. Thoracic vertebral fractures could increase the kyphotic curvature of the thoracic spine [4], and may therefore cause a flexed posture [5]. In chapter 3 and 4, we screened older patients for vertebral fractures, measured the degree of thoracic kyphosis, and the occiput-to-wall distance (as indicator for a flexed posture) when they visited the geriatric outpatient clinic. Most of these patients had a combination of two or three of these osteoporosis-related factors. Therefore, regression analyses were performed to examine the associations between vertebral fractures, increased thoracic kyphosis and a flexed posture.

A multivariate regression analysis revealed no significant association between an increased thoracic kyphosis and the presence of vertebral fractures (chapter 3). Other studies found similar results: only a third of the individuals with severe thoracic kyphosis have one or more vertebral fractures [6, 7]. The association between vertebral fractures,

increased thoracic kyphosis and consequently a flexed posture could probably not be found because there are different causes for an increased thoracic kyphosis and consequently a flexed posture, such as degenerative disc diseases, or muscle weakness [8, 9]. Of these factors, only grip strength, as indicator of overall muscle strength, was assessed in the present studies. However, grip strength was not significantly associated with a flexed posture in the multivariate regression analyses (chapter 3). To obtain more in-depth insight in the relationship between vertebral fractures, increased thoracic kyphosis and consequently a flexed posture, future studies should examine the association between vertebral fractures, increased thoracic kyphosis, and other potential causes for a flexed posture in a longitudinal study design. These insights could subsequently be used to offer and/or improve interventions aimed at correcting patients' posture, such as anti-osteoporotic medications, exercise aimed at trunk stabilization, and manual therapy [10].

Association between osteoporosis-related factors and postural control

Because vertebral fractures, thoracic kyphosis, and a flexed posture may affect motor function, the association between these osteoporosis-related factors and postural control was investigated in chapter 2 and 3 of this thesis. In the literature study (chapter 2), after reviewing eighteen cross-sectional studies it was concluded that postural control was generally affected in patients with prevalent vertebral fractures, an increased thoracic kyphosis and/or a flexed posture. This was affirmed in the cross-sectional study described in chapter 3, where was demonstrated that patients with a flexed posture had overall a more variable and less structured gait pattern, and a more irregular trunk acceleration pattern in the anterior-posterior direction than patients with normal upright posture. This can be explained by the fact that in these patients the body's center of mass is shifted forward [11, 12]. As postural control can be defined as the ability to maintain the center of mass within the support base [13], this would suggest that patients with a forward spinal curvature require correcting responses from dorsal musculature and ligaments to maintain balance. In severe cases of patients with a flexed posture, this is expressed by flexed knees and protrusion of the head [5, 14]. This presumably leads to impairments in postural control mainly in the anterior-posterior direction as was expressed by more postural sway while standing still [15, 16], slower walking speed and smaller step and stride lengths [5, 15]. In addition, arm sway and trunk movements and rotation may be reduced due to the changed flexed posture and altered functioning of muscles and ligaments. Because dynamics of arms, head and

trunk are important mechanisms to maintain balance [17], it is likely that the ability to react to (small) perturbations during walking is diminished in patients with a flexed posture, increasing the risk of falls.

Risk of falling in osteoporotic patients

Based on the previous described findings, it is suggested that patients with vertebral fractures, increased thoracic kyphosis and/or flexed posture will have an increased risk of falling due to the impairments in postural control. Retrospective studies showed that the presence of both vertebral fractures and an increased thoracic kyphosis are related with increased fall risk [18–20]. In the prospective study presented in chapter 4, we found that older patients with an increased thoracic kyphosis are more likely to fall within the next year.

Since older adults with an increased thoracic kyphosis may thus have an increased fall risk, clinical attention is suggested for these patients, because the consequences of vertebral fractures, increased thoracic kyphosis, flexed posture and falls in the long term may be severe. As concluded in the first part of this thesis, these osteoporosis-related conditions could lead to impaired postural control, and an increased fracture risk. Furthermore, patients with prevalent vertebral fractures, an increased thoracic kyphosis, and/or a flexed posture may experience pain, restrictive respiratory disease, decline in physical functioning, loss of quality of life, and/or mortality [4, 21–24]. Due to the high observed prevalence of vertebral fractures, increased thoracic kyphosis, and flexed posture in the examined older patient population in this thesis, it is recommended to clinicians to screen for these conditions. As part of the comprehensive geriatric assessment, X-rays of the chest are often performed to visualize heart and lungs. These routinely made lateral chest X-rays are reliable to diagnose vertebral fractures [25], and could also be used to measure the degree of thoracic kyphosis by the Cobb angle [15]. A flexed posture can be easily assessed in clinical practice by measuring the occiput-to-wall distance [5], as done in chapter 3 and 4. When one (or more) of these conditions is prevalent, adequate treatment should be provided. Several studies have shown improvements in the degree of osteoporosis, reduced number of new vertebral fractures and increased thoracic kyphosis by prescribing anti-osteoporotic medications, supplementation of calcium and vitamin D, exercise aimed at trunk stabilization and manual therapy [10, 26]. These interventions might also reduce the risk of falls and resultant fractures in older patients. In order to prevent adverse outcomes associated with the described osteoporosis-related conditions, the aforementioned clinical

examinations could be easily implemented in the screening at the geriatric outpatient clinic, with minimal extra work for both patient and physician.

