G. Ziere

Risk Factors for Falls and Fall-related Fractures in the Elderly

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The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University Rotterdam, the Netherlands Organization for Scientific Research (NMW), the Netherlands Organization for Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII) and the Municipality of Rotterdam

The contributions of general practitioners and pharmacists of the Ommoord district to the Rotterdam Study are greatly acknowledged.

The study reported in chapter 3 was supported by a grant from the Inspectorate for Health Care, the Hague, the Netherlands.

The publication of this thesis was financially supported by Servier Nederland Farma BV and Novartis Pharma BV.

Layout: Jorrit M. van der Velden, Dordrecht, www.vdvelden.eu
Cover Photograph: Jan Koeman, member of the Philippus Lansbergen Public Observatory, Middelburg

Printed by Optima Grafische Communicatie, Rotterdam

ISBN: 978-90-8559-326-3

Risk Factors for Falls and Fall-related Fractures in the Elderly

Risicofactoren voor vallen en val-gerelateerde fracturen bij ouderen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 5 december 2007 om 15.45 uur

door

Gijsbertus Ziere

geboren te Rotterdam

Promotiecommissie

Promotor:	Prof.dr. B.H.Ch. Stricker
Overige leden:	Prof. J.H.P. Wilson
	Prof.dr. H.A.P Pols
	Prof.dr. M.G.M. Olde Rikkert
Copromotoren:	Dr. J.P. Dieleman
	Dr. T.J.M. van der Cammen

Voor Ageeth, Gijs en Johanneke

Ter nagedachtenis aan Thierry Gideon le Fèvre

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Chapter 1 **| General introduction**

Historical context

By the appearance of *homo erectus*, the "Upright Man", approximately 500,000 years ago, a new episode in the development of mankind started: the challenge of coping with gravity. Consequently, man was facing a new problem, namely, that he could fall as well.

For ages, falls and fall-related injuries were considered accidents, that is "acts of God" (*fatum*), random or chance events without observable or understandable explanations. Otherwise, as described in Rome's religious history[1], they could be a result of not paying due attention to the gods, invoking the wrath of the god Salus (*ira deum*).

First descriptions of falls in ancient medicine

In ancient medicine, little attention was paid to fall-accidents, presumably because there were few opportunities for successful interventions. However, the results of an injurious fall, especially fractures, are dealt with extensively by Hippocrates[2]. One of the first written descriptions of a fall accident is found in "the history of Rome" by Titus Livius[3], where consul Marcellus, a veteran general of more than sixty years old, fell from his horse and died. Even in modern times, there is still a belief that falls are an inevitable part of the aging process[4 5]

Falls in geriatric medicine

As from the 1960s, beginning with the early studies by Droller[6], Sheldon[4], and Fine[7], falls have increasingly been recognized as predictable, and potentially preventable, health problems warranting careful investigation. As evidenced by their association with other functional problems, such as incontinence, and by a high mortality rate for reasons other than injury, falls in the very frail elderly may simply be markers for deterioration. However, falls by elderly persons other than the very frail appear to result from either a single specific cause or, more often, from the accumulated effect of multiple identifiable risk factors[8].

The incidence of falls as well as the severity of fall-related complications rises steeply beyond the age of 60. Among all community dwelling persons of 65 and over, 30-40% have at least one fall each year and the incidence increases with age[9, 10]. The incidence of falls in nursing homes and hospitals is almost three times as high as in the community[9].

Consequences of falls in the elderly

Not all falls of older adults result in injury, but 4% to 5% of the falls cause a fracture, and an additional 5% to 11% of falls cause other serious injuries, e.g., serious soft tissue contusions, joint distortions and dislocations, severe wounds and lacerations, and head injuries[11-13]. This is compounded further by the psychological *sequelae* of loss of confidence, increased fear of falling, lower quality of life[14]

and post-fall anxiety syndrome[15]. Fifty percent of fallers will have a further fall within the next 12 months[16]. Recurrent falls are the main reason for nursing home admission representing 40% of the admissions[17]. Fall-related injuries accounted for 6% of all medical expenditures for people aged 65 and over in the United States[18]. Unintentional injuries are the fifth leading cause of death in older adults, and falls are responsible for two-thirds of the deaths resulting from unintentional injuries. Three quarter of deaths due to falls in the United States occur in the 13% of the population above the age of 65[19].

Risk factors and interventions

A number of studies have identified risk factors for falling[9, 20-30], which are outlined in table 1. A commonly used classification for falls distinguishes between intrinsic factors (e.g., lower extremity weakness, poor grip strength, balance disorders, functional and cognitive impairment, visual deficits) and extrinsic factors (e.g., polypharmacy of four or more prescription medications and environmental factors such as poor lighting, loose carpets, and lack of bathroom safety equipment)[9].

