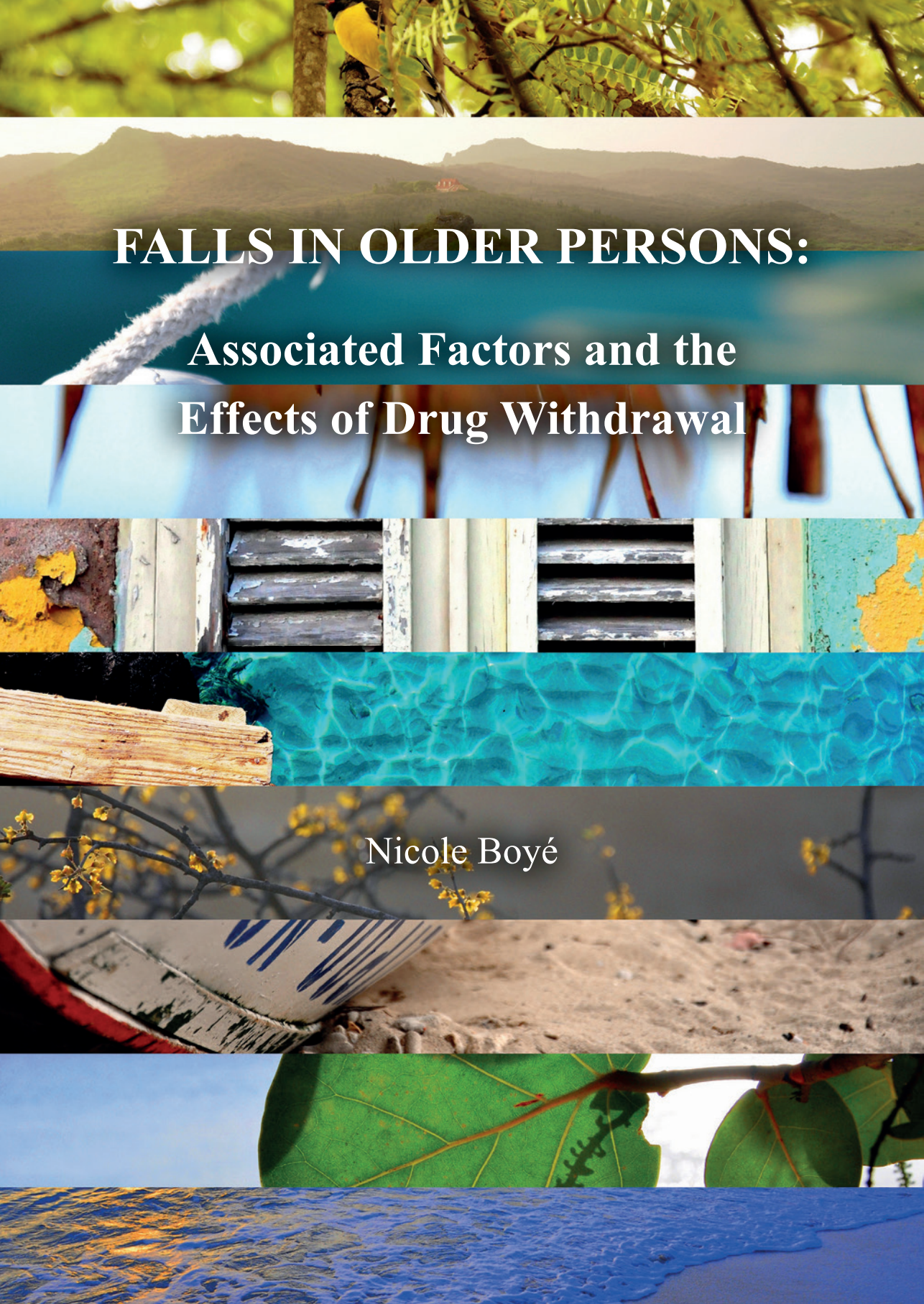


FALLS IN OLDER PERSONS:

Associated Factors and the Effects of Drug Withdrawal

Nicole Boyé

Falls in Older Persons: Associated Factors and the Effects of Drug Withdrawal

Nicole Danielle Ariane Boyé

Printing of this thesis was financially supported by:

ABN AMRO

ErasmusMC, University Medical Center Rotterdam

Funding for the research of this thesis was provided by the Netherlands Organization for Health Research and Development (ZonMw, research grant number 170.885.607).

Cover: Nicole Boyé

Layout and printing: Ridderprint BV, the Netherlands.

ISBN: 978-94-6299-179-8

Falls in older persons:

Associated factors and the effects of drug withdrawal

Valincidenten in de oudere populatie:

Gerelateerde factoren en het effect van het afbouwen

van valrisicoverhogende geneesmiddelen

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de

rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

vrijdag 9 oktober 2015 om 13:30 uur door

Nicole Danielle Ariane Boyé

geboren op 24 augustus 1986 te Willemstad, Curaçao

Promotiecommissie

Promotors:

Prof.dr. P. Patka

Prof.dr. T.J.M. van der Cammen

Overige leden:

Prof.dr. S.E.J.A. de Rooij

Prof.dr. A. Burdorf

Prof.dr. M.H.J. Verhofstad

Copromotor:

Dr. E.F. van Beeck

Contents

Part I

Chapter 1.1

The Impact of Falls in the Elderly

Nicole D.A. Boyé, Esther M.M. van Lieshout, Ed F. van Beeck, Klaas A. Hartholt, Tischa J.M. van der Cammen, Peter Patka

Trauma 01/2013; 15(1):29-35.

Abstract

The number of falls in the elderly is a major public health problem in our society. In the past decade life expectancy increased from 75 years in 1990 to 79 years in 2009 in the United States (US). It has been estimated that the number of persons aged 65 years and older in the US will double by 2050.

In 2000 falls accounted for 45% of all injury-related inpatient stays, with almost 750,000 hospitalizations. Fractures were the most common primary injury diagnosis, including 314,006 hip fractures. Injury following a fall is associated with a decreased quality of life and poor functional outcome, in severe injuries these effects continue for a prolonged period of time.

In 2006 fall-related medical costs in the population aged ≥65 in the US amounted to US$19 billion for non-fatal and US$0.2 billion for fatal injuries.

In this paper we provide a literature overview on the impact of falls in the elderly, the demands on healthcare and the costs for our society.

INTRODUCTION

The number of falls in the elderly is a major public health problem in our society. In past decades life expectancy has risen from 77 years in 1990 to 81 years in 2009 in the Netherlands. Similar trends were noted in other countries; from 75 to 79 years in the US, and from 76 to 80 years in the UK. This gives an estimate of the increasing life expectancy in western countries worldwide [2]. In 2010 Vincent et al. estimated that the number of persons aged 65 years and older in the US will double by 2050 [3]. In 2010 14 percent of the population in the US was 85 years or older, by 2050 that proportion is expected to increase to more than 21 percent. Currently 15.6 percent of the population in the Netherlands is aged 65 years or older; this is estimated to increase to 25 percent by 2050 [4].

How should we prepare our society for the growing number of elderly and the array of health problems associated with increased age? Approximately one out of three persons aged ≥ 65 years experiences a fall every year [5]. The most important risk factors for falls are old age (>80 years), a history of falls, gait deficit, balance deficit, use of assistive device, visual deficit, arthritis, impaired activities of daily living (ADL), depression, and cognitive impairment. Other risk factors include the environment (*e.g.*, insufficient lighting, rugs, and loose wiring), and comorbidities like orthostatic hypotension, vertigo, and Parkinson's disease [6-9]. Approximately 33 percent of persons over 65 years use so-called fall-risk-increasing drugs (FRIDs) such as cardiovascular and psychotropic drugs [10-12].

Low-level falls are deemed as fairly innocent in the young, yet falls in the older population are associated with substantial higher morbidity and mortality rates. This will put a substantial burden on healthcare workers and institutions, and will result in rising healthcare costs as long as the population of elderly continues to grow. In order to solve this public health problem we need insight into the outcome of falls in the older population, such as the

type of injury, mortality, disability, fear of falling, and social isolation. Also, the burden of falls on healthcare systems including emergency departments (ED), hospitals, long-term care and rehabilitation facilities, and the costs of falls for our society and economy need to be investigated. Falls-prevention programs provided by healthcare givers are now being developed and implemented worldwide, assessing and managing risk factors for falls. In this paper we provide a literature overview on the impact of falls in the elderly, including predominant injuries following a fall, the quality of life after a fall, the costs of treatment, and the effectiveness of fall prevention.

Burden on Healthcare

In 2009 the number of persons aged 65 and older treated at an ED for a non-fatal fall in the US was 1,594,335 [13]. Greenspan et al. showed that of all injury-related hospitalizations in 2000, discharge rates from hospitals were highest for those aged 65 years and older; adults 85 years and older had the highest hospitalization rates of any age group (5,499 per 100,000). Falls were the leading cause of hospitalization. With almost 750,000 hospitalizations, falls accounted for 45% of all inpatient stays. Fractures were the most common primary injury diagnosis, including 314,006 hip fractures [14].

Falls are also the leading cause of traumatic brain injury, between 2002 and 2006, an average of 144,338 persons aged ≥65 sustained traumatic brain injury in the US annually, of which 107,221 visited the ED, 29,860 were hospitalized and 7,257 resulted in death [15].

In 2008 there were 34,091 fall related hospitalizations including 14,258 with hip fractures [16] and 3,010 with significant traumatic head injury [17] in persons aged 65 years and older in the Netherlands. In 1999, there were over 647,721 fall-related ED visits in the UK for persons aged 60 or older, leading to 204,424 hospital admissions [18].

Close et al. documented healthcare use of older fallers (≥ 70 years old) in Australia. From 2008 through 2010, older fallers constituted 17% of all ED visits, which led to hospital admission in 42.7% of the cases, after hospitalization 9.5% became first-time resident of long-term care facilities [19].

Predominant Injuries

In 2006 there were 10,300 fatal and 2.6 million non-fatal fall-related injuries in the population aged ≥65 in the US [20]. Accidental injury, often resulting from a fall, ranks as the ninth leading cause of death among people over 65 years of age in the US [21].

Older adults are more prone to injury than younger persons, and similar injury mechanisms will result in more severe consequences for the elderly. For instance, the increased fracture incidence at older age is partly attributable to osteoporosis. The most common injuries due to falls in persons aged 65 years or older in the Netherlands are superficial injuries, hip fractures, upper extremity fractures, and traumatic brain injury [16]. About 30% of people with a hip fracture will die in the following year, and many more will experience significant functional loss [22]. Data from recent studies in Europe and North America indicate that the incidence of hip fractures is declining [22-25]. This decline has been observed since 1985 [25] and by some as early as 1950 [26]. Having an explanation for this trend could be helpful in developing programs for further reduction of the hip fracture incidence rate. However, there seems yet to be no clear answer to this incidence decline. One of the most striking observations is the disparity in decline of the male and female incidence rates, Chevalley et al. reported no decrease in hip fracture rates between 1991 and 2000 in males in Switzerland [23], and Hartholt et al. reported a continuing increase in hip fracture rates in the oldest men aged 80 years and older in the Netherlands between 1980 and 2008 [27]. One

explanation for this observation could be the lack of awareness and preventive measures against osteoporosis in men. However, the overall decline in hip fracture incidence rates observed in both males and females in the US and Canada cannot be explained by this [22,25]. Several other explanations have been suggested such as improved nutrition status, increasing body weight, declining smoking rates, and hormone replacement therapy yet there is no definitive answer. A combination of all these factors is probably the reason for the lower incidence rate of hip fractures in western countries.

Traumatic brain injury is associated with serious consequences. Recent studies in the US [15], the Netherlands [17], and Finland [28] showed an increase in fall-related traumatic brain injury. Falls cause 60.7% of traumatic brain injuries among persons aged 65 years and older in the US [15]. Rates for ED visits, hospitalization and death due to traumatic brain injury in the US all increased from 2002 to 2006, with hospitalization rates increasing from 67.6 to 90.7 per 100,000 in persons aged 65 or older [15]. A similar increase in hospitalization rates after traumatic brain injury was also seen in the Netherlands [17]. A definite cause is yet unknown, the observed increase could in part be due to the increased mobility of the elderly, the implementation of new treatment guidelines, the increased use of radiographic imaging, or the rising life expectancy in western countries.

Health-Related Quality of Life

In addition to the effects on morbidity and mortality as described above, falls result in a significant reduction in health-related quality of life and substantial functional impairment one year after sustaining a hip fracture [29,30]. Compared with the general older population, fallers with hip factures, upper extremity fractures or skull/brain injury all displayed a higher prevalence of functional problems. In a Dutch population-based study, patients aged 65 years

or older who had sustained a hip fracture reported problems in all domains of the EuroQol-5D (EQ-5D), including mobility (90% of patients), self-care (54%), usual activities (73%), pain/discomfort (69%), anxiety/depression (28%) and cognition (38%) up to nine months after the fall [31]. Marottoli et al. studied physical function following a hip fracture in persons aged 65 and older; at baseline, 86% of patients could dress independently versus 49% at six months. Similarly, 90% could transfer independently versus 32% at six months; 75% could walk across a room independently versus 15% at six months; 63% could climb a flight of stairs versus 8% at six months; and 41% could walk one-half mile versus 6% at six months [32]. Injury following a fall is associated with a decreased quality of life and poor functional outcome, in severe injuries these effects continue for a prolonged period of time.

Healthcare Costs

In 2006 fall-related medical costs in the population aged ≥65 years in the US amounted to US$19 billion (equivalent to €13.8 billion) for non-fatal and US$0.2 billion (€0.15 billion) for fatal injuries [20]. The estimated population aged ≥65 in 2006 in the US was 37 million [33,34], which amounts to a per capita cost of US$517 (€382). Between 2003 and 2007 the average annual cost for fall-related injuries in the Netherlands was US$ 0.64 billion (€0.47 billion), in 2005 the population aged ≥65 in the Netherlands was 2.3 million [35], which amounts to a per capita cost of US$280 (€207). In 1999, the total cost to the UK government from unintentional falls in persons aged 60 or older was US$1.6 billion (€1.15 billion) [18], the UK population aged ≥60 in 1999 was 12.2 million [36] thus the per capita cost was approximately US$130 (€96). In 2005 Roudsari et al., estimated the mean cost per fall-related hospitalization in the US to be US$17,483 (€12,674), the mean cost per ED visit US$236 (€171) and the mean cost per outpatient visit US$412 (€299) [37]. Between 2003 and 2007 the average cost per

hip fracture in the Netherlands was US$24,639 (€18,223), the cost per patient admitted to a hospital with traumatic brain injury after a fall was US$19,309 (€14,281) and overall cost per fall US$9,530 (€7,048) [31].

Falls Prevention Initiatives

Much effort has been put into prevention programs, assessing risk factors, such as previous falls, impaired balance and gait, and fall-risk-increasing drugs. There have been successful single intervention studies, implementing exercise programs which mainly consisted of muscle strengthening and balance exercises [38,39], and a study featuring withdrawal of fall-risk-increasing drugs (FRIDs) [40]. The withdrawal of FRIDs should place minimal burden on the healthcare system, fallers taking FRIDs are easily identified, and withdrawal is shown to be safely possible and effective for both cardiovascular and psychotropic drugs [41]. Campbell et al. demonstrated how withdrawal of psychotropic medication significantly reduced falls; however, permanent withdrawal was difficult to achieve [40]. There are also falls prevention programs with multiple interventions; these are called multifactorial intervention programs. The most common interventions featured in successful multifactorial intervention studies are exercise, medication review, an assessment of vision, hearing, cardiovascular function and psychological state with proper referrals, and an assessment of the home environment and assistive devices [5,9,42-46]. Efficacy of such interventions varies, and in some multifactorial intervention studies no reduction in falls could be shown [47,48]. Thus there is room for improvement and further research concerning this complex problem. Identifying the population that will benefit most from falls-prevention programs and determining which components of multifactorial interventions are most effective could improve current results. With such a broad range of risk factors, falls-prevention is not a simple task.

DISCUSSION

In this paper, different aspects of falls and the impact of falls on the elderly, healthcare systems, and society have been reviewed based on current literature. In the past decades there has been a growing awareness in western societies, concerning the increasing burden of falls. Although the mortality rate following a fall and the incidence rates of hip fractures have decreased, hospitalization rates for traumatic brain injury are increasing. The absolute number of falls and injury following a fall continues to rise, as do the costs. Factors which have reduced injury severity following a fall are preventative measures and treatment for osteoporosis, an improved nutrition status, increasing body weight, declining smoking rates, hormone replacement therapy, and more recently falls-prevention programs. Yet the decline in hip fracture rates is not explained by these factors alone, a definitive answer concerning the reduction in hip fracture rates could help us further in preventing fractures following falls. Falls affect a large proportion of the elderly population and have a substantial impact, with consequences such as higher morbidity and mortality rates, disability, fear of falling, social isolation, loss of independence, and institutionalization. Fall-related injuries and loss of function, quality of life and independence place a substantial burden on healthcare systems due to the large amount of visits to emergency departments, hospital admissions, admissions to long-term care and rehabilitation facilities, and other healthcare services needed. The elderly population in our society will continue to increase during the coming decades. This may be a reflection of the change in life style and the advances in public health and medical care, yet this will challenge us with rising healthcare budgets worldwide.

REFERENCES

1. Holick MF. Vitamin D deficiency. *N Engl J Med.* Jul 19 2007;357(3):266-281.

2. WHO. Global Health Data Repository: life expectancy. . 2011.

3. Vincent GK, Velkoff VA. THE NEXT FOUR DECADES, The Older Population in the United States: 2010 to 2050. In: U.S. Census Bureau W, DC, ed: Current Population Reports; 2010:25-1138.

4. CBS. Kerncijfers van de bevolkingsprognose, 2010-2060. Centraal Bureau Statistiek 2010. 2010.

5. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med.* Sep 29 1994;331(13):821-827.

6. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* Dec 29 1988;319(26):1701-1707.

7. Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls. A prospective study. *Jama.* May 12 1989;261(18):2663-2668.

8. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc.* Jul 2004;52(7):1121-1129.

9. AGS/BGS/AAOS. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* May 2001;49(5):664-672.

10. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* Nov 23 2009;169(21):1952-1960.

11. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):40-50.

12. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):30-39.

13. CDC. Web-based Injury Statistics Query and Reporting System (WISQARS). In: Centers for Disease Control and Prevention A, ed2004.

14. Greenspan AI, Coronado VG, Mackenzie EJ, Schulman J, Pierce B, Provenzano G. Injury hospitalizations: using the nationwide inpatient sample. *J Trauma.* Nov 2006;61(5):1234-1243.

15. Faul M, Xu, L., Wald, M., and Coronado, V. . Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006. . *Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: Atlanta.* 2010.

16. Hartholt KA, van der Velde N, Looman CW, van Lieshout EMM, Panneman MJ, van Beeck EF, et al. Trends in fall-related hospital admissions in older persons in the Netherlands. *Arch Intern Med.* May 24 2010;170(10):905-911.

17. Hartholt KA, Van Lieshout EMM, Polinder S, Panneman MJ, Van der Cammen TJM, Patka P. Rapid increase in hospitalizations resulting from fall-related traumatic head injury in older adults in The Netherlands 1986-2008. *J Neurotrauma.* May 2011;28(5):739-744.

18. Scuffham P, Chaplin S, Legood R. Incidence and costs of unintentional falls in older people in the United Kingdom. *J Epidemiol Community Health.* Sep 2003;57(9):740-744.

19. Close JC, Lord SR, Antonova EJ, Martin M, Lensberg B, Taylor M, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. *Emerg Med J.* Oct 1 2011.

20. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev.* Oct 2006;12(5):290-295.

21. Kochanek KD, Xu JQ, Murphy SL, al. e. Deaths: Preliminary data for 2009. . Vol National vital statistics reports; vol 59 no 4.: Hyattsville, MD: National Center for Health Statistics. ; 2011.

22. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *Jama.* Oct 14 2009;302(14):1573-1579.

23. Chevalley T, Guilley E, Herrmann FR, Hoffmeyer P, Rapin CH, Rizzoli R. [Incidence of hip fracture: reversal of a secular trend]. *Rev Med Suisse.* Jun 13 2007;3(115):1528-1530, 1532-1523.

24. Kannus P, Niemi S, Parkkari J, Palvanen M, Vuori I, Jarvinen M. Nationwide decline in incidence of hip fracture. *J Bone Miner Res.* Dec 2006;21(12):1836-1838.

25. Leslie WD, O'Donnell S, Jean S, Lagace C, Walsh P, Bancej C, et al. Trends in hip fracture rates in Canada. *Jama.* Aug 26 2009;302(8):883-889.

26. Melton LJ, 3rd, Atkinson EJ, Madhok R. Downturn in hip fracture incidence. *Public Health Rep.* Mar-Apr 1996;111(2):146-150; discussion 151.

27. Hartholt KA, Oudshoorn C, Zielinski SM, Burgers PT, Panneman MJ, van Beeck EF, et al. The epidemic of hip fractures: are we on the right track? *PLoS One.* 2011;6(7):e22227.

28. Kannus P, Niemi S, Parkkari J, Palvanen M, Sievanen H. Alarming rise in fall-induced severe head injuries among elderly people. *Injury.* Jan 2007;38(1):81-83.

29. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. *Osteoporos Int.* Feb 2004;15(2):87-94.

30. Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. *Osteoporos Int.* 2000;11(5):460-466.

31. Hartholt KA, van Beeck EF, Polinder S, van der Velde N, van Lieshout EMM, Panneman MJ, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* Sep 2011;71(3):748-753.

32. Marottoli RA, Berkman LF, Cooney LM, Jr. Decline in physical function following hip fracture. *J Am Geriatr Soc.* Sep 1992;40(9):861-866.

33. Census-Bureau. Intercensal Estimates of the Resident Population by Sex and Age for the United States: April 1, 2000 to July 1, 2010. U.S. Census Bureau, Population Division. 2010.

34. Lord SR, Ward JA, Williams P, Anstey KJ. Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc.* Oct 1994;42(10):1110-1117.

35. CBS. Bevolking; kerncijfers. Centraal Bureau voor de Statistiek (http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=37296ned&D1=a&D2=0,10,20,30,40,50,(l-1)-l&HD=111128-1323&HDR=G1&STB=T). Last accessed on November 20, 2011. 2011.

36. ONS. Key Population and Vital Statistics - Annex A1: National populations at Mid-1999 by single year of age and sex. No. 26, 1999 Edition. Office for National Statistics. 1999.
37. Roudsari BS, Ebel BE, Corso PS, Molinari NA, Koepsell TD. The acute medical care costs of fall-related injuries among the U.S. older adults. *Injury.* Nov 2005;36(11):1316-1322.
38. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Falls prevention over 2 years: a randomized controlled trial in women 80 years and older. *Age Ageing.* Oct 1999;28(6):513-518.
39. Province MA, Hadley EC, Hornbrook MC, Lipsitz LA, Miller JP, Mulrow CD, et al. The effects of exercise on falls in elderly patients. A preplanned meta-analysis of the FICSIT Trials. Frailty and Injuries: Cooperative Studies of Intervention Techniques. *Jama.* May 3 1995;273(17):1341-1347.
40. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc.* Jul 1999;47(7):850-853.
41. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. *Br J Clin Pharmacol.* Feb 2007;63(2):232-237.
42. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet.* Jan 9 1999;353(9147):93-97.
43. Davison J, Bond J, Dawson P, Steen IN, Kenny RA. Patients with recurrent falls attending Accident & Emergency benefit from multifactorial intervention--a randomised controlled trial. *Age Ageing.* Mar 2005;34(2):162-168.
44. Jensen J, Lundin-Olsson L, Nyberg L, Gustafson Y. Fall and injury prevention in older people living in residential care facilities. A cluster randomized trial. *Ann Intern Med.* May 21 2002;136(10):733-741.
45. Spice CL, Morotti W, George S, Dent TH, Rose J, Harris S, et al. The Winchester falls project: a randomised controlled trial of secondary prevention of falls in older people. *Age Ageing.* Jan 2009;38(1):33-40.
46. AGS/BGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc.* Jan 2010;59(1):148-157.
47. Hartholt KA, Boyé NDA, Van der Velde N, Van Lieshout EMM, Polinder S, De Vries OJ, et al. [Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study). *BMC Geriatr.* 2011;11:48.
48. Mahoney JE, Shea TA, Przybelski R, Jaros L, Gangnon R, Cech S, et al. Kenosha County falls prevention study: a randomized, controlled trial of an intermediate-intensity, community-based multifactorial falls intervention. *J Am Geriatr Soc.* Apr 2007;55(4):489-498.

Chapter 1.2

General introduction and thesis outline

In this thesis

Part I starts with a literature overview on the impact of falls in the elderly, the burden on healthcare, and the costs for society.

Part II is descriptive, providing insight into various factors related to falls. An important aspect regarding falls in older adults are the circumstances leading to injurious falls. Falls are the most significant cause of traumatic brain injuries (TBI) and hip fractures in older adults, and these circumstances highlight subgroups that may benefit from targeted falls prevention strategies [1-3]. The location and activity surrounding falls requiring an emergency department (ED) visit, falls resulting in TBI, and falls resulting in hip fractures, are discussed in **Chapter 2.1**. In **Chapter 2.2** the association between serum 25-hydroxy-vitamin D and physical performance in older men and women is presented. A decrease in physical performance, such as impaired mobility, reduced muscle strength or poor balance, predisposes to falls and related injuries [4-6]. Muscle tissue is an important target tissue of vitamin D [7]. Furthermore, vitamin D deficiency has been shown to be a key contributor to a decline in physical performance and an increase in fall incidence [8-15]. Additionally, guidelines concerning falls prevention make a clear distinction between single and recurrent fallers [16]. Iin **Chapter 2.3** the differences in functional status, physical performance and health related quality of life between single and recurrent fallers are discussed.

And finally, **Part III** presents the background of and data from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) Study. Including the study protocol in **Chapter 3.1**, the main outcomes in **Chapter 3.2**, and the cost-utility analysis in **Chapter 3.3**. The use of certain drugs, i.e. the so-called fall-risk increasing drugs (FRIDs) [17-20], mainly psychotropic and cardiovascular drugs, has been associated with

increased risk of falls and related injuries [17, 18, 20, 21], and withdrawal of FRIDs appears to be feasible and effective [19, 22-24]. Although FRIDs withdrawal is frequently incorporated in multifactorial intervention trials, evidence regarding overall FRID withdrawal as a single intervention is scarce [25].

The aim of the IMPROveFALL study and this thesis is to gain insight into the [cost]-effectiveness of FRIDs withdrawal as a method for falls reduction in older adults.

REFERENCES

1. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. Jama 2009;302:1573-9.
2. Faul M, Xu L, Wald MM, Coronado VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006. In: Centers for Disease Control and Prevention NCfIPaC, ed.; 2010.
3. Hartholt KA, Van Lieshout EMM, Polinder S, Panneman MJ, Van der Cammen TJM, Patka P. Rapid increase in hospitalizations resulting from fall-related traumatic head injury in older adults in The Netherlands 1986-2008. J Neurotrauma 2011;28:739-44.
4. Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994;331:821-7.
5. Toraman A, Yildirim NU. The falling risk and physical fitness in older people. Arch Gerontol Geriatr 2009;51:222-6.
6. Whitney SL, Wrisley DM, Marchetti GF, Gee MA, Redfern MS, Furman JM. Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the Five-Times-Sit-to-Stand Test. Phys Ther 2005;85:1034-45.
7. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
8. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr 2004;80:752-8.
9. Dukas L, Bischoff HA, Lindpaintner LS, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc 2004;52:230-6.
10. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab 2001;86:3618-28.
11. Gerdhem P, Ringsberg KA, Obrant KJ, Akesson K. Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. Osteoporos Int 2005;16:1425-31.
12. Okuno J, Tomura S, Yabushita N, et al. Effects of serum 25-hydroxyvitamin D(3) levels on physical fitness in community-dwelling frail women. Arch Gerontol Geriatr 2010;50:121-6.
13. Pfeifer M, Begerow B, Minne HW, et al. Vitamin D status, trunk muscle strength, body sway, falls, and fractures among 237 postmenopausal women with osteoporosis. Exp Clin Endocrinol Diabetes 2001;109:87-92.
14. Stewart JW, Alekel DL, Ritland LM, Van Loan M, Gertz E, Genschel U. Serum 25-hydroxyvitamin D is related to indicators of overall physical fitness in healthy postmenopausal women. Menopause 2009;16:1093-101.
15. Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 2007;92:2058-65.
16. AGS/BGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc 2010;59:148-57.
17. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. J Am Geriatr Soc 1999;47:40-50.
18. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc 1999;47:30-9.

19. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. Br J Clin Pharmacol 2007;63:232-7.
20. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 2009;169:1952-60.
21. Sterke CS, Ziere G, van Beeck EF, Looman CW, van der Cammen TJ. Dose-response relationship between selective serotonin re-uptake inhibitors and injurious falls: a study in nursing home residents with dementia. Br J Clin Pharmacol 2012;73:812-20.
22. Alsop K, Mac Mahon M. Withdrawing cardiovascular medications at a syncope clinic. Postgrad Med J 2001;77:403-5.
23. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. J Am Geriatr Soc 1999;47:850-3.
24. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. Med J Aust 2007;187:23-30.
25. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;9:CD007146.

Part II

Chapter 2.1

Circumstances leading to injurious falls in older men and women in the Netherlands

Nicole D.A. Boyé, Francesco U.S. Mattace-Raso, Nathalie van der Velde, Esther M.M. van Lieshout, Oscar J. de Vries, Klaas A. Hartholt, Albert J.H. Kerver, Milko M.M. Bruijninckx, Tischa J.M. van der Cammen, Peter Patka, Ed F van Beeck, and the IMPROveFALL trial collaborators

Injury. 2014 Aug;45(8):1224-30.
doi: 10.1016/j.injury.2014.03.021.

ABSTRACT

Background: Fall-induced injuries in persons aged 65 years and older are a major public health problem. Data regarding circumstances leading to specific injuries, such as traumatic brain injury (TBI) and hip fractures in older adults are scarce.

Objective: To investigate the activity distributions leading to indoor and outdoor falls requiring an Emergency Department (ED) visit, and those resulting in TBIs and hip fractures.

Participants: 5880 older adults who visited the ED due to a fall.

Methods: Data is descriptive and stratified by age and gender.

Results: Two-thirds of all falls occurred indoors. However, there were higher proportions of outdoor falls at ages 65-79 years (48%). Walking up or down stairs (51%) and housekeeping (17%) were the most common indoor activities leading to a TBIs. Walking (42%) and sitting or standing (16%) were the most common indoor activities leading to a hip fracture. The most common outdoor activities were walking (61% for TBIs and 57% for hip fractures) and cycling (10% for TBIs and 24% for hip fractures).

Conclusion: In the present study we found that the indoor activities distribution leading to TBIs and hip fractures differed. Notably, about half of the traumatic brain injuries and hip fractures in men and women aged 65-79 years occurred outdoors. This study provides new insights into patterns leading to injurious falls by age, gender and injury type, and may guide the targeting of falls prevention at specific activities and risk groups, including highly functional older men and women.

INTRODUCTION

Falls affect approximately a third of the population aged 65 years and older, and are associated with major adverse consequences such as disability, loss of quality of life, institutionalization, and high morbidity and mortality rates [1-8]. Furthermore, falls place a substantial burden on healthcare systems due to the large amount of visits to emergency departments, hospital admissions, admissions to long-term care and rehabilitation facilities, and related healthcare costs [3,4,7,9-11] making falls prevention a public health priority [12,13].

The most common injuries due to falls in the population aged 65 years and older in the Netherlands are superficial injuries, hip fractures, upper extremity fractures, and traumatic brain injury (TBI)[10]. Approximately 30% of people with a hip fracture will die within a year, and many more will experience significant functional loss [2]. Similarly, TBI is associated with serious consequences. Falls cause 61% of TBIs among persons aged 65 years and older in the United States [14]. Furthermore, recent studies in the United States [14], the Netherlands [15], and Finland [16] showed an increase in fall-related TBIs.

An important yet overlooked aspect regarding falls in the elderly is the paucity of evidence regarding patterns in the circumstances leading to injurious falls. Falls are the most important cause of TBIs and hip fractures in older adults, thus these patterns are valuable because they could highlight subgroups that may benefit from targeted falls prevention strategies [2,15,17]. However, data on circumstances leading to major consequences of falls in older adults, such as hip fractures and TBIs are scarce; and the number of events in the available studies is relatively low [18-21].

In this study, we investigated the indoor and outdoor activities leading to injurious falls in a large number of older men and women who visited the Emergency Department (ED) after experiencing a fall.