Part II: Medication-use

Older patients often have multiple chronic diseases and use consequently multiple medications [27]. Some psychotropic and cardiac medication classes are associated with an increased risk of falls [28–32], and are therefore called fall-risk increasing drugs (FRIDs). Especially psychotropic drugs are known to increase fall risk due to their sedative side-effects, inducing muscle relaxation and decreased grip strength [33], and might therefore impair postural control [13]. In chapter 5, this assumption was confirmed by 71 out of 94 reviewed studies, which found an increase in parameters quantifying body sway, and/or slower walking speed, smaller step length and/or lower cadence after using psychotropic drugs. The effects were more pronounced when people were older, used higher daily dosages of psychotropics, with longer half-lives or for a longer period of time. Importantly, two intervention studies concluded that these effects seem to be reversible when medications are discontinued [34, 35], although it is not clear whether this would also reduce falls [36].

When analyzing the effects of medication-use on fall risk or postural control, it is important to not only investigate the effects of the drug, but also to consider the effects of the underlying disease [37]. For example, antidepressants are known to be associated with an increased risk of falling [28–31] and an impaired postural control (chapter 5). Also depressive symptomatology is a risk factor for falls independent of antidepressant use [38] due to the physical factors, including impaired balance and reduced muscle strength, and cognitive functioning [39, 40]. Studies examining the effects of medication-use on postural control should thus take the underlying illness into account.

In chapter 6, a multifactorial model was therefore created to examine the association between medication-use, the prevalence of several chronic diseases, frailty-related factors and gait performance in older patients. These patients often have multiple diseases simultaneously and consequently chronically use multiple medications. This is in contrast to the reviewed study populations in chapter 5 that consisted of relatively young and healthy adults and tested only single-drug effects. In the examined older patient population of chapter 6, only a moderate association was observed between the use of antiepileptics and antidepressants with impaired gait ability, while hardly any association with other psychotropic drug classes was found, contrary to our expectations based on the literature review described in chapter 5. Interestingly, a strong association

was found between frailty-related factors, including unintentional weight loss, self-reported exhaustion, low physical activity, and low grip strength, with impaired gait performance as expressed by lower walking speed, higher mean stride times, increased variability of stride times and less consistent steps. These findings were in line with previous research [41, 42] which suggested that the impaired gait ability that was found might reflect the multisystem reduction in neurophysiological capacity in frailty.

In chapter 6, we also found drugs to be associated with impaired gait ability that were not expected to be. Laxatives, agents acting on sensory organs (e.g., artificial tears), and drugs for peptic ulcer and reflux disease were strongly associated with impaired gait performance. Although these drugs are suggested not to have a direct effect on postural control, they are frequently prescribed in individuals with indicators of frailty, and may therefore act as "frailty markers" [43, 44]. Because the frailty-related factors were stronger associated with impaired gait ability than the use of psychotropic drugs, it was suggested that possibly, at a certain frailty-level, the effect of the deterioration in physical functioning is so large, that the instability provoking sedative side-effects of psychotropic drugs have less impact on gait.

Nevertheless, the findings of the second part of this thesis enhance the necessity for physicians to take the adverse effects of psychotropic drugs on postural control and consequently on fall risk into account when evaluating or prescribing these drugs to older patients. Recent studies found that when a patient presents himself/herself with complaints about dizziness, balance problems or falls to a general practitioner, the adjustment of FRIDs is carried out less often than other management strategies [45, 46]. Evaluation of the use of FRIDs in older patients is therefore recommended. Preferably, psychotropic drugs should only be administered after consideration of other non-pharmacological and/or pharmacological interventions with potentially less effect on postural control. And when psychotropic drugs are administered, then only at the lowest effective dose, with a short half-live, and for limited time [47].

Part III: Classification of fallers

Based on the previously discussed chapters and other studies [42, 48–51], it is known that multiple, interrelated factors caused by natural age and/or pathology are related to falling and changes in the gait pattern in older patients. The multifactorial nature of falls in this population makes it challenging to predict who will fall, and thus whom to offer preventive intervention. Therefore, in chapter 7 a multi-factorial statistical approach was used to build three models including categories of modifiable fall risk factors among

geriatric patients in order to identify fallers with highest accuracy. The first model including patient characteristics, e.g., handgrip strength, medication use, and frailty-related factors, already achieved high classification accuracy (AUC=0.86). Although sensitivity of this first model was quite high (80%), specificity remained relatively low (60%). This could result in misclassification of non-fallers, following unnecessary interventions, and potentially induce a fear of falling which in itself could increase the risk of falling [52, 53].

When cognitive functions and three gait components, namely 'pace', 'variability' and 'coordination' (extracted from eleven gait parameters by factor analysis) were added to the model, it's specificity increased to 80% with an area under the receiver operating curve of 0.93. The results showed that combining gait characteristics derived from instrumented gait analysis, combined with patient characteristics (including the use of FRIDs, the degree of thoracic kyphosis, hand grip strength, the severity of comorbid diseases), and cognitive functioning has high accuracy to identify fallers. This emphasizes the need for the development of a multifactorial fall risk assessment for older patients, including the abovementioned modifiable factors. When any of the identified fall-related factors is prevalent, targeted individualized interventions should be started to reduce the risk of falling. For example, when impairments in gait performance are prevalent, it is recommended to start an individualized preventive multi-component exercise program targeting strength, balance, flexibility, and/or endurance [54, 55]. Osteoporosis, vertebral fractures and increased thoracic kyphosis could be treated with anti-osteoporotic medications, calcium and vitamin D supplementation and/or exercise aimed at trunk stabilization [10, 26]. Medication-use should be evaluated by a patient's physician, for example by using the BEERS or STOPP/START criteria [56, 57], in order to avoid potentially inappropriate medication-use and to decrease adverse drug events in older adults. For cognitive functioning, the effectiveness of therapies, such as cognitive stimulation (or 'mental exercise'), aerobic exercise and/or medications, is not yet clear [58–60].