The risk of falling, i.e., the chance to experience one or more falls per year, increases dramatically if the number of risk factors increases: the fall risk of community dwelling older persons increases from 27% in the presence of one risk factor to 78% in the presence of four or more risk factors[31]. Comparable results have been found for hospitalised older persons[32]. To reduce the fall risk within the older population all risk factors need to be assessed. Special efforts should be made to identify modifiable risk factors which can be useful for undertaking effective interventions.

Table 1 | **Most Common Risk Factors for Falls**

Risk Factor	Mean RR-OR#
Muscle weakness	4.4
History of falls	3.0
Gait deficit	2.9
Balance deficit	2.9
Use assistive device	2.6
Visual deficit	2.5
Arthritis	2.4
Impaired ADL*	2.3
Depressive symptoms	2.2
Cognitive impairment	1.8
Female Gender	1.9
Age> 80 years	1.7
Psychotropics	1.7
Urinary incontinence	1.6

\# Relative risk ratios (RR) calculated for prospective studies. Odds ratios (OR) calculated for retrospective studies.

* ADL = activities of daily living.

Sources: [9, 20, 22]

Fall risk and drugs

Drugs constitute a major part of modifiable risk factors for falls in the elderly. In guidelines for the prevention of falls in older persons recommendations are made that the influence of drugs on fall risk of older persons need further investigation[9, 20].

There are no precise percentages of drug-induced falls in community dwelling elderly. One study on drug use and chronic deseases in elderly women, showed a prevalence of 16.9%[33].

Although there are no randomized controlled studies of the effect of modifications in pharmacological treatment regimens as a sole intervention, reduction of medications was a prominent component of effective fall-reducing interventions in community-based and long-term care multifactorial studies[16, 34-37]. These multifactorial studies suggest that a reduction in the number of medications in patients who are taking more than four preparations is beneficial.

Some studies have tried to identify drugs that increase fall risk. Most studies were small and often retrospective. A meta-analysis in 1999 showed an increased fall risk with diuretics, type IA anti-arrhythmics, digoxin, hypnotics/sedatives, neuroleptics, and antidepressants (tricyclic and SSRIs)[21, 22]. Across all settings (i.e., community, long-term care, hospital, and rehabilitation), there is a consistent association between psychotropic medication use (i.e., neuroleptics, benzodiazepines, and antidepressants) and falls.

A recent prospective cohort study showed that withdrawal of fall-risk-increasing drugs was effective as a single intervention for falls prevention in a geriatric outpatient setting. The effect was greatest for withdrawal of cardiovascular drugs[38]. It is important to recognize falls as a potential adverse drug reaction in order to adequately reduce the risk.

Falls and the cardiovascular system

Although many risk factors for falls have been identified in the last two decades, research regarding cardiovascular risk factors is less abundant[9]. The reported studies pertain to vascular risk factors, such as orthostatic hypotension, systolic hypertension, carotid sinus hypersensitivity and vasovagal collapse[39]. Besides a recent cohort study by our research group, in which echocardiographic abnormalities were studied as a risk factor in geriatric outpatients, to our knowledge there are no data regarding structural cardiac abnormalities as possible risk factor for falls[40]. This is remarkable, since structural cardiac abnormalities are undisputed risk factors for syncope[41, 42]. Older persons suffering from syncope will incorrectly be classified as a simple fall in approximately 50% of cases, mainly because of amnesia for the temporary loss of consciousness[43]. Syncope, or falls, will occur when circulatory demands outweigh the ability of the heart to increase its output. It is thought that in this situation a transient shortage of cerebral perfusion occurs, resulting in a fall or syncope[41].

Aims and outline of this thesis

The objective of this thesis was to investigate the occurrence and consequences of falls in the Netherlands, to address risk factors for falls and to explore the association of drug use with falls and fall related fractures in more depth.

For this purpose, we used two population-based data sources. Main analyses were performed in the Rotterdam Study, a prospective population- based cohort study among 7983 older adults living in Ommoord, a suburb of Rotterdam[44]. Additionally, we were able to use the 'Landelijke Medische Registratie' (LMR) database, a registry that stores discharge information from all hospitalizations in the Netherlands. We were able to combine both data sources by record linkage.

To gain more insight into the present and future burden of illness due to falls on a population level we describe time-trends in the cumulative incidence and characteristics of fall-related hospitalisations in the Netherlands using the national registry of hospital admissions in chapter 2.