METHODS

Study population

For the present study, screening data were extracted from the IMPROveFALL study [22]. The IMPROveFALL study is a randomized multicenter trial investigating the effect of withdrawal of fall-risk increasing drugs versus 'care as usual' on reducing falls in community-dwelling older men and women. Patients meeting the following criteria were screened for potential enrolment in the IMPROveFALL study: aged 65 years or older, visited the ED due to a fall. A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions, *e.g.* stroke, or exogenous factors such as a traffic accident [23]. All patients meeting the screening criteria were included in the current study. Screening was performed at two academic and five regional hospitals in the Netherlands, all located in highly urbanized areas. Screening started in October 2008 and was completed in October 2011. The local Medical Research Ethics Committees at all participating sites approved the study.

Data collection

Data regarding age, gender, dwelling, date of ED visit, location of fall, activity during fall, and injuries sustained were collected from ED records. Records were made by ED personnel, were free-form, and paper or electronic depending on the hospital. Records were collected and managed by the research nurse and research physician. ED personnel were not aware of specific data being collected from records, therefore, there was a fair amount of missing data. Regarding the location of the fall, 27% of the data were missing; and regarding activity prior to the fall, 34% of the data was missing. Data regarding hospital stay and hospital mortality were not collected.

Age was categorised as 65 to 79 years old or 80 years and older. Dwelling was categorised as community-dwelling or living in a care facility (assisted living facility or nursing home). Location at time of fall was categorised as indoors or outdoors. Activity at time of fall was categorised as walking, sitting or standing, walking up or down stairs, lavatory visit, sports and recreation, out of bed, housekeeping, cycling, or other. Season during which fall occurred was categorised as winter (December, January and February), spring (March. April and May), summer (June, July and August) , and autumn (September, October and November). Injuries were defined by the International Classification of Diseases 10th revision (ICD-10) [24] and categorised as superficial injury, open wound, head injuries (*i.e.*, superficial injury, open wound, skull/facial fracture, and TBI), and fractures (*i.e.*, spine, rib, shoulder and upper arm, elbow and forearm, wrist and hand, pelvis, hip, knee and lower leg, or ankle and foot). Activity distributions leading to indoor and outdoor falls were described separately for all falls, and for the two major fall-related injuries, *i.e.* TBIs and hip fractures.

RESULTS

In total data of 5880 fall-related ED visits of persons aged 65 years and older were included in this study. The mean age was 80 years with a standard deviation of 8, and the study population consisted of 1824 (31%) men and 4056 (69%) women.

The overall gender and age specific circumstances surrounding a fall are shown in table 1. Data concerning dwelling was obtained from 5489 patients. Most patients were community-dwelling (n=4734, 86%), with 95% of both men and women aged 65-79 years, and 83% of the men and 75% of women aged ≥ 80 years being community-dwelling, the remaining were residing in a care facility. Data concerning location of the fall were obtained from 4279 patients. Most falls occurred indoors (n=2773, 65%).

Table 1. Circumstances surrounding injurious falls stratified by gender and age

	Total	**Men**			**Women**		
		65-79y	≥ 80y	Total	65-79y	≥ 80y	Total
	n = 5880	n = 1095	n = 729	n = 1824	n = 1851	n = 2205	n = 4056
Dwelling	n = 5489	n = 1065	n = 673	n = 1738	n = 1753	n = 1998	n = 3751
Community	4734 (86)	1013 (95)	561 (83)	1574 (91)	1663 (95)	1497 (75)	3160 (84)
Care facility	755 (14)	52 (5)	112 (17)	164 (9)	90 (5)	501 (25)	591 (16)
Location	n = 4279	n = 815	n = 562	n = 1377	n = 1306	n = 1596	n =2902
Indoor	2773 (65)	428 (53)	390 (69)	818 (59)	673 (52)	1282 (80)	1955 (67)
Outdoor	1506 (35)	387 (48)	172 (31)	559 (41)	633 (48)	314 (20)	947 (33)
Activity	n = 3871	n = 818	n = 472	n = 1290	n = 1302	n = 1279	n = 2581
Walking	1898 (49)	314 (38)	232 (49)	546 (42)	690 (53)	662 (52)	1352 (52)
Sitting & Standing	371 (10)	63 (8)	56 (12)	119 (9)	90 (7)	162 (13)	252 (10)
Walking up or down stairs	409 (11)	142 (17)	45 (10)	187 (15)	142 (11)	80 (6)	222 (9)
Lavatory visit	161 (4)	22 (3)	21 (4)	43 (3)	42 (3)	76 (6)	118 (5)
Sports & Recreation	51 (1)	21 (3)	3 (1)	24 (2)	20 (2)	7 (1)	27 (1)
Out of bed	107 (3)	15 (2)	18 (4)	33 (3)	19 (2)	55 (4)	74 (3)
Housekeeping	331 (9)	85 (10)	38 (8)	123 (10)	88 (7)	120 (9)	208 (8)
Cycling	200 (5)	74 (9)	13 (3)	87 (7)	88 (7)	25 (2)	113 (4)
Other	343 (9)	82 (10)	46 (10)	128 (10)	123 (9)	92 (7)	215 (8)
Season	n = 5880	n = 1095	n = 729	n = 1824	n = 1851	n = 2205	n = 4056
Winter	1258 (21)	265 (24)	160 (22)	425 (23)	437 (24)	396 (18)	833 (21)
Spring	1472 (25)	292 (27)	194 (27)	486 (27)	448 (24)	538 (24)	986 (24)
Summer	1802 (31)	306 (28)	201 (28)	507 (28)	549 (30)	746 (34)	1295 (32)
Autumn	1348 (23)	232 (21)	174 (24)	406 (22)	417 (23)	525 (24)	942 (23)

Data are given as number (percentages).

However, this differed between the age and gender categories; there were higher proportions of outdoor falls at ages 65-79 years (48%), and overall 41% of the men fell outdoors. Data concerning activity were obtained from 3871 participants. Overall, the most common activity

at time of the fall was walking (n=1898, 49%). Other common activities were walking up or down stairs (n=409, 11%) and sitting / standing (n=371, 10%). Data concerning the season during which the fall occurred was obtained from all 5880 patients. Overall most falls occurred during summer (n=1802, 31%), 28% of men and 32% of women fell during summer. The least amount of falls occurred during autumn (22%) for men, and winter (21%) for women.

Of the ED records with missing data regarding either the location or activity at time of the fall, the mean age was 81 years with a standard deviation of 8, and the population consisted of 687 (27%) men, and 1822 (73%) women. Furthermore, 1819 (81%) were community-dwelling, and 421 (19%) resided in a care-facility.

The age and gender specific injuries following a fall are shown in table 2. Data concerning injury were collected from all 5880 patients. Falls caused superficial injury in 1951 patients (33%), open wounds in 461 (8%), TBIs in 254 (4%) and fractures in 2700 (46%) of the population. The most common fracture was a hip fracture (n=883, 15%).

All injurious falls

The location and activity surrounding a fall requiring an ED visit was obtained from 3371 records and are shown in figure 1. The overall most common indoor activities were walking (n=658, 34%) and walking up or down stairs (n=322, 17%) [Figure 1 A, B]. The overall most common outdoor activities were walking (n=946, 66%) and cycling (n=200, 14%) [Figure 1 C, D].

Traumatic brain injury

Overall, 254 falls resulted in a TBI. The location and activity surrounding a fall leading to a TBI was obtained from 176 records and are shown in figure 2. Falls resulting in TBIs had a

similar indoor (n=92, 52%) and outdoor (n=84, 48%) prevalence. The most common indoor activities were walking up or down stairs (n=47, 51%) and housekeeping (n=16, 17%) [Figure 2 A, B]. The most common outdoor activities were walking (n=51, 61%) and cycling (n=8, 10%) [Figure 2 C, D].

Table 2. Injuries following a fall stratified by gender and age

	Total	**Men**			**Women**		
		65-79y	≥ 80y	Total	65-79y	≥ 80y	Total
	n = 5880	n = 1095	n = 729	n = 1824	n = 1851	n = 2205	n = 4056
Superficial injury	1951 (33)	385 (35)	244 (34)	629 (35)	603 (33)	719 (33)	1322 (33)
Open wound	461 (8)	103 (9)	96 (13)	199 (11)	109 (6)	153 (7)	262 (7)
Injuries to the head							
SI head	629 (11)	150 (14)	97 (13)	247 (14)	160 (9)	222 (10)	382 (9)
Open wound of head	289 (5)	69 (6)	74 (10)	143 (8)	66 (4)	79 (4)	145 (4)
Skull/facial fracture	82 (1)	19 (2)	8 (1)	27 (2)	26 (1)	29 (1)	55 (1)
Traumatic brain injury	254 (4)	81 (7)	42 (6)	123 (7)	67 (4)	64 (3)	131 (3)
Fractures							
All fractures	2700 (46)	349 (32)	274 (38)	623 (34)	929 (50)	1148 (52)	2077 (51)
Spine	127 (2)	24 (2)	12 (2)	36 (2)	37 (2)	54 (2)	91 (2)
Rib	92 (2)	35 (3)	14 (2)	49 (3)	13 (1)	30 (1)	43 (1)
Shoulder and upper arm	400 (7)	53 (5)	38 (5)	91 (5)	160 (9)	149 (7)	309 (8)
Elbow and forearm	517 (9)	57 (5)	19 (3)	76 (4)	248 (13)	193 (9)	441 (11)
Wrist and hand	289 (5)	42 (4)	20 (3)	62 (3)	139 (8)	88 (4)	227 (6)
Pelvis	133 (2)	9 (1)	10 (1)	19 (1)	33 (2)	81 (4)	114 (3)
Hip	883 (15)	86 (8)	143 (20)	229 (13)	170 (9)	484 (22)	654 (16)
Knee and lower leg	106 (2)	15 (1)	9 (1)	24 (1)	43 (2)	39 (2)	82 (2)
Ankle and foot	174 (3)	22 (2)	9 (1)	31 (2)	93 (5)	50 (2)	143 (4)

Data are given as number (percentages). SI: superficial injury.

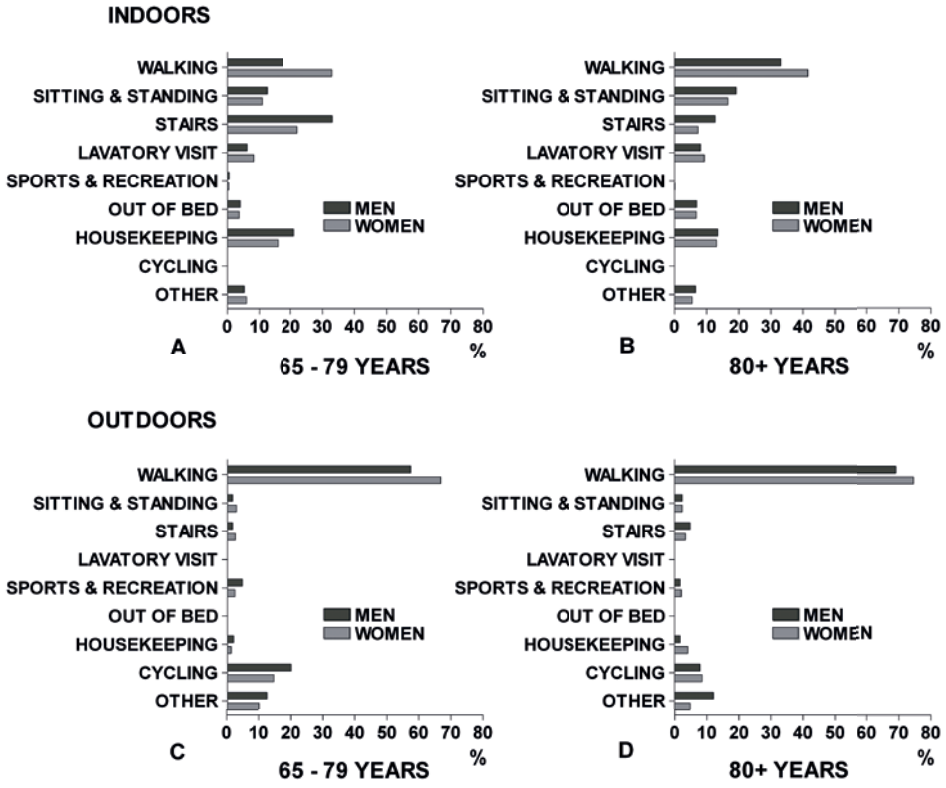
Hip fractures

Overall, 883 falls resulted in a hip fracture. The location and activity surrounding a fall leading to a hip fracture was obtained from 468 records and are shown in figure 3. A fall resulting in a hip fracture most commonly occurred indoors (n=341, 73%) except for the men aged 65-79 years, in whom hip fractures most commonly occurred outdoors (n=33, 54%). The most common indoor activities were walking (n=144, 42%) and sitting or standing (n=55, 16%) [Figure 3 A, B]. The most common outdoor activities were walking (n=72, 57%) and cycling (n=30, 24%) [Figure 3 C, D].

Falls by season

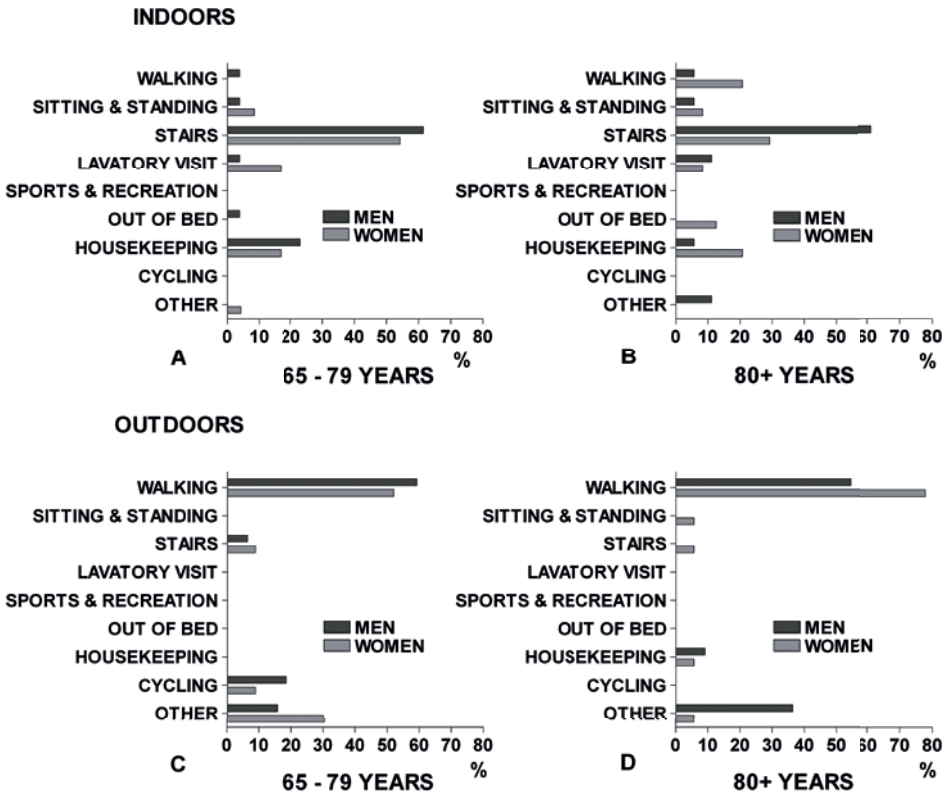
The season, location and activity surrounding a fall requiring an ED visit was obtained from 3371 records and are shown in supplementary figure X. The most common indoor activities surrounding a fall during winter were walking (n=123, 33%) and walking up or down stairs (n=65, 18%). The most common outdoor activities surrounding a fall during winter were walking (n=300, 77%) and cycling (n=37, 10%). The most common indoor activities during spring were walking (n=160, 33%) and walking up or down stairs (n=79, 16%) and housekeeping (n=79, 16%). The most common outdoor activities during spring were walking (n=224, 64%) and cycling (n=44, 13%). The most common indoor activities during summer were walking (n=192, 33%) and walking up or down stairs (n=100, 17%). The most common outdoor activities during summer were walking (n=227, 59%) and cycling (n=84, 22%). The most common indoor activities during autumn were walking (n=183, 36%) and housekeeping (n=87, 17%). The most common outdoor activities during autumn were walking (n=195, 65%) and cycling (n=35, 12%).

Figure 1. Circumstances leading to all injurious falls, stratified by age and gender.



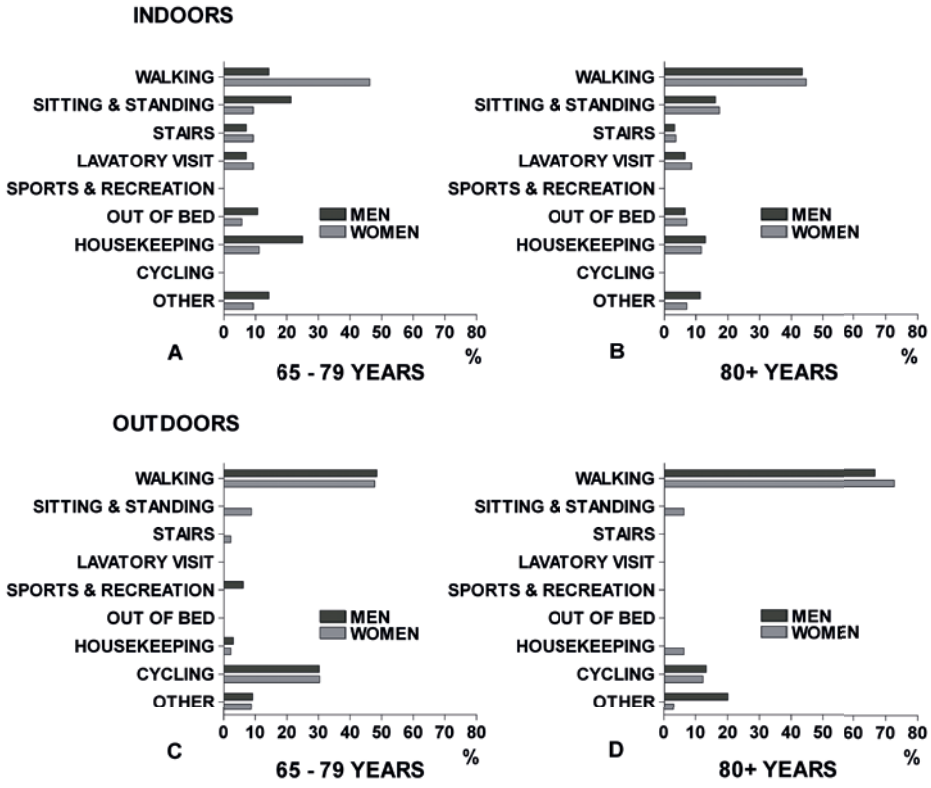
Indoor (A, B) and outdoor (C, D) activities leading to a fall requiring an Emergency Department visit, stratified by the age categories 65-79 years (A, C) and 80+ years (B, D). Data are shown in percentages.

Figure 2. Circumstances surrounding falls leading to traumatic brain injury, stratified by age and gender.



Indoor (A, B) and outdoor (C, D) activities leading to a traumatic brain injury, stratified by the age categories 65-79 years (A, C) and 80+ years (B, D). Data are shown in percentages.

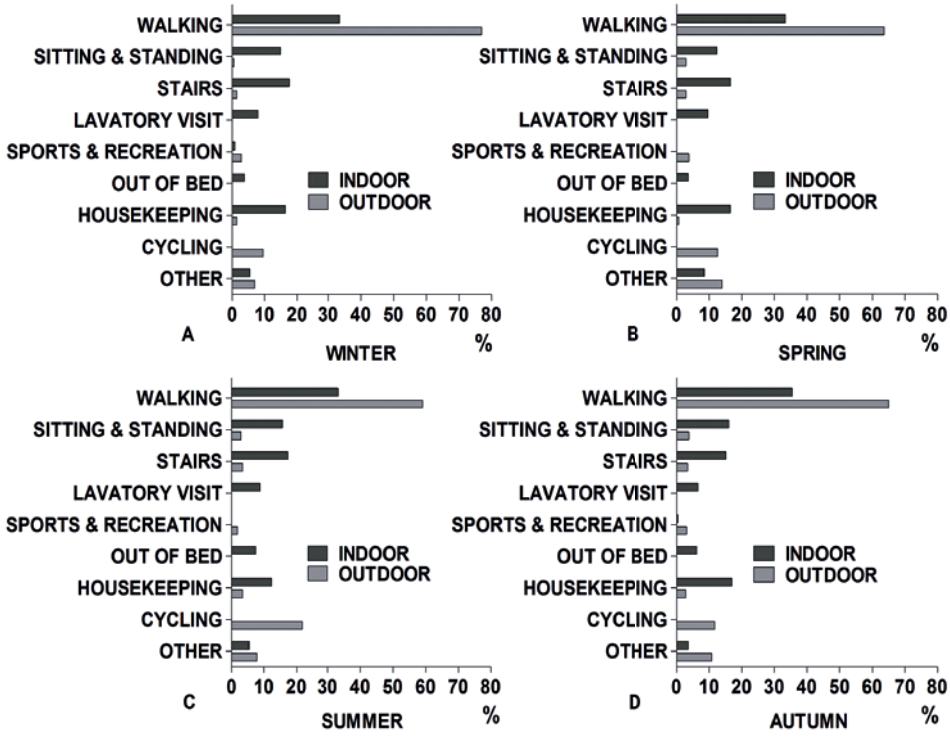
Figure 3. Circumstances surrounding falls leading to a hip fracture, stratified by age and gender.



Indoor (A, B) and outdoor (C, D) activities leading to a hip fracture, stratified by the age categories 65-79 years (A, C) and 80+ years (B, D). Data are shown in percentages.

SUPPLEMENTARY

Figure X. Circumstances surrounding all falls, stratified by location and season.



Activities leading to a fall stratified by the seasons, winter (A), spring (B), summer (C), autumn (D), and location (indoor and outdoor). Data are shown in percentages.

DISCUSSION

In this study two-thirds of all falls occurred indoors. However, this differed between the age and gender categories, with higher proportions of outdoor falls at ages 65-79 years and among men. The overall most common indoor activities leading to injurious falls were walking and walking up or down stairs. The overall most common outdoor activities were walking and cycling. We found that the indoor activities leading to major injuries, *i.e.* TBIs and hip fractures differed. Walking up or down stairs and housekeeping were the most common activities leading to a TBIs whereas walking and sitting / standing were the most common activities leading to a hip fracture. Notably, about half of the traumatic brain injuries and hip fractures in men and women aged 65-79 years occurred outdoors. The most common outdoor activities leading to both injuries were walking and cycling. To our knowledge this is the largest study investigating patterns leading to fall-related TBIs and hip fractures in community dwelling older adults.

Falls are the leading cause of TBIs and hip fractures in the elderly population [4,15,17]. Falls cause 61% of traumatic brain injuries in persons aged 65 years and older in the US [17], and recent studies in the US, the Netherlands, and Finland showed an increase in fall-related TBIs [15-17]. About 30% of people with a hip fracture will die in the following year, and many more will experience significant functional loss [2]. Furthermore, TBIs and hip fractures contribute considerably to healthcare costs [4]. Therefore, interventions targeted toward this group have the potential to be very (cost-) effective. The two most common indoor activities leading to a TBI were walking up or down stairs and housekeeping. Furthermore, about half of the hip fractures in men and women aged 65-79 years occurred outdoors, and approximately a third of those while cycling. These all suggest high activity levels. Up to now, little to no special attention has been paid to outdoor activities such as cycling and

'higher level' activities such as housekeeping. Few have incorporated strategies for falls prevention derived from these specific circumstances. Partly, this can be accomplished by education of the risk groups. Healthy and highly functional older adults may be unaware that their higher activity levels may increase their risk for falling and subsequent injuries [25]. Another possibility is the elimination of outdoor environmental hazards involving sidewalks, curbs, and streets, such as by promptly repairing uneven surfaces, removing debris, and painting curbs [26,27]. Furthermore, promotion of measures which can reduce the severity of injuries following a fall, such as bicycle helmets, should also be considered [28].

It should be noted that in the Netherlands about 27% of all travel is done by bicycle. As a consequence, the data presented is more relevant in countries where cycling is common. Other western countries where cycling is a common mode of transportation are, Denmark (18% of all travel), Finland (11%), Germany (10%), and Sweden (10%) [29]. Whereas in the United States and the United Kingdom only 1% of all trips are by bicycle [29].

In this study, most falls occurred during summer (31%), and the least during winter (21%), this differed from other studies [30-32], where most falls occurred during winter, and a recent study which showed seasons had no effect on fall rates [33]. Possibly more falls occurred during summer due to people being more active during the warm summer months compared to winter. Furthermore, snow and ice might not have been a major factor as in previous studies, due to the relatively mild winters in urban areas of the Netherlands. The most common indoor and outdoor activities leading to a fall during the four seasons were similar, noteworthy were the rates for walking outdoors during winter (77%), and cycling outdoors during summer (22%).

Various studies have investigated circumstances surrounding falls in older adults [25-27,34-45]. However, these studies investigated falls in general and not falls resulting in major injuries. Furthermore, the study population of two of the latest studies consisted of older

adults dwelling in care-facilities, an older and frailer population, in which the majority of falls occurred indoors [33,44]. Two recent studies suggest that different types of fall-risk assessment are needed for indoor and outdoor fallers. And propose that, prevention recommendations would be more effective if targeted differently for frail, inactive older people at risk for indoor falls and relatively active healthy older people at risk for outdoor falls [41,42].

The following limitations should be acknowledged when interpreting the results of this study. First, all data were gathered from ED records, we did not include persons who visited a general practitioner or persons who did not seek medical attention after a fall. Therefore, this is not a report on circumstances surrounding all falls in older adults. Nevertheless, our objective was to investigate falls resulting in injuries, not falls in general. Second, the Netherlands has more bicyclists and pedestrians that most Western countries, reducing the generalizability. Third, part of the data regarding either the location or the activity at time of fall was missing from ED records, which may have introduced bias into the results. Overall, the patient characteristics of the missing records differed slightly regarding age, gender and dwelling. However, the most significant difference was the hospital where data was gathered, possibly due to differences in recordkeeping methods. Furthermore, these results are otherwise scarce and remain valuable, especially for the subgroup of older men and women with 'higher level' activities. Strengths of this study include the study population size, and that data was collected from ED records and thus included detailed information concerning injuries sustained.

In conclusion, in the present study we found distinct fall and injury patterns, *i.e.* where and how, leading to TBIs and hip fractures in older men and women. Notably, about half of the traumatic brain injuries and hip fractures in men and women aged 65-79 years occurred outdoors. This study provides new insights into patterns leading to injurious falls by age,

gender and injury type, and may guide the targeting of falls prevention at specific activities and risk groups, including highly functional older men and women.

REFERENCES

1. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. *Osteoporos Int.* Feb 2004;15(2):87-94.

2. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *Jama.* Oct 14 2009;302(14):1573-1579.

3. Close JC, Lord SR, Antonova EJ, Martin M, Lensberg B, Taylor M, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. *Emerg Med J.* Oct 1 2011.

4. Hartholt KA, van Beeck EF, Polinder S, van der Velde N, van Lieshout EM, Panneman MJ, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* Sep 2010;71(3):748-753.

5. Kochanek KD, Xu JQ, Murphy SL, al. e. Deaths: Preliminary data for 2009. . Vol National vital statistics reports; vol 59 no 4.: Hyattsville, MD: National Center for Health Statistics. ; 2011.

6. Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. *Osteoporos Int.* 2000;11(5):460-466.

7. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev.* Oct 2006;12(5):290-295.

8. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med.* Sep 29 1994;331(13):821-827.

9. Greenspan AI, Coronado VG, Mackenzie EJ, Schulman J, Pierce B, Provenzano G. Injury hospitalizations: using the nationwide inpatient sample. *J Trauma.* Nov 2006;61(5):1234-1243.

10. Hartholt KA, van der Velde N, Looman CW, van Lieshout EMM, Panneman MJ, van Beeck EF, et al. Trends in fall-related hospital admissions in older persons in the Netherlands. *Arch Intern Med.* May 24 2010;170(10):905-911.

11. Scuffham P, Chaplin S, Legood R. Incidence and costs of unintentional falls in older people in the United Kingdom. *J Epidemiol Community Health.* Sep 2003;57(9):740-744.

12. AGS/BGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc.* Jan 2010;59(1):148-157.

13. AGS/BGS/AAOS. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* May 2001;49(5):664-672.

14. Faul M, Xu, L., Wald, M., and Coronado, V. . Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006. . *Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: Atlanta.* 2010.

15. Hartholt KA, Van Lieshout EMM, Polinder S, Panneman MJ, Van der Cammen TJM, Patka P. Rapid increase in hospitalizations resulting from fall-related traumatic head injury in older adults in The Netherlands 1986-2008. *J Neurotrauma.* May 2011;28(5):739-744.

16. Kannus P, Niemi S, Parkkari J, Palvanen M, Sievanen H. Alarming rise in fall-induced severe head injuries among elderly people. *Injury.* Jan 2007;38(1):81-83.

17. Faul M, Xu L, Wald MM, Coronado VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006. In: Centers for Disease Control and Prevention NCfIPaC, ed2010.

18. Abolhassani F, Moayyeri A, Naghavi M, Soltani A, Larijani B, Shalmani HT. Incidence and characteristics of falls leading to hip fracture in Iranian population. *Bone.* Aug 2006;39(2):408-413.

19. Aharonoff GB, Dennis MG, Elshinawy A, Zuckerman JD, Koval KJ. Circumstances of falls causing hip fractures in the elderly. *Clin Orthop Relat Res.* Mar 1998(348):10-14.

20. Allander E, Gullberg B, Johnell O, Kanis JA, Ranstam J, Elffors L. Circumstances around the fall in a multinational hip fracture risk study: a diverse pattern for prevention. MEDOS Study Group). Mediterranean Osteoporosis Study. *Accid Anal Prev.* Sep 1998;30(5):607-616.

21. Harvey LA, Close JC. Traumatic brain injury in older adults: characteristics, causes and consequences. *Injury.* Nov 2012;43(11):1821-1826.

22. Hartholt KA, Boyé NDA, Van der Velde N, Van Lieshout EMM, Polinder S, De Vries OJ, et al. [Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study). *BMC Geriatr.* 2011;11:48.

23. KIWG. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan Med Bull.* Apr 1987;34 Suppl 4:1-24.

24. WHO. ICD-10: International statistical classification of diseases and related health problems 10th Rev. ed.: World Health Organization 2008.

25. Bath PA, Morgan K. Differential risk factor profiles for indoor and outdoor falls in older people living at home in Nottingham, UK. *Eur J Epidemiol.* Jan 1999;15(1):65-73.

26. Lai PC, Wong WC, Low CT, Wong M, Chan MH. A small-area study of environmental risk assessment of outdoor falls. *J Med Syst.* Dec 2011;35(6):1543-1552.

27. Li W, Keegan TH, Sternfeld B, Sidney S, Quesenberry CP, Jr., Kelsey JL. Outdoor falls among middle-aged and older adults: a neglected public health problem. *Am J Public Health.* Jul 2006;96(7):1192-1200.

28. Macpherson A, Spinks A. Bicycle helmet legislation for the uptake of helmet use and prevention of head injuries. *Cochrane Database Syst Rev.* 2008(3):CD005401.

29. Pucher J, Buehler J. Making Cycling Irresistible: Lessons from the Netherland, Denmark, and Germany. *Transport Reviews.* July 2008 2008;28(4):495–528.

30. Berg WP, Alessio HM, Mills EM, Tong C. Circumstances and consequences of falls in independent community-dwelling older adults. *Age Ageing.* Jul 1997;26(4):261-268.

31. Kojima S, Furuna T, Ikeda N, Nakamura M, Sawada Y. Falls among community-dwelling elderly people of Hokkaido, Japan. *Geriatr Gerontol Int.* Dec 2008;8(4):272-277.

32. Nachreiner NM, Findorff MJ, Wyman JF, McCarthy TC. Circumstances and consequences of falls in community-dwelling older women. *J Womens Health (Larchmt).* Dec 2007;16(10):1437-1446.

33. Rapp K, Becker C, Cameron ID, Konig HH, Buchele G. Epidemiology of falls in residential aged care: analysis of more than 70,000 falls from residents of bavarian nursing homes. *J Am Med Dir Assoc.* Feb 2012;13(2):187 e181-186.

34. Ashley MJ, Gryfe CI, Amies A. A longitudinal study of falls in an elderly population II. Some circumstances of falling. *Age Ageing.* Nov 1977;6(4):211-220.

35. Bergland A, Pettersen AM, Laake K. Falls reported among elderly Norwegians living at home. *Physiother Res Int.* 1998;3(3):164-174.

36. Bleijlevens MH, Diederiks JP, Hendriks MR, van Haastregt JC, Crebolder HF, van Eijk JT. Relationship between location and activity in injurious falls: an exploratory study. *BMC Geriatr.* 2010;10:40.