Future perspectives for research and clinical geriatric practice

This thesis was able to answer some important questions regarding factors that are associated with postural control and falling in older patients. This group is specifically relevant because falls and their adverse results occur more often when people are older and have more comorbidities [61]. Paradoxically, in the past this frail group was often not included in fall risk studies [62, 63]. Based on the results of this thesis, it was concluded that multiple, interrelated factors are related to falling and changes in the gait pattern in older patients.

Multifactorial approach for future research in the geriatric population

When investigating gait and/or falls in older patients, it should be taken into account that these patients form a heterogeneous study population with many comorbid factors prevalent. In fact, as many as 400 variables have been suggested to be of interest to investigate in relation to falling [64], and according to chapter 7 and the study of Van Schooten *et al*. [65] multifactorial models including gait parameters showed high classification accuracy. A multifactorial study design is therefore recommended when examining gait and/or falls in older adults.

In these type of studies, methodological difficulties and properties of the data must be considered when choosing statistical methods. In previous studies, logistic regression analyses have often been used [66, 67] to determine the mean effect of a predicting variables, such as gait speed, grip strength, or medical history, on an outcome variable, for example fall incidence in a 1-year follow-up. Consequently, only variables that are important to the entire population are extracted, while variables of importance to a subgroup of the heterogeneous population are difficult to detect [68]. Furthermore, in heterogeneous study populations a large dispersion in predicting and outcome variables is common [69], as was also found in the studies described in this thesis, which makes it more difficult to detect variables of importance to the entire study population.

In addition to the heterogeneity of the study population, another problem is the correlation among variables that are of interest in relation to falls. For example, when analyzing gait, it should be taken into account that gait parameters are not independent, but are both interrelated and complimentary to each other [70–72]. In more conventional regression analyses multicollinearity leads to an increased standard error of regression coefficients [68]. For studies examining gait and/or falls in older adults, it is therefore recommended to use statistical methods where the dependency among variables is taken into account.

In chapter 6 and 7 of this thesis, therefore Partial Least Squares (PLS) regression analyses were used to model multiple variables, including patient characteristics, comorbid diseases, medication-use and cognitive functioning, in relation to gait parameters and fall-status, respectively. PLS analyses are not impeded by collinearity among variables [73–75], and they are particularly useful in studies in which a set of dependent variables is predicted from a relatively large set of independent variables in a relatively small study population [76–78]. Therefore, PLS regression analyses might be a useful statistical method to explore the interplay between multiple variables of interest in relation to gait and/or falls in the heterogeneous population of older patients.

Gait analysis in clinical geriatric practice

In the included studies of the literature reviews described in chapter 2 and 5 of this thesis, postural control during standing or walking was investigated with a large variety of instruments. Functional performance tests are easy-to-use in clinical practice, but seem to be less sensitive than computerized instruments according to the reviewed literature in chapter 2. More objective measures derived from computerized instruments, such as accelerometry as used in the present thesis, are therefore recommended to detect whether patients have impairments in postural control and to obtain more insight into the underlying mechanisms. Recent studies found that smart devices, such as smart phones or the iPod Touch, are valid and reliable to use for such purposes, and that they have the potential to be used for clinical gait assessments since they are light, inexpensive, and easy to handle [79–81]. Easy-to-use applications should be developed to assess postural control during walking in older patients and to monitor interventions targeted at improving postural control. Based on the results of chapter 7 and previous studies [62, 63, 81], it is recommended to include in these applications a combination of gait parameters indicating ‘pace’ (that is, speed-related gait measures, such as walking speed, stride time, and the amplitude of trunk accelerations), ‘variability’ and ‘coordination’ (that are gait properties that reflect the dynamics of gait), since this combination would increase the accuracy to classify (potential) fallers as found in chapter 7.

Because older patients visiting a geriatric outpatient clinic represent a vulnerable population with an increased risk of falling and resultant injuries, the need for a multifactorial approach in fall risk assessment is of great importance. Based on the findings of this thesis, such assessment should include an analysis of the gait pattern combined with a comprehensive evaluation of patient characteristics, osteoporosis-

related factors (such as vertebral fractures, increased thoracic kyphosis and/or a flexed posture), medication-use, frailty-related factors (such as, grip strength and weight loss), and cognitive functioning. Ultimately, these fall risk factors should be targeted by individualized interventions to reduce fall risk, such as exercise targeting strength, balance, flexibility, and/or endurance [54, 55], an evaluation of medication-use for example by using the BEERS or STOPP/START criteria [56, 57], and/or starting osteoporosis-medication and calcium and vitamin D supplementation to reduce the risk of a fracture [26].