In chapter 3 we present analyses in the baseline cohort of the Rotterdam Study to examine multiple risk factors for falls in a single population, including drug use as a important modifiable risk factor. Consequently, in more depth in chapter 4, the association between hypovolemia and falls in a population-based study is described. In chapter 5, we focus on polypharmacy and elaborate on our hypothesis that drugs can be an independent risk factor for falling but that polypharmacy itself is not a risk factor.

The study described in chapter 6 aims at the association between left ventricular function and serious fall incidents in older persons. In chapter 7, we describe a prospective population-based cohort study of the association of non-vertebral fracture and use of antidepressants, in which we address the issue of confounding by indication. The association between benzodiazepine use, certain cytochrome - P450 gene poymorphisms and serious fall incidents in older persons is presented in chapter 8.

Finally, in chapter 9 the strengths and limitations of this thesis are discussed, together with an implication of our results for future research.

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02

Chapter 2 | **Fall - Related Hospitalisations: A Nationwide Study in the Netherlands**

ABSTRACT

Objective:
To evaluate the incidence and characteristics of fall-related acute hospitalisations in the Netherlands in the period 2001-2004.

Study design:
Nationwide cohort-study of all hospital admissions in the years 2001-2004.

Setting:
Population based using the national morbidity registration and general population statistics of the Netherlands.

Participants:
All inhabitants in the Netherlands.

Measurements:
Acute hospitalisations, coded as fall-related, to all Dutch academic and general hospitals were selected. Age, sex, and calendar year specific cumulative incidences were calculated. Time trends in incidence as well as duration of hospitalisation, risk of fatal most frequent main diagnoses were analysed.

Results:
162,696 (5.45%) of acute admissions were considered as fall-related. In the study period the cumulative incidence of fall-related hospitalisations increased from 2.3 (95% CI 2.3-2.4) per 1,000 inhabitants to 2.7 (95% CI 2.7-2.7). The risk increase was highest in persons aged 99 years and above accumulating to a 30% risk increase for persons of 99 years and older. The most frequent main diagnosis implicated 'fracture of neck of femur' (33.9%). A general decline in in-hospital mortality was observed. The mortality reduction was independent of the observed trend towards shorter hospitalisations.

Conclusion:
We observed a steady increase in fall-related hospitalisations which exceeds the annual growth of the ageing population. Consequently, in the future more hospital beds are needed.

INTRODUCTION

Falls are among the most common and serious problems in elderly persons. Approximately 30% of the older persons living in the community and more than 50% of those living in geriatric long-stay facilities fall every year[1-3]. Falling is associated with considerable mortality, morbidity, reduced functioning, and premature nursing home admissions[4-6]. Four to 5% of falls in the elderly result in a fracture, and an additional 5% to 11% of falls cause other serious injuries, such as serious soft tissue contusions, joint distortions and dislocations, severe wounds and lacerations, and head injuries[3, 5, 7]. Ultimately, 23.5% of falls requires health services and 17.2% requires treatment[8]. The public health impact is considerable as falls account for over 80% of injury-related admissions to hospital of people older than 65 years[9].

Studies that examined time trends on a population level and therefore can inform us about potential future risks and public health impact are scanty. Most epidemiological studies evaluating the extent of fall-related hospitalisations were conducted within (single) units, departments or hospitals[8, 10-13] . Because of the variability in applied methodologies and confined settings, it is difficult to reliably extrapolate the incidence and prevalence figures to other geographic areas and to provide insight into future risks and the impact of the problem on a population level.

To gain more insight into the present and future burden of illness due to falls on a population level we assessed time-trends in the cumulative incidence and characteristics of fall-related hospitalisations in the Netherlands using a national registry of hospital admissions.

METHODS

Setting

Data were retrieved from a nationwide computer database for hospital discharge records (National Morbidity Registration, LMR) in the Netherlands. The registry contains among others basic patient characteristics, date of admission and discharge, one discharge diagnosis (ICD-9 coded), secondary diagnoses (ICD-9 coded), procedures, treating medical specialism (coded) and special aetiological codes indicating fall-related hospitalisations (E-codes), based on the ICD-9-CM coding system[14]. For every admission, one discharge / main diagnosis (mandatory), and up to 9 secondary diagnoses (optional) are registered. All general (n=100) and university (n=8) hospitals in the Netherlands participate in the registry. Characteristics of all hospitalisations are registered by medical doctors on the basis of hospital discharge letters and coded by professional code clerks. The coding is independent of reimbursement of hospital or specialist. All diagnoses are submitted in the same format, mostly electronically.