37. Campbell AJ, Borrie MJ, Spears GF, Jackson SL, Brown JS, Fitzgerald JL. Circumstances and consequences of falls experienced by a community population 70 years and over during a prospective study. *Age Ageing.* Mar 1990;19(2):136-141.

38. Coutinho ES, Bloch KV, Rodrigues LC. Characteristics and circumstances of falls leading to severe fractures in elderly people in Rio de Janeiro, Brazil. *Cad Saude Publica.* Feb 2009;25(2):455-459.

39. Hill K, Schwarz J, Flicker L, Carroll S. Falls among healthy, community-dwelling, older women: a prospective study of frequency, circumstances, consequences and prediction accuracy. *Aust N Z J Public Health.* Feb 1999;23(1):41-48.

40. Jensen J, Lundin-Olsson L, Nyberg L, Gustafson Y. Falls among frail older people in residential care. *Scand J Public Health.* 2002;30(1):54-61.

41. Kelsey JL, Berry SD, Procter-Gray E, Quach L, Nguyen US, Li W, et al. Indoor and outdoor falls in older adults are different: the maintenance of balance, independent living, intellect, and Zest in the Elderly of Boston Study. *J Am Geriatr Soc.* Nov 2010;58(11):2135-2141.

42. Kelsey JL, Procter-Gray E, Berry SD, Hannan MT, Kiel DP, Lipsitz LA, et al. Reevaluating the implications of recurrent falls in older adults: location changes the inference. *J Am Geriatr Soc.* Mar 2012;60(3):517-524.

43. Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. *J Gerontol.* Sep 1991;46(5):M164-170.

44. Robinovitch SN, Feldman F, Yang Y, Schonnop R, Leung PM, Sarraf T, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet.* Jan 5 2012;381(9860):47-54.

45. Yasumura S, Haga H, Niino N. Circumstances of injurious falls leading to medical care among elderly people living in a rural community. *Arch Gerontol Geriatr.* Sep-Oct 1996;23(2):95-109.

Chapter 2.2

Vitamin D and physical performance in older men and women visiting the emergency department because of a fall

Nicole D.A. Boyé, Christian Oudshoorn, Nathalie van der Velde, Esther M.M. van Lieshout, Oscar J. de Vries, Paul Lips, Ed F. van Beeck, Peter Patka, Tischa J.M. van der Cammen

J Am Geriatr Soc. 2013 Nov;61(11):1948-52.
doi: 10.1111/jgs.12499.

ABSTRACT

Background: Vitamin D deficiency is considered a key contributor to impaired physical performance. However, many studies demonstrating this relationship were conducted in female-only populations, and recent studies investigating men specifically found no association. Nevertheless, evidence regarding an underlying gender-specific mechanism is lacking.

Objectives: To investigate whether serum 25-hydroxy vitamin D [25(OH)D] is associated with physical performance in both men and women.

Design: Cross-sectional.

Setting: Community.

Participants: 616 older adults who visited the Emergency Department due to a fall.

Measurements: Physical performance was assessed with the Timed "Up & Go" test, the "Five Time Sit to Stand" test, handgrip strength, and the tandem stand test. Multivariate linear regression was used to assess the association between physical performance, and (log transformed) serum 25 (OH)D concentration, and adjust for potential confounders.

Results: In men, the serum 25(OH)D concentration was significantly associated with better handgrip strength, with a regression coefficient (B) and [95% CI] of 3.86 [2.04; 5.69], faster TUG times -2.82 [-4.91; -0.73], and faster FTSS times -3.39 [-5.67; -1.11]. In women, a higher serum 25(OH)D concentration was significantly associated with faster TUG times -2.68 [-4.87; -0.49].

Conclusion: In the present study, we found a positive association between vitamin D and physical performance in both men and women. Intervention studies are needed which include vitamin D deficient, older, community-dwelling men and women, to further investigate the effect of vitamin D supplementation in this particular group.

INTRODUCTION

A decrease in physical performance, such as impaired mobility, reduced muscle strength or poor balance, predisposes to falls and related injuries [1-3]. Furthermore, it results in loss of quality of life [4], threatens functional independence [5-7], and increases the risk of morbidity and mortality [8,9]. Therefore, identification of modifiable causes of physical impairment can aid in the prevention of decline of functional-independence, future falls, associated morbidity, and loss of quality of life [10].

Muscle tissue is an important target tissue of vitamin D [11]. Furthermore, vitamin D deficiency has been shown to be a key contributor to a decline in physical performance and increase in fall incidence [12-19]. However, most studies demonstrating the relationship between vitamin D levels and physical performance were conducted in female-only populations [12,15-18]. In addition, recent studies investigating the relationship between serum 25(OH)D levels and physical performance in men found no significant associations [20,21]. However, these studies were conducted in a population of highly functional, younger men with a low prevalence of vitamin D deficiency. Furthermore, evidence regarding an underlying gender-specific mechanism is lacking.

Therefore, we assessed whether serum 25(OH)D was associated with physical performance in community-dwelling older men and women who visited the emergency department (ED) after experiencing a fall. We hypothesized that this association is as strong in men as previously demonstrated in women.

METHODS

Data collection

For this study, baseline data of the IMPROveFALL study were used, a detailed description of the methods can be found elsewhere [22]. In short, patients meeting the following inclusion criteria were eligible for enrolment: aged 65 years or older, visited the ED due to a fall, use of one or more fall-risk increasing drugs [22-26]; Mini-Mental State Examination (MMSE) score of at least 21 out of 30 points [27], ability to walk independently, community dwelling, and provision of written informed consent by patient. Enrolment started in October 2008 and was completed in October 2011. The local Medical Research Ethics Committee approved the study protocol.

Covariates

A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions, *e.g.* stroke, or exogenous factors such as a traffic accident [28]. At the baseline assessment, a geriatric assessment was performed. Medical history, prescription medication, supplements and lifestyle factors (*e.g.*, education, smoking, and alcohol intake) were documented. The number of comorbidities was derived from the following chronic comorbidities: any malignancy, diabetes mellitus, cardiac disease (*i.e.* hypertension, myocardial infarction, cardiomyopathy, congestive heart failure, arrhythmia, and valve disease), chronic obstructive pulmonary disease, stroke, neurological disorders (*i.e.* Parkinson's disease, epilepsy, neuropathy, myopathy, spinal disc herniation, and multiple sclerosis), peripheral vascular disease, renal insufficiency, and arthritis. Collected data were verified with records from the patient's general physician and local pharmacist. Height and weight were measured using standardized equipment and procedure. Body mass index (BMI) was calculated as body weight (in kilograms) divided by height² (in meters).

Biochemistry

Non-fasting blood samples were collected at the baseline assessment. Serum 25(OH)D_3 levels (in nmol/l) were measured using a radio-immuno-assay (DiaSorin, Saluggia (Vercelli) - Italy). Intra-assay and inter-assay coefficients of variation were <10%. Serum 25(OH)D groups were chosen based on levels of vitamin D deficiency as described in the literature [11,29]; i.e. severe vitamin D deficiency < 25 nmol/l, moderate vitamin D deficiency 25 – 49.9 nmol/L, and sufficient vitamin D levels, of 50-74.9 nmol/L, and ≥ 75 nmol/L.

Physical performance

Physical performance was assessed with handgrip strength measurements, the Timed "Up & Go" (TUG) test, the Five Time Sit to Stand (FTSS) test, and the tandem stand test. Handgrip strength [30], was measured in kilograms using a digital strain-gauged dynamometer (Takei TKK 5401, Takei Scientific Instruments Co, Ltd., Tokyo, Japan). The participant was asked to stand upright with arms hanging beside his or her body. Subsequently, grip strength was measured with the left and right hand. In the TUG test [31,32], time was measured while the participant stood up from a sitting position, walked three meters along a line, performed a 180 degree turn, walked back to the chair and sat down, as fast as safely possible. In the FTSS test [3,31], time was measured while the participant stood up and sat down five consecutive times, as fast as safely possible. The participant was not permitted to use their hands or the chair's arm supports during standing up or sitting down. In the tandem stand test, the participant had to stand fully independent for 10 seconds with one foot in front of the other. The test was scored as completed (1) or failed (0) [31]. All tests were performed twice and the best score was recorded.

Statistical analysis

All analyses were performed using the Statistical Package of the Social Sciences (SPSS version 17.0, Chicago, Ill.). Baseline characteristics were compared using Student t-test analyses for continuous variables and chi-square analyses for dichotomous variables. Linear regression and binary logistic regression models were constructed to adjust for potential confounders. The crude model was solely age-adjusted. Potential confounders that were considered for inclusion in the multivariate model besides age, were number of comorbidities, degree of urbanization, marital status, level of education, current or past smoker, alcohol units p/day, MMSE, and BMI. Confounders that led to a change in the regression coefficient (B) of 10% or more were retained in the multivariate-adjusted regression model. Participants with incomplete or missing performance test measures were excluded from related analyses, handgrip strength (n=7), TUG test (n=55), FTSS test (n=95), and the tandem stand test (n=4). Missing measures were mostly due to injuries following fall (e.g. upper or lower extremity fractures), or pre-existing conditions. Due to a right-skewed distribution, serum 25-(OH)D levels were log transformed (natural log) for the regression models. Furthermore, a general linear model (GLM) was used to multivariately compare all continuous outcomes, and chi-square analyses to compare the tandem stand outcomes. All analyses were stratified by gender, and a p-value < 0.05 was considered statistically significant.

RESULTS

In total, 616 participants were enrolled in the IMPROveFALL study. Serum 25(OH)D concentration was obtained from 600 participants, 230 (38%) men and 370 (62%) women respectively. The gender-specific baseline characteristics are shown in Table 1; the mean age was 76 years with a standard deviation (SD) of 7. The mean ± SD serum 25(OH)D concentration was 59 ± 29 nmol/L.

Table 1. Baseline characteristics according to gender

		Men (n=230)	**Women** (n=370)	***p*-value**
Age (years)		76.4 ± 6.7	76.5 ± 7.0	0.820
Serum 25(OH)D		58.9 ± 30.9	58.7 ± 27.8	0.939
Mini Mental State Examination score		27.0 ± 2.3	26.9 ± 2.4	0.716
Body mass index (kg/m^2)		27.1 ± 3.9	27.9 ± 4.9	0.027
Level of education (secondary)		185 (80)	250 (68)	<0.001
Degree of urbanization (urban)		190 (83)	323 (87)	0.142
Smoking				
	Current	28 (12)	40 (11)	0.609
	Past	152 (66)	122 (33)	<0.001
	Never	76 (33)	245 (66)	<0.001
Alcohol units p/day				<0.001
	0	92 (40)	212 (57)	
	<1	24 (10)	63 (17)	
	1-3	66 (29)	78 (21)	
	>3	48 (21)	17 (5)	
Vitamin D supplements		14 (6)	61 (17)	<0.001
Number of comorbidities		2.1 ± 1.2	2.1 ± 1.2	0.654
Number of medications		5.9 ± 2.9	6.5 ± 3.5	0.027
Number of FRIDs		2.5 ± 1.5	2.7 ± 1.6	0.378

Data are given as mean values ± standard deviation, or as number (percentages). FRID: fall-risk increasing drugs.

Stratification according to vitamin D status is shown in Table 2. Of the participants, 55 (9%) had severe vitamin D deficiency (25(OH)D < 25 nmol/L), 209 participants (35%) had moderate vitamin D deficiency (25(OH)D 25-49.9 nmol/L), 172 participants (29%) were vitamin D-sufficient and had 25(OH)D levels of 50-74.9 nmol/L, and 164 participants (27%) had 25(OH)D levels ≥ 75 nmol/L.

Table 2. Serum 25 (OH)D groups stratified by gender

	Men (n=230)		**Women** (n=370)	
25(OH)D < 25 nmol/L	19	(8)	36	(10)
25(OH)D 25 – 49.9 nmol/L	83	(36)	126	(34)
25(OH)D 50 – 74.9 nmol/L	72	(31)	100	(27)
25(OH)D ≥ 75 nmol/L	56	(24)	108	(29)

Data are shown as number (percentage)

Regression models of the physical performance according to log-transformed serum 25(OH)D concentration were constructed (Table 3). The results for the men were as follows, in the fully adjusted model a higher serum 25(OH)D concentration was significantly associated with better handgrip strength, with a regression coefficient (B) and [95% CI] of 3.86 [2.04; 5.69], faster TUG times -2.82 [-4.91; -0.73], and faster FTSS times -3.39 [-5.67; -1.11]. In women, a higher serum 25(OH)D concentration was significantly associated with faster TUG times -2.68 [-4.87; -0.49].

Table 3. Results of regression analysis of strength and physical performance according to log transformed serum 25 (OH)D concentration and gender

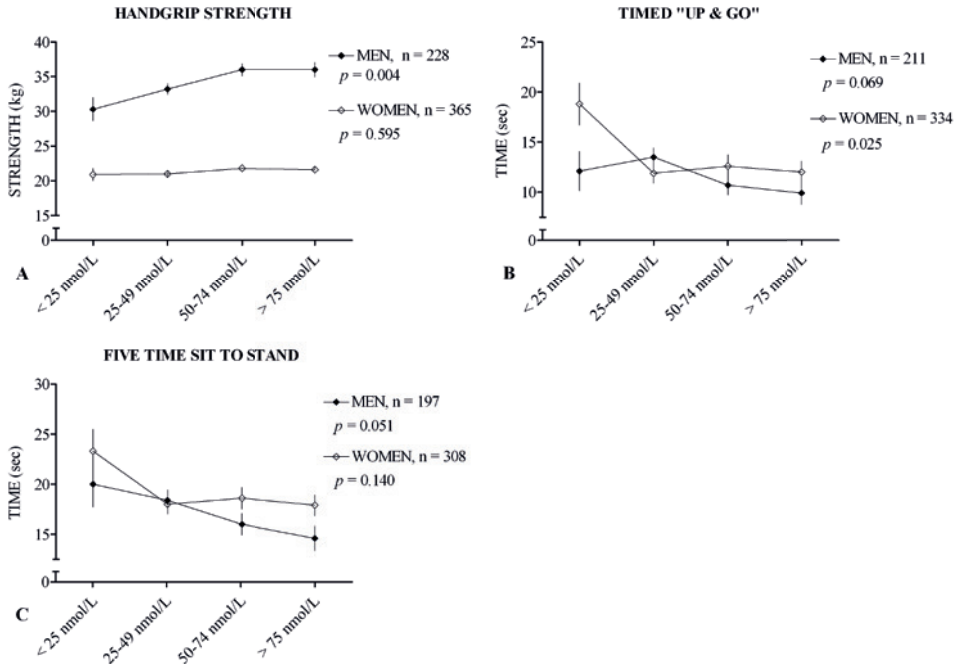
	Model 1		Model 2	
Men (n = 230)				
Handgrip strength (n=228)	4.02	[2.30; 5.75]***	3.86	[2.04; 5.69]***
Timed "Up & Go" (n=211)	-3.02	[-5.03; -1.02]**	-2.82	[-4.91; -0.73]**
Five Time Sit to Stand (n=197)	-3.11	[-5.27; -0.94]**	-3.39	[-5.67; -1.11]**
Tandem stand (n=230)	0.59	[1.05; 3.11]*	0.55	[0.93; 3.19]
Women (n = 370)				
Handgrip strength (n=365)	0.80	[-0.13; 1.72]	0.67	[-0.26; 1.61]
Timed "Up & Go" (n=334)	-3.19	[-5.34; -1.04]**	-2.68	[-4.87; -0.49]*
Five Time Sit to Stand (n=308)	-2.69	[-4.90; -0.49]*	-2.13	[-4.30; 0.04]
Tandem stand (n=366)	0.15	[0.77; 1.76]	0.04	[0.68; 1.59]

Data are shown as B with the 95% confidence interval between square brackets.

Model 1: adjusted for age. Model 2: adjusted for age, number of comorbidities, smoking, degree of urbanization, body mass index, and Mini Mental State Examination score. *p < 0.05; **p < 0.01; ***p < 0.001.

A general linear model was used in order to compare the means of the handgrip strength, TUG, and FTSS (Figure 1 A, B and C) according to gender and vitamin D group. The percentage of completed tandem stands according to vitamin D group in men was 68%, 59%, 64% and 86% respectively, $p = 0.009$. The percentage of completed tandem stands according to vitamin D group in women was 44%, 61%, 66% and 63% respectively, $p = 0.153$.

Figure 1. Strength and physical performance according to serum 25 (OH) D group and gender



General linear model analysis of the handgrip strength (A), Timed "Up & Go" test (B), and Five Time Sit to Stand test (C) with mean ± standard error. Adjusted for age, number of comorbidities, smoking, degree of urbanization, body mass index, and Mini Mental State Examination score.

DISCUSSION

As was hypothesized, serum 25(OH)D levels were significantly associated with physical performance, not only in community-dwelling older women, but also in men.

As mentioned in the introduction, there are several studies which have demonstrated the relationship between vitamin D and physical performance [15-21,33,34]. Although most of these were conducted with female-only populations [15-18], some studies including both men and women had similar results [12,19,33].This includes a 3-year follow-up study which reported poorer physical performance and a greater decline in physical performance in older vitamin D deficient men and women [19]. However, recent studies investigating men specifically did not find an association between vitamin D levels and physical performance [20,21,34]. Lack of an association in the previously mentioned populations may be due to the target population; young, healthy men, and the low prevalence of vitamin D deficiency [20,21,34]. Our population consisted of older men with a mean age of 76 years, of which a large proportion was vitamin D deficient, 44% had 25(OH)D levels <50 nmol/L. Making it a particularly adequate population to investigate the relationship between vitamin D and physical performance. Furthermore, community-dwelling elderly who have recently experienced a fall are certainly part of the target group, which have the greatest need for fall prevention strategies. A recent meta-analysis assessing the effects of interventions designed to reduce the incidence of falls in older people living in the community observed that only trials recruiting participants with lower vitamin D levels at enrolment had a reduction in rate of falls and risk of falling [35].

The following limitations should be taken into account when interpreting our results. First, the cross-sectional design of the study limits the ability to infer a causal relationship between serum 25(OH)D levels and physical performance, and does not dismiss the possibility of reverse causality. Nevertheless, the comparable population characteristics argue

against this, all participants had experienced a recent fall and were community-dwelling (similar frailty). Furthermore, similar to previous studies, the analyses were multivariately adjusted for a wide range of confounders including comorbidities and BMI (with the exception of nutrition and physical activity). Second, serum parathyroid hormone (PTH) levels were not determined. Vitamin D deficiency leads to an increase of serum PTH which increases bone turnover and bone loss, and is related to a decrease in muscle strength [36]. Third, the use of the MMSE as an exclusion criterion could have resulted in the exclusion of the frailest persons. A major strength of this study is the substantial proportion of the participants deficient in vitamin D included in the study, which enabled analysis of the physical performance in both vitamin D deficient and sufficient men and women.

In addition, it was striking to note how few of the older fallers in our study were prescribed vitamin D supplements, especially in the male population; though 44% of the men and women were deficient in vitamin D, only 6% of the men and 17% of the women used vitamin D supplements. The under-prescribing of vitamin D in this age group has previously been reported [37]. Yet, despite evidence that vitamin D supplementation has been shown to increase muscle strength and reduce the risk of falls [38], vitamin D deficiency is still common in community-dwelling elderly, with a prevalence of 40-100% in U.S. and European older men and women [11]. Furthermore, while we set the levels ≥50 nmol/L as vitamin D sufficient, another opinion is that optimal vitamin D levels should be ≥75 nmol/L (39). This is interesting to note when considering figure 1, where it seems levels closer to 75 nmol/L result in continued physical performance benefits, especially in men.

In conclusion, in the present study higher serum 25(OH)D concentrations were associated with better strength and physical performance in community-dwelling older men and women. Intervention studies are needed to further investigate the effect of vitamin D supplementation in this particular group.

REFERENCES

1. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med.* Sep 29 1994;331(13):821-827.

2. Toraman A, Yildirim NU. The falling risk and physical fitness in older people. *Arch Gerontol Geriatr.* Sep-Oct 2009;51(2):222-226.

3. Whitney SL, Wrisley DM, Marchetti GF, Gee MA, Redfern MS, Furman JM. Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the Five-Times-Sit-to-Stand Test. *Phys Ther.* Oct 2005;85(10):1034-1045.

4. Takata Y, Ansai T, Soh I, Awano S, Yoshitake Y, Kimura Y, et al. Quality of life and physical fitness in an 85-year-old population. *Arch Gerontol Geriatr.* May-Jun 2009;50(3):272-276.

5. Giampaoli S, Ferrucci L, Cecchi F, Lo Noce C, Poce A, Dima F, et al. Hand-grip strength predicts incident disability in non-disabled older men. *Age Ageing.* May 1999;28(3):283-288.

6. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med.* Mar 2 1995;332(9):556-561.

7. Hairi NN, Cumming RG, Naganathan V, Handelsman DJ, Le Couteur DG, Creasey H, et al. Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. *J Am Geriatr Soc.* Nov 2010;58(11):2055-2062.

8. Al Snih S, Markides KS, Ray L, Ostir GV, Goodwin JS. Handgrip strength and mortality in older Mexican Americans. *J Am Geriatr Soc.* Jul 2002;50(7):1250-1256.

9. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. *J Geriatr Phys Ther.* 2008;31(1):3-10.

10. Hartholt KA, van Beeck EF, Polinder S, van der Velde N, van Lieshout EM, Panneman MJ, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* Sep 2010;71(3):748-753.

11. Holick MF. Vitamin D deficiency. *N Engl J Med.* Jul 19 2007;357(3):266-281.

12. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *Am J Clin Nutr.* Sep 2004;80(3):752-758.

13. Dukas L, Bischoff HA, Lindpaintner LS, Schacht E, Birkner-Binder D, Damm TN, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. *J Am Geriatr Soc.* Feb 2004;52(2):230-236.

14. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. *J Clin Endocrinol Metab.* Aug 2001;86(8):3618-3628.

15. Gerdhem P, Ringsberg KA, Obrant KJ, Akesson K. Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. *Osteoporos Int.* Nov 2005;16(11):1425-1431.

16. Okuno J, Tomura S, Yabushita N, Kim MJ, Okura T, Tanaka K, et al. Effects of serum 25-hydroxyvitamin D(3) levels on physical fitness in community-dwelling frail women. *Arch Gerontol Geriatr.* Mar-Apr 2010;50(2):121-126.

17. Pfeifer M, Begerow B, Minne HW, Schlotthauer T, Pospeschill M, Scholz M, et al. Vitamin D status, trunk muscle strength, body sway, falls, and fractures among 237 postmenopausal women with osteoporosis. *Exp Clin Endocrinol Diabetes.* 2001;109(2):87-92.

18. Stewart JW, Alekel DL, Ritland LM, Van Loan M, Gertz E, Genschel U. Serum 25-hydroxyvitamin D is related to indicators of overall physical fitness in healthy postmenopausal women. *Menopause.* Nov-Dec 2009;16(6):1093-1101.

19. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, et al. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab.* Jun 2007;92(6):2058-2065.

20. Ceglia L, Chiu GR, Harris SS, Araujo AB. Serum 25-hydroxyvitamin D concentration and physical function in adult men. *Clin Endocrinol (Oxf).* Mar 2011;74(3):370-376.

21. Dam TT, von Muhlen D, Barrett-Connor EL. Sex-specific association of serum vitamin D levels with physical function in older adults. *Osteoporos Int.* May 2009;20(5):751-760.

22. Hartholt KA, Boyé NDA, Van der Velde N, Van Lieshout EMM, Polinder S, De Vries OJ, et al. [Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study). *BMC Geriatr.* 2011;11:48.

23. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):40-50.

24. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):30-39.

25. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. *Br J Clin Pharmacol.* Feb 2007;63(2):232-237.

26. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* Nov 23 2009;169(21):1952-1960.

27. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* Nov 1975;12(3):189-198.

28. KIWG. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan Med Bull.* Apr 1987;34 Suppl 4:1-24.

29. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev.* Aug 2001;22(4):477-501.

30. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. *J Gerontol.* Jul 1989;44(4):M112-117.

31. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* Mar 1994;49(2):M85-94.

32. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc.* Feb 1991;39(2):142-148.
33. Dhesi JK, Jackson SH, Bearne LM, Moniz C, Hurley MV, Swift CG, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing.* Nov 2004;33(6):589-595.
34. Kenny AM, Biskup B, Robbins B, Marcella G, Burleson JA. Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. *J Am Geriatr Soc.* Dec 2003;51(12):1762-1767.
35. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev.* 2012;9:CD007146.
36. Oudshoorn C, van der Cammen TJ, McMurdo ME, van Leeuwen JP, Colin EM. Ageing and vitamin D deficiency: effects on calcium homeostasis and considerations for vitamin D supplementation. *Br J Nutr.* Jun 2009;101(11):1597-1606.
37. Lang PO, Hasso Y, Drame M, Vogt-Ferrier N, Prudent M, Gold G, et al. Potentially inappropriate prescribing including under-use amongst older patients with cognitive or psychiatric co-morbidities. *Age Ageing.* May 2012;39(3):373-381.
38. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of Vitamin D on falls: a meta-analysis. *Jama.* Apr 28 2004;291(16):1999-2006.

Chapter 2.3

Physical performance and quality of life in single and recurrent fallers

Nicole D.A. Boyé, Francesco U.S. Mattace-Raso, Esther M.M. van Lieshout, Klaas A. Hartholt, Ed F. van Beeck, Tischa J.M. van der Cammen

Geriatr Gerontol Int. 2015 Mar;15(3):350-5.
doi: 10.1111/ggi.12287.

ABSTRACT

Background: Although guidelines concerning falls prevention make a clear distinction between single and recurrent fallers, differences in functional status, physical performance and quality of life in single and recurrent fallers have not been thoroughly investigated. Therefore we investigated the differences in functional status, physical performance and health related quality of life (HRQoL) between single and recurrent fallers.

Methods: From October 2008 to October 2011 616 community-dwelling older adults, who visited the Emergency Department due to a fall were enrolled. Physical performance was assessed with the Timed "Up & Go" (TUG) test, the "Five Time Sit to Stand" (FTSS) test, handgrip strength, and the tandem stand test. Functional status was measured using the Activities of Daily Living and Instrumental Activities of Daily Living scales. HRQoL was measured using the EQ-5D, and the SF-12 version 2. A general linear model was used to compare means of the scores.

Results: Recurrent falls in community dwelling elderly were associated with poorer physical performance as measured with the TUG test ($p < 0.001$), FTSS test ($p = 0.011$), handgrip strength ($p < 0.001$), and tandem stand ($p < 0.001$), and lower HRQoL scores as measured with the EQ-5D ($p = 0.006$) and SF-12 ($p = 0.006$ and $p = 0.012$).

Conclusion: Our findings provide further evidence that recurrent fallers have poorer physical performance and quality of life than single fallers. Recurrent falls might be a symptom of underlying disease and frailty, and reason for further assessment.

INTRODUCTION

Falls affect a large proportion of the population aged 65 years and older and are associated with consequences such as disability, loss of quality of life, institutionalization [1-3], and high morbidity and mortality rates [4,5]. In order to reduce the incidence of falls, guidelines on falls prevention recommend detailed assessments and a multifactorial intervention for persons with a history of recurrent falls [6]. Fallers are classified in different ways. A single faller is generally defined as someone who has fallen at least once during a defined time period, usually 6 or 12 months. A recurrent faller is someone who has fallen twice or more during a defined time period [7].

Several studies have reported specific differences between single and recurrent fallers, using varying outcome measures like sensory and motor function outcomes [8], certain physical performance tests [9-11], the Mini-Mental State Examination (MMSE) [12], posturography [13,14], and dual-tasking tests [15,16]. Most studies compared the prevalence of specific risk factors in single and recurrent fallers [17-20]. In addition to investigating physical performance and functional status, we assessed the health related quality of life (HRQoL). To the best of our knowledge, no previous study has investigated quality of life measures in single and recurrent fallers.

Therefore the aim of this descriptive study was to determine physical functioning and HRQoL in community-dwelling older men and women who visited the Emergency Department (ED) after experiencing a fall [21], and to evaluate if these differed in single and recurrent fallers. Validated and commonly used tools of measuring physical performance, functional status, and HRQoL were used.

METHODS

Study population

For this study, baseline data of the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) study were used, a detailed description of the methods can be found elsewhere [21]. In short, patients meeting the following inclusion criteria were eligible for enrolment: aged 65 years or older, visited the ED due to a fall, use of one or more fall-risk increasing drugs [22], Mini-Mental State Examination (MMSE) score of at least 21 out of 30 points [23], ability to walk independently, community dwelling, and provision of written informed consent by patient. Enrolment was performed in two academic and four regional hospitals, started in October 2008 and was completed in October 2011. The local Medical Research Ethics Committees at all participating sites approved the study.

Fall history

A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by an acute medical condition, *e.g.*, stroke, or exogenous factors such as a traffic accident [24]. The history of falls was ascertained during an interview with the clinical investigator. The number of falls in the 12 months prior to the outpatient research clinic visit was used to divide participants into two groups, single and recurrent fallers. A single faller was defined as someone who had fallen once in the 12 months preceding inclusion, a recurrent faller was defined as someone who had fallen twice or more in the 12 months preceding inclusion.

Data collection

At the baseline assessment, a geriatric assessment was performed. Medical history, prescription medication, and sociodemographic factors were documented. The number of comorbidities was derived from the following chronic comorbidities; any malignancy, diabetes mellitus, cardiac disease (*i.e.* hypertension, myocardial infarction, cardiomyopathy, congestive heart failure, arrhythmia, and valve disease), chronic obstructive pulmonary disease, stroke, neurological disorders (*i.e.* Parkinson's disease, epilepsy, neuropathy, myopathy, spinal disc herniation, and multiple sclerosis), peripheral vascular disease, renal insufficiency, and arthritis. Collected data were verified with records from the patient's general physician and local pharmacist. Height and weight were measured using standardized equipment and procedure. Body mass index (BMI) was calculated as body weight (in kilograms) divided by height² (in meters).

Physical performance

Physical performance was assessed with the Timed "Up & Go" (TUG) test, the Five Time Sit to Stand (FTSS) test, handgrip strength, and the tandem stand test. In the TUG test, time was measured while the participant stood up from a sitting position, walked three meters along a line, performed a 180 degree turn, walked back to the chair, and sat down, as fast as safely possible [25,26]. In the FTSS test, time was measured while the participant stood up and sat down five consecutive times, as fast as safely possible. The participant was not permitted to use their hands or the chair's arm supports during standing up or sitting down [25,27]. Handgrip strength was measured in kilograms using a digital strain-gauged dynamometer (Takei TKK 5401, Takei Scientific Instruments Co, Ltd., Tokyo, Japan). The participant was asked to stand upright with arms hanging beside his or her body. Subsequently, grip strength was measured with the left and right hand [28]. In the tandem stand test, the participant had to stand

fully independent for 10 seconds with one foot in front of the other. The test was scored as completed or failed [25]. All tests were performed twice and the best score was recorded.

Functional status

Functional status was measured using the activities of daily living (ADL) score [29] which evaluates independence while bathing, dressing, going to the toilet, continence, getting around the house, and feeding. And the instrumental activities of daily living (IADL) score [30] which evaluates independence while using the telephone, handling finances, taking medications, preparing light meals, housekeeping, shopping, and using transportation outside of home. ADL is scored 0-12 points, a higher score indicates greater disability; and IADL is scored 0-14 points, a higher score also indicates greater disability.

Health related quality of life

Based on the recommendations of *Prevention of Falls Network Europe* (ProFaNe), HRQoL was measured using the Dutch versions of the EQ-5D utility score, and the Short Form-12 (SF-12) version 2 [31]. The EQ-5D questionnaire covers five health domains (*i.e.*, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-5D is a validated and extensively used general health questionnaire to measure quality of life [32]. The SF-12 contains 12 questions and is designed and validated to assess the quality of life in large population studies; it consists of eight items measuring physical and mental health outcomes. These items are physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Information from these items is used to construct the physical and mental component summary measures (PCS and MCS) [33].

Statistical analysis

Analyses were performed using the Statistical Package of the Social Sciences (SPSS version 17.0, Chicago, Ill.).Baseline characteristics between single fallers and recurrent fallers were compared using Student t-test analyses for continuous variables and Chi-squared analyses for dichotomous variables. A general linear model was used to compare means of the TUG, FTSS, handgrip strength, ADL, IADL, EQ-5D utility score, SF-12 PCS and SF-12 MCS scores. Data were adjusted for age, gender, BMI, MMSE and number of comorbidities. The individual domains of the EQ-5D and the tandem stand test were assessed with Chi-squared analyses. Participants with incomplete or missing functional status, performance tests or HRQoL scores were excluded from related analyses, TUG test (n=57), FTSS test (n=99), handgrip strength (n=7), tandem stand test (n=4), and SF-12 (n=4). The missing measures of the physical performance tests were mostly due to injuries following fall (e.g. upper or lower extremity fractures). A p-value < 0.05 was used as a threshold for statistical significance.