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APPENDICES

APPENDICES

Summary

A

Summary

Falls are a serious problem for older patients visiting a geriatric outpatient clinic: it is the combination of a high fall incidence together with the high susceptibility to injuries that makes a relatively mild fall potentially dangerous to these old persons. Falling is a multifactorial problem, but postural instability during daily activities, such as walking, is suggested to be the most consistent predictor of falls. Age-related physiological changes (i.e., the loss of visual ability, proprioception, vestibular sensitivity, motor and cognitive functions), and a high prevalence of clinical diseases result in a slower and less coordinated gait. These changes can be quantified by a wide variety of gait parameters, each characterizing different aspects of the gait pattern. Several studies among relatively young and healthy older adults have shown that gait characteristics, such as gait speed, stride-to-stride variability, gait asymmetry, harmonic ratios, and sample entropy, can differentiate fallers from non-fallers. However, the results of these studies cannot be extrapolated to geriatric patients, although paradoxically this is the group of older adults that is most vulnerable to falls and resultant injuries. In geriatric patients there are, besides the normal age-related neurophysiological changes, additional comorbid factors present that might affect the walking pattern, and that consequently might increase fall risk.

Therefore, in the present thesis, we examined the association between several phenomena that occur common in geriatric patients, including osteoporosis-related factors, medication-use, and frailty-related factors with postural control during walking in older patients visiting a geriatric outpatient clinic. This provided new insights into the interplay between geriatric phenomena and different properties of the gait pattern. The results could be used for future classification of fallers.

Part I: Osteoporosis-related factors

Osteoporosis can cause vertebral fractures, which might lead to a flexed posture, and consequently to impaired postural control and an increased risk of falling. In the first part of this thesis, we investigated these associations. In chapter 2, our literature study among 18 cross-sectional studies revealed that postural control was generally affected in patients with prevalent vertebral fractures, an increased thoracic kyphosis and/or a flexed posture. Impairments in postural control among these patients can be best established when assessed by computerized instruments, such as accelerometry. Unfortunately, in the majority of the reviewed studies the presence and severity of

vertebral fractures, the degree of the thoracic kyphosis, and/or flexed posture were not specified, and the association between these clinical entities in relation to walking remained unclear. Therefore, in chapter 3 we investigated postural control during walking in older patients with a flexed posture, and possible causes for a flexed posture were explored, i.e., the degree of thoracic kyphosis, the presence of vertebral fractures and grip strength as indicator for overall muscle strength. In a study population of 56 older patients, 45% had a flexed posture (occiput-to-wall distance ≥5 cm). These patients demonstrated overall a more variable and less structured gait pattern, and a more irregular trunk acceleration pattern than patients with normal posture. Having a flexed posture was significantly associated with an increased thoracic kyphosis (defined as a Cobb angle >50°) , but not with other phenomena, such as vertebral fractures and low grip strength.

Based on the results of chapter 2 and 3, we speculated that patients with a flexed posture, increased thoracic kyphosis and/or prevalent vertebral fractures have an increased risk of falling due to their impairments in postural control during walking. However, this hypothesis had not yet been prospectively investigated. Therefore, in chapter 4 we performed a prospective cohort study among 51 older patients to examine the association between vertebral fractures, increased thoracic kyphosis and flexed posture with fall incidents within the next year. In this group, 39% had at least one prevalent vertebral fracture, 55% had an increased thoracic kyphosis, and 44% had a flexed posture. In the presence of an increased thoracic kyphosis, falls were more likely to occur.

Most of the patients that were included in the studies described in chapter 3 and 4 had a combination of two or three of the above-mentioned clinical entities. We suggest that osteoporotic vertebral fractures may contribute to the manifestation of an increased thoracic kyphosis, and in turn to a flexed posture. Due to an increased forward spinal curvature, it is hypothesized that the body's center of mass is shifted forward, causing an increased forward bending moment. This requires correcting responses from dorsal musculature and ligaments, which changes trunk alignment and functioning of muscles and ligaments. Therefore, it is likely that the ability of these older patients to respond on small perturbations during walking is diminished.

Based on this first part of the thesis, we recommend to screen older patients for vertebral fractures, increased thoracic kyphosis and/or a flexed posture, and to assess postural control in these patients, since impairments in postural control are an important risk factor for falls and future fractures in this patient group. Computerized instruments, such as easy-to-use ambulant motion-sensing technology, seem to be most

sensitive to detect these impairments. When impairments in postural control are present in these patients, we recommended to offer them multi-component exercise interventions targeting strength, balance, flexibility, and/or endurance combined with anti-osteoporotic treatment when osteoporosis is diagnosed.

Part II: Medication-use

Older patients often have multiple chronic diseases, and therefore often use multiple medications. Meta-analyses showed that psychotropic drugs (antidepressants, neuroleptics, benzodiazepines, antiepileptic drugs) and some cardiac drugs (digoxin, type IA antiarrhythmics, diuretics) are associated with increased fall risk. Because balance and gait disorders are the most consistent predictors of future falls, falls due to these fall-risk-increasing drugs (FRIDs) might be partly caused by impairments of postural control that these drugs can induce. In the second part of this thesis, we therefore examined associations between medication use and postural control. Our literature review in chapter 5 among 94 controlled research articles showed that postural control was impaired when using psychotropic FRIDs. These effects were more pronounced when people were older, used psychotropic drugs at higher daily doses, with longer half-lives, and/or were administered for a longer period of time. The sedative effects of these drugs on postural control are reversible, as was proven in intervention studies where FRIDs were withdrawn. The findings of chapter 5 confirm that the use of psychotropic drugs should be discouraged in the older population, or when usage is necessary, to prescribe these drugs only at the lowest effective dose and for a limited period of time in order to minimize the instability-provoking side-effects.