Demographic data on the Dutch population for the period 2001 up to and including 2004 were retrieved from the Central Bureau for Statistics in the

Netherlands (CBS, http://statline.cbs.nl/StatWeb/, last accessed 5-9-2006).

Study population

The study population comprised all inhabitants in the Netherlands during the 4-year period 2001 through 2004. Population characteristics that were available from both data sources (i.e. CBS and LMR) included age and gender. Persons were categorized into 5 different age groups including <20 years, 20 through 40 years, 41 through 65 years, 66 through 80 years and ≥ 81 years. To further explore time trends in the "oldest old", we also considered the age groups of 90 to 98 years and ≥ 99 years.

Fall-related hospital admissions

All acute (non-planned) admissions to a Dutch hospital between 2001 and 2004 were identified in the admission registry (n=2,987,580). The year 2004 was chosen, as this was the last complete year available in the registry. A fall-related hospitalisation was defined as a hospitalisation with an E-code E880 through E888 in the first secondary diagnosis, because a fall is not a medical diagnosis, but an etiology and cannot be chosen by hospitals as the main discharge diagnosis. When relevant, the first secondary diagnosis is often used for an aetiological E-code indicating the cause of the main discharge diagnosis. Hospital admissions were described in terms of length of hospital stay, type of injury involved, and outcome of admission (i.e. died in hospital, institutionalized, returned home).

ANALYSIS

For each calendar year and for each age group, we calculated the proportion of fall-related hospitalisations by dividing the number of fall-related acute admissions by the total number of acute admissions to Dutch hospitals. In addition, we calculated median duration of hospital stay and the in-hospital mortality. Differences between fall-related admissions and other admissions were tested by using Chi-squared statistics for categorical variables and standard t-test for continuous variables. Non-normally distributed data were analyzed after normalisation through log-transformation.

Cumulative incidences or risks were calculated by dividing the number of acute fall-related hospital admissions by the number of persons available in the Dutch population. Although we used a nationwide registry covering the entire population, which provides exact figures, we did calculate 95% confidence intervals (95% CI) assuming a normal distribution.

The risk of fall-related hospital admission was modelled against time (in years) assuming a linear relationship. The resulting equation was used to extrapolate the results up to the year 2010. Relative changes over time were calculated by subtracting the estimates for 2001 from the estimates for 2004 and by dividing this difference by the estimates for 2001. Relative risk of fall-related hospital

admission was calculated by dividing cumulative incidences. The influence of duration of hospital stay on the mortality risk per year was analyzed by using a Cox-regression model with duration of hospital stay as time axis. Analyses were performed using SPSS, version 11.0.1 for Windows (SPSS Inc., Chicago, IL).

RESULTS

During the study period the Dutch population grew from approximately 15.99 million in 2001 to 16.26 million inhabitants in 2004 (table 1). The proportion of persons above 80 years of age increased from 3.2% to 3.4%. Of all 9,729,819 admissions during the study period, 30.7% (n= 2,987,580) were acute. The most frequent main diagnoses were of cardiovascular nature including chest pain, myocardial infarction, heart failure and stroke (13.5% of all acute admissions)[15]. The mean duration of acute admissions was 8.8 days and 4.9% of all acute admissions had a fatal course.

Table 1 **| Time trends in population characteristics and fall related hospital admissions in the Netherlands between 2001 and 2004**