RESULTS

From October 2008 to October 2011, 616 community-dwelling men and women who visited the ED due to a fall were enrolled in the IMPROveFALL study, of which 338 (55%) reported no prior falls, and 278 (45%) reported one or more prior falls in the 12 months preceding inclusion. The baseline characteristics are shown in table 1. Age, gender, MMSE scores and BMI, smoking, alcohol intake and number of comorbidities did not differ between single and recurrent fallers.

The physical performance, functional status and HRQoL outcomes are shown in table 2. Recurrent fallers scored significantly poorer than the single fallers in all the physical performance tests. The mean ADL an IADL scores did not differ significantly between single and recurrent fallers. Finally, recurrent fallers scored significantly lower than single fallers in

all of the HRQoL measures. Furthermore, the recurrent fallers reported significantly more problems than the single fallers, in all five domains of the EQ-5D (table 3).

Table 1. Baseline characteristics according to history of falls

	Single fallers (n=338)	**Recurrent fallers (n=278)**	***p*-value**
Age (years)	76.0 ± 6.7	77.0 ± 7.1	0.069
Gender (female)	199 (59)	182 (66)	0.094
Mini Mental State Examination score	27.1 ± 2.3	26.8 ± 2.3	0.054
Body mass index (kg/m^2)	27.3 ± 4.5	28.0 ± 4.7	0.072
Smoking	42 (12)	29 (10)	0.440
Alcohol (units per day)			0.834
0	165 (49)	145 (52)	
<1	51 (15)	38 (14)	
1-3	83 (25)	67 (24)	
>3	39 (12)	28 (10)	
Number of comorbidities	2.1 ± 1.1	2.1 ± 1.3	0.410

Continuous data are shown as mean values ± standard deviation and were analyzed using a Student's t-test. Categorical data are given as number with percentages, and were analyzed with a Chi-squared analysis.

Table 2. Physical performance, functional status, and health-related quality of life according to history of falls

	Single fallers (n=338)	Recurrent fallers (n=278)	*p*-value
Physical Performance			
Timed "Up & Go" (seconds)	10.9 ± 0.5	14.2 ± 0.6	< 0.001
Five Time Sit to Stand (seconds)	17.0 ± 0.6	19.3 ± 0.7	0.011
Hand Grip strength (kg)	27.2 ± 0.3	25.3 ± 0.4	< 0.001
Tandem stand (completed)	237 (70)	152 (55)	< 0.001
Functional Status			
ADL scale score	0.8 ± 0.2	0.8 ± 0.2	0.893
IADL scale score	1.4 ± 0.3	1.4 ± 0.3	0.979
Health Related Quality of Life			
EQ-5D utility score	0.78 ± 0.01	0.72 ± 0.01	0.006
SF-12 Physical Component Summary	46.5 ± 0.5	44.4 ± 0.6	0.006
SF-12 Mental Component Summary	53.9 ± 0.5	51.9 ± 0.6	0.012

Data was analyzed using general linear models, adjusted for age, gender, body mass index, Mini Mental State Examination and the number of comorbidities and given as mean ± standard error. ADL, Activities of Daily Living (range: 0-12, a higher number indicates higher impairment); IADL, Instrumental Activities of Daily Living (range: 0-14, a higher number indicates higher impairment); SF-12, Short-Form 12; EQ-5D, EuroQol 5D questionnaire.

Table 3. Prevalence of problems on the five dimensions of the EQ-5D according to history of falls

	Single fallers (n=338)	Recurrent fallers (n=278)	*p*-value
Mobility	137 (41)	178 (64)	< 0.001
Self-Care	41 (12)	65 (23)	< 0.001
Usual Activities	107 (32)	115 (41)	0.012
Pain / Discomfort	174 (52)	173 (62)	0.007
Anxiety / Depression	74 (22)	94 (34)	0.001

Data are shown as number (percentage) and were analyzed using Chi-squared analyses.

DISCUSSION

In the present study we found that recurrent fallers had poorer physical performance, and lower EQ-5D and SF-12 scores than single fallers. The functional status scores did not differ significantly between single and recurrent fallers.

Participants with a history of recurrent falls performed significantly poorer than single fallers at all the physical performance tests, these tests measure mobility, muscle strength and balance. In previous literature, 12 seconds has been suggested as a practical cut-off value for the TUG test, and has been found useful in detecting mobility impairment in elderly persons [34]. In the current study population recurrent fallers had below normal TUG test scores, and were significantly slower than the single fallers who had normal scores. Furthermore, poor muscle strength is a known risk factor for falls [35], it predicts disability [36], and mortality [37], and is one of the criteria used to define frailty [38].

The recurrent fallers also reported lower HRQoL scores than the single fallers, including significantly lower EQ-5D utility scores and more problems in all the five EQ-5D domains. In addition, the recurrent fallers scored below the Dutch population norm for the SF-12 PCS and MCS, while the single fallers scored above the norm. The Dutch SF-12 PCS and MCS population norms for the ≥ 65 age group are 45.2 and 52.9 [33]. Previous studies have reported lower quality of life scores in older fallers, than in older adults without a previous fall [3,39]. However, in these studies no comparison was made between single and recurrent fallers. The scores from the current study demonstrate how dissimilar single and recurrent fallers are. It is striking to note that regardless of age, gender, MMSE, BMI, and the number of comorbidities being similar in both groups, the measures of mobility, muscle strength, balance and quality of life showed significant differences between single and recurrent fallers. This suggests that recurrent falls could be a symptom of underlying disease severity and frailty [38]. Although guidelines concerning falls prevention make a clear distinction between single and recurrent fallers [6], these groups have not been thoroughly investigated. Previous studies report differences between single and recurrent fallers, with varying study methods. In some studies the population consisted of older adults admitted to hospital or aged-care facilities [11-13,15,20], generally an older and frailer population than the community dwelling older men and women who participated in the current study. Another study only assessed community-dwelling women [8]. Furthermore, varying outcome measures were used in the previous studies [8-20]. In addition to investigating the TUG and FTSS tests, which has been done previously [10], we used physical performance tests. And, as far as we are aware, this is the first time, that health related quality of life is assessed. Finally, the current study consisted of a large number of recurrent fallers, whereas other studies included relatively low numbers of recurrent fallers, the number of recurrent fallers included in the abovementioned studies ranged between 18 and 237.

The functional status scores did not differ between single and recurrent fallers, despite of recurrent fallers having poorer physical performance and lower HRQoL scores. A potential explanation for this finding is that the study population consisted of community-dwelling older adults. Being able to perform the individual components of ADL and IADL is a prerequisite for living independently. Possibly the sensitivity of the ADL and IADL questionnaires was not sufficient to detect differences in functional status.

The following limitations should be acknowledged when interpreting the results of this study. First, the cross-sectional design limits the ability to infer a causal relationship between poor functional status, physical performance, HRQoL, and recurrent falls. Second, recall bias with respect to the history of falls in the 12 months prior to inclusion cannot be ruled out. If any, this effect is likely to be small, since usually patients can accurately recall whether they have experienced one or more prior falls in the preceding 12 months, and the participants' medical records of the year preceding inclusion were made available to us. Third, the self-report nature of ADL and IADL scales can be influenced by the interviewer, and the mood and personality of the participant. Nevertheless these instruments are validated and are widely used by healthcare professionals to determine functional status. Finally, the study population only included older men and women who visited the ED after a fall. Thus these results are not applicable to the general population. However, this is an important group of fallers, representing those with injurious falls. Strengths of this study are the study population size, the validated tests used to assess physical performance and that we adhered to current recommendations regarding HRQoL outcome measures [31].

In conclusion, in the present study we found that compared to single falls, a history of recurrent falls was associated with poorer physical performance, and lower HRQoL scores in older community dwelling men and women.

REFERENCES

1. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. *Osteoporos Int.* Feb 2004;15(2):87-94.
2. Close JC, Lord SR, Antonova EJ, Martin M, Lensberg B, Taylor M, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. *Emerg Med J.* Sep 2012;29(9):742-747.
3. Hartholt KA, van Beeck EF, Polinder S, van der Velde N, van Lieshout EM, Panneman MJ, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* Sep 2010;71(3):748-753.
4. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *Jama.* Oct 14 2009;302(14):1573-1579.
5. Minino AM, Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2008. *Natl Vital Stat Rep.* Dec 7 2011;59(10):1-126.
6. AGS/BGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc.* Jan 2010;59(1):148-157.
7. Masud T, Morris RO. Epidemiology of falls. *Age Ageing.* Nov 2001;30 Suppl 4:3-7.
8. Lord SR, Ward JA, Williams P, Anstey KJ. Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc.* Oct 1994;42(10):1110-1117.
9. Anstey KJ, Wood J, Kerr G, Caldwell H, Lord SR. Different cognitive profiles for single compared with recurrent fallers without dementia. *Neuropsychology.* Jul 2009;23(4):500-508.
10. Buatois S, Perret-Guillaume C, Gueguen R, Miget P, Vancon G, Perrin P, et al. A simple clinical scale to stratify risk of recurrent falls in community-dwelling adults aged 65 years and older. *Phys Ther.* Apr 2010;90(4):550-560.
11. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. *Am J Med.* Mar 1986;80(3):429-434.
12. Chen X, Van Nguyen H, Shen Q, Chan DK. Characteristics associated with recurrent falls among the elderly within aged-care wards in a tertiary hospital: the effect of cognitive impairment. *Arch Gerontol Geriatr.* Sep-Oct 2011;53(2):e183-186.
13. Bigelow KE, Berme N. Development of a protocol for improving the clinical utility of posturography as a fall-risk screening tool. *J Gerontol A Biol Sci Med Sci.* Feb 2011;66(2):228-233.
14. Buatois S, Gueguen R, Gauchard GC, Benetos A, Perrin PP. Posturography and risk of recurrent falls in healthy non-institutionalized persons aged over 65. *Gerontology.* 2006;52(6):345-352.
15. Beauchet O, Annweiler C, Allali G, Berrut G, Herrmann FR, Dubost V. Recurrent falls and dual task-related decrease in walking speed: is there a relationship? *J Am Geriatr Soc.* Jul 2008;56(7):1265-1269.
16. Faulkner KA, Redfern MS, Cauley JA, Landsittel DP, Studenski SA, Rosano C, et al. Multitasking: association between poorer performance and a history of recurrent falls. *J Am Geriatr Soc.* Apr 2007;55(4):570-576.
17. Fletcher PC, Hirdes JP. Risk factors for falling among community-based seniors using home care services. *J Gerontol A Biol Sci Med Sci.* Aug 2002;57(8):M504-510.

18. Melzer I, Kurz I. Self reported function and disability in late life: a comparison between recurrent fallers and non-fallers. *Disabil Rehabil.* 2009;31(10):791-798.

19. Rossat A, Fantino B, Nitenberg C, Annweiler C, Poujol L, Herrmann FR, et al. Risk factors for falling in community-dwelling older adults: which of them are associated with the recurrence of falls? *J Nutr Health Aging.* Nov 2010;14(9):787-791.

20. Vassallo M, Sharma JC, Allen SC. Characteristics of single fallers and recurrent fallers among hospital in-patients. *Gerontology.* May-Jun 2002;48(3):147-150.

21. Hartholt KA, Boyé NDA, Van der Velde N, Van Lieshout EMM, Polinder S, De Vries OJ, et al. [Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study). *BMC Geriatr.* 2011;11:48.

22. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* Nov 23 2009;169(21):1952-1960.

23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* Nov 1975;12(3):189-198.

24. KIWG. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan Med Bull.* Apr 1987;34 Suppl 4:1-24.

25. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* Mar 1994;49(2):M85-94.

26. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc.* Feb 1991;39(2):142-148.

27. Whitney SL, Wrisley DM, Marchetti GF, Gee MA, Redfern MS, Furman JM. Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the Five-Times-Sit-to-Stand Test. *Phys Ther.* Oct 2005;85(10):1034-1045.

28. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. *J Gerontol.* Jul 1989;44(4):M112-117.

29. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies Of Illness In The Aged. The Index Of Adl: A Standardized Measure Of Biological And Psychosocial Function. *Jama.* Sep 21 1963;185:914-919.

30. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* Autumn 1969;9(3):179-186.

31. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc.* Sep 2005;53(9):1618-1622.

32. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy.* Dec 1990;16(3):199-208.

33. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol.* Nov 1998;51(11):1171-1178.

34. Bischoff HA, Stahelin HB, Monsch AU, Iversen MD, Weyh A, von Dechend M, et al. Identifying a cut-off point for normal mobility: a comparison of the timed 'up and go' test in community-dwelling and institutionalised elderly women. *Age Ageing.* May 2003;32(3):315-320.

35. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc.* Jul 2004;52(7):1121-1129.
36. Hairi NN, Cumming RG, Naganathan V, Handelsman DJ, Le Couteur DG, Creasey H, et al. Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. *J Am Geriatr Soc.* Nov 2010;58(11):2055-2062.
37. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. *J Geriatr Phys Ther.* 2008;31(1):3-10.
38. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* Mar 2001;56(3):M146-156.
39. Polinder S, van Beeck EF, Essink-Bot ML, Toet H, Looman CW, Mulder S, et al. Functional outcome at 2.5, 5, 9, and 24 months after injury in the Netherlands. *J Trauma.* Jan 2007;62(1):133-141.

Part III

Chapter 3.1

[Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study)

Klaas A. Hartholt, Nicole D.A. Boyé, Nathalie van der Velde, Esther M.M. van Lieshout, Suzanne Polinder, Oscar J. de Vries, Albert J.H. Kerver, Gijsbertus Ziere, Milko M.M. Bruijninckx, Mark R. de Vries, Francesco U.S. Mattace-Raso, André G. Uitterlinden, Ed F. van Beeck, Paul Lips, Peter Patka, Tischa J.M. van der Cammen

BMC Geriatr. 2011 Aug 21;11:48.
doi: 10.1186/1471-2318-11-48.

ABSTRACT

Background: Fall incidents represent an increasing public health problem in aging societies worldwide. A major risk factor for falls is the use of fall-risk increasing drugs. The primary aim of the study is to compare the effect of a structured medication assessment including the withdrawal of fall-risk increasing drugs on the number of new falls versus 'care as usual' in older adults presenting at the Emergency Department after a fall.

Methods/Design: A prospective, multi-center, randomized controlled trial will be conducted in hospitals in the Netherlands. Persons aged ≥65 years who visit the Emergency Department due to a fall are invited to participate in this trial. All patients receive a full geriatric assessment at the research outpatient clinic. Patients are randomized between a structured medication assessment including withdrawal of fall-risk increasing drugs and 'care as usual'. A 3-monthly falls calendar is used for assessing the number of falls and associated injuries over a one-year follow-up period. Measurements will be at three, six, nine, and 12 months and include functional outcome, healthcare consumption, socio-demographic characteristics, and clinical information. After one year a second visit to the research outpatient clinic will be performed, and adherence to new medication regimen in the intervention group will be measured. The primary outcome will be the incidence of new falls. Secondary outcome measurements are possible health effects of medication withdrawal, health-related quality of life (Short Form-12 and EuroQol-5D), costs, and cost-effectiveness of the intervention. Data will be analyzed using an intention-to-treat analysis.

Conclusions: The successful completion of this trial will provide evidence on the effectiveness of withdrawal of fall-risk increasing drugs in older patients as a falls reduction option.

BACKROUND

Falls form one of the most common and serious public health problems in older populations. Fall incidents are associated with considerable morbidity and mortality.[1, 2] Even a low energetic trauma, such as a unintended fall, can lead to major injuries in older adults with long-term consequences.[3, 4] The incidence of falls and the severity of fall-related complications rises steeply beyond the age of 65 years.[1-5] Approximately 72,000 older adults visit an Emergency Department in the Netherlands each year due to a fall. Hereof, over 30,000 are hospitalized, and 1,600 elderly die due to a fall per year.[6] The large burden of fall-related healthcare consumption is leading to high healthcare costs in western societies.[4, 7, 8] Over the last decades several risk factors for falls have been identified. Major risk factors include one or more previous falls, mobility impairments, high age, and the use of fall-risk increasing drugs.[9, 10] The majority (73%) of older persons use one or more drugs.[11] In 2008, nearly half of all drug prescriptions in the Netherlands were delivered to persons aged 65 years and older who constituted only 15% of the Dutch population in that year.[12] Adverse Drug Reactions are frequently seen in older adults.[13] A meta-analysis of observational studies showed an increased fall risk with certain drug groups, *i.e.*, psychotropic[14] and cardiovascular drugs.[15] Approximately three-quarters of the community dwelling elderly used at least one prescribed drug, and about a third used at least one fall-risk increasing drug.[11]

There is evidence that withdrawal, reduction, or substitution of fall-risk increasing drugs can reduce fall risk in older adults. Only one small, randomized controlled trial on drug withdrawal has been performed.[16] Campbell *et al.* found that withdrawal of psychotropic medication significantly reduced the risk of falling, but permanent withdrawal proved very difficult to achieve. Therefore the authors made recommendations for a larger randomized controlled trial (RCT) to study the single effect of drugs assessment and drugs modification

on fall risk. A recent prospective cohort study with a two-month follow-up period showed that the withdrawal of fall-risk increasing drugs was associated with a reduction in falls.[17]

An increased susceptibility to certain adverse drug reactions may partly be due to genetic polymorphisms that alter responses of individual persons to various drugs.[13] A possible cause might be the pathway of hepatic drug metabolization by the cytochrome P-450 family of biotransformation enzymes [18]. Consequently, poor, extensive and ultra-rapid metabolizers for certain cytochrome pathways and membrane bound transporters can be distinguished,[19] which influence the pharmacodynamics and pharmacokinetics. The majority of fall-risk increasing drugs are metabolized by a small number of enzymes, the major ones being CYP450 2D6, 2C9, 2C19 and 3A4/5.[20]

A systematic fall-related drugs assessment combined with medication changes and a one-year follow-up assessment among older fallers may contribute to a reduction in the incidence of new falls and related consequences.[17] At this moment a structured medication assessment is not a standard part of the current care of older fallers presenting at the Emergency Department. In the Netherlands, the current care of fall-related injuries consists of treatment of the consequences of the fall. However, before a systemic fall-related medication assessment can be incorporated in the routine work-up of older persons presenting with a fall, further evidence is required. The aim of this randomized controlled trial is to compare the effect of withdrawal of fall-risk increasing drugs versus ‘care as usual’ on future falls. The primary outcome of this study is be the number of new falls. Secondary outcome measurements are possible health effects of medication withdrawal, health-related quality of life, costs, and cost-effectiveness of the intervention.

METHODS

The study is designed as a multicenter RCT with a one-year follow-up period in the Netherlands. The Medical Ethics review board of the Erasmus MC, University Medical Center, approved the study protocol. The study started in October 2008.

Study population

Patients aged 65 years and over, who visit the Emergency Department of a participating hospital due to a fall, are eligible for inclusion. A fall is defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions, *e.g.* ,stroke, or exogenous factors like a traffic accident.[21]

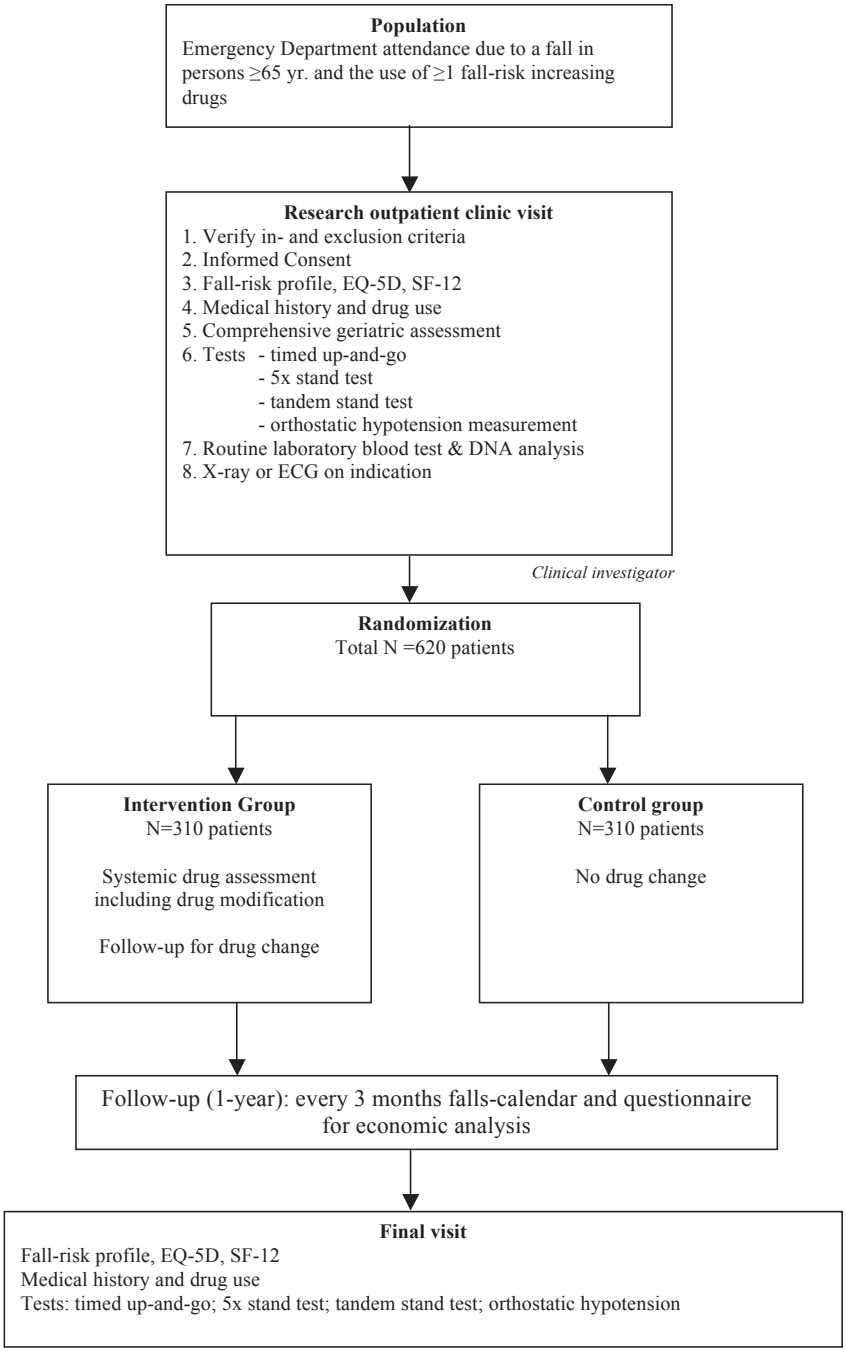
Patients meeting the following inclusion criteria are eligible for enrollment:

1. Aged 65 years or older (no upper age limit)
2. Attended the Emergency Department due to a fall incident
3. Taking one or more fall-risk increasing drugs for at least two weeks prior to the fall
4. Mini-Mental State Examination score of 21/30 points or over
5. Able to walk independently
6. Community dwelling
7. Provision of informed consent by patient

If any of the following criteria applies, patients will be excluded:

1. Patient participation in another trial
2. Fall not meeting criteria of specified definition
3. Likely problems, in the judgment of the investigators, with maintaining follow-up (*e.g.*, patients with no fixed address)
4. Not willing to complete the research protocol (such as attending for a control visit)

Figure 1. Flow chart



Procedure

All persons visiting the Emergency Department due to a fall receive care as usual for their injuries. Within two weeks following the Emergency Department attendance, patients are contacted by telephone with information about the study. All eligible study participants will receive written information about the study and all interested patients will receive an appointment for the research outpatient clinic. The appointments take place within two months after Emergence Department presentation. If the patient meets all eligibility criteria and no exclusion criteria are present at the research outpatient clinic, the patient will be asked to sign the Informed Consent Form before the study procedures take place. Patients who do not meet the inclusion criteria will be excluded. During the outpatient clinic visit a falls risk profile (FRP), falls history, health-related quality of life (HRQoL) and physical performance are measured in all patients. Furthermore, a geriatric assessment and a standardized medication assessment will take place in all patients. Eligible patients will be randomized to one of the treatment arms, the intervention group versus 'care as usual'. The aim in the intervention group will be to reduce fall-risk increasing drugs, and in the 'care as usual' group no medication change will be made. All included participants receive a Falls Calendar for reporting falls during a one-year follow-up period as well as a cost-evaluation form at three, six, nine and 12 months after the research outpatient clinic visit. One year after the first visit, the study participants are invited for a final visit to the research outpatient clinic in order to reassess the falls risk profile, falls history, HRQoL, and physical performance. Adherence to their medication is also evaluated. After the first and last visit to the outpatient clinic a brief information letter about the study start and completion will be sent to the patient's General Practitioner. Table 1 shows the flow chart of this study.

Randomization

Participants will be allocated to one of two treatment arms using a web-based randomization program that will be available 24 hours a day. Variable block randomization will be accomplished via a trial website. Allocation will be random. It is not possible to blind the geriatrician and patients for the allocation. In order to reduce bias, the patient's General Practitioner receives a letter from the attending physician that the patient was enrolled in a study.

Intervention

The single intervention will consist of a systematic fall-related medication assessment combined with drug withdrawal or modification, if safely possible. Fall-risk increasing drugs, as defined in the literature,[14, 15, 17, 22] will be stopped, reduced or substituted with potentially safer drugs in the intervention group. A complete list of fall-risk increasing drugs is shown in Table 2, determined on the basis of the currently available evidence from the literature.

For each drug, the clinical investigator will assess whether the initial indication still exists. Proposed changes in medication will be discussed with a senior geriatrician and the participant's General Practitioner and with the prescribing doctor if other than the General Practitioner. If consensus is obtained, fall-risk increasing drugs will be stopped when considered redundant, reduced in dose over a one-month period, if safely possible, or substituted for potentially safer drugs if necessarily and available. For each drug modification, the clinical investigator will follow the standardized instructions of the Dutch National Formulary,[23] and the clinical pharmacologist will be available for advice when needed. A research nurse will offer counseling and evaluate possible negative effects by weekly telephone calls over a period of 1 month, and discuss any problems with the clinical investigator and the geriatrician (project leader).

Table 2. Drugs classified as fall-risk increasing drugs in the IMPROveFALL study

Category	Drug type
Central nervous system	**anxiolytics/hypnotics** (benzodiazepines and others); **antidepressants (**tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors), **neuroleptics** (dopamine D2-receptor agonists and serotonin dopamine receptor antagonists)
Cardiovascular	**Antihypertensives** (diuretics, beta-adrenoceptor blockers, alpha-adrenoceptor blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers); **Anti-arrhythmic drugs** (Antiarrhythmics, nitrates, digoxin, vasodilators)
Anti-inflammation	NSAIDs
Gastro-Intestinal	Antacids (H-2 receptor antagonists)
Analgesics	Opioids
Pulmonal	Sympaticamometica, anti-histaminics
Diuretics	Thiazide, loop diuretics

Outcome measures

The primary outcome measure will be the incidence of new falls, based on the Falls Calendar. Secondary outcome measures will be fall-related injuries, generic health-related HRQoL, compliance, quality adjusted life years (QALY), genetic polymorphisms associated with increased adverse drug reactions, and positive or negative health effects, cost, and cost-effectiveness.

Measurements

Medication use

Medication use will be assessed by registering the drug names directly from the medication boxes. For each drug, both prescription and over-the-counter (OTC), the name, intake frequency, dosage, start and stop dates, and whether the drug has been prescribed after the fall will be registered. The information will be verified and compared with data retrieved from the General Practitioner and local pharmacist of the patient.

Quality of life

The level of independency of the activity of daily living (ADL) will be examined using the Barthel Index (ranging from zero for full independency to 20 for full dependency).[24] Quality of life will be measured using the Dutch version of the SF-12 and EQ-5D (EuroQol) questionnaire. The EQ-5D has been designed by the Euro-HRQoL Group to assess the experienced general quality of life in large populations in order to provide a simple, generic measure of health for clinical and economic appraisal.[25] The EQ-5D questionnaire covers five health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a Visual Analogue Scale (VAS) to record the current experienced health status. The EuroQol (EQ-5D) is a validated and extensively used general health questionnaire to measure quality of life.[26, 27] It is recommended for the assessment of HRQoL in trauma patients, especially for economic assessments.[28] The SF-12 contains 12 questions and has been designed and validated to assess the quality of life in large population studies [29, 30]. Fall-risk will be assessed using a validated FRP.[31] The FRP contains five questions, two measurements (handgrip strength and body weight), and two interacting items. Hand grip strength will be measured using a digital strain-gauged dynamometer (Takei TKK 5401, Takei Scientific Instruments Co, Ltd., Tokyo, Japan). Body weight will be measured with a calibrated beam scale. For each item points are scored and summed (range 0-30), where zero represents a low risk of recurrent falling and 11 and over indicates a high risk of recurrent falling (2 or more falls in the next 12 months).[31]

Physical performance

In order to assess the physical activity, three tests will be conducted. First, the chair stand test, which is a standardized test in which the participant stands up and sits down five constitutive times. The patient is not allowed to use the chair's arms supports during standing or sitting.[32]

The Timed Up-and-Go test (TUG-test), in which the participant has to stand up from sitting position and walks three meters along a line, perform a 180 degree turn and walk back to the chair and sit down will be conducted.[32] A tandem stand test will be used in order to assess balance. The test will be performed in standing position, in which the patient has to stand fully independently for 10 seconds with both feet in front of each other, and is scored as correct or failed. All three mobility tests are conducted twice, and the best time (where appropriate) will be used.

Orthostatic hypotension will be measured by using a calibrated sphygmomanometer, in supine position followed by five minutes standing straight up. The blood pressure will be measured in supine position, one, two, three, four, and five minutes standing. The blood pressure is registered in millimetres of mercury (mmHg), heart rate in beats per minute. Orthostatic hypotension is defined as a decrease of 20 mmHg systolic, of 10 mmHg diastolic in standing position.[33]

Costs

The total direct and indirect costs of both fall-risk increasing drugs withdrawal and 'care as usual' will be measured. All analysis will be performed in accordance with Dutch guidelines for economic evaluations.[34] Direct healthcare costs include the additional costs of the systematic fall-related drugs assessment and modification, drug consumption (including the costs for substitution drugs), and fall-related and non-fall-related healthcare consumption during one year of follow-up (*e.g.,* General Practitioner, outpatient visits, and hospital admissions).

Real medical costs were calculated by multiplying the volumes of health care use with the corresponding unit prices. For the intervention (systematic fall-related drugs assessment) the full cost price will be calculated and for the other health care costs standard cost prices will be

used as published by Oostenbrink.[34] The full cost price of patient identification at the Emergency Department and the systematic fall-related drugs assessment will be determined based upon time measurements and employment of personnel. Costs of medication use will be recorded in the study, and unit costs will be determined with information from the National Dutch Formulary.[23]

Healthcare consumption, both fall and non-fall related, and patient costs will be recorded from the Hospital Information System for hospital care, and three-monthly written questionnaires for other healthcare and patient costs. These will be supplemented with data on healthcare costs of injury from previous research.[7] The number of injuries prevented will be calculated with data recorded in the study, supplemented with epidemiological data on falls and injury risks.

Cost-effectiveness was assessed by calculating the incremental cost-effectiveness ratio, defined here as the difference in average costs between medication assessment including withdrawal of fall-risk increasing drugs and 'care as usual' and by the difference in prevented fall-related injury. Secondary, a cost-utility analysis will be performed, *i.e.*, as cost per Quality Adjusted Life Years (QALY). Policy makers and health economists have proposed that costs varying from €25,000 up to €75,000 per QALY may be considered as acceptable.[35, 36]. The QALY combines mortality and morbidity into a single number. The morbidity component is referred to as health-related HRQoL and is based on a descriptive health-state measure. Because of a long track record in health economic analyses, the EQ-5D measure will be used for this purpose.[26] Furthermore, the lifetime health effects (cardiovascular events such as myocardial infarction, stroke, and mortality) due to possible increased cardiovascular risks (*i.e.*, cardiac failure, rebound hypertension) will be calculated with existing models for cardiovascular disease risk management. In accordance with guidelines for differential discounting, effects will be discounted at a rate of 1.5% and costs at 4% per year.[37]

Full blood for DNA isolation will be drawn during the first visit (5 mL). The blood will be stored by -80 degrees Celsius, until DNA-isolation will take place. After DNA isolation, polymorphisms will be analyzed using the TaqMan allelic discrimination assays on the ABI Prism 9700 HT sequence detection system.