The current literature on the effects of psychotropics on postural control, as described in chapter 5, only examined acute single-drug effects on postural control during quiet standing in relatively healthy young elderly. Consequently, it was unclear what the impact of the long-term drug use is on gait performance in frail older persons with multiple comorbid diseases and polypharmacy. In chapter 6, we therefore explored the association between the use of psychotropics, multiple other medications, frailty-related parameters and gait performance among 80 older patients. A multivariate Partial Least Squares (PLS) regression analysis revealed that frailty-related parameters were stronger associated with impaired gait performance than the use of psychotropic drugs. It is suggested that the effect of the deterioration in physical functioning in these frail older adults is so large that the instability-provoking side-effects of psychotropic drugs have less impact on gait. This is in accordance to our hypothesis that results from studies

in healthy and relatively young elderly cannot be extrapolated to the frail population, because many complicating factors are present in this older population that might influence postural control. Therefore, it is recommended to future studies among older patients to include frailty-related parameters in their analyses since there are important confounding factors.

Part III: Classification of fallers

Since falling is a multifactorial problem, and walking is also influenced by many factors that could be simultaneously present in the investigated population, we created in chapter 7 a model of frailty-related parameters supplemented with cognitive functioning and gait performance to discriminate fallers from non-fallers. Because gait parameters are related to each other, first a factor analysis was performed on eleven gait parameters to determine underlying properties of the gait pattern, revealing three latent factors that were labeled 'pace', 'variability', and 'coordination'. Thereafter, Partial Least Squares Discriminant Analyses (PLS-DA) were used to discriminate fallers from non-fallers. The classification accuracy increased when cognitive variables and the gait components were added to frailty-related factors and cognitive functioning. The results of this study highlight the need for a multifactorial approach in fall risk assessment, including an analysis of gait performance, frailty-related factors, and specific cognitive functions. Future studies should examine these results more extensively in a prospective design with a larger study population.

Conclusions and future perspectives

Based on the studies described in the present thesis, it can be concluded that in older patients visiting a geriatric outpatient clinic impaired postural control during walking is associated with many factors, including osteoporosis-related factors, medication-use, and frailty related factors. In the first part of this thesis, we concluded that patients with a flexed posture, an increased thoracic kyphosis and/or prevalent vertebral fractures have an impaired postural control. This might be the underlying mechanism for the increased fall incidence that was found in patients with an increased thoracic kyphosis. In the second part of this thesis, we described that postural control was impaired in healthy young and older adults when they use psychotropic FRIDs. These effects were not so clearly manifested in older patients, since frailty-related parameters in this

population were stronger associated with impaired gait performance than the use of psychotropic medications.

Since impairments in gait and balance are the main risk factors for falls, this emphasizes the need for a multifactorial approach in fall risk assessment as described in the third part of this thesis, including gait analysis, medication review, and screening for frailty- and osteoporosis-related factors, in order to detect patients at risk for falling in an early stage and offer them an individualized intervention tailored to the identified intrinsic and extrinsic fall risk factors.

APPENDICES

Samenvatting
(Summary in Dutch)

A

Samenvatting

Vallen is een groot probleem bij oudere patiënten die de dagkliniek geriatrie bezoeken. Door het grote aantal valincidenten en het relatief hoge risico op verwondingen, kan een milde val een potentieel gevaar vormen voor deze kwetsbare groep. Een val ontstaat vaak door een combinatie van intrinsieke en extrinsieke factoren; desalniettemin lijkt de beste voorspeller voor vallen een instabiele houding tijdens dagelijkse activiteiten zoals lopen, te zijn. Een langzamer en ongecoördineerder looppatroon kan veroorzaakt worden door allerlei medische aandoeningen, maar kan ook het resultaat zijn van "normale" leeftijdsgerelateerde neurofysiologische veranderingen, zoals een verminderd gezichtsvermogen, een verslechterd gevoel voor evenwicht, en/of verminderde cognitieve en motorische functies. Deze veranderingen in het looppatroon kunnen gemeten worden met een verscheidenheid aan variabelen die ieder een ander aspect van het looppatroon kwantificeren. Diverse studies onder relatief jonge en gezonde ouderen lieten zien dat verschillende loopkarakteristieken, waaronder de loopsnelheid, de variabiliteit in schredetijden, een minder symmetrisch looppatroon, een minder vloeiend lopen en een lagere stabiliteit van het lopen, in staat blijken om vallende en niet-vallende ouderen van elkaar te onderscheiden. De resultaten van deze studies kunnen echter niet (gemakkelijk) geëxtrapoleerd worden naar de populatie van geriatrische patiënten, omdat deze oudere patiënten naast normale leeftijds-gerelateerde neurofysiologische veranderingen vaak ook andere co-morbiditeiten hebben die het looppatroon kunnen beïnvloeden en tevens het risico op een val kunnen verhogen. Dat is opvallend, aangezien deze groep oudere patiënten het grootste risico heeft om te vallen met daarbij een hoog risico op verwondingen gezien hun kwetsbare fysieke staat.

In dit proefschrift is daarom bij patiënten die de dagkliniek geriatrie bezochten het looppatroon onderzocht in relatie tot een groot aantal geriatrische factoren, waaronder osteoporose-gerelateerde factoren, medicatiegebruik en *frailty*-gerelateerde factoren. Dit heeft nieuwe inzichten opgeleverd in de samenhang tussen deze geriatrische fenomenen en verschillende aspecten van het looppatroon. In de toekomst kunnen de resultaten van dit onderzoek gebruikt worden voor het ontwikkelen van een instrument om ouderen met een verhoogd valrisico vroegtijdig te identificeren aan de hand van een analyse van hun looppatroon.