Follow-up

Patients will be followed for one year. After the first visit to the research outpatient clinic patients receive a Falls Calendar.[31] During a one-year follow-up period, the participant will be asked to record every week whether they experienced a fall that week. The 3-monthly calendar sheet will be returned once per 3-months by mail. Cost-effectiveness will be measured using a cost-evaluation questionnaire. Participant can register the number of visits to physicians, therapists, day care centers, hospitalizations, adaptations of the living area, and the current living location (*e.g.*, home or nursing home). The cost-evaluation questionnaire will be returned with the falls calendar at three, six, nine, and 12 months after the first visit to the research outpatient clinic. In case no calendar sheet or questionnaire is received, or when it is completed incorrectly, the calendar sheet or questionnaire will be completed by telephone.

During the last visit to the outpatient clinic, one year after the first visit, all physical performance tests are conducted, as well as questionnaires regarding medical history, drug use, quality of life, and fall risk profile. Adherence to the drug-use recommendations (complete withdrawal, lowering of dosage, or substitution) will be evaluated by reassessment of drug use as described above. Information of the participants regarding medical history and drug use will be verified by information of the General Practitioner and local pharmacist.

Table 1. Schedule of events

	Screening	**1 visit**	**3 months**	**6 months**	**9 months**	**12 months**
Telephone call	X					
Information package	X					
Informed Consent		X				
Randomization		X				
Baseline data		X				
EQ-5D		X				X
SF-12		X				X
FRP		X				X
Orthostatic hypotension test		X				X
Complications			X	X	X	X
Falls calendar			X	X	X	X
Healthcare consumption			X	X	X	X
ADL		X				X
Physical functioning (VAS)		X				X

EQ-5D, EuroQol 5-D questionnaire; SF-12, Short Form-12; FRP, Fall Risk Profile; ADL, Activities of Daily living; VAS, Visual Analogue Scale.

Sample size calculation

A total number of 620 patients will be included in the study, 310 in the control group and 310 in the intervention group. Calculation of the required sample size is based on the assumption that the annual cumulative incidence of further falling is 50% without intervention,[38] a 15% drop-out (including death), drug withdrawal being possible in 50% of the participants in the intervention group and a 50% decrease of further falls among participants with successful withdrawal. A single-sided test with an alpha level of 0.05 and a beta of 0.2 indicates that 310 patients in both groups is sufficient in order to detect a 25% decrease of respondents reporting further falls in the intervention group.

Statistical analysis

Data will be primarily analyzed according to the intention-to-treat principle. Patients with protocol violations will be followed up, and data will be recorded. Data will be analyzed with and without inclusion of patients with protocol violation. At baseline, differences in baseline characteristics will be compared between the intervention and control group in order to assess

comparability between the two groups. Student's T-test (parametric numeric data), Mann-Whitney U-test (nonparametric numeric data) or Chi-square test (categorical data). Data will be presented as mean ± SD (parametric data) or medians and percentiles (non-parametric data).

The hazard ratio for falling will be calculated using a Cox-regression model. Herein, the time between the intervention (*i.e.*, drug assessment/change or not) and the first and/or second fall will serve as the primary outcome measure. Fallers will be defined as those who will fall once or more during the one-year follow-up. Differences in cumulative incidence of falls will be analyzed using log-linear or Poisson regression, adjusted for over dispersion because of interdependence among the dependent variable (falls). Differences in adverse health effects between both trial arms will be assessed using Chi^2 testing. Several subgroups will be distinguished in order to examine whether the effect of the intervention depends upon sex, age, race and risk of future falls. Since healthcare costs per patient are typically highly skewed, non-parametric techniques will be used to derive a 95% confidence interval for the differences in distributions of the costs. In a sensitivity analysis the impact on cost-effectiveness of statistical uncertainty on the main study outcomes will be determined (uni- and multi-variable).

The association between polymorphisms and falls history will be evaluated using a multivariate logistic regression analysis. A *p*-value of <0.05 will be used as threshold for statistical significance.

Ethical considerations

The study will be conducted according to the principles of the Declaration of Helsinki (59th World Medical Association General Assembly, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The Medical Ethics review

board of the Erasmus MC acts as central ethics committee for this trial (reference number MEC-2008-254; NTR1593). In addition approval has been obtained from the local Medical Ethics review boards in all participating hospitals. An information letter notifying the patients' participation and severe abnormal findings will be sent to their general practitioners, unless a patient does not agree with this.

Liability insurance has been obtained, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th 2003). This insurance provides cover in case of damage to research subjects through injury or death caused by the study.

DISCUSSION

The strength of this study is that a single intervention, the withdrawal of fall-risk increasing drugs, will be studied versus 'usual care' using a randomized controlled approach. The study results will provide valuable knowledge for clinicians and healthcare policymakers on the necessity of withdrawal of fall-risk increasing drugs in falls prevention strategies in the older population. If proven effective and cost-effective, fall-risk increasing drugs withdrawal in persons with a high risk of recurrent falling, might lower the risk of future falls and consequently contribute to reductions in fall-related injuries, related healthcare consumption, and costs. As far as we are aware, up till now no large RCT's have been published reporting the effects of withdrawal, dose reduction or substitution of fall-risk increasing drugs after a fall. The inclusion of patients started October 2008 and is expected to be complete by July 2011. Because of the one-year follow-up period, presentation of data can be expected in the second half of 2012.

REFERENCES

1. Hartholt KA, van der Velde N, Looman CW, et al. Trends in fall-related hospital admissions in older persons in the Netherlands. *Arch Intern Med.* May 24 2010;170(10):905-911.

2. Kannus P, Parkkari J, Koskinen S, et al. Fall-induced injuries and deaths among older adults. *Jama.* May 26 1999;281(20):1895-1899.

3. Stevens JA, Sogolow ED. Gender differences for non-fatal unintentional fall related injuries among older adults. *Inj Prev.* Apr 2005;11(2):115-119.

4. Hartholt KA, van Beeck EF, Polinder S, et al. Societal Consequences of Falls in the Older Population: Injuries, Healthcare Costs, and Long-Term Reduced Quality of Life. *J Trauma.* Nov 1 2010;In Press.

5. Hartholt KA, van Lieshout EM, Polinder S, Panneman MJ, van der Cammen TJ, Patka P. Rapid increase in hospitalizations due to fall-related head injury in older adults in the Netherlands 1986-2008. *J Neurotrauma.* Mar 1 2011;In Press.

6. Statistics Netherlands. [Official-Cause-of-Death statistics in The Netherlands]. Internet]. May 28, 2009; http://statline.cbs.nl/StatWeb/publication/default.aspx?DM=SLNL&PA=7052_95&D1=84&D2=15-21&D3=1-2&D4=a&HDR=G3%2cG2%2cG1&STB=T&VW=T. Accessed December 22, 2009.

7. Meerding WJ, Mulder S, van Beeck EF. Incidence and costs of injuries in The Netherlands. *Eur J Public Health.* Jun 2006;16(3):272-278.

8. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev.* Oct 2006;12(5):290-295.

9. Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med.* Sep 29 1994;331(13):821-827.

10. Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med.* May 11 2009;169(9):894-900.

11. Ziere G, Dieleman JP, Hofman A, Pols HA, van der Cammen TJ, Stricker BH. Polypharmacy and falls in the middle age and elderly population. *Br J Clin Pharmacol.* Feb 2006;61(2):218-223.

12. Foundation for Pharmaceutical Statistics (SFK). [Nearly half of all medication prescriptions are for the older adult]. *Pharmaceutisch Weekblad.* May 14th 2009;144(20).

13. Hartholt KA, van der Velde N, Looman CW, et al. Adverse drug reactions related hospital admissions in persons aged 60 years and over, The Netherlands, 1981-2007: less rapid increase, different drugs. *PLoS One.* 2010;5(11):e13977.

14. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):30-39.

15. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):40-50.

16. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc.* Jul 1999;47(7):850-853.

17. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. *Br J Clin Pharmacol.* Feb 2007;63(2):232-237.

18. Shapiro LE, Shear NH. Drug interactions: Proteins, pumps, and P-450s. *J Am Acad Dermatol.* Oct 2002;47(4):467-484; quiz 485-468.

19. Montellano Od. Human cytochrome P450 enzymes. In: FP G, ed. Vol 2nd. New York: Plenum; 2000:473-535.

20. Blonk MI, van der Velde N, van den Bemt PM, van Schaik RH, van der Cammen TJ. CYP2D6*4, CYP3A5*3 and ABCB1 3435T polymorphisms and drug-related falls in elderly people. *Pharm World Sci.* Feb 2010;32(1):26-29.

21. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan Med Bull.* Apr 1987;34 Suppl 4:1-24.

22. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* Nov 23 2009;169(21):1952-1960.

23. Dutch National Formulary. http://www.fk.cvz.nl.

24. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. *Md State Med J.* Feb 1965;14:61-65.

25. The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* Dec 1990;16(3):199-208.

26. Brooks R. EuroQol: the current state of play. *Health Policy.* Jul 1996;37(1):53-72.

27. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. *Ned Tijdschr Geneeskd.* Jul 9 2005;149(28):1574-1578.

28. Van Beeck EF, Larsen CF, Lyons RA, Meerding WJ, Mulder S, Essink-Bot ML. Guidelines for the conduction of follow-up studies measuring injury-related disability. *J Trauma.* Feb 2007;62(2):534-550.

29. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* Mar 1996;34(3):220-233.

30. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol.* Nov 1998;51(11):1171-1178.

31. Pluijm SM, Smit JH, Tromp EA, et al. A risk profile for identifying community-dwelling elderly with a high risk of recurrent falling: results of a 3-year prospective study. *Osteoporos Int.* 2006;17(3):417-425.

32. Guralnik JM, Winograd CH. Physical performance measures in the assessment of older persons. *Aging (Milano).* Oct 1994;6(5):303-305.

33. Medow MS, Stewart JM, Sanyal S, Mumtaz A, Sica D, Frishman WH. Pathophysiology, diagnosis, and treatment of orthostatic hypotension and vasovagal syncope. *Cardiol Rev.* Jan-Feb 2008;16(1):4-20.

34. Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. *Pharmacoeconomics.* 2002;20(7):443-454.

35. Report of the Commission on Macroeconomics and Health. *Macroeconomics and health: Investing in health for economic development.* Geneva: WHO Commision on Macroeocnomics and Health.; 2001.
36. Towse A, Pritchard, C. National Institute for Clinical Excellence (NICE): Is economic appraisal working? *Pharmacoeconomics.* 2002;20 Suppl 3:95-105.
37. Oostenbrink JB, Bouwmans, C.A.M., Koopmanschap, M.A., Rutten, F.F.H. *[Handleiding voor kostenonderzoek. Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg].* Diemen: College voor Zorgverzekeringen; 2004.
38. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet.* Jan 9 1999;353(9147):93-97.

Chapter 3.2

The Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) Study: results from a Randomized Controlled Trial in Older Fallers

Nicole D.A. Boyé, Nathalie van der Velde, Oscar J. de Vries, Esther M.M. van Lieshout, Klaas A. Hartholt, Francesco U.S. Mattace-Raso, Paul Lips, Peter Patka, Ed F. van Beeck, Tischa J.M. van der Cammen, and the IMPROveFALL trial collaborators

Submitted

ABSTRACT

Importance: Fall incidents represent a public health problem in aging societies worldwide. A major risk factor for falls is the use of fall-risk increasing drugs (FRIDs).

Objectives: To investigate the effect of withdrawal of FRIDs versus 'care as usual' on reducing falls in community-dwelling older men and women.

Design: Randomized multicenter trial.

Setting: Community, Primary care, Geriatric care.

Participants: 612 older adults who visited an Emergency Department because of a fall.

Interventions: A structured medication assessment including withdrawal of FRIDs.

Main Outcomes and Measures: A 3-monthly falls calendar was used for assessing the number of falls and associated injuries during 12 months of follow-up. Primary outcome was incidence of falls. Secondary outcome measures were falls requiring a general practitioner consultation or Emergency Department visit, and possible health effects of medication withdrawal. Data were analyzed using an intention-to-treat (primary) and a per protocol (secondary) analysis. Both overall FRID withdrawal as well as major subgroups (psychotropic and cardiovascular drugs) were assessed. The hazard ratios for time-to-fall were calculated using a Cox-regression model. Differences in cumulative incidence of falls were analysed using Poisson regression.

Results: During the 12 months follow-up, 91 (34%) of the control participants and 115 (37%) of the intervention participants experienced a fall. FRIDs withdrawal did not have a significant effect on the time to the first fall (hazard ratio [HR] 1.17; 95% confidence interval [CI] 0.89-1.54), the time to the second fall (1.19; 0.78-1.82), the time to the first general practitioner consultation because of a fall (0.66; 0.42-1.06), or the time to the first Emergency

Department visit because of a fall (0.85; 0.43-1.68). Cardiovascular FRID withdrawal increased the time to the first general practitioner consultation because of a fall (0.57; 0.34-0.93). Per-protocol analyses did not alter the results.

Conclusions and Relevance: The risk of falls did not differ between the usual care and intervention groups. There was a tendency towards fewer healthcare visits in the intervention group, and this was significant in the cardiovascular-drugs withdrawal subgroup. Surprisingly, no effect of psychotropic drug withdrawal was seen.

Trial Registration: Netherlands Trial Register NTR1593 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1593).

INTRODUCTION

Falls affect a large proportion of persons aged 65 years and older [1], and are associated with negative consequences such as high morbidity and mortality rates [2-4], disability, loss of quality of life, and institutionalization [5-8]. Furthermore, fall-related injuries place a substantial burden on healthcare systems due to the large number of visits to Emergency Departments (ED), hospital admissions, and admissions to long-term care and rehabilitation facilities [6,9-12]. In order to reduce the prevalence of falls, risk factors have been identified and documented [13-15], and a substantial number of falls-prevention trials has been published [1,16,17].

The use of certain drugs, i.e. the so-called fall-risk increasing drugs (FRIDs) [18-21], mainly psychotropic and cardiovascular drugs, has been associated with increased risk of falls and related injuries [18,19,21,22], and withdrawal of FRIDs appears to be feasible and effective [20,23-25]. Although FRIDs withdrawal is frequently incorporated in multifactorial intervention trials, evidence regarding overall FRID withdrawal as a single intervention is scarce [17].

In the present study, we investigated the effect of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' on reducing falls in community-dwelling older men and women, who visited the ED after experiencing a fall [26].

METHODS

Study population

The IMPROveFALL study is a randomized, multicenter trial, assessing the effect of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' as a method for falls reduction [26]. Patients meeting the following inclusion criteria were eligible for enrolment: aged 65 years or older, visited the ED of a participating hospital because of a

fall, use of one or more fall-risk increasing drugs [18,19,21,26] (Table 1), Mini-Mental State Examination (MMSE) score of at least 21 out of 30 points [27,28], ability to walk independently, and community dwelling. Participating hospitals included two academic and four regional hospitals in the Netherlands. Enrolment started in October 2008 and was completed in October 2011. The follow-up period was 12 months. The study was performed in accordance with the Declaration of Helsinki and all participants gave written informed consent. The local Medical Research Ethics Committees in all participating hospitals approved the study protocol.

Covariates

All persons visiting the ED because of a fall received care as usual for their injuries. Following the ED visit, patients were contacted by telephone. Subsequently, eligible and interested potential study participants received an appointment for the research outpatient clinic (OPC). The visits to the research OPC took place within two months after the fall-related ED visit. If the patient met all eligibility criteria, the patient was asked to sign the Informed Consent Form. During the visit to the research OPC a fall-related assessment was performed by the clinical investigator. This included a falls history (a single faller was defined as someone who had fallen once in the 12 months preceding inclusion, a recurrent faller was defined as someone who had fallen twice or more in the 12 months preceding inclusion), a fall-risk questionnaire [29], medical history and physical examination, physical performance tests, and a blood sample. The blood sample was used for measuring 25-hydroxyvitamin D levels, and to screen for hematologic, electrolyte, and liver and kidney function abnormalities. During the baseline assessment and at the follow-up research OPC visit, participants completed questionnaires on generic Health Related Quality of Life (HRQoL). HRQoL was measured using the Dutch versions of the EuroQol five dimensions [30],

and the Short Form-12 version 2 [31], at baseline and at 12 months-follow-up. A detailed description of the study protocol can be found elsewhere [26].

Randomization

Participants were randomized to one of the treatment arms, the intervention group versus 'care as usual', using a web-based variable block randomization program that was available 24 hours a day. Randomization using the trial website was done by the research physician. A block randomization with a block size of 4 was used. Due to the nature of the intervention, participants, research physicians, and care-givers could not be blinded to group assignment.

Intervention

All participants received a structured medication assessment, which included withdrawal of FRIDs in the intervention group only. In the 'care as usual' group, the medication was not changed. The intervention consisted of a systematic FRIDs assessment combined with drug withdrawal or modification, when safely possible. FRIDs, as defined in the literature [18-21,26], were discontinued, reduced or substituted with potentially safer drugs in the intervention group. A complete list of FRIDs, based on current literature, is shown in Table 1. For each drug, the clinical investigator assessed whether the initial indication still existed. Proposed changes in medication were discussed with a senior geriatrician, and if necessary with the prescribing physician. The participant's General Practitioner (GP), and the prescribing physician if other than the GP were informed of any changes. For each drug modification, the clinical investigator followed the standardized instructions of the Dutch National Formulary [32], and a clinical pharmacologist was available for advice when needed. A research nurse offered counselling, evaluated possible negative effects via a standardized telephone follow-

up, and discussed any problems regarding the drug modification with the clinical investigator and geriatrician.

All participants with follow-up were included in the intention-to-treat analyses. Regarding the per protocol analyses, the intervention group included both participants in whom FRID withdrawal/substitution was successful and participants in whom FRID withdrawal was not necessary or safely possible. In the event of more than one attempted FRID withdrawal, the successful withdrawal/substitution of at least one FRID was considered successful. The control group only included the participants in the "care as usual" group in whom we did not withdraw/substitute FRIDs during the first research OPC visit.

Definition fall incident

A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions, *e.g.*, stroke, or exogenous factors such as a traffic accident [33]. The history of falls was ascertained during a structured interview with the use of a falls questionnaire [29].

All participants received a Falls Calendar for reporting falls during a one-year follow-up period. Falls were recorded weekly on the Falls Calendars and had to be returned every three months. Follow-up started two weeks after completed intervention or two weeks after initial research OPC visit when no intervention was performed.

Laboratory values

Non-fasting blood samples were collected at the baseline assessment. Vitamin D deficiency was defined as serum 25(OH)D < 50 nmol/l [34,35]. Anemia was defined as hemoglobin levels < 8.1 mmol/L for men and < 7.5 mmol/L for women.

Statistical analyses

All analyses were performed using the Statistical Package of the Social Sciences (SPSS version 17.0, Chicago, Ill.). A p-value of < 0.05 was used as threshold for statistical significance.

After sample size calculations, our aim was to include a total number of 620 participants in the study, 310 in the control group and 310 in the intervention group [26]. Calculation of the required sample size was based on the assumption that the annual cumulative incidence of further falling is 50% without intervention [36], a 15% drop-out rate (including death) [1], drug withdrawal being possible in 50% of the participants in the intervention group and a 50% decrease of further falls among participants with successful withdrawal [24]. A single-sided test with an alpha level of 0.05 and a beta of 0.2 indicated that 310 patients in each group would be sufficient in order to detect a 25% decrease of participants reporting further falls in the intervention group [26].

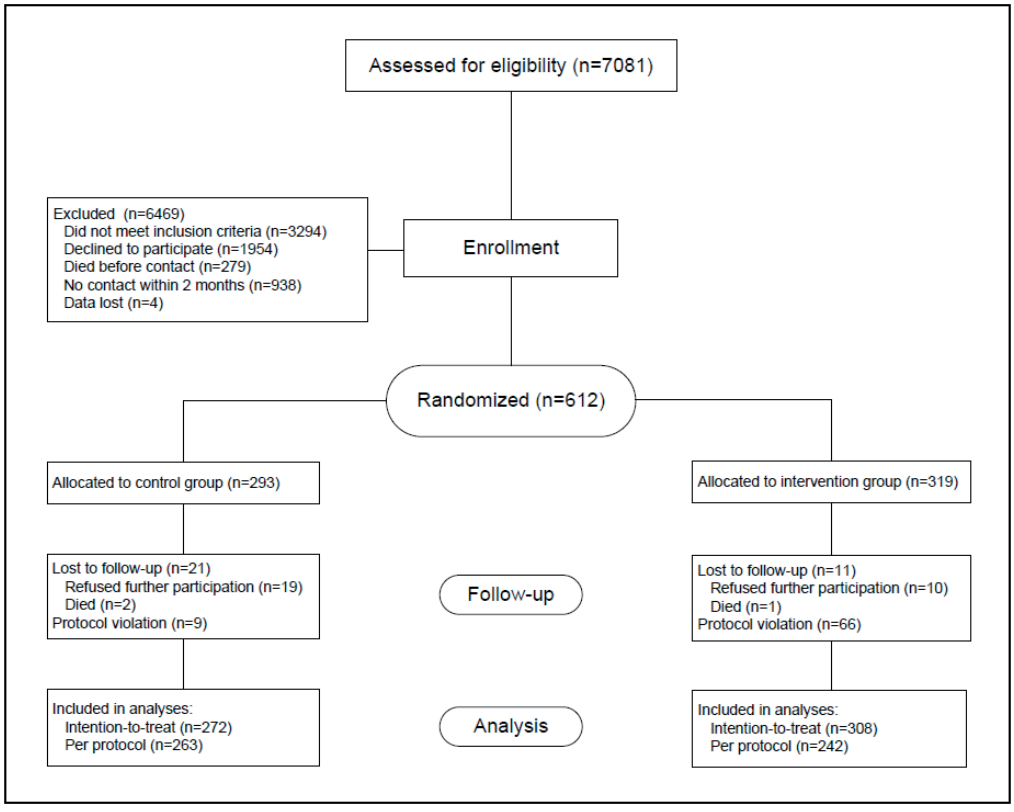
Data were analyzed according to the intention-to-treat principle (primary), and per-protocol (secondary). The per-protocol analysis only included participants without a protocol violation as mentioned above. The hazard ratios for falling were calculated using a Cox-regression model. Herein, the time between the start of follow-up and the first fall served as the primary outcome measure. The time between the start of follow-up and the second fall, first GP consultation and first ED visit because of a fall were also analyzed. Differences in cumulative incidence of falls, GP consultations and ED visit were analyzed using Poisson regression, adjusted for overdispersion because of interdependence among the dependent variable (falls). Subgroup analyses were performed, assessing the separate effect of cardiovascular and psychotropic drug withdrawal.

Predefined models were constructed in order to adjust for age, gender and potential confounders. Potential predefined confounders that were considered for inclusion in the

multivariate model were MMSE, BMI, the Charlson Comorbidity index, vitamin D deficiency, anemia HRQoL, physical performance, number of drugs, the number of FRIDs, smoking, alcohol intake, history of recurrent falls, use of walking aid, urinary incontinence, vision problems, fear of falling, and dizziness. Confounders that led to a change in the regression coefficient (B) of 10% or more were retained in the multivariate-adjusted regression model.

RESULTS

Figure 1. Flowchart of study participants



*Of the participants that died during follow-up, most were included in the analyses, except for two in the usual care and one in the intervention group.

In total, 7,081 ED visits were screened for possible trial participants, of which 3,294 were not eligible, and 1,954 refused to participate. Subsequently, 612 participants were randomized in the IMPROveFALL study (Figure 1). Randomization resulted in 293 participants being allocated to the control group and 319 participants to the intervention group (Figure 1). For the intention-to-treat analyses, 21 participants in the control group and 11 participants in the intervention group were excluded due to withdrawal from study or death. For the per protocol analyses, 9 participants in the control group and 66 participants in the intervention group were excluded due to protocol violations (Figure 1).

The mean age was 76 years, and 62% of the study population was female. No obvious differences in baseline characteristics were noted between the intervention and control group (Table 2). The mean number of drugs and FRIDs used at baseline were six ± three and four ± two, respectively. Table 3 specifies the interventions according to FRID categories and specific drug types, and also includes details on compliance to attempted interventions. Notably, in 40% of all FRIDs, 62% of cardiovascular FRIDs, 32% of psychotropic FRIDs, and 78% of other FRIDs, an intervention was not deemed possible or necessary. Of all attempted interventions 35% failed (37% of cardiovascular FRID interventions,48% of psychotropic FRID interventions, and 31% of other FRID interventions), either due to non-compliance or a return of the primary reason for which the drug was prescribed.

The percentage of participants using ≥ 3 FRIDs at baseline was 72% in the control group and 70% in the intervention group, these percentages did not decrease after 1 year follow-up, 75% and 70% respectively. Furthermore, in the intervention group 66 participants (22%) used a higher number of FRIDs after 12 months of follow-up than they used at baseline, compared to 68 (25%) in the control group (Supplementary data).

Table 1. Fall-risk increasing drugs

Drug category	Drug type	Therapeutic subgroups	ATC code
Psychotropic	Analgesics	Opioids	N02A
	Anti-epileptic	Barbiturates, fatty-acid derivatives, carboxamide derivatives, other	N03
	Anti-Parkinson	Dopaminergics, anticholenergics	N04
	Neuroleptics	Dopamine D2-receptor agonists and serotonin dopamine receptor antagonists	N05A
	Anxiolytics & Sedative/Hypnotics	Benzodiazepines and others	N05B N05C
	Antidepressants	Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors	N06
	Other	Anti-vertigo agents	N07CA
Cardiovascular	Cardiac therapy	Digitalis, anti-arrhythmics, nitrates	C01
	Anti-hypertensives	Alpha-adrenoceptor blockers, centrally acting antihypertensives	C02
	Diuretics	Thiazide diuretics, loop diuretics	C03
	Beta-blockers		C07
	Calcium-channel blockers		C08
	ACE/Angiotensin-II inhibitors		C09
	HMG CoA reductase inhibitors		C10AA
Other drugs	Gastro-Intestinal	Anticholenergics Hypoglycemics	A03AA A10
	Urogenital system	α –blockers, spasmolytics	G04BD G04CA
	Anti-inflammatory	Steroids Non-steroidal anti-inflammatory drugs (NSAID) Anti-gout	H02AB, R01AD B01AC06/08, M01A M04
	Muscle relaxant	Hydroquinine	M09AA
	Pulmonary	Sympathomimetics, cough suppressants, anti-histaminics	R03AC, R05DA, R06A

*According to study protocol [26]. ATC, Anatomical Therapeutic Chemical.

The number of participants in the control group (n=91; 34%) and intervention group (n=115; 37%) experiencing a fall during the one-year follow-up did not differ significantly ($p = 0.33$). Similarly, the number of participants in the control group (n=38; 14%) and intervention group

(n=50; 16%) experiencing a recurrent fall during the one-year follow-up did not differ significantly ($p = 0.45$).

Table 2. Baseline characteristics

	Control n = 293	Intervention n = 319
Demographics		
Age (year)	76.4 ± 6.6	76.5 ± 7.2
Gender (female)	182 (62)	198 (62)
MMSE	27.0 ± 2.4	27.0 ± 2.3
BMI (m^2/kg)	27.6 ± 4.7	27.6 ± 4.6
Home care	69 (24)	82 (26)
Fall risk factors		
Charlson Comorbidity Index	1.9 ± 1.6	1.9 ± 1.6
Number of drugs	6.4 ± 3.3	6.3 ± 3.3
Number of FRIDs	3.9 ± 2.0	3.9 ± 2.1
History of recurrent falls	128 (44)	148 (46)
Use of walking aid	72 (27)	78 (27)
Urinary incontinence	37 (13)	52 (16)
Vision problems	85 (30)	98 (32)
Nycturia	177 (60)	181 (57)
Fear of falling	104 (36)	118 (37)
Dizziness	75 (26)	102 (32)
Indoor fall	107 (37)	148 (46)
Smoking	37 (13)	34 (11)
Alcohol intake (≥ 3 units/day)	33 (11)	34 (11)
Functional status		
Activities of Daily Living	0.80 ± 4.5	0.80 ± 3.3
Instrumental Activities of Daily Living	1.39 ± 5.4	1.37 ± 4.0
Biochemical		
Vitamin D deficiency	119 (41)	135 (42)
Anemia	34 (13)	58 (19)

Continuous data are shown as mean values ± standard deviation, categorical data as number with percentage. MMSE, Mini-Mental State Examination; BMI, Body Mass Index; FRID, Fall-Risk Increasing Drugs.

Furthermore, the number of fallers requiring a GP consultation (n=46; 17% vs. 36; 12%, *p*=0.07) or ED visit (n=21; 8% vs. 16; 5%, *p*=0.22) did not differ significantly. The mean number of falls during follow-up in the control group was 0.83 and the mean number of falls in the intervention group was 0.80 (*p* = 0.88). The mean number of GP consultations because of a fall in the control and intervention group were 0.21 and 0.16 respectively, *p*=0.25. The mean number of ED visits because of a fall in the control and intervention group were 0.08 and 0.06 respectively, *p*=0.51.

In the intention-to-treat analysis, cox-regression analyses adjusted for age and gender showed that FRIDs withdrawal had no significant effect on the time to first fall (hazard ratio [HR] 1.17; 95% confidence interval [CI] 0.89-1.54), or on the time to the second fall (1.19; 0.78-1.82) (Table 4). Similarly, no significant effect on the time to the first GP consultation because of a fall (0.66; 0.42-1.06) or the time to the first ED visit because of a fall (0.85; 0.43-1.68) was found (Table 4). Subgroup analyses of cardiovascular and psychotropic FRIDs withdrawal were similar, except for an increased time until the first GP consultation because of a fall for cardiovascular FRIDs withdrawal (0.57; 0.34-0.93). The per protocol analyses did not alter the results.

Poisson regression analyses showed FRIDs withdrawal did not have a significant effect on the cumulative incidence of falls (β -0.05; 95% confidence interval [CI] -0.52-0.42), or on the cumulative incidence of GP consultations (-0.28; -0.75- 0.18) or ED visits (-0.22; -0.88- 0.44) because of a fall. Subgroup analyses of cardiovascular and psychotropic FRIDs withdrawal were again similar, and per protocol analyses did not alter these results (Supplementary data).

During the 12-months follow-up, 28 participants in the control group and 27 participants in the intervention group sustained an injurious fall (*p* = 0.64). Seven participants in the control group and six participants in the intervention group sustained a fracture because

of a fall ($p = 0.66$). Two participants, both in the control group, sustained a traumatic brain injury because of a fall ($p = 0.14$). Six participants died in the control group, causes were a ruptured coronary artery during a coronary angiography [1], kidney failure [1], esophageal cancer [1], leukemia [1], motor vehicle collision [1], and unknown [1]. Thirteen participants died in the intervention group, causes were sepsis [4], cancer [3], cerebrovascular accident [2], encephalopathy [1], cardiac failure [1], and unknown [2] ($p = 0.15$).

Table 3. Specification of interventions and compliance in intervention group

	Intervention group	No withdrawal*	Attempted withdrawal	Failed withdrawal	Successful withdrawal
All FRIDs	308	122	186	66	120
Cardiovascular FRIDs	265	164	101	37	64
Digitalis	4	3	1	1	0
Anti-arrhythmics	16	14	2	2	0
Nitrates	28	24	4	1	3
Antihypertensives	8	6	2	0	2
Diuretics	123	83	40	20	20
Beta-blockers	132	99	33	15	18
Calcium channel blockers	64	49	15	7	8
ACE/Angiotensin-II inhibitors	143	121	22	3	19
HMG CoA reductase inhibitors	119	117	2	0	2
Psychotropic FRIDs	114	37	77	37	40
Opioids	20	15	5	1	4
Anti-epileptic	10	8	2	1	1
Anti-Parkinson	9	6	3	0	3
Neuroleptics	3	1	2	2	0
Anxiolytics	27	4	23	10	13
Sedatives/Hypnotics	43	10	33	22	11
Antidepressants	36	20	16	8	8
Anti-vertigo	5	3	2	0	2
Other FRIDs	222	174	48	15	33
Anticholinergics (GI)	4	3	1	1	0
Hypoglycemics	51	49	2	1	1
Anti-spasmodics (GU)	15	6	9	5	4
Alfa-blockers (GU)	23	16	7	2	5
Steroids	16	15	1	0	1
NSAID	144	135	9	2	7
Anti-gout	12	10	2	1	1
Hydroquinine (muscle relaxant)	5	3	2	1	1
Adrenergics (respiratory)	25	23	2	0	2
Cough suppressants (opioids)	18	12	6	2	4
Antihistamines	11	2	9	3	6

*Participants in intervention group where withdrawal, dose reduction and/or substitution of FRID was not necessary or safely possible. FRID, Fall-Risk Increasing Drugs; ACE, Angiotensin-Converting-Enzyme; GI, Gastrointestinal; GU, Genitourinary; NSAID, Non-steroidal anti-inflammatory drug. Data are shown as number of patients.

Table 4. Cox-regression analyses including subgroup analyses

	Intention to treat			Per protocol		
	HR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
All FRIDs						
First fall	1.17	0.89; 1.54	0.27	1.19	0.89; 1.60	0.24
Second fall	1.19	0.78; 1.82	0.41	1.26	0.80; 1.99	0.31
GP consultation	0.66	0.42; 1.06	0.09	0.61	0.37; 1.02	0.06
ED visit	0.85	0.43; 1.68	0.64	0.78	0.37; 1.63	0.50
Cardiovascular FRIDs						
First fall	1.10	0.82; 1.49	0.51	1.12	0.81; 1.54	0.49
Second fall	1.21	0.78; 1.88	0.41	1.31	0.81; 2.12	0.27
GP consultation	0.57	0.34; 0.93	0.03	0.52	0.30; 0.91	0.02
ED visit	0.77	0.38; 1.58	0.48	0.68	0.31; 1.50	0.34
Psychotropic FRIDs						
First fall	1.28	0.84; 1.94	0.26	1.44	0.91; 2.29	0.12
Second fall	1.17	0.64; 2.15	0.60	1.37	0.71; 2.67	0.35
GP consultation	0.74	0.37; 1.48	0.40	0.88	0.42; 1.85	0.74
ED visit	0.78	0.28; 2.16	0.64	0.93	0.32; 2.69	0.89

Adjusted for age and gender. FRID, fall-risk increasing drug.

eTable 1. Amount of FRIDs at baseline and at 12 months follow-up

	Control n=272	Intervention n=308
Baseline FRIDs		
0 - 1	31 (11)	36 (11)
2	45 (17)	58 (19)
≥ 3	196 (72)	214 (70)
Follow-up FRIDs		
0 - 1	30 (11)	52 (17)
2	37 (14)	41 (13)
≥ 3	205 (75)	215 (70)
Change in amount of FRIDs		
Decrease	53 (20)	115 (38)
No change	151 (56)	127 (41)
Increase	68 (25)	66 (22)

Categorical data are given as number with percentages.

eTable 2. Poisson distribution of fall incidence

	Intention to treat			Per protocol		
	β	**95% CI**	***p*-value**	**β**	**95% CI**	***p*-value**
All FRIDs						
Falls	-0.05	-0.52; 0.42	0.84	-0.01	-0.53; 0.52	0.98
GP consultations	-0.28	-0.75; 0.18	0.23	-0.28	-0.78; 0.22	0.27
ED visits	-0.22	-0.88; 0.44	0.51	-0.37	-1.08; 0.34	0.30
Cardiovascular FRIDs						
Falls	-0.06	-0.57 5; 0.46	0.83	-0.01	-0.59; 0.57	0.97
GP consultations	-0.34	-0.84; 0.16	0.18	-0.35	-0.88; 0.20	0.21
ED visits	-0.19	-0.90; 0.52	0.59	-0.38	-1.16; 0.39	0.33
Psychotropic FRIDs						
Falls	0.31	-0.22; 0.84	0.25	0.53	-0.05; 1.10	0.07
GP consultations	-0.32	-1.03; 0.40	0.38	-0.15	-0.91; 0.61	0.70
ED visits	-0.25	-1.26; 0.75	0.62	-0.17	-1.22; 0.89	0.76

Adjusted for age and gender. FRID, fall-risk increasing drug.

DISCUSSION

In the present randomized controlled trial we found that a structured medication assessment including withdrawal of FRIDs did not reduce the risk of falls in community dwelling elderly with a history of previous fall. There was a tendency towards fewer healthcare visits in the intervention group, which was significant in the cardiovascular-drug withdrawal subgroup. In previous studies, the withdrawal of FRIDs has been shown to be safely possible and effective [20,23-25]. However, evidence regarding FRIDs withdrawal as single intervention is scarce [17,24,25]. In a study by Pit *et al.* the intervention was carried out by the participants' GP, probably increasing and sustaining the number of successful withdrawals due to the more substantial doctor-patient relationship [25]. Campbell *et al.* performed a psychotropic drug withdrawal intervention that was complete and double-blinded, demonstrating the effectiveness of total psychotropic drug withdrawal on preventing falls [24]. Yet this complete withdrawal was difficult to maintain. This was also a limitation in our study. Notably, in our study the withdrawal of cardiovascular FRIDs appeared to reduce risk of GP consultations because of a fall, possibly due to fewer injurious falls. Most studies associate greater fall risk with psychotropic drugs [19,21], however, besides our finding, another study has also reported greater risk reduction after withdrawal of cardiovascular drugs [20]. Furthermore, a recent large study found that antihypertensive medications were associated with an increased risk of serious fall injuries [37].

There are several possible explanations for our findings. First, since in the last decade, falls prevention guidelines have been incorporated into usual care, this may well have blunted the effect of the intervention. Second, in our intervention group a large proportion of FRIDs were prescribed adequately and thus withdrawal was not appropriate (Table 3). Third, a large proportion of the participants in the intervention group was not compliant to the intervention,

especially concerning psychotropic drugs withdrawal. Fourth, it might be possible that participants in the intervention group were more diligent when filling out their Falls Calendars than the usual care group. The time till first and second fall were recorded from the Falls Calendars which participants from both group filled out and the time till the first GP consultation and ED visit were recorded from GP data. Although not statistically significant, the intervention group displayed a tendency towards a shorter time until the first fall, yet a longer time until the first GP consultation or ED visit because of a fall. Furthermore, when studying the participants in the successful withdrawal group individually, it was apparent that although one or more FRIDs were successfully withdrawn, reduced, or substituted, several participants were prescribed additional FRIDs during the follow-up year by their GP or other specialist, often for new conditions. Furthermore, the percentage of participants using ≥ 3 FRIDs in the intervention group (70%) was not decreased at 1 year follow-up.

Notably, during follow-up, six participants in the control group and thirteen participants in the intervention group died, however, this was not a significant difference. Furthermore, looking at the separate causes of death the distribution of these deaths seem coincidental and not due to adverse effects of drug withdrawal. Also, another falls prevention trial including FRID withdrawal observed the opposite distribution [16].

In addition to the potential explanations mentioned above, the following limitations should be taken into account when interpreting our results. First, recruiting participants proved challenging. Possible reasons for refusing to participate have been reported previously [38]. Most common reasons for refusal were the added burden of additional visits to the hospital; highly independent older adults feeling “too healthy”; and personal opinions regarding the cause of the fall. Second, possibly the method of reporting falls was not as accurate as anticipated; as mentioned above, the intervention group reported as many falls as the control group, but the numbers of healthcare visits because of a fall (which were verified with GP

records) were higher in the control group. The newest guidelines state fall incidence is best monitored with weekly phone calls instead of self-report calendars [39]. Third, as mentioned before, in the intervention group compliance with withdrawal was limited, especially in the group with psychotropic drug withdrawal. This might be improved if the prescribing physician performs the withdrawal, as was the case in the study by Pit *et al.* [25]. A major strength of this study is that current recommendations regarding falls prevention studies were followed [40], i.e., addressing a single intervention in a randomized controlled trial. Furthermore, participants included were high-risk fallers, i.e., older men and women who visited the ED because of a fall. In this target group even a small reduction of their fall risk might prevent loss of independence.

Overall, FRIDs withdrawal did not result in reduced incidence of falls, whereas, cardiovascular FRIDs withdrawal did reduce healthcare visits because of a fall. Surprisingly, no effect of psychotropic drug withdrawal was seen, which might have been caused by low compliance to the intervention. This study increases insight into both the effectiveness of FRIDs withdrawal as a method for falls reduction in older adults, and into the complexity of this intervention in an older, multi-morbid population. The current study adds to the understanding of effective falls-prevention interventions. Further research is warranted focusing on the optimal method for implementation, thus ensuring participation and compliance of sustained FRID withdrawal in older fallers.

REFERENCES

1. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med.* Sep 29 1994;331(13):821-827.

2. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *Jama.* Oct 14 2009;302(14):1573-1579.

3. Kochanek KD, Xu JQ, Murphy SL, al. e. Deaths: Preliminary data for 2009. . Vol National vital statistics reports; vol 59 no 4.: Hyattsville, MD: National Center for Health Statistics. ; 2011.

4. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev.* Oct 2006;12(5):290-295.

5. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. *Osteoporos Int.* Feb 2004;15(2):87-94.

6. Close JC, Lord SR, Antonova EJ, Martin M, Lensberg B, Taylor M, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. *Emerg Med J.* Sep 2012;29(9):742-747.

7. Hartholt KA, van Beeck EF, Polinder S, van der Velde N, van Lieshout EM, Panneman MJ, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* Sep 2010;71(3):748-753.

8. Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. *Osteoporos Int.* 2000;11(5):460-466.

9. Greenspan AI, Coronado VG, Mackenzie EJ, Schulman J, Pierce B, Provenzano G. Injury hospitalizations: using the nationwide inpatient sample. *J Trauma.* Nov 2006;61(5):1234-1243.

10. Hartholt KA, van der Velde N, Looman CW, van Lieshout EMM, Panneman MJ, van Beeck EF, et al. Trends in fall-related hospital admissions in older persons in the Netherlands. *Arch Intern Med.* May 24 2010;170(10):905-911.

11. Hartholt KA, Van Lieshout EMM, Polinder S, Panneman MJ, Van der Cammen TJM, Patka P. Rapid increase in hospitalizations resulting from fall-related traumatic head injury in older adults in The Netherlands 1986-2008. *J Neurotrauma.* May 2011;28(5):739-744.

12. Scuffham P, Chaplin S, Legood R. Incidence and costs of unintentional falls in older people in the United Kingdom. *J Epidemiol Community Health.* Sep 2003;57(9):740-744.

13. AGS/BGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc.* Jan 2010;59(1):148-157.

14. AGS/BGS/AAOS. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* May 2001;49(5):664-672.

15. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* Dec 29 1988;319(26):1701-1707.

16. de Vries OJ, Peeters GM, Elders PJ, Muller M, Knol DL, Danner SA, et al. Multifactorial intervention to reduce falls in older people at high risk of recurrent falls: a randomized controlled trial. *Arch Intern Med.* Jul 12 2011;170(13):1110-1117.

17. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev.* 2012;9:CD007146.

18. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):40-50.

19. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):30-39.

20. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. *Br J Clin Pharmacol.* Feb 2007;63(2):232-237.

21. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* Nov 23 2009;169(21):1952-1960.

22. Sterke CS, Ziere G, van Beeck EF, Looman CW, van der Cammen TJ. Dose-response relationship between selective serotonin re-uptake inhibitors and injurious falls: a study in nursing home residents with dementia. *Br J Clin Pharmacol.* May 2012;73(5):812-820.

23. Alsop K, Mac Mahon M. Withdrawing cardiovascular medications at a syncope clinic. *Postgrad Med J.* Jun 2001;77(908):403-405.

24. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc.* Jul 1999;47(7):850-853.

25. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. *Med J Aust.* Jul 2 2007;187(1):23-30.

26. Hartholt KA, Boyé NDA, Van der Velde N, Van Lieshout EMM, Polinder S, De Vries OJ, et al. [Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study). *BMC Geriatr.* 2011;11:48.

27. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. *J Am Geriatr Soc.* Jul 1988;36(7):613-616.

28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* Nov 1975;12(3):189-198.

29. Pluijm SM, Smit JH, Tromp EA, Stel VS, Deeg DJ, Bouter LM, et al. A risk profile for identifying community-dwelling elderly with a high risk of recurrent falling: results of a 3-year prospective study. *Osteoporos Int.* 2006;17(3):417-425.

30. Brooks R. EuroQol: the current state of play. *Health Policy.* Jul 1996;37(1):53-72.

31. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol.* Nov 1998;51(11):1171-1178.

32. *Farmacotherapeutisch Kompas.* Diemen, Netherlands: College voor zorgverzekeringen; 2012.

33. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan Med Bull.* Apr 1987;34 Suppl 4:1-24.
34. Holick MF. Vitamin D deficiency. *N Engl J Med.* Jul 19 2007;357(3):266-281.
35. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev.* Aug 2001;22(4):477-501.
36. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet.* Jan 9 1999;353(9147):93-97.
37. Tinetti ME, Han L, Lee DS, McAvay GJ, Peduzzi P, Gross CP, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA Intern Med.* Apr 1 2014;174(4):588-595.
38. Elskamp AB, Hartholt KA, Patka P, van Beeck EF, van der Cammen TJ. Why older people refuse to participate in falls prevention trials: a qualitative study. *Exp Gerontol.* Apr 2012;47(4):342-345.
39. Reelick MF, Faes MC, Lenferink A, Esselink RA, Olde Rikkert MG. The fall telephone for falls assessment in frail older persons; feasibility, reliability, and validity. *J Am Geriatr Soc.* Feb 2011;59(2):372-373.
40. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc.* Sep 2005;53(9):1618-1622.

Chapter 3

Cost-Utility Analysis of the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) Study

Nicole D.A. Boyé, Esther M.M. van Lieshout, Francesco U.S. Mattace-Raso, Nathalie van der Velde, Klaas A. Hartholt, Oscar J. de Vries, Paul Lips, Tischa J.M. van der Cammen, Peter Patka, Ed F. van Beeck, Suzanne Polinder, and the IMPROveFALL trial collaborators

Manuscript in preparation

ABSTRACT

Background: Falls affect a large proportion of the persons aged 65 years and older, and are associated with substantial loss of quality of life, and high cost.

Objectives: To investigate the effect of a structured medication assessment including withdrawal of fall-risk increasing drugs versus 'care as usual' on the costs, health-related quality of life (HRQoL), and cost-utility in community-dwelling older men and women.

Design: Randomized multicenter trial.

Participants: 612 older adults who visited an Emergency Department due to a fall.

Measurements: HRQoL was measured at baseline and at 12 months follow-up using the EuroQol-5D and Short Form-12 version 2. Cost-utility was assessed by calculating the cost per Quality Adjusted Life Years (QALY) gained.

Results: Costs for the intervention were €39 higher than usual care. The control group had a greater decline in EuroQol-5D utility score during the 12 month follow-up than the intervention group ($p = 0.02$). The change in the Short Form-12 Physical Component Summary and Mental Component Summary scores did not differ significantly between the two groups. Incremental cost-utility of the intervention was €780/QALY gained.

Conclusion: Compared to usual care, FRID withdrawal led to higher costs, but was associated with less decline in HRQoL as measured with the EQ-5D utility score.

Trial Registration: Netherlands Trial Register NTR1593 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1593).

INTRODUCTION

Falls affect a large proportion of the persons aged 65 years and older and are associated with consequences such as loss of quality of life and high cost [1-5]. In 2000 the fall-related medical costs in the population 65 years and older in the United States amounted to US$19 billion for non-fatal injuries and US$200 million for fatal injuries [6]. Between 2003 and 2007 the average annual cost for fall-related injuries in the Netherlands was US$ 640 million (€470 million), and the overall cost per fall was US$9,530 (€7,048) [7]. In order to reduce the prevalence of falls, risk factors have been well documented [8-10], and there have been a substantial amount of fall-prevention trials [5,11-20].

However, past variations in outcome definitions and measures of fall-prevention trials have hindered comparative research and meta-analysis, and thus the *Prevention of Falls Network Europe* (ProFaNE) established a common set of outcome definitions and measures for use in trials. These include cost, health-related quality of life (HRQoL) outcomes, and a follow-up duration of 12 months [21]. To our knowledge no studies have reported the cost-utility of withdrawal of fall-risk increasing drug (FRID) as a single intervention [22-35]. Furthermore, few fall-prevention trials have documented quality of life outcomes [15,36-39], and only one reported HRQoL as recommended by ProFaNE [15].

The use of certain drugs has been associated with increased risk of falls and related injuries [40-43], and in previous literature the withdrawal of FRIDs was shown to be safely possible and to generate significant cost savings [11,20,44]. The present study investigated the costs, the effect on HRQoL, and the cost-utility of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' in community-dwelling older men and women, who visited the emergency department (ED) after experiencing a fall [45].

METHODS

Study population

The IMPROveFALL study was a randomized, multicenter trial, assessing the effect of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' as a method for falls reduction [45]. Patients meeting the following inclusion criteria were eligible for enrolment: aged 65 years or older, visited the ED of a participating hospital due to a fall, use of one or more fall-risk increasing drugs [40,41,43,45], Mini-Mental State Examination (MMSE) score of at least 21 out of 30 points [46], ability to walk independently, community dwelling, and provision of written informed consent by the patient. Participating hospitals included two academic and four regional hospitals in the Netherlands. Enrolment started in October 2008 and was completed in October 2011. The follow-up period was 12 months. The study was performed in accordance with the Declaration of Helsinki and all participants gave written informed consent. The local Medical Research Ethics Committees in all participating hospitals approved the study protocol.

All persons visiting the ED due to a fall received care as usual for their injuries and were contacted by telephone after their ED visit. Eligible study participants received written information concerning the study and those interested in participating were invited to the research outpatient clinic. The visits to the outpatient clinic took place within two months after the ED visit. During the visit at the outpatient clinic a fall-related assessment was performed by the clinical investigator and supervised by a geriatrician. A detailed description of the study protocol can be found elsewhere [45].

Definition fall incident

A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions, *e.g.*, stroke, or exogenous factors such as a traffic accident [47]. All participants received a Falls Calendar for reporting falls during a one-year follow-up period. Falls were recorded weekly on the Fall Calendars and had to be returned every three months. Follow-up started two weeks after completed intervention or two weeks after initial research clinic visit when no intervention was performed. The number of injuries prevented was calculated with data recorded in the study, supplemented with epidemiological data on falls and injury risks.

Costs

The total direct and indirect costs of both FRID withdrawal and 'care as usual' were measured. Costs were calculated by multiplying the volumes of healthcare use with the corresponding unit prices (Table 1). Direct healthcare costs included the costs of the FRID assessment and modification, drug consumption (*i.e.*, the cost of substitution drugs), and fall-related healthcare consumption during one year of follow-up (*e.g.*, outpatient visits, hospital admissions, General Practitioner consultations, home care, nursing home care). Indirect costs included patient travel costs. For the intervention (systematic fall-related drugs assessment) the full cost was calculated and for the other healthcare costs standard Dutch cost prices were used as published by *Hakkaart-van Roijen et al.* [48]. Costs of medication use were recorded in the study, and unit costs were determined with information from the National Dutch Formulary [49]. Healthcare consumption, both fall and non-fall related, and patient costs were recorded from the three-monthly questionnaires for healthcare consumption and patient costs and data received from the participants' General Practitioner.

Health-related quality of life

During the baseline assessment and at the follow-up clinic visit, all participants completed questionnaires on generic HRQoL under supervision of the clinical investigator or research nurse. Based upon the recommendations of ProFaNE [21], HRQoL was measured using the Dutch versions of the EuroQol-5D (EQ-5D) [50] and the Short Form-12 (SF-12) version 2 [51] at baseline and at 12 months-follow-up. The EQ-5D utility score covers five health domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has three levels; no problem, moderate problem, or severe problem. In addition, a scoring algorithm based on empiric valuations from the United Kingdom general population and subsequent statistical modeling is available by which each health status description can be expressed into a utility score [52]. This utility score ranges from 1 for full health to 0 for death, and can be interpreted as a judgment on the relative desirability of a health status compared with perfect health. The EQ-5D is a validated and extensively used general health questionnaire to measure quality of life [50]. It is recommended for the assessment of HRQoL in trauma patients, especially for economic assessments [53]. The SF-12 contains eight domains measuring physical and mental health outcomes; physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Data from all eight domains is used to construct the physical and mental component summary measures (PCS and MCS) [51].

Cost-utility analysis

The long-term effectiveness of the interventions was expressed in terms of the cumulative number of life years and quality-adjusted life years (QALYs) gained. The QALY combines morbidity and mortality into a single number. QALYs were calculated by weighting life years for the quality of life using the EQ-5D utility score. The gain in QALY is equal to difference between QALY measures.

Finally, the cost per QALY gained was calculated as the ratio of total intervention costs minus savings in fall-related healthcare costs compared with control divided by the cumulative QALYs gained compared with control. All analyses were performed in accordance with Dutch guidelines for economic evaluations [54].

Statistical analyses

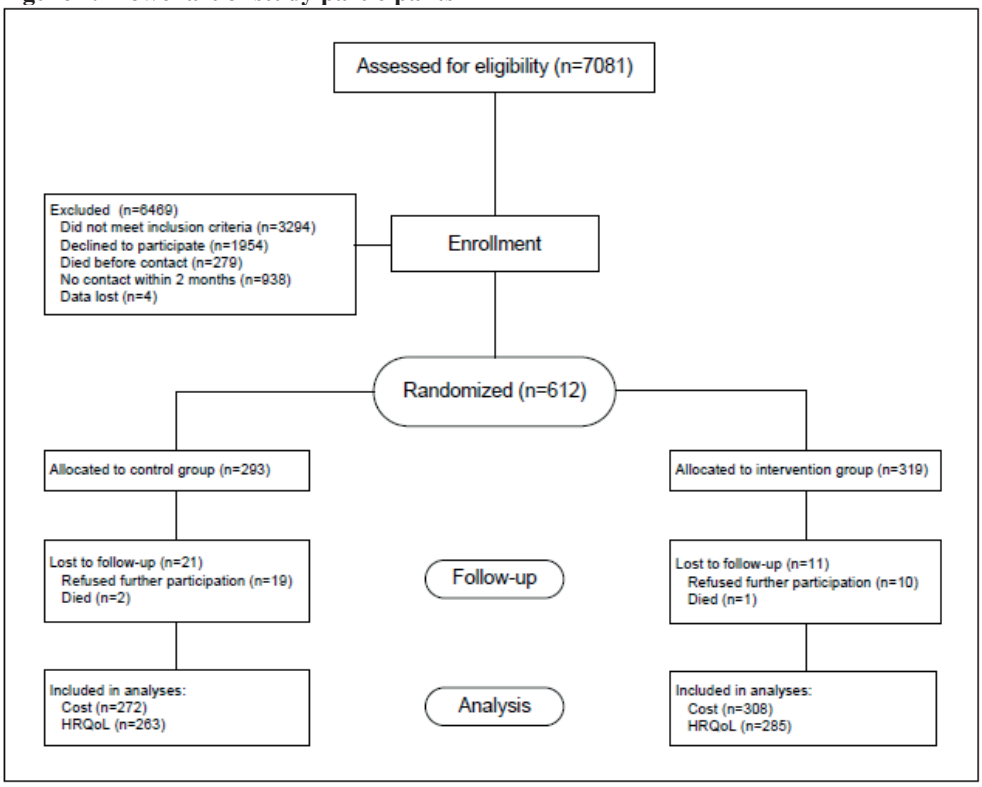
All analyses were performed using the Statistical Package of the Social Sciences (SPSS version 17.0, Chicago, Ill.) and a p-value < 0.05 was considered statistically significant. Baseline characteristics were compared using Student t-test analyses for continuous variables and chi-squared analyses for dichotomous variables. The change in EQ-5D utility score and SF-12 PCS and MCS scores over 12 months (*i.e.*, after 12 months follow-up versus baseline data) within the control and intervention groups were compared using the Wilcoxon Signed Rank test for continuous variables and the McNemar test for dichotomous variables. The change in scores between the control and intervention groups were compared using a two-way analysis of variance (ANOVA). Analyses of the individual health domains of the EQ-5D and SF-12 were also performed. Secondary analyses were performed, comparing the HRQoL scores of the participants with and without a fall during follow-up.

RESULTS

In total, 7,081 patients visiting the ED were screened for possible trial participants, subsequently 612 participants were randomized in the IMPROveFALL study (Figure 1). Randomization resulted in 293 participants being allocated to the control group and 319 participants to the intervention group, of those 265 and 287 had complete quality of life assessments at baseline and at 12 months follow-up (Figure 1). The mean age was 76 years

and 62% of the study population was female. No significant differences in baseline characteristics were found between the control and intervention group (Table 2).

Figure 1. Flowchart of study participants



*Of the participants who died during follow-up, most were included in the analyses, except for two in the control and one in the intervention group. **Nine and 23 participants in the control and intervention group declined or were unable to complete EQ-5D questionnaires after 12-months follow-up.

Table 3 specifies the interventions according to FRID categories and specific drug types, and also includes details on compliance to attempted interventions. Notably, in 40% of all FRIDs, an intervention was not deemed possible or necessary. Of all attempted interventions 36% failed, either due to non-compliance or a return of the primary indication for which the drug

was prescribed. The number of participants in the control group and intervention group experiencing a fall or recurrent fall during the one-year follow-up did not differ significantly (Chapter 3.2).

Table 1. List of costs

Cost categories	Parameter	Cost price (€, 2009)
Intervention costs	*	Variable
Medication costs	DDD	Variable
Hospital stay costs	Day	457
Emergency Department costs	Visit	151
General Practitioner costs	Consultation	28
Specialist consult costs	Consultation	72
Home care costs	Per hour	35
Physical therapy costs	Visit	36
Nursing home costs	Day	238
Intermediate care facility costs	Day	90
Rehabilitation center costs	Day	340
Patient costs (travel costs)	Per kilometer	Variable**

DDD: Defined Daily Dose; GP, General Practitioner. *Geratric consultation (€72) + routine blood test (€20) + extra consults (€72). **Private motor vehicle / public transportation / taxi.

Costs

The mean cost of the FRIDs intervention was €120 which included the initial Geriatric consultation (€72), routine blood tests (€20) and necessary additional consultations (€72). The

mean costs saved with medication withdrawal, dose reduction and drug substitution was €38 per participant. The savings in fall-related healthcare costs of the intervention group (€ 2324 - 2285 = €39) compared with control did not differ significantly (Table 4).

Table 2. Baseline characteristics of the control and intervention group

	Control	**Intervention**
	n = 293	**n = 319**
Demographics		
Age (year)	76.4 ± 6.6	76.5 ± 7.2
Female gender	182 (62)	198 (62)
MMSE	27.0 ± 2.4	27.0 ± 2.3
BMI (m^2/kg)	27.6 ± 4.7	27.6 ± 4.6
Fall risk factors		
Charlson Comorbidity Index	1.9 ± 1.6	1.9 ± 1.6
Number of drugs	6.4 ± 3.3	6.3 ± 3.3
Number of FRIDs	3.9 ± 2.0	3.9 ± 2.1
History of recurrent falls	128 (44)	148 (46)
Smoking	37 (13)	34 (11)
Alcohol intake (≥ 3 units/day)	33 (11)	34 (11)
Functional status		
Home care	69 (24)	82 (26)
Activities of Daily Living	0.80 ± 4.5	0.80 ± 3.3
Instrumental Activities of Daily Living	1.39 ± 5.4	1.37 ± 4.0

Continuous data are shown as mean values ± standard deviation, categorical data as number with percentage. MMSE, Mini-Mental State Examination; BMI, Body Mass Index; FRID, Fall-Risk Increasing Drugs.

Table 3. Specification of interventions and compliance in intervention group

	Intervention group	No withdrawal*	Attempted withdrawal	Failed withdrawal	Successful withdrawal
All FRIDs	308	122	186	66	120
Cardiovascular FRIDs	265	164	101	37	64
Psychotropic FRIDs	114	37	77	37	40
Other FRIDs	222	174	48	15	33

*Participants in intervention group where withdrawal, dose reduction and/or substitution of FRID was not necessary or safely possible. FRID, Fall-Risk Increasing Drugs. Data are shown as number of patients.

Health-related quality of life

9 and 23 participants in the control and intervention group declined or were unable to complete EQ-5D questionnaires after 12-months follow-up, and an additional 5 and 2 participants in the control and intervention group had incomplete SF-12 questionnaires after 12-months follow-up.

The baseline and follow-up HRQoL scores of the control and intervention group are shown in Table 5. The control group had a greater decline in EQ-5D utility score during the 12 month follow-up compared to the intervention group, ($p = 0.02$). The decline in the SF-12 PCS and MCS score did not differ significantly between the intervention and control group ($p = 0.08$ and $p = 0.90$). The problems in the EQ-5D domains of the control and intervention group reported at baseline and at follow-up are shown in Table 6.

Table 4. Mean costs of the control and intervention group during 12 months follow-up.

Cost categories	Control (n=272)	Intervention (n=308)	*p*-value
Intervention costs	-	120[†]	*
General Practitioner consult costs	29	20	*
Specialist consult costs	51	40	
Emergency Department costs	12	10	
Hospital stay costs	360	383	
Home care costs	662	630	
Physical therapy costs	290	218	
Intermediate care facility costs	220	74	
Nursing home costs	424	156	
Rehabilitation center costs	229	708	
Patient costs (travel costs)	3	2	
Medication cost saved	-3	-38	*
Total costs	2285	2324	

Data are given as mean values in euro (€).[†]Average;* < 0.05

The overall mean baseline EQ-5D utility score of those with and without a fall during follow-up was 0.69 ± 0.27 and 0.80 ± 0.21, respectively ($p < 0.01$; data not shown). The overall mean baseline SF-12 PCS scores of those with and without a fall during follow-up were 44.4 ± 9.9, and 46.6 ± 9.6, $p = 0.01$. The overall mean baseline SF-12 MCS scores of those with and without a fall during follow-up were 53.2 ± 10.0, and 53.3 ± 9.0, $p = 0.87$. Thus, the participants who fell during follow-up had significantly lower EQ-5D and SF-12 PCS scores at baseline. A secondary analysis was performed of the decline in HRQoL in the participants

of the control and intervention group with and without a fall during follow-up (Table 7). In the participants with a fall during follow-up, the change in quality of life did not differ significantly between both groups. In the participants without a fall during follow-up, the control group had a greater decline in the SF-12 PCS score ($p = 0.01$), when compared to the intervention group.

Table 5. Quality of life scores of the control and intervention groups at baseline and 12 months follow-up, and the change over 12 months

	Group	N[†]	Baseline	Follow-up	*p*-values*	Change	*p*-values**
EQ-5D utility score	C	263	0.78 ± 0.22	0.74 ± 0.25	0.01	-0.04 ± 0.22	0.02
	I	285	0.74 ± 0.26	0.75 ± 0.26	0.75	0.01 ± 0.24	
SF-12 PCS score	C	258	46.2 ± 9.9	42.2 ± 11.6	<0.01	-3.9 ± 8.5	0.08
	I	283	45.6 ± 9.5	43.0 ± 10.7	<0.01	-2.6 ± 8.5	
SF-12 MCS score	C	258	53.2 ± 9.0	52.5 ± 9.2	0.28	-0.7 ± 9.7	0.90
	I	283	53.3 ± 9.5	52.5 ± 9.0	0.20	-0.8 ± 9.7	

C, control; I, intervention. Data are given as mean values ± standard deviation.

[†]9 and 23 participants in the control and intervention group declined or were unable to complete EQ-5D questionnaires after 12-months follow-up, an additional 5 and 2 participants in the control and intervention group had incomplete SF-12 questionnaires after 12-months follow-up. *Wilcoxon Signed Rank test (comparing baseline and follow-up), **Two-way ANOVA of the change over 12 months.

Cost-utility

The mean QALY difference between both groups was 0.05 QALY (gained by the intervention group) over the trial period. The costs in the intervention group were €39 higher

per patient than usual care. This results in an incremental cost-utility ratio of €780/QALY gained.

Table 6. Prevalence of problems on the five dimensions of the EQ-5D in the control and intervention groups at baseline and 12 months follow-up

	Group	N[†]	Baseline	Follow-up	*p*-value*
Mobility	C	263	119 (45)	141 (54)	0.01
	I	285	152 (53)	150 (53)	0.90
Self-Care	C	263	37 (14)	37 (14)	1.00
	I	285	48 (17)	37 (13)	0.08
Usual Activities	C	263	80 (30)	89 (34)	0.30
	I	285	104 (37)	97 (34)	0.49
Pain/Discomfort	C	263	138 (53)	152 (58)	0.13
	I	285	165 (58)	151 (53)	0.12
Anxiety/Depression	C	263	74 (28)	78 (30)	0.70
	I	285	73 (26)	84 (30)	0.19

C, control; I, intervention. Data are presented as number and percentages (%).

[†]9 and 23 participants in the control and intervention group declined or were unable to complete EQ-5D questionnaires after 12-months follow-up. *McNemar test.