Deel I: Osteoporose-gerelateerde factoren

Wervelfracturen ontstaan door osteoporose en kunnen een gekromde houding veroorzaken, wat vervolgens tot een verminderde houdingscontrole en een hoger risico op vallen zou kunnen leiden. Deze hypothese werd in het eerste gedeelte van dit proefschrift onderzocht. Een literatuuronderzoek onder 18 cross-sectionele studies (zie hoofdstuk 2) liet zien dat bij patiënten met prevalente wervelfracturen, een vergrote thoracale kyfose en/of een gekromde houding de houdingscontrole over het algemeen was verminderd. Dit werd het sterkst waargenomen wanneer gecomputeriseerde meetinstrumenten, zoals accelerometrie, werden gebruikt voor het analyseren van de houdingscontrole. Op basis van het literatuuronderzoek kon er echter geen causaal verband vastgesteld worden tussen de aanwezigheid van wervelfracturen, de mate van thoracale kyfose en een gekromde houding, doordat het grootste deel van de geïncludeerde studies slechts één van deze entiteiten onderzocht had in relatie tot de mate van houdingscontrole.

Daarom is in hoofdstuk 3 bij een groep oudere patiënten met een gekromde houding de houdingscontrole tijdens het lopen onderzocht, waarbij tevens de relatie met mogelijke oorzaken voor de gekromde houding werd geanalyseerd, waaronder de mate van thoracale kyfose, de aanwezigheid van wervelfracturen en de mate van handknijpkracht als indicator voor algehele spierkracht. Van de 56 onderzochte ouderen had 45% een gekromde houding (gedefinieerd als een achterhoofd-tot-muur-afstand van meer dan 5 cm). Deze patiënten lieten over het algemeen een variabeler en minder gestructureerd looppatroon zien, en hadden tevens een onregelmatiger patroon van rompversnellingen dan ouderen met een normale, rechtopstaande houding. Het hebben van een gekromde houding was significant geassocieerd met het hebben van een vergrote thoracale kyfose, maar niet met andere onderzochte factoren.

Op basis van de resultaten van hoofdstuk 2 en 3 werd verondersteld dat patiënten met een gekromde houding, een vergrote thoracale kyfose en/of prevalente wervelfracturen een hoger risico om te vallen hadden doordat zij een verminderde houdingscontrole hadden tijdens het lopen. Omdat deze hypothese nog niet eerder prospectief onderzocht was, is in hoofdstuk 4 een cohortstudie onder 51 oudere patiënten beschreven waarbij de aanwezigheid van wervelfracturen, een vergrote thoracale kyfose en een gekromde houding is onderzocht in relatie tot valincidenten die binnen een jaar na bezoek aan de dagkliniek optraden. Binnen deze onderzochte groep patiënten had 39% één of meerdere prevalente wervelfracturen, 55% had een vergrote

thoracale kyfose, en 44% had een gekromde houding. Wanneer een vergrote thoracale kyfose aanwezig was, bleek de kans op een valincident groter.

De meeste patiënten die geïncludeerd waren in de studies die beschreven staan in hoofdstuk 3 en 4 hadden een combinatie van twee of drie van de eerder genoemde osteoporose-gerelateerde factoren. Er wordt daarom verondersteld dat wervelfracturen die door osteoporose veroorzaakt zijn bijdragen aan het ontwikkelen van een vergrote thoracale kyfose wat vervolgens kan leiden tot een gekromde houding. Door deze voorwaartse kromming van de wervelkolom, verschuift het lichaamszwaartepunt naar voren wat een voorwaarts flexiemoment veroorzaakt. Dit vereist een corrigerende respons van de dorsale rugspieren en -ligamenten, wat de houding van de romp doet veranderen en ook het functioneren van spieren en ligamenten kan beïnvloeden. Het is daarom aannemelijk dat ouderen die een gekromde houding hebben minder goed kunnen reageren op (kleine) balansverstoringen tijdens het lopen, zoals beschreven in hoofdstuk 3, waardoor het risico op een val groter wordt.

Op basis van de resultaten van het eerste gedeelte van dit proefschrift, adviseren we om oudere patiënten te screenen op de aanwezigheid van wervelfracturen, een vergrote thoracale kyfose en/of een gekromde houding. Tevens raden we aan om bij deze patiënten het looppatroon te analyseren, aangezien houdings- en balansproblemen tijdens het lopen belangrijke risicofactoren zijn voor ontstaan van valincidenten en mogelijk daaropvolgende fracturen. Wanneer een patiënt problemen heeft met het handhaven van de balans, wordt het aanbevolen om een gepersonaliseerde interventie aan te bieden die bestaat uit het trainen van de spierkracht, balanshandhaving, flexibiliteit en/of uithoudingsvermogen gecombineerd met een anti-osteoporosebehandeling wanneer de botdichtheid ernstig verlaagd is.

Deel II: Medicatiegebruik

Oudere patiënten hebben vaak meerdere chronische aandoeningen waarvoor zij vaak meerdere medicijnen gebruiken. Meta-analyses hebben aangetoond dat psychofarmaca (waaronder antidepressiva, neuroleptica, benzodiazepines en anti-epileptica) en een aantal cardiale medicijnen (waaronder digoxine, type IA antiaritmica en diuretica) geassocieerd zijn met een verhoogd valrisico. Aangezien balans- en loopproblemen de meest consistente voorspellers zijn voor toekomstige valproblematiek, werd er beredeneerd dat een medicatie-gerelateerde val mogelijk veroorzaakt wordt door balansproblemen die ontstaan zijn door de bijwerkingen van deze medicijnen. In het tweede gedeelte van dit proefschrift werd daarom de relatie tussen medicatiegebruik

en houdingscontrole onderzocht. Hoofdstuk 5 beschrijft een literatuuronderzoek bij 94 gecontroleerde onderzoeksartikelen waaruit blijkt dat de houdingscontrole verminderd was bij deelnemers die psychofarmaca gebruikten. Deze effecten werden duidelijker waargenomen wanneer participanten ouder waren, een hogere dosis psychofarmaca gebruikten, medicijnen met een langere halfwaardetijd hadden, en/of wanneer medicijnen voor langere tijd gebruikt werden. De sedatieve effecten van deze medicijnen bleken reversibel te zijn, wat aangetoond werd door interventiestudies waarbij het gebruik van valrisicoverhogende medicatie werd afgebouwd. De resultaten van hoofdstuk 5 bevestigen dat het gebruik van psychofarmaca ontmoedigd zou moeten worden bij de oudere patiëntenpopulatie, of wanneer gebruik noodzakelijk is, deze medicijnen alleen worden voorgeschreven in de laagst effectieve dosering en voor een beperkte periode teneinde de balansverstorende bijwerkingen van deze medicijnen tot een minimum te beperken.

De huidige literatuur naar de effecten van psychofarmaca op houdingscontrole, zoals beschreven in hoofdstuk 5, heeft alleen acute effecten van enkelvoudig medicijngebruik op de balanshandhaving tijdens stilstaan onderzocht bij relatief jonge gezonde ouderen. Het bleef dus onduidelijk wat de invloed is van het op lange termijn gebruiken van deze medicijnen op het looppatroon bij oudere fragiele patiënten met meerdere aandoeningen en polyfarmacie. Daarom werd in hoofdstuk 6 de associatie tussen het gebruik van psychofarmaca, verschillende andere medicijnen, frailty-gerelateerde factoren en loopparameters onderzocht bij 80 oudere patiënten. Een multivariate Partial Least Square (PLS) regressieanalyse liet zien dat frailty-gerelateerde factoren sterker geassocieerd waren met een langzamer en onregelmatiger looppatroon dan het gebruik van valrisicoverhogende medicatie. Er wordt gesuggereerd dat de achteruitgang in fysiek functioneren bij deze fragiele ouderen zo sterk was, dat de sedatieve bijwerkingen van de psychofarmaca minder invloed hadden op het looppatroon. Dit kwam overeen met de stelling dat resultaten van studies bij gezonde, relatief jonge ouderen niet gemakkelijk extrapoleerbaar zijn naar de fragiele oudere populatie, omdat in deze oudere patiëntenpopulatie veel complicerende factoren aanwezig zijn die de houdingscontrole kunnen beïnvloeden. Voor toekomstig onderzoek naar vallen en lopen bij kwetsbare ouderen wordt daarom aangeraden om frailty-gerelateerde factoren mee te nemen in analyses omdat dit belangrijke beïnvloeders van de resultaten kunnen zijn.

Deel III: Classificatie van vallers

Aangezien vallen een multifactorieel probleem is, en lopen ook beïnvloed wordt door diverse factoren die tegelijkertijd aanwezig kunnen zijn, werd in hoofdstuk 7 een model gecreëerd van frailty-gerelateerde factoren aangevuld met indicatoren voor het cognitief functioneren en loopparameters met als doel om vallers van niet-vallers te onderscheiden. Aangezien loopparameters gerelateerd zijn aan elkaar, werd eerst een factoranalyse uitgevoerd met elf loopparameters om de onderliggende eigenschappen van het looppatroon te bepalen. Uit deze analyse kwamen drie latente factoren naar voren die we gelabeld hebben als “tred”, “variabiliteit” en “coördinatie”. Vervolgens is een Partial Least Square Discriminant Analyse (PLS-DA) uitgevoerd om vallers van niet-vallers te onderscheiden. De nauwkeurigheid van de classificatie werd hoger toen cognitieve factoren en de drie loopcomponenten werden toegevoegd aan een model van frailty-gerelateerde factoren. De resultaten van dit hoofdstuk lieten zien dat een multifactoriële benadering voor het schatten van het valrisico gewenst is, waarbij met name een analyse van het looppatroon, het onderzoeken van frailty-gerelateerde factoren, en een beoordeling van specifieke cognitieve functies aan bod zouden moeten komen. Toekomstige studies zouden de resultaten van het uitgevoerde onderzoek nog uitvoeriger kunnen onderzoeken in een prospectief design met een grotere onderzoekspopulatie.

Conclusies en toekomstperspectief

Op basis van dit promotieonderzoek kan geconcludeerd worden dat bij ouderen die de dagkliniek geriatrie bezoeken een verminderde houdingscontrole tijdens het lopen gerelateerd is met vele factoren, waaronder osteoporose-gerelateerde factoren, medicatiegebruik, en frailty-gerelateerde factoren. In het eerste gedeelte van deze thesis werd geconcludeerd dat patiënten met een gekromde houding, een vergrote thoracale kyfose en/of prevalente wervelfracturen een verminderde houdingscontrole hebben. Dit is mogelijk de onderliggende oorzaak van de hogere valincidentie die bij deze patiënten gevonden werd. In het tweede deel van dit proefschrift is beschreven dat de houdingscontrole was verminderd bij zowel oudere als jongere proefpersonen wanneer zij valrisicoverhogende psychofarmaca gebruikten. Deze effecten waren echter minder duidelijk bij de onderzochte oudere patiënten, omdat frailty-gerelateerde factoren in deze populatie sterker gerelateerd waren met een aangedaan looppatroon dan het gebruik van psychofarmaca.