Table 7. Quality of life scores of the participants with and without a fall during follow-up

Fall	**Group**	**N**	**Baseline**	**Follow-up**	***p*-values***	**Change**	***p*-values****
EQ-5D utility score	UC	87	0.71 ± 0.25	0.64 ± 0.28	0.01	-0.07 ± 0.29	0.13
	I	101	0.68 ± 0.29	0.67 ± 0.28	0.70	-0.01 ± 0.27	
SF-12 PCS score	UC	88	44.0 ± 10.4	39.3 ± 13.1	<0.01	-4.7 ± 9.8	0.72
	I	107	44.8 ± 9.5	40.7 ± 11.2	<0.01	-4.2 ± 10.2	
SF-12 MCS score	UC	88	53.6 ± 9.1	51.6 ± 10.5	0.14	-1.9 ± 10.8	0.56
	I	107	52.4 ± 10.6	51.7 ± 9.2	0.25	-1.0 ± 11.1	
No fall	**Group**	**N**	**Baseline**	**Follow-up**	***p*-values***	**Change**	***p*-values****
EQ-5D utility score	UC	169	0.81 ± 0.19	0.80 ± 0.22	0.27	-0.02 ± 0.16	0.08
	I	180	0.77 ± 0.24	0.80 ± 0.23	0.44	0.02 ± 0.16	
SF-12 PCS score	UC	172	47.3 ± 9.6	43.9 ± 10.4	<0.01	-3.5 ± 7.8	0.01
	I	178	46.1 ± 9.6	44.5 ± 10.2	<0.01	-1.5 ± 7.1	
SF-12 MCS score	UC	172	53.1 ± 9.0	53.0 ± 8.5	0.76	-0.1 ± 9.2	0.46
	I	178	53.9 ± 8.8	53.0 ± 8.9	0.40	-0.9 ± 8.8	

C, control; I, intervention. Data are given as mean values ± standard deviation. *Wilcoxon Signed Rank test, **Two-way ANOVA.

DISCUSSION

To the best of our knowledge this is the first cost-utility analysis comparing a structured medication assessment including withdrawal of FRIDs versus 'care as usual' in community-dwelling older men and women. The total cost did not differ significantly between the control and intervention group, whereas, the total healthcare related costs in the intervention group were €39 higher than usual care. Notably, the control group reported a significantly greater decline in HRQoL during the 12 month follow-up as measured with the EQ-5D utility score than the intervention group. The intervention resulted in an incremental cost-utility ratio of

€780/QALY gained. Policy makers and health economists have proposed that costs up to €20,000 per QALY are considered as acceptable [55].

Various studies have reported cost and cost-effectiveness data regarding fall prevention trials with varying results, however, most studies evaluated multifactorial interventions [23,25,26,28-31,33-35,56]. One study reported on the cost-effectiveness of FRID withdrawal as a single intervention, and reported significant national cost savings [44]. In this study, the total healthcare related costs in the intervention group were €39 higher than usual care, yet no reduction in fall risk was found. Possible reasons for this lack of fall risk reduction are extensively discussed elsewhere (Chapter 3.2). In short, since in the last decade fall prevention guidelines have been incorporated into usual care, this may well have blunted the effect of the intervention. Second, a large proportion of FRIDs turned out to be prescribed adequately and thus withdrawal was not appropriate. In addition, a large proportion of the participants was not compliant to the intervention, especially with respect to psychotropic drugs (Table 2). Higher compliance rates might have led to lower fall risk and lower related healthcare costs, and increased savings due to reduced medication costs (mean reduction of €38 per participant in this study). Furthermore, a less costly method of FRID withdrawal could be accomplished by having the GP perform the intervention, thus further lowering costs per QALY.

The mean EQ-5D utility score of the entire study population at baseline was 0.75 ± 0.25, and the overall percentage of problems reported at baseline were 52% for mobility, 17% for self-care, 36% for usual activities, 57% for pain/discomfort, and 28% for anxiety/depression. These rates were higher than the Dutch population norms for the 70-79 age group, which are 43% for mobility, 9% for self-care, 23% for usual activities, and 42% for pain/discomfort, and 12% for anxiety/depression [57]. The mean SF-12 PCS and MCS

scores at baseline were 45.5 ± 9.8 and 53.0 ± 9.5, respectively. These were similar to the Dutch population norms for the 65-74 age group [51].

Until now, only one fall prevention trial reported HRQoL as recommended by ProFaNE, a multifactorial intervention trial, and reported no significant change in EQ-5D and SF-12 scores between the intervention and control group [15]. Four other trials used varying methods to measure HRQoL. Two found no difference in SF-36 score between the control and intervention group [36,37]. Another multifactorial fall prevention trial, which used the 15D instrument, concluded the intervention produced positive effects in some dimensions of HRQoL [39]. Still another trial used the World Health Organization Quality of Life instrument WHOQoL) and measured higher quality of life in one of the treatment groups [38]. It is difficult to compare results, partly due to varying outcome measures. Another reason is the diversity of interventions, an intervention such as exercise training will most likely improve quality of life [38], while withdrawal of certain drugs might do the opposite.

It is important to note that except for a structured medication assessment, including the withdrawal of FRIDs, both groups received identical care. Furthermore, withdrawal of certain commonly prescribed FRIDs such as benzodiazepines, antidepressants and opiates [45], could have resulted in lower quality of life scores in the intervention group. Nonetheless, in this study the withdrawal of FRIDs did not lower the HRQoL. Remarkably, in the secondary analysis comparing the participants without a fall during follow-up the intervention group had lesser decline in the SF-12 PCS score than the control group. The fact that the intervention did not lower the HRQoL and possibly even improved it, is on its own an important outcome. Notably, the participants who fell during follow-up had significantly lower EQ-5D and SF-12 PCS scores at baseline. This is in a group of community-dwelling elderly who all recently visited the ED due to a fall; those who fell during follow-up had lower quality of life scores ahead of the recurrent fall. To the best of our knowledge, this finding has not been reported in

previous literature, and is valuable for future investigations regarding risk factors associated with falls in community-dwelling older men and women.

An unexpected finding was that regardless of similar baseline characteristics including age, gender, and number of comorbidities, the baseline EQ-5D utility score was lower in the intervention group. This could not be attributed to differences in reporting procedures, as the method and timing of HRQoL questionnaire completion were identical for the control and intervention groups. Another possible reason could be the presence of more severe injuries in the intervention group at baseline, however, the injuries sustained by the participants at baseline were similar in both groups (data not shown).

The following limitations should be taken into account when interpreting our results. First, the dropout during the 12 month follow-up could be due to the selected study population which had a high risk of falling. These patients often had mobility impairments and other comorbid conditions that may have resulted in a refusal to continue participating in the study and visit our outpatient clinic after 12 months follow-up. Thus the most at-risk and frail participants could have been excluded from the analysis, however, the randomization would have equally divided these patients across the intervention and control group. Second, the SF-12 has been evaluated for use in large group comparisons, this may not be correct for our secondary analyses where we solely included participants with and without a fall during follow-up [51]. Third, as mentioned before, in the intervention group compliance with withdrawal was limited, especially in the group with psychotropic drug withdrawal. This might be improved if the prescribing physician performs the withdrawal, as was the case in the study by Pit *et al.* [58]. Fourth, the main aim of this study was to study the effectiveness of the intervention that is why the power calculation was based on a falls reduction rather than QALYs or costs. A major strength of this study is that it was a single intervention study, making it easier to be included in comparative research and meta-analysis, and it follows

current recommendations regarding HRQoL outcome measures [21]. Furthermore, participants included were high-risk fallers, *i.e.*, older men and women who visited the ED due to a fall.

In this study comparing withdrawal of FRIDs versus 'care as usual' in community-dwelling older men and women, the total healthcare related costs in the intervention group were €39 higher than the control group. The incremental cost-utility ratio was €780/QALY gained and remained below the €20,000 per QALY which is considered acceptable by policy makers. Notably, the withdrawal of FRIDs reduced medication costs with a mean of €38 per participant, this in combination with less decline in HRQoL should not be overlooked.

REFERENCES

1. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. *Osteoporos Int.* Feb 2004;15(2):87-94.
2. Close JC, Lord SR, Antonova EJ, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. *Emerg Med J.* Sep 2012;29(9):742-747.
3. Hartholt KA, van Beeck EF, Polinder S, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* Sep 2010;71(3):748-753.
4. Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. *Osteoporos Int.* 2000;11(5):460-466.
5. Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med.* Sep 29 1994;331(13):821-827.
6. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev.* Oct 2006;12(5):290-295.
7. Hartholt KA, van Beeck EF, Polinder S, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* Sep 2011;71(3):748-753.
8. AGS/BGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc.* Jan 2010;59(1):148-157.
9. AGS/BGS/AAOS. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* May 2001;49(5):664-672.
10. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* Dec 29 1988;319(26):1701-1707.
11. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc.* Jul 1999;47(7):850-853.
12. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Falls prevention over 2 years: a randomized controlled trial in women 80 years and older. *Age Ageing.* Oct 1999;28(6):513-518.
13. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet.* Jan 9 1999;353(9147):93-97.
14. Davison J, Bond J, Dawson P, Steen IN, Kenny RA. Patients with recurrent falls attending Accident & Emergency benefit from multifactorial intervention--a randomised controlled trial. *Age Ageing.* Mar 2005;34(2):162-168.
15. de Vries OJ, Peeters GM, Elders PJ, et al. Multifactorial intervention to reduce falls in older people at high risk of recurrent falls: a randomized controlled trial. *Arch Intern Med.* Jul 12 2011;170(13):1110-1117.
16. Jensen J, Lundin-Olsson L, Nyberg L, Gustafson Y. Fall and injury prevention in older people living in residential care facilities. A cluster randomized trial. *Ann Intern Med.* May 21 2002;136(10):733-741.

17. Mahoney JE, Shea TA, Przybelski R, et al. Kenosha County falls prevention study: a randomized, controlled trial of an intermediate-intensity, community-based multifactorial falls intervention. *J Am Geriatr Soc.* Apr 2007;55(4):489-498.

18. Province MA, Hadley EC, Hornbrook MC, et al. The effects of exercise on falls in elderly patients. A preplanned meta-analysis of the FICSIT Trials. Frailty and Injuries: Cooperative Studies of Intervention Techniques. *Jama.* May 3 1995;273(17):1341-1347.

19. Spice CL, Morotti W, George S, et al. The Winchester falls project: a randomised controlled trial of secondary prevention of falls in older people. *Age Ageing.* Jan 2009;38(1):33-40.

20. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. *Br J Clin Pharmacol.* Feb 2007;63(2):232-237.

21. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc.* Sep 2005;53(9):1618-1622.

22. Salkeld G, Cumming RG, O'Neill E, Thomas M, Szonyi G, Westbury C. The cost effectiveness of a home hazard reduction program to reduce falls among older persons. *Aust N Z J Public Health.* Jun 2000;24(3):265-271.

23. Sach TH, Logan PA, Coupland CA, et al. Community falls prevention for people who call an emergency ambulance after a fall: an economic evaluation alongside a randomised controlled trial. *Age Ageing.* Sep 2012;41(5):635-641.

24. Sach TH, Foss AJ, Gregson RM, et al. Falls and health status in elderly women following first eye cataract surgery: an economic evaluation conducted alongside a randomised controlled trial. *Br J Ophthalmol.* Dec 2007;91(12):1675-1679.

25. Robertson MC, Devlin N, Gardner MM, Campbell AJ. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 1: Randomised controlled trial. *BMJ.* Mar 24 2001;322(7288):697-701.

26. Peeters GM, Heymans MW, de Vries OJ, Bouter LM, Lips P, van Tulder MW. Multifactorial evaluation and treatment of persons with a high risk of recurrent falling was not cost-effective. *Osteoporos Int.* Jul 2011;22(7):2187-2196.

27. Lee RH, Weber T, Colon-Emeric C. Comparison of cost-effectiveness of vitamin D screening with that of universal supplementation in preventing falls in community-dwelling older adults. *J Am Geriatr Soc.* May 2013;61(5):707-714.

28. Jenkyn KB, Hoch JS, Speechley M. How much are we willing to pay to prevent a fall? Cost-effectiveness of a multifactorial falls prevention program for community-dwelling older adults. *Can J Aging.* Jun 2012;31(2):121-137.

29. Irvine L, Conroy SP, Sach T, et al. Cost-effectiveness of a day hospital falls prevention programme for screened community-dwelling older people at high risk of falls. *Age Ageing.* Nov 2010;39(6):710-716.

30. Hendriks MR, Evers SM, Bleijlevens MH, van Haastregt JC, Crebolder HF, van Eijk JT. Cost-effectiveness of a multidisciplinary fall prevention program in community-dwelling elderly people: a randomized controlled trial (ISRCTN 64716113). *Int J Technol Assess Health Care.* Spring 2008;24(2):193-202.

31. Heinrich S, Rapp K, Stuhldreher N, Rissmann U, Becker C, Konig HH. Cost-effectiveness of a multifactorial fall prevention program in nursing homes. *Osteoporos Int.* Apr 2013;24(4):1215-1223.

32. van Haastregt JC, Zijlstra GA, Hendriks MR, Goossens ME, van Eijk JT, Kempen GI. Cost-effectiveness of an intervention to reduce fear of falling. *Int J Technol Assess Health Care.* Jul 2013;29(3):219-226.

33. Davis JC, Marra CA, Robertson MC, et al. Economic evaluation of dose-response resistance training in older women: a cost-effectiveness and cost-utility analysis. *Osteoporos Int.* May 2011;22(5):1355-1366.

34. Church J, Goodall S, Norman R, Haas M. An economic evaluation of community and residential aged care falls prevention strategies in NSW. *N S W Public Health Bull.* Jun 2011;22(3-4):60-68.

35. Campbell AJ, Robertson MC, La Grow SJ, et al. Randomised controlled trial of prevention of falls in people aged > or =75 with severe visual impairment: the VIP trial. *BMJ.* Oct 8 2005;331(7520):817.

36. Clemson L, Cumming RG, Kendig H, Swann M, Heard R, Taylor K. The effectiveness of a community-based program for reducing the incidence of falls in the elderly: a randomized trial. *J Am Geriatr Soc.* Sep 2004;52(9):1487-1494.

37. Elley CR, Robertson MC, Garrett S, et al. Effectiveness of a falls-and-fracture nurse coordinator to reduce falls: a randomized, controlled trial of at-risk older adults. *J Am Geriatr Soc.* Aug 2008;56(8):1383-1389.

38. Lin MR, Wolf SL, Hwang HF, Gong SY, Chen CY. A randomized, controlled trial of fall prevention programs and quality of life in older fallers. *J Am Geriatr Soc.* Apr 2007;55(4):499-506.

39. Vaapio S, Salminen M, Vahlberg T, et al. Effects of risk-based multifactorial fall prevention on health-related quality of life among the community-dwelling aged: a randomized controlled trial. *Health Qual Life Outcomes.* 2007;5:20.

40. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):40-50.

41. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):30-39.

42. Sterke CS, Ziere G, van Beeck EF, Looman CW, van der Cammen TJ. Dose-response relationship between selective serotonin re-uptake inhibitors and injurious falls: a study in nursing home residents with dementia. *Br J Clin Pharmacol.* May 2012;73(5):812-820.

43. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* Nov 23 2009;169(21):1952-1960.

44. van der Velde N, Meerding WJ, Looman CW, Pols HA, van der Cammen TJ. Cost effectiveness of withdrawal of fall-risk-increasing drugs in geriatric outpatients. *Drugs Aging.* 2008;25(6):521-529.

45. Hartholt KA, Boyé NDA, Van der Velde N, et al. [Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study). *BMC Geriatr.* 2011;11:48.

46. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* Nov 1975;12(3):189-198.

47. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan Med Bull.* Apr 1987;34 Suppl 4:1-24.

48. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek. College voor zorgverzekeringen; 2010.

49. *Farmacotherapeutisch Kompas.* Diemen, Netherlands: College voor zorgverzekeringen; 2012.

50. Brooks R. EuroQol: the current state of play. *Health Policy.* Jul 1996;37(1):53-72.
51. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol.* Nov 1998;51(11):1171-1178.
52. Dolan P. Modeling valuations for EuroQol health states. *Med Care.* Nov 1997;35(11):1095-1108.
53. Van Beeck EF, Larsen CF, Lyons RA, Meerding WJ, Mulder S, Essink-Bot ML. Guidelines for the conduction of follow-up studies measuring injury-related disability. *J Trauma.* Feb 2007;62(2):534-550.
54. Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. *Pharmacoeconomics.* 2002;20(7):443-454.
55. NICE guide to the methods of health technology appraisal. London: National Institute for Health and Clinical Excellence; 2004.
56. Rizzo JA, Baker DI, McAvay G, Tinetti ME. The cost-effectiveness of a multifactorial targeted prevention program for falls among community elderly persons. *Med Care.* Sep 1996;34(9):954-969.
57. Hoeymans N, van Lindert H, Westert GP. The health status of the Dutch population as assessed by the EQ-6D. *Qual Life Res.* Apr 2005;14(3):655-663.
58. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. *Med J Aust.* Jul 2 2007;187(1):23-30.

Part IV

Chapter 4.1

General discussion

Falls affect a large proportion of persons aged 65 years and older [1], and are associated with serious consequences such as high morbidity and mortality rates [2-4], disability, loss of quality of life, and institutionalization [5-8]. Furthermore, fall-related injuries place a substantial burden on healthcare systems due to the large number of visits to emergency departments (ED), hospital admissions, and admissions to long-term care and rehabilitation facilities [6, 9-12]; and high medical costs[7].

Approximately one out of three persons aged ≥ 65 years experiences a fall every year [1]. A fall is usually defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by an acute medical condition, *e.g.* stroke, or exogenous factors, such as a traffic accident [13]. Falls are precipitated by a number of risk factors, these can be grouped into intrinsic and extrinsic factors. Intrinsic risk factors include old age (>80 years), a history of falls, gait deficit, balance deficit, visual impairment, cognitive impairment, cardiovascular problems (*e.g.* orthostatic hypotension, arrhythmia), and urinary incontinence. Vitamin D deficiency has also been shown to be a key contributor to a decline in physical performance and increase in fall incidence [14-21]. Extrinsic risk factors include the environment (*e.g.*, poor lighting, rugs, and loose wiring), and improper use of walking aids [22-25]. Furthermore, approximately 33 percent of persons over 65 years use so-called fall-risk-increasing drugs (FRIDs) such as cardiovascular and psychotropic drugs [26-28].

The most common injuries due to falls in persons aged 65 years or older in the Netherlands are superficial injuries, hip fractures, wrist fractures, and traumatic brain injury (TBI) [10]. In addition to the effects on morbidity and mortality, falls result in a significant reduction in health-related quality of life and substantial functional impairment [5, 8]. Furthermore, between 2003 and 2007 the average annual cost for fall-related injuries in the Netherlands was US$ 640 million (€470 million), and the overall cost per fall was US$9,530 (€7,048) [7].

AIM

As stated above, falls in older adults are a major public health problem, yet essentially preventable. The rationale for the studies presented in this thesis is to gain insight into falls prevention in older adults. Researchers started documenting fall-related risk-factors in the 1980s, afterwards the first fall prevention trials were conducted [1, 22, 23, 29, 30]. Early on Campbell *et al.* performed a psychotropic drug withdrawal intervention that was complete and double-blinded, demonstrating the effectiveness of total psychotropic drug withdrawal on preventing falls [29]. The use of certain drugs, i.e. the so-called fall-risk increasing drugs (FRIDs) [26-28, 31], mainly psychotropic and cardiovascular drugs, has been associated with increased risk of falls and related injuries [26-28, 32], and withdrawal of FRIDs appears to be feasible and effective [29, 31, 33, 34]. Although FRIDs withdrawal is frequently incorporated in multifactorial intervention trials, evidence regarding overall FRIDs withdrawal as a single intervention is scarce [35].

The aim of this thesis was twofold. First, we investigated factors associated with falls in older adults. We separated these into several components starting with the circumstances surrounding injurious falls [36], then we investigated the effect of serum vitamin D on physical performance [37], and finally we compared functional, physical and health related quality of life scores between single and recurrent fallers [38]. Second, we conducted a multicenter randomized controlled trial and investigated the effect of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' on reducing falls in community-dwelling older men and women, who visited the ED after experiencing a fall [39]. We also investigated the related costs, the effect on health related quality of life, and the cost-utility of the intervention.

In this chapter we summarize the main findings and discuss the strengths and limitations of this study. In addition we present the clinical implications of our findings and our recommendations for future research.

MAIN FINDINGS

Chapter 2.1 Circumstances surrounding injurious falls

We investigated the activity distributions leading to indoor and outdoor falls requiring an emergency department visit, and those resulting in traumatic brain injuries and hip fractures. In total 5880 fall-related emergency department visits were included. Two-thirds of all falls occurred indoors. However, this differed between age and gender categories, with higher proportions of outdoor falls at ages 65-79 years and among men. The overall most common indoor activities leading to injurious falls were walking and walking up or down stairs. The overall most common outdoor activities leading to injurious falls were walking and cycling. We found that the indoor activities leading to major injuries, *i.e.* TBIs and hip fractures, differed. Walking up or down stairs and housekeeping were the most common activities leading to a TBI whereas walking and sitting or standing were the most common activities leading to a hip fracture. Notably, about half of the traumatic brain injuries and hip fractures in men and women aged 65-79 years occurred outdoors. The most common outdoor activities leading to both injuries were walking and cycling. It should be noted that in the Netherlands about 27% of all travel is done by bicycle. As a consequence, the data presented is more relevant in countries where cycling is common.

Falls are the leading cause of TBIs and hip fractures in the elderly population [7, 40, 41]. Falls cause 61% of traumatic brain injuries in persons aged 65 years and older in the US [40], and recent studies in the US, the Netherlands, and Finland showed an increase in fall-related

TBIs [11, 40, 42]. About 30% of people with a hip fracture will die in the following year, and many more will experience significant functional loss [2]. Furthermore, TBIs and hip fractures contribute considerably to healthcare costs [7]. These results provide new insights into patterns leading to injurious falls by age, gender and injury type, and may guide the targeting of falls prevention at specific activities and risk groups.

Up to now, little to no special attention has been paid to outdoor activities such as cycling and 'higher level' activities such as housekeeping. Few have incorporated strategies for falls prevention derived from these specific circumstances. Partly, this can be accomplished by education of the risk groups. Healthy and highly functional older adults may be unaware that their higher activity levels may increase their risk for falling and subsequent injuries [43]. Another possibility is the elimination of outdoor environmental hazards involving sidewalks, curbs, and streets, such as by promptly repairing uneven surfaces, removing debris, and painting curbs [44, 45]. Furthermore, promotion of measures which can reduce the severity of injuries following a fall, such as bicycle helmets, should also be considered [46].

Chapter 2.2 Vitamin D and physical performance

We investigated whether higher serum 25-hydroxy vitamin D [25(OH)D] concentrations were associated with better strength and physical performance. Muscle tissue is an important target tissue of vitamin D [47]. Furthermore, vitamin D deficiency has been shown to be a key contributor to a decline in physical performance and increase in fall incidence [14-21]. However, most studies demonstrating the relationship between vitamin D levels and physical performance were conducted in female-only populations [14, 17-20]. In addition, recent studies investigating the relationship between serum 25(OH)D levels and physical performance in men found no significant associations [48, 49]. However, these studies were conducted in a

population of highly functional, younger men with a low prevalence of vitamin D deficiency. Furthermore, evidence regarding an underlying gender-specific mechanism is lacking.

As was hypothesized, serum 25(OH)D levels were significantly associated with muscle strength and physical performance, not only in community-dwelling older women, but also in men. Furthermore, it was striking to note how few of the older fallers in our study were prescribed vitamin D supplements, especially in the male population; though 44% of the men and women were deficient in vitamin D, only 6% of the men and 17% of the women used vitamin D supplements. The under-prescribing of vitamin D in this age group has previously been reported [50]. Yet, despite evidence that vitamin D supplementation has been shown to increase muscle strength and reduce the risk of falls [51], vitamin D deficiency is still common in community-dwelling elderly, with a prevalence of 40-100% in U.S. and European older men and women [47]. Furthermore, while we set the levels ≥50 nmol/L as vitamin D sufficient, another opinion is that optimal vitamin D levels should be ≥75 nmol/L [52]. This is interesting to note when considering our results, where it seems levels closer to 75 nmol/L result in continued physical performance benefits, especially in men.

Chapter 2.3 Single and Recurrent fallers

Fallers are classified in different ways. A single faller is generally defined as someone who has fallen at least once during a defined time period, usually 6 or 12 months. A recurrent faller is someone who has fallen twice or more during a defined time period [53]. Guidelines concerning falls prevention make a clear distinction between single and recurrent fallers, a recurrent faller is at greater risk for future falls [25, 54].

Several studies have reported specific differences between single and recurrent fallers, using varying outcome measures like sensory and motor function outcomes [55], certain physical performance tests [56-58], the Mini-Mental State Examination (MMSE) [59],

posturography [60, 61], and dual-tasking tests [62, 63]. Most studies compared the prevalence of specific risk factors in single and recurrent fallers [64-67]. In addition to investigating the differences in physical performance and functional status between single and recurrent fallers, we assessed differences in health related quality of life (HRQoL).

Recurrent fallers scored significantly poorer than the single fallers in all the physical performance tests, these tests measure mobility, muscle strength and balance. In previous literature, 12 seconds has been suggested as a practical cut-off value for the Timed "Up & Go" test, and has been found useful in detecting mobility impairment in elderly persons [68]. In the current study population recurrent fallers had below normal Timed "Up & Go" test scores, and were significantly slower than the single fallers who had normal scores. Furthermore, poor muscle strength is a known risk factor for falls [24], it predicts disability [69], and mortality [70], and is one of the criteria used to define frailty [71]. The recurrent fallers also reported lower HRQoL scores than the single fallers, including significantly lower EQ-5D utility scores and more problems in all the five EQ-5D domains. In addition, recurrent fallers scored below the Dutch population norm for the SF-12 PCS and MCS, while the single fallers scored above the norm. Surprisingly, the functional status scores did not differ between single and recurrent fallers, despite of recurrent fallers having poorer physical performance and lower HRQoL scores. A potential explanation for this finding is that the study population consisted of community-dwelling older adults. Being able to perform the individual components of ADL and IADL is a prerequisite for living independently. Possibly the sensitivity of the ADL and IADL questionnaires was not sufficient to detect differences in functional status.

Chapter 3.2 The effect of fall-risk increasing drug withdrawal on reducing incidence of falls

The use of FRIDs [26-28, 31], mainly psychotropic and cardiovascular drugs, has been associated with increased risk of falls and related injuries [26-28, 32], and withdrawal of FRIDs appears to be

feasible and effective [29, 31, 33, 34]. Although FRIDs withdrawal is frequently incorporated in multifactorial intervention trials, evidence regarding overall FRID withdrawal as a single intervention is scarce [35].

We investigated the effect of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' on reducing falls in community-dwelling older men and women, who visited the ED after experiencing a fall [39]. Overall, FRIDs withdrawal did not result in reduced incidence of falls, whereas, cardiovascular FRIDs withdrawal did reduce healthcare visits because of a fall. Surprisingly, no effect of psychotropic drug withdrawal was seen.

There are several possible explanations for our findings. First, since in the last decade, falls prevention guidelines have been incorporated into usual care, this may well have blunted the effect of the intervention. Second, in our intervention group a large proportion of FRIDs were prescribed adequately and thus withdrawal was not appropriate . Third, a large proportion of the participants in the intervention group was not compliant to the intervention, especially concerning psychotropic drugs withdrawal. Fourth, it might be possible that participants in the intervention group were more diligent when filling out their Falls Calendars than the usual care group. The time till first and second fall were recorded from the Falls Calendars which participants from both group filled out and the time till the first GP consultation and ED visit were recorded from GP data. Although not statistically significant, the intervention group displayed a tendency towards a shorter time until the first fall, yet a longer time until the first GP consultation or ED visit because of a fall. Furthermore, when studying the participants in the successful withdrawal group individually, it was apparent that although one or more FRIDs were successfully withdrawn, reduced, or substituted, several participants were prescribed additional FRIDs during the follow-up year by their GP or other

specialist, often for new conditions. The percentage of participants using ≥ 3 FRIDs in the intervention group (70%) was not decreased at 1 year follow-up.

In a study by Pit *et al.* the intervention was carried out by the participants' GP, probably increasing and sustaining the number of successful withdrawals due to the more substantial doctor-patient relationship [34]. Campbell *et al.* performed a psychotropic drug withdrawal intervention that was complete and double-blinded, demonstrating the effectiveness of total psychotropic drug withdrawal on preventing falls [29]. Yet this complete withdrawal was difficult to maintain. Notably, in our study the withdrawal of cardiovascular FRIDs appeared to reduce risk of GP consultations because of a fall, possibly due to fewer injurious falls. Most studies associate greater fall risk with psychotropic drugs [26, 28], however, besides our finding, another study has also reported greater risk reduction after withdrawal of cardiovascular drugs [31]. Furthermore, another recent large study found that antihypertensive medications were associated with an increased risk of serious fall injuries [72].

Chapter 3.3 The costs, the effect on HRQoL, and the cost-utility of FRID withdrawal

Falls affect a large proportion of the persons aged 65 years and older and are associated with consequences such as loss of quality of life and high cost [1, 5-8]. In 2000 the fall-related medical costs in the population 65 years and older in the United States amounted to US$19 billion for non-fatal injuries and US$200 million for fatal injuries [4]. Between 2003 and 2007 the average annual cost for fall-related injuries in the Netherlands was US$ 640 million (€470 million), and the overall cost per fall was US$9,530 (€7,048) [7]. Various studies have reported cost and cost-effectiveness data regarding fall prevention trials with varying results, however, most studies evaluated multifactorial interventions [73-83]. One study reported on the cost-effectiveness of FRID withdrawal as a single intervention, and reported significant national cost savings [84].

We investigated the costs, the effect on HRQoL, and the cost-utility of a structured medication assessment including withdrawal of FRIDs versus 'care as usual'. The total healthcare related costs in the intervention group were €39 higher than usual care. FRID withdrawal was associated with less decline in HRQoL as measured with the EQ-5D utility score. The intervention resulted in an incremental cost-utility ratio of €780/QALY gained. Policy makers and health economists have proposed that costs up to €20,000 per QALY are considered as acceptable [85].

Higher compliance rates might have led to lower fall risk and lower related healthcare costs, and increased savings due to reduced medication costs (mean reduction of €38 per participant in this study). Furthermore, a less costly method of FRID withdrawal could be accomplished by having the GP perform the intervention, thus further lowering costs per QALY.

Notably, the control group reported a significantly greater decline in HRQoL during the 12 month follow-up as measured with the EQ-5D utility score than the intervention group. It is important to note that except for a structured medication assessment, including the withdrawal of FRIDs, both groups received identical care. Furthermore, withdrawal of certain commonly prescribed FRIDs such as benzodiazepines, antidepressants and opiates [39], could have resulted in lower quality of life scores in the intervention group. Nonetheless, in this study the withdrawal of FRIDs did not lower the HRQoL. Remarkably, in the secondary analysis comparing the participants without a fall during follow-up the intervention group had lesser decline in the SF-12 PCS score than the control group. The fact that the intervention did not lower the HRQoL and possibly even improved it, is on its own an important outcome.

STRENGTHS AND LIMITATIONS

A major strength of this study is that current recommendations regarding falls prevention studies were followed [86], i.e., addressing a single intervention in a randomized controlled trial. Furthermore, participants included were high-risk fallers, i.e., older men and women who visited the ED because of a fall. In this target group even a small reduction of their fall risk might prevent loss of independence. In addition, the study population size, the validated tests used to assess physical performance and HRQoL outcome measures are also strengths [86]. Finally, the execution of the *IMPROveFALL study* came very close to current clinical practice, thus our results can be applied directly.

The following limitations should be taken into account when interpreting our results. First, recruiting participants proved challenging. Possible reasons for refusing to participate have been reported previously [87]. Most common reasons for refusal were the added burden of additional visits to the hospital; highly independent older adults feeling "too healthy"; and personal opinions regarding the cause of the fall. Second, possibly the method of reporting falls was not as accurate as anticipated; as mentioned above, the intervention group reported as many falls as the control group, but the numbers of healthcare visits because of a fall (which were verified with GP records) were higher in the control group. The newest guidelines state fall incidence is best monitored with weekly phone calls instead of self-report calendars [88]. Third, as mentioned before, in the intervention group compliance with withdrawal was limited, especially in the group with psychotropic drug withdrawal. This might be improved if the prescribing physician performs the withdrawal, as was the case in the study by Pit *et al.* [34]. Fourth, the dropout during the 12 month follow-up could be due to the selected study population which had a high risk of falling. These patients often had mobility impairments and other comorbid conditions that may have resulted in a refusal to continue participating in the study and visit our outpatient clinic after 12 months follow-up. Thus the most at-risk and frail participants could have been excluded from the analysis,

however, the randomization would have equally divided these patients across the intervention and control group.

And solely regarding the cost-utility analyses, the SF-12 has been evaluated for use in large group comparisons, this may not be correct for our secondary analyses where we solely included participants with and without a fall during follow-up [89]. Furthermore, the main aim of this study was to study the effectiveness of the intervention that is why the power calculation was based on a falls reduction rather than QALYs or costs.

CLINICAL IMPLICATIONS AND FUTURE RESEARCH

This study increases insight into both the effectiveness of FRIDs withdrawal as a method for falls reduction in older adults, and into the complexity of this intervention in an older, multi-morbid population. The current study adds to the understanding of effective falls-prevention interventions. Overall, FRIDs withdrawal did not result in reduced incidence of falls, whereas, cardiovascular FRIDs withdrawal did reduce healthcare visits because of a fall. Surprisingly, no effect of psychotropic drug withdrawal was seen, which might have been caused by low compliance to the intervention. The potential harm versus benefit of antihypertensive medications should be weighed in older adults with multiple chronic conditions [72]. The method of implementation of fall-risk increasing drugs withdrawal is essential, compliance might be improved if the prescribing physician performs the withdrawal. Further research is warranted focusing on the optimal method for implementation, thus ensuring participation and compliance of sustained FRID withdrawal in older fallers.

REFERENCES

1. Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994;331:821-7.
2. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. Jama 2009;302:1573-9.
3. Kochanek KD, Xu JQ, Murphy SL, al. e. Deaths: Preliminary data for 2009. . In: Hyattsville, MD: National Center for Health Statistics. ; 2011.
4. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. Inj Prev 2006;12:290-5.
5. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. Osteoporos Int 2004;15:87-94.
6. Close JC, Lord SR, Antonova EJ, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. Emerg Med J 2012;29:742-7.
7. Hartholt KA, van Beeck EF, Polinder S, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. J Trauma 2011;71:748-53.
8. Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. Osteoporos Int 2000;11:460-6.
9. Greenspan AI, Coronado VG, Mackenzie EJ, Schulman J, Pierce B, Provenzano G. Injury hospitalizations: using the nationwide inpatient sample. J Trauma 2006;61:1234-43.
10. Hartholt KA, van der Velde N, Looman CW, et al. Trends in fall-related hospital admissions in older persons in the Netherlands. Arch Intern Med 2010;170:905-11.
11. Hartholt KA, Van Lieshout EMM, Polinder S, Panneman MJ, Van der Cammen TJM, Patka P. Rapid increase in hospitalizations resulting from fall-related traumatic head injury in older adults in The Netherlands 1986-2008. J Neurotrauma 2011;28:739-44.
12. Scuffham P, Chaplin S, Legood R. Incidence and costs of unintentional falls in older people in the United Kingdom. J Epidemiol Community Health 2003;57:740-4.
13. KIWG. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. Dan Med Bull 1987;34 Suppl 4:1-24.
14. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr 2004;80:752-8.
15. Dukas L, Bischoff HA, Lindpaintner LS, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc 2004;52:230-6.
16. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab 2001;86:3618-28.
17. Gerdhem P, Ringsberg KA, Obrant KJ, Akesson K. Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. Osteoporos Int 2005;16:1425-31.
18. Okuno J, Tomura S, Yabushita N, et al. Effects of serum 25-hydroxyvitamin D(3) levels on physical fitness in community-dwelling frail women. Arch Gerontol Geriatr 2010;50:121-6.

19. Pfeifer M, Begerow B, Minne HW, et al. Vitamin D status, trunk muscle strength, body sway, falls, and fractures among 237 postmenopausal women with osteoporosis. Exp Clin Endocrinol Diabetes 2001;109:87-92.
20. Stewart JW, Alekel DL, Ritland LM, Van Loan M, Gertz E, Genschel U. Serum 25-hydroxyvitamin D is related to indicators of overall physical fitness in healthy postmenopausal women. Menopause 2009;16:1093-101.
21. Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 2007;92:2058-65.
22. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701-7.
23. Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls. A prospective study. Jama 1989;261:2663-8.
24. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2004;52:1121-9.
25. AGS/BGS/AAOS. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. J Am Geriatr Soc 2001;49:664-72.
26. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 2009;169:1952-60.
27. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. J Am Geriatr Soc 1999;47:40-50.
28. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc 1999;47:30-9.
29. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. J Am Geriatr Soc 1999;47:850-3.
30. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. Lancet 1999;353:93-7.
31. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. Br J Clin Pharmacol 2007;63:232-7.
32. Sterke CS, Ziere G, van Beeck EF, Looman CW, van der Cammen TJ. Dose-response relationship between selective serotonin re-uptake inhibitors and injurious falls: a study in nursing home residents with dementia. Br J Clin Pharmacol 2012;73:812-20.
33. Alsop K, Mac Mahon M. Withdrawing cardiovascular medications at a syncope clinic. Postgrad Med J 2001;77:403-5.
34. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. Med J Aust 2007;187:23-30.
35. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;9:CD007146.
36. Boyé ND, Mattace-Raso FU, Van der Velde N, et al. Circumstances leading to injurious falls in older men and women in the Netherlands. Injury 2014;45:1224-30.
37. Boyé ND, Oudshoorn C, van der Velde N, et al. Vitamin D and physical performance in older men and women visiting the emergency department because of a fall: data from the improving medication prescribing to reduce risk of falls (IMPROveFALL) study. J Am Geriatr Soc 2013;61:1948-52.
38. Boyé ND, Mattace-Raso FU, Van Lieshout EM, Hartholt KA, Van Beeck EF, Van der Cammen TJ. Physical performance and quality of life in single and recurrent fallers: Data

from the Improving Medication Prescribing to Reduce Risk of Falls study. Geriatr Gerontol Int 2014.
39. Hartholt KA, Boyé NDA, Van der Velde N, et al. [Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study). BMC Geriatr 2011;11:48.
40. Faul M, Xu L, Wald MM, Coronado VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006. In: Centers for Disease Control and Prevention NCfIPaC, ed.; 2010.
41. Hartholt KA, van Beeck EF, Polinder S, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. J Trauma 2010;71:748-53.
42. Kannus P, Niemi S, Parkkari J, Palvanen M, Sievanen H. Alarming rise in fall-induced severe head injuries among elderly people. Injury 2007;38:81-3.
43. Bath PA, Morgan K. Differential risk factor profiles for indoor and outdoor falls in older people living at home in Nottingham, UK. Eur J Epidemiol 1999;15:65-73.
44. Lai PC, Wong WC, Low CT, Wong M, Chan MH. A small-area study of environmental risk assessment of outdoor falls. J Med Syst 2011;35:1543-52.
45. Li W, Keegan TH, Sternfeld B, Sidney S, Quesenberry CP, Jr., Kelsey JL. Outdoor falls among middle-aged and older adults: a neglected public health problem. Am J Public Health 2006;96:1192-200.
46. Macpherson A, Spinks A. Bicycle helmet legislation for the uptake of helmet use and prevention of head injuries. Cochrane Database Syst Rev 2008:CD005401.
47. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
48. Ceglia L, Chiu GR, Harris SS, Araujo AB. Serum 25-hydroxyvitamin D concentration and physical function in adult men. Clin Endocrinol (Oxf) 2011;74:370-6.
49. Dam TT, von Muhlen D, Barrett-Connor EL. Sex-specific association of serum vitamin D levels with physical function in older adults. Osteoporos Int 2009;20:751-60.
50. Lang PO, Hasso Y, Drame M, et al. Potentially inappropriate prescribing including under-use amongst older patients with cognitive or psychiatric co-morbidities. Age Ageing 2012;39:373-81.
51. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. Jama 2004;291:1999-2006.
52. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713-6.
53. Masud T, Morris RO. Epidemiology of falls. Age Ageing 2001;30 Suppl 4:3-7.
54. AGS/BGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc 2010;59:148-57.
55. Lord SR, Ward JA, Williams P, Anstey KJ. Physiological factors associated with falls in older community-dwelling women. J Am Geriatr Soc 1994;42:1110-7.
56. Anstey KJ, Wood J, Kerr G, Caldwell H, Lord SR. Different cognitive profiles for single compared with recurrent fallers without dementia. Neuropsychology 2009;23:500-8.
57. Buatois S, Perret-Guillaume C, Gueguen R, et al. A simple clinical scale to stratify risk of recurrent falls in community-dwelling adults aged 65 years and older. Phys Ther 2010;90:550-60.
58. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. Am J Med 1986;80:429-34.
59. Chen X, Van Nguyen H, Shen Q, Chan DK. Characteristics associated with recurrent falls among the elderly within aged-care wards in a tertiary hospital: the effect of cognitive impairment. Arch Gerontol Geriatr 2011;53:e183-6.

60. Bigelow KE, Berme N. Development of a protocol for improving the clinical utility of posturography as a fall-risk screening tool. J Gerontol A Biol Sci Med Sci 2011;66:228-33.
61. Buatois S, Gueguen R, Gauchard GC, Benetos A, Perrin PP. Posturography and risk of recurrent falls in healthy non-institutionalized persons aged over 65. Gerontology 2006;52:345-52.
62. Beauchet O, Annweiler C, Allali G, Berrut G, Herrmann FR, Dubost V. Recurrent falls and dual task-related decrease in walking speed: is there a relationship? J Am Geriatr Soc 2008;56:1265-9.
63. Faulkner KA, Redfern MS, Cauley JA, et al. Multitasking: association between poorer performance and a history of recurrent falls. J Am Geriatr Soc 2007;55:570-6.
64. Fletcher PC, Hirdes JP. Risk factors for falling among community-based seniors using home care services. J Gerontol A Biol Sci Med Sci 2002;57:M504-10.
65. Melzer I, Kurz I. Self reported function and disability in late life: a comparison between recurrent fallers and non-fallers. Disabil Rehabil 2009;31:791-8.
66. Rossat A, Fantino B, Nitenberg C, et al. Risk factors for falling in community-dwelling older adults: which of them are associated with the recurrence of falls? J Nutr Health Aging 2010;14:787-91.
67. Vassallo M, Sharma JC, Allen SC. Characteristics of single fallers and recurrent fallers among hospital in-patients. Gerontology 2002;48:147-50.
68. Bischoff HA, Stahelin HB, Monsch AU, et al. Identifying a cut-off point for normal mobility: a comparison of the timed 'up and go' test in community-dwelling and institutionalised elderly women. Age Ageing 2003;32:315-20.
69. Hairi NN, Cumming RG, Naganathan V, et al. Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. J Am Geriatr Soc 2010;58:2055-62.
70. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. J Geriatr Phys Ther 2008;31:3-10.
71. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
72. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med 2014;174:588-95.
73. Campbell AJ, Robertson MC, La Grow SJ, et al. Randomised controlled trial of prevention of falls in people aged > or =75 with severe visual impairment: the VIP trial. BMJ 2005;331:817.
74. Church J, Goodall S, Norman R, Haas M. An economic evaluation of community and residential aged care falls prevention strategies in NSW. N S W Public Health Bull 2011;22:60-8.
75. Davis JC, Marra CA, Robertson MC, et al. Economic evaluation of dose-response resistance training in older women: a cost-effectiveness and cost-utility analysis. Osteoporos Int 2011;22:1355-66.
76. Heinrich S, Rapp K, Stuhldreher N, Rissmann U, Becker C, Konig HH. Cost-effectiveness of a multifactorial fall prevention program in nursing homes. Osteoporos Int 2013;24:1215-23.
77. Hendriks MR, Evers SM, Bleijlevens MH, van Haastregt JC, Crebolder HF, van Eijk JT. Cost-effectiveness of a multidisciplinary fall prevention program in community-dwelling elderly people: a randomized controlled trial (ISRCTN 64716113). Int J Technol Assess Health Care 2008;24:193-202.

78. Irvine L, Conroy SP, Sach T, et al. Cost-effectiveness of a day hospital falls prevention programme for screened community-dwelling older people at high risk of falls. Age Ageing 2010;39:710-6.
79. Jenkyn KB, Hoch JS, Speechley M. How much are we willing to pay to prevent a fall? Cost-effectiveness of a multifactorial falls prevention program for community-dwelling older adults. Can J Aging 2012;31:121-37.
80. Peeters GM, Heymans MW, de Vries OJ, Bouter LM, Lips P, van Tulder MW. Multifactorial evaluation and treatment of persons with a high risk of recurrent falling was not cost-effective. Osteoporos Int 2011;22:2187-96.
81. Rizzo JA, Baker DI, McAvay G, Tinetti ME. The cost-effectiveness of a multifactorial targeted prevention program for falls among community elderly persons. Med Care 1996;34:954-69.
82. Robertson MC, Devlin N, Gardner MM, Campbell AJ. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 1: Randomised controlled trial. BMJ 2001;322:697-701.
83. Sach TH, Logan PA, Coupland CA, et al. Community falls prevention for people who call an emergency ambulance after a fall: an economic evaluation alongside a randomised controlled trial. Age Ageing 2012;41:635-41.
84. van der Velde N, Meerding WJ, Looman CW, Pols HA, van der Cammen TJ. Cost effectiveness of withdrawal of fall-risk-increasing drugs in geriatric outpatients. Drugs Aging 2008;25:521-9.
85. NICE guide to the methods of health technology appraisal. In. London: National Institute for Health and Clinical Excellence; 2004.
86. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. J Am Geriatr Soc 2005;53:1618-22.
87. Elskamp AB, Hartholt KA, Patka P, van Beeck EF, van der Cammen TJ. Why older people refuse to participate in falls prevention trials: a qualitative study. Exp Gerontol 2012;47:342-5.
88. Reelick MF, Faes MC, Lenferink A, Esselink RA, Olde Rikkert MG. The fall telephone for falls assessment in frail older persons; feasibility, reliability, and validity. J Am Geriatr Soc 2011;59:372-3.
89. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998;51:1171-8.

Chapter 4.2

Summary and Conclusions

Summary and Conclusions

Part I starts with a literature overview on the impact of falls in the elderly, the burden on healthcare, and the costs for society. Falls affect a large proportion of persons aged 65 years and older, and are associated with serious consequences such as high morbidity and mortality rates, disability, loss of quality of life, and institutionalization. Furthermore, fall-related injuries place a substantial burden on healthcare systems due to the large number of visits to emergency departmenst (ED), hospital admissions, admissions to long-term care and rehabilitation facilities; and high medical costs.

Part II provides insight into various factors associated with falls in older adults. We separated these into several components starting with the circumstances surrounding injurious falls, then we investigated the effect of serum vitamin D on physical performance, and finally we compared functional, physical and health related quality of life scores between single and recurrent fallers. **Chapter 2.1** provides an overview of the activity distributions leading to indoor and outdoor falls requiring an ED visit, and those resulting in traumatic brain injuries (TBI) and hip fractures. Two-thirds of all falls occurred indoors. The overall most common indoor activities leading to injurious falls were walking and walking up or down stairs. The overall most common outdoor activities leading to injurious falls were walking and cycling. We found that the indoor activities leading to major injuries, *i.e.* TBIs and hip fractures differed. Walking up or down stairs and housekeeping were the most common activities leading to a TBI whereas walking and sitting or standing were the most common activities leading to a hip fracture. Notably, about half of the traumatic brain injuries and hip fractures in men and women aged 65-79 years occurred outdoors. The most common outdoor activities leading to both injuries were walking and cycling. In **Chapter 2.2** we demonstrate that serum

25(OH)D levels are significantly associated with muscle strength and physical performance, not only in community-dwelling older women, but also in men. And in **Chapter 2.3** we present evidence supporting current guidelines, which state that recurrent fallers should have a multifactorial fall risk assessment. Recurrent fallers scored significantly poorer than the single fallers in all the physical performance tests, these tests measure mobility, muscle strength and balance. Furthermore, recurrent fallers also reported lower health related quality of life scores than the single fallers, including significantly lower EQ-5D utility scores and more problems in all the five EQ-5D domains.

Part III includes the IMPROveFALL study protocol in **Chapter 3.1** [16]. **The IMPROveFALL study is** a multicenter randomized controlled trial investigating the effect of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' on reducing falls in community-dwelling older men and women, who visited the ED after experiencing a fall. **Chapter 3.2** discusses the results of the IMPROveFALL study. Overall, FRIDs withdrawal did not result in a reduced incidence of falls. However, cardiovascular FRIDs withdrawal did reduce visits to the general practitioner because of a fall. Surprisingly, no effect of psychotropic drug withdrawal was seen. **Chapter 3.3** describes the related costs, the effects on health related quality of life, and the cost-utility of the intervention. The total healthcare related costs in the intervention group were €39 higher than usual care. FRID withdrawal was associated with less decline in HRQoL as measured with the EQ-5D utility score. The intervention resulted in an incremental cost-utility ratio of €780/QALY gained. Policy makers and health economists have proposed that costs up to €20,000 per QALY are considered as acceptable.

Part IV starts with the general discussion, wherein we summarize the main findings and discuss the strengths and limitations of the IMPROveFALL study. In addition we present the clinical implications of our findings and our recommendations for future research.

This study increases our insights into both the effectiveness of FRIDs withdrawal as a method for falls reduction in older adults, and into the complexity of this intervention in an older, multi-morbid population. The study adds to the understanding of effective falls-prevention interventions. Overall, FRIDs withdrawal did not result in a reduced incidence of falls. However,cardiovascular FRIDs withdrawal did reduce visits to the general practitioner because of a fall. The potential harm versus benefit of antihypertensive medications should be weighed in older adults with multiple chronic conditions. The method of implementation of fall-risk increasing drugs withdrawal is essential, compliance might be improved if the prescribing physician performs the withdrawal.

Samenvatting en Conclusies

Deel I is een overzicht van de literatuur over de effecten van valincidenten op de oudere persoon, de gezondheidszorg en de kosten voor de samenleving. Een groot aantal ouderen van 65 jaar en ouder maakt in een jaar één of meerdere valincidenten door. Valincidenten leiden tot ernstige problemen zoals hoge morbiditeit en mortaliteit, verminderd fysiek functioneren, verlies in kwaliteit van leven, en verlies van zelfstandigheid met als gevolg langdurige opnames in zorginstellingen. Verder drukken valgerelateerde letsels op de gezondheidszorg met een groot aantal spoedeisende hulp bezoeken, ziekenhuisopnames, opnames in verpleeg- en revalidatie-instellingen en veroorzaken deze letsels hoge gezondheidszorgkosten.

Deel II biedt inzicht in diverse factoren die aan valincidenten in de oudere populatie gerelateerd zijn. Deze factoren, zoals de omstandigheden die leiden tot schadelijke valincidenten en het effect van vitamine D op fysieke prestaties worden besproken. Tenslotte wordt een vergelijking van functionele, fysieke en gezondheidsgerelateerde kwaliteit van leven scores in eenmalige en frequente vallers gemaakt. **Hoofdstuk 2.1** is een overzicht van de activiteiten binnenshuis en buitenshuis die hebben geleid tot valincidenten die een bezoek aan de spoedeisende hulp vereisen en valincidenten die hebben geleid tot ernstige verwondingen zoals traumatisch hersenletsel en heupfracturen. Twee derde van alle valincidenten vond binnenshuis plaats. De meest voorkomende activiteiten voorafgaand aan een val met letsels binnenshuis waren lopen en traplopen. De meest voorkomende activiteiten voorafgaand aan een val met letsels buitenshuis waren lopen en fietsen. Activiteiten binnenshuis die leidden tot traumatisch hersenletsel respectievelijk heupfracturen verschilden. Traplopen en huishoudelijke werkzaamheden waren de meest voorkomende activiteiten voorafgaand aan traumatisch hersenletsel, terwijl lopen en zitten of staan behoorden tot de meest voorkomende activiteiten voorafgaand aan heupfracturen. Opmerkelijk was dat

ongeveer de helft van alle traumatische hersenletsels en heupfracturen bij mannen en vrouwen tussen 65-79 jaar buitenshuis zijn opgetreden. De meest voorkomende activiteiten buitenshuis die leidden tot beide letsels waren lopen en fietsen. In **Hoofdstuk 2.2** laten we zien dat de serum 25(OH)D-spiegel significant gerelateerd is aan spierkracht en fysieke prestatie in de studie-populatie van zelfstandig-wonende oudere mannen en vrouwen. In **Hoofdstuk 2.3** worden gegevens gepresenteerd die richtlijnen ondersteunen waarin gesteld wordt dat frequente vallers een indicatie hebben voor een multifactoriële evaluatie van valgerelateerde risicofactoren. Deze groep vallers scoorden significant minder goed in alle fysieke prestatie toetsen (mobiliteit, spierkracht en balans). Verder hadden frequente vallers lagere gezondheidsgerelateerde kwaliteit van leven scores, inclusief significant lagere EQ-5D scores en meer problemen in alle vijf de EQ-5D domeinen.

Deel III beschrijft het protocol van de IMPROveFALL studie (**Hoofdstuk 3.1)**. De IMPROveFALL studie is een multicenter gerandomiseerd onderzoek dat het effect van het gestructureerd afbouwen van valrisicoverhogende geneesmiddelen vergelijkt met 'gebruikelijke zorg' op het voorkomen van valincidenten bij zelfstandig wonende oudere mannen en vrouwen. **Hoofdstuk 3.2** vermeldt de resultaten van de IMPROveFALL studie. In het algemeen heeft het afbouwen van valrisicoverhogende geneesmiddelen niet geleid tot een vermindering van valincidenten in het follow-up jaar. Echter, het afbouwen van cardiovasculaire geneesmiddelen resulteerde in een lager aantal huisartsbezoeken vanwege een val ten opzichte van de controle groep. Verrassend was dat er geen effect op de valincidentie werd gevonden na het afbouwen van psychotropica. **Hoofdstuk 3.3** biedt inzicht in de gezondheidszorg gerelateerde kosten, het effect op de gezondheidsgerelateerde kwaliteit van leven en de kosten-utiliteit van de interventie. De totale gezondheidszorggerelateerde kosten in de interventiegroep waren €39 hoger dan in de controle groep. Het afbouwen van valrisicoverhogende geneesmiddelen was gerelateerd aan

minder achteruitgang van gezondheidsgerelateerde kwaliteit van leven zoals gemeten met de EQ-5D score. De interventie had een incrementele kosten-utiliteits ratio van €780 per gewonnen QALY. Beleidsmakers en gezondheid economen hebben eerder € 20.000 per gewonnen QALY voorgesteld als acceptabel

Deel IV bevat een algemene discussie met een samenvatting van de uitkomsten en een bespreking van de beperkingen en sterke punten van de IMPROveFALL studie. De gevolgen van de studieresultaten voor de kliniek worden hier besproken evenals de aanbevelingen voor toekomstig onderzoek.

Dit proefschrift verbreedt het inzicht in het effect van het afbouwen van valrisicoverhogende geneesmiddelen als methode voor het reduceren van valincidenten in een populatie van thuiswonende oudere mannen en vrouwen. De complexiteit van deze interventie in een oudere populatie met multimorbiditeit wordt aan de orde gesteld. In het algemeen heeft het afbouwen van valrisicoverhogende geneesmiddelen niet geleid tot een vermindering van valincidenten. Echter, het afbouwen van cardiovasculaire geneesmiddelen heeft het aantal huisartsbezoeken vanwege een val wel verminderd. De methode van implementeren van deze interventie is essentieel. Mogelijk is de implementatie effectiever als de behandelend arts deze uitvoert.

Acknowledgements

Curriculum Vitae

List of publications

PhD Portfolio

Dankwoord

Onderzoek doe je niet alleen. Dit proefschrift zou niet tot stand zijn gekomen zonder samenwerking van een grote groep toegewijde mensen. Een aantal van hen wil ik graag hier in het bijzonder noemen.

Mijn promotor, prof.dr. P. Patka. Geachte professor Patka, ik ben ontzettend dankbaar dat u mij vier jaar geleden de gelegenheid gaf dit promotietraject in te gaan. Ik heb uw inzet tijdens de maandelijkse vergaderingen en achter de schermen enorm gewaardeerd. Dank voor uw scherpe inzicht, nuttige commentaar en fijne samenwerking.

Mijn tweede promotor, prof.dr. T.J.M. van der Cammen. Beste Tischa, uw enthousiasme en toewijding aan dit onderzoek is aan niemand voorbij gegaan. Dank voor de altijd interessante gesprekken en discussies met uitslagen uit de meest recente literatuur. Alle tijd en moeite die u in mijn proefschrift heeft geïnvesteerd waardeer ik enorm.

Mijn copromotor, dr. E.F. van Beeck. Beste Ed, ik heb bewondering voor uw kennis en inzicht, en uw inzet om deze over te brengen aan jonge onderzoekers. Na onze gesprekken kwam ik altijd weg met nieuwe ideeën en een verse kijk op alle data en uitslagen. Hartelijk dank voor de goede begeleiding.

De leescommissie, prof. dr. S.E.J.A. de Rooij, prof. dr. A. Burdorf en prof. dr. M.H.J. Verhofstad, dank voor het lezen en beoordelen van mijn proefschrift.

Beste Esther, in 2010 kwam ik als jonge student bij jou terecht voor mijn keuze-onderzoek. In deze periode heb je mij enthousiast gemaakt voor wetenschappelijk onderzoek, ik ben tenslotte via jou beland in dit mooie promotietraject. Jouw gedrevenheid, gestructureerde manier van werken en enthousiasme voor onderzoek zijn ongeëvenaard. Jouw deur was altijd open om mijn vragen te beantwoorden en te helpen als ik vastliep. Dank voor lezen van mijn

manuscripten in de avonduren, dank voor jou altijd kritische blik. Maar bovenal dank voor alle steun en vertrouwen afgelopen jaren.

Nathalie, hartelijk dank voor alle tijd en energie die jij in dit proefschrift hebt gestoken. Als jonge onderzoeker heb ik veel gehad aan jouw kennis en ervaring. Tevens is het fundament voor de IMPROveFALL studie mede door jouw inspanningen gelegd.

Francesco, dankzij de manier waarop wij met elkaar omgingen ben ik nooit met tegenzin naar het D-gebouw gegaan. Je enthousiasme en warme persoonlijkheid maakten het heel prettig om samen te werken. Besprekingen met jou waren altijd erg effectief, bespreken wat er besproken moet worden en dan weer aan de slag. Je hulp bij het tot stand komen van artikelen was erg leerzaam. *Molte grazie!*

Klaas, dank voor jouw aandeel bij het opstartten van de IMPROveFALL inclusie. Het was erg fijn om op een rijdende trein te kunnen stappen. Je was altijd bereikbaar en bereid om te helpen in de jaren daarna. Ik wens je alle succes toe in de toekomst, gaat helemaal goed komen met je ambities.

Beste Oscar en prof. Lips, ontzettend veel dank voor alle hulp, waardevolle feedback en prettige samenwerking. Beste Suzanne, dank voor de prettige en ontspannen samenwerking! Beste Carolien, fijn dat ik altijd bij jou terecht kon voor een kop koffie (en ook alle vragen). Beste Liz, Dineke, en Ingrid hartelijk dank voor alle moeite die jullie hebben gedaan voor de IMPROveFALL deelnemers en studie. Jullie waren onmisbaar voor de uitvoering van dit onderzoek en ik heb veel gehad aan jullie inzet. Alle studenten die hard hebben gewerkt aan het verzamelen van data wil ik ook hartelijk danken: Sama Najidh, Steven Venema, Eunice Comvalius, Carla Cok, Els van Leest en Tiemen Lammerink.

Gijs en Kiran mijn ‘roomies’ en ook Steven, Stephanie, Paul en Siebe, mijn mede Z-flat bewoners, dankzij jullie was het altijd gezellig werken! Stephanie van Hoppe en Kiran

Mahabier, mijn paranimfen, ik ben blij dat jullie 9 oktober, letterlijk en figuurlijk achter mij staan.

Collegae in het Maasstad en nu het Hagaziekenhuis, hartelijk dank voor de tot nu toe geweldige tijd in de kliniek!

Masha danki na mi mayornan, bosnan nunka a pone limitashon riba mi soñonan. Ta un honor pa ta boso yu.

Mi dushi, Josuah*,* jij bent mijn thuis. Bedankt voor de vrijheid die jij me geeft om te zijn wie ik ben en te doen wat ik doe.

Curriculum vitae

Nicole Boyé werd op 24 augustus 1986 geboren te Willemstad, Curaçao. Ze behaalde in 2004 haar VWO diploma aan het Radulphus College te Curaçao. In 2004 startte zij met de opleiding Geneeskunde, zij bracht tijdens haar coschappen drie maanden door bij de Traumachirurgie en Oncologie in het Groote Schuur Hospital in Kaapstad en vervolgens drie maanden bij de Heelkunde in St. Vincent's Medical Center in Bridgeport, VS. In 2011 behaalde zij haar artsexamen aan het Erasmus Universiteit Rotterdam. Na het afstuderen werkte zij als arts-onderzoeker bij de afdelingen Heelkunde en Interne Geneeskunde in het Erasmus MC in Rotterdam. In 2013 begon zij als arts-assistent heelkunde in het Maasstad Ziekenhuis in Rotterdam. En in 2014 begon zij met de opleiding tot chirurg in het HagaZiekenhuis in Den Haag (opleiders: dr. J.J. Wever en prof. dr. J.F. Hamming).

List of Publications

[Cost] effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study).
Hartholt KA, Boyé ND, Van der Velde N, Van Lieshout EM, Polinder S, De Vries OJ, Kerver AJ, Ziere G, Bruijninckx MM, De Vries MR, Mattace-Raso FU, Uitterlinden AG, Van Beeck EF, Lips P, Patka P, Van der Cammen TJ.
BMC Geriatr. 2011 Aug 21;11:48.

The Impact of Falls in the Elderly
Nicole D.A. Boyé, Esther M.M. van Lieshout, Ed F. van Beeck, Klaas A. Hartholt, Tischa J.M. van der Cammen, Peter Patka
Trauma 01/2013; 15(1):29-35.

Single-nucleotide polymorphisms in the Toll-like receptor pathway increase susceptibility to infections in severely injured trauma patients.
Bronkhorst MW, Boyé ND, Lomax MA, Vossen RH, Bakker J, Patka P, Van Lieshout EM.
J Trauma Acute Care Surg. 2013 Mar;74(3):862-70.

Vitamin D and physical performance in older men and women visiting the emergency department because of a fall: data from the improving medication prescribing to reduce risk of falls (IMPROveFALL) study.
Boyé ND, Oudshoorn C, van der Velde N, van Lieshout EM, de Vries OJ, Lips P, van Beeck EF, Patka P, van der Cammen TJ.
J Am Geriatr Soc. 2013 Nov;61(11):1948-52.

Physical performance and quality of life in single and recurrent fallers: Data from the Improving Medication Prescribing to Reduce Risk of Falls study.
Boyé ND, Mattace-Raso FU, Van Lieshout EM, Hartholt KA, Van Beeck EF, Van der Cammen TJ.
Geriatr Gerontol Int. 2014 Apr 15.

Circumstances leading to injurious falls in older men and women in the Netherlands
Nicole D.A. Boyé, Francesco U.S. Mattace-Raso, Nathalie van der Velde, Esther M.M. van Lieshout, Oscar J. de Vries, Klaas A. Hartholt, Albert J.H. Kerver, Milko M.M. Bruijninckx, Tischa J.M. van der Cammen, Peter Patka, Ed F van Beeck, and the IMPROveFALL trial collaborators
Injury. 2014 Aug;45(8):1224-30.

PhD Portfolio

ERASMUS UNIVERSITEIT ROTTERDAM

Summary of PhD-training and teaching	
Name PhD student: Nicole D.A. Boyé	PhD period:
Erasmus MC Department:	June 2011 – December 2014
Surgery – Traumatology	Promotor:
Internal Medicine – Geriatrics	Prof. dr. P. Patka
Research School: MUSC	Copromotors:
	Dr. T.J.M van der Cammen
	Dr. E.F. van Beeck

1. PhD training	**Year**	**Workload (ECTS)**
Courses		
Scientific Writing	2012	2.0
BROK - Basiscursus Regelgeving en Organisatie van Klinische trials (GCP course)	2012	1.5
NIHES - Classical Methods for data-analysis	2012	5.7
Presentations		
Stafdag Heelkunde	2012	2.0
10th Congress of the EUGMS, Rotterdam	2014	2.0
Landelijk valsymposium	2014	2.0

2. Teaching	**Year**	**Workload (ECTS)**
Lecturing		
Lecturing at Department of Internal Medicine	2012	1.0
Lecturing at Department of Surgery	2011-2012	2.0
Supervising practicals and excursions		
Examination of Basic Life Support of medical students	2011-2012	1.0
Supervising Master's theses		
Sama Najidh, *master-student pharmacology*	2011-2012	2.0
Steven Venema, *medical student*	2011-2012	2.0
Eunice Comvalius, *medical student*	2012	2.0
Carla Cok, *medical student*	2012	2.0
Els van Leest, *medical student*	2012	2.0
Tiemen Lammerink, *master-student pharmacology*	2012-2013	2.0