Aangezien houdings- en balansproblemen de belangrijkste risicofactoren zijn voor een val, is het van groot belang om het risico op een val te bepalen op basis van een analyse van het looppatroon, aangevuld met een medicatie-review en het screenen op frailty- en osteoporose-gerelateerde factoren. Door tijdige identificatie van ouderen met een risico om te vallen, kan in een vroeg stadium een gepersonaliseerde interventie aangeboden worden gericht op het verbeteren van de geïdentificeerde intrinsieke en extrinsieke valrisicoverhogende factoren.

APPENDICES

Dankwoord
(Acknowledgements in Dutch)

A

Dankwoord

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Maartje

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Curriculum Vitae

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Curriculum Vitae

Maartje de Groot werd geboren op 20 november 1986 in Aduard en groeide op in Roden. In Juli 2005 behaalde zij in Leek aan RSG de Borgen haar VWO-diploma, waarna zij startte met de Bachelor Bewegingswetenschappen aan de Rijksuniversiteit Groningen. Deze opleiding werd in Maart 2010 afgerond. Ondertussen begon zij in September 2008 alvast met de Master Human Movement Sciences (HMS), eveneens aan de Rijksuniversiteit Groningen. Tijdens de Master rondde zij aan de Vrije Universiteit in Amsterdam aan de Faculteit der Bewegingswetenschappen de opleiding tot HBO-docent af.

In september 2010 startte Maartje met haar afstudeerproject van de Master HMS, waarvoor zij begon met een onderzoeksstage bij de Dagkliniek Geriatrie in het Slotervaartziekenhuis in Amsterdam, onder supervisie van Claudine Lamoth, Jos van Campen en Hanna Willems. In augustus 2010 rondde zij haar afstudeerproject af met de afstudeerscriptie “The influence of vertebral fractures and thoracic kyphosis on variability and stability of walking among geriatric patients”, waarmee zij haar diploma voor de Master HMS behaalde. Na haar afstuderen kreeg zij de mogelijkheid om in het Slotervaartziekenhuis haar afstudeeronderzoek uit te breiden tot een promotie-onderzoek. Het resultaat hiervan ligt nu voor u.

In november 2014 begon Maartje aan een (tijdelijke) baan als docent bij de opleiding Podotherapie van Saxion Hogescholen in Enschede. Inmiddels werkt zij sinds juni 2015 met veel plezier als docent bij de opleiding Voeding & Diëtetiek aan de Haagse Hogeschool.

APPENDICES

Publications & Presentations

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Publications

M.H. de Groot, J.P.C.M. van Campen, N.M. Kosse, O.J. de Vries, J.H. Beijnen, C.J.C. Lamoth. The association of medication-use and frailty-related factors with gait performance in older patients. *PLoS ONE* 2016; 11 (2): e0149888.

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Presentations

International congress presentations

Oral presentation "Can gait variability measures predict falls in geriatric outpatients? A prospective validation study" at the symposium "Instrumented analysis of gait variability as diagnostic instrument in geriatric medicine" at the 10th International Congress of the EUGMS (abstract nr. SS4.04). 17-19 September 2014, Rotterdam. Abstract published in: *European Geriatric Medicine* 2014; 5 (Suppl. 1): S29-S30.

Oral presentation "The relationship between medication-use and gait variability in frail elderly: from FRIDs to frail" at the 10th International Congress of the EUGMS (abstract nr. O1.13). 17-19 September 2014, Rotterdam. Abstract published in: *European Geriatric Medicine* 2014; 5 (Suppl. 1): S49.

Poster presentation "The effect of fall-risk-increasing drugs (FRIDs) on gait variability in frail elderly" at the ISPGR World Congress (abstract nr. P1-H-32). 29 June–3 July 2014, Vancouver, BC, Canada.

Oral presentation "Do patients with vertebral fractures and/or increased thoracic kyphosis fall more often? Preliminary results of a study among geriatric patients about the relation between falling and gait variability and stability" at the 1st Joint World Congress of ISPGR and Gait & Mental Function (abstract nr. O.15.3). 24-28 June 2012, Trondheim, Norway.

Poster presentation "The influence of vertebral fractures and thoracic kyphosis on variability and stability of walking among geriatric patients" at the "2011 Alliance for Healthy Aging Symposium on Frailty and Healthspan" (p. 88). 20-22 October 2011, Groningen.

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Onderzoekspitch in het kader van de Stimuleringsprijs Geriatrie van de Nederlandse Vereniging voor Klinische Geriatrie (NVKG) tijdens de Geriatriedag. 13 februari 2014, ’s-Hertogenbosch.

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Posterpresentatie “Kan het effect van psychofarmaca op balans geobjectiveerd worden? Een literatuurreview” tijdens de Geriatriedagen (p. 125). 6-8 februari 2013, ’s-Hertogenbosch.

Posterpresentatie “Vallen patiënten met wervelfracturen en/of thoracale kyfose vaker? Een onderzoek naar de relatie tussen het looppatroon en vallen bij geriatrische patiënten” tijdens de Geriatriedagen (pp. 129-130). 8-10 februari 2012, ’s-Hertogenbosch.

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