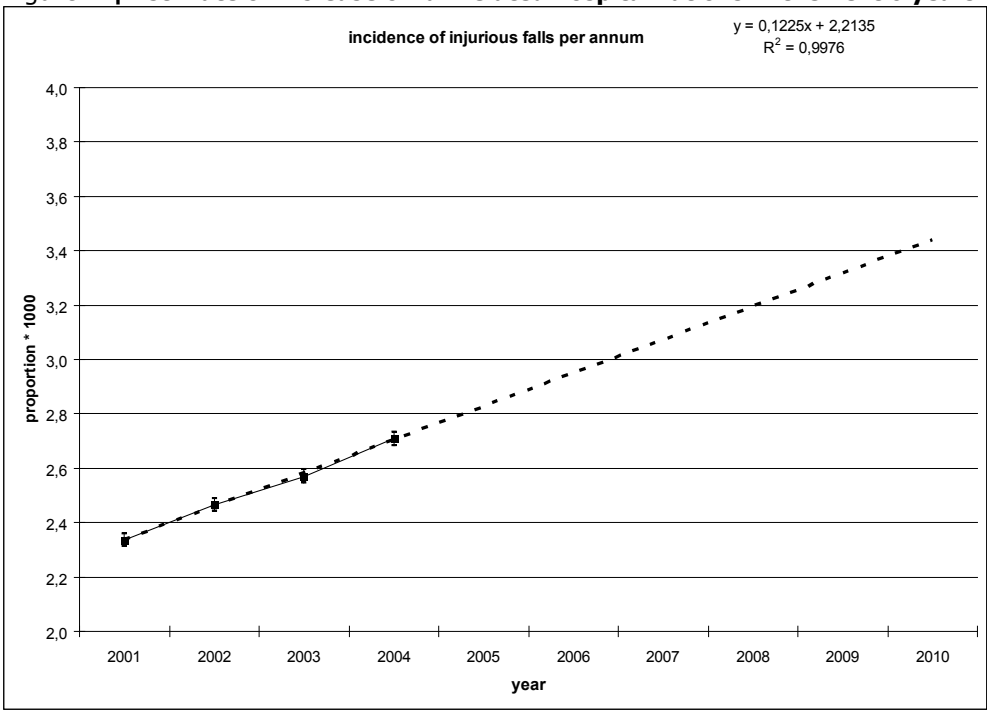
Characteristic	2001	2002	2003	2004
Dutch population	15,987,075	16,105,285	16,192,572	16,258,032
Female sex (%)	50.5	50.5	50.5	50.5
mean age (years)	38,3	38,4	38,6	38,7
age 65 - 80 years (%)	10,4	10,4	10,4	10,4
age > 80 years (%)	3,2	3,3	3,4	3,4
Acute hospital admissions (n)	669,279	725,221	772,062	821,045
Female sex (%)	53.4	53.5	53.6	53.6
Mean age (years)	48.4	48.7	49.3	49.8
age 65 - 80 years (%)	23.8	23.5	23.6	23.4
age > 80 years (%)	12.9	13.1	13.6	13.8
In hospital mortality				
65 - 80 years	9.8	9.0	8.1	7.1
> 80 years	16.2	15.5	14.1	12.2
Total	5.6	5.2	4.8	4.2
Fall related acute admissions (n)	37,334	39,702	41,623	44,037
Fall related, (% of acute admissions)	5.6%	5.5%	5.4%	5.4%
Female sex (%)	60.8	59.8	60.1	60.2
Mean age (years)	58.7	57.6	57.8	57.4
age 65 - 80 years (%)	23.6	22.6	22.3	21.5
age > 80 years (%)	31.6	31.1	31.9	31.6
In hospital mortality				
65 - 80 years (%)	3.8	3.6	3.5	3.0
> 80 years (%)	9.5	8.9	7.9	6.6
Total (%)	4.2	3.8	3.5	2.9

Trends in fall-related hospital admissions

In total 162,696 (5.45%) of acute admissions were considered as fall-related (table 1). The number of hospitalisations coded as fall-related rose from 37,334 in 2001 to 44,037 in 2004. The cumulative incidence of fall-related hospitalisations in the Netherlands was 2.3 (95% CI 2.3 – 2.4) per 1,000 inhabitants in 2001 and 2.7 (95% CI 2.7 – 2.7) per 1,000 inhabitants in 2004. The overall risk increase of fall-related admissions between 2001 and 2004 was 15.8%.

Modelling the risk of fall-related admissions against time resulted in the following equation: risk=0.1225*year+2.2135. Assuming continuation of the linear trend, thereby assuming a change of underlying determinants at a similar rate for 6 years, the estimated risk of fall-related hospital admissions in 2010 would be 3.5 per 1000 persons (figure 1).

Figure 1 **| Estimate of increase of fall related hospitalizations in the next 6 years**



Age specific cumulative incidence figures showed an increase in fall-related hospital admissions across all age groups over time but especially in the young (<20 years) and the very old (>99 years, table 2). Unlike other acute admissions the fall related admissions showed a strong age dependency among the group above 80 years. The relative increases during the study period ranged from 30% in the young and very old to 5.3% in the group aged 65 to 80 years. Across all study years the 80 or above year olds, consistently had the highest cumulative

Table 2 | **Age specific cumulative Incidence (per 1000 inhabitants) of fall-related and non fall-related acute admissions from 2001 to 2004**

	2001		2002		2003		2004		Relative increase
Age category	**Cum. Inc.**	**(95% CI)**	**Cum. Inc.**	**(95% CI)**	**Cum. Inc.**	**(95% CI)**	**Cum. Inc.**	**(95% CI)**	
Acute admissions	**41.9**	**(41.8 - 42.0)**	**45.0**	**(44.9 - 45.1)**	**47.7**	**(47.6 - 47.8)**	**50.5**	**(50.4 - 50.6)**	**20.6%**
< 20 years	29.6	(29.5-29.8)	30.9	(30.7-31.1)	31.7	(31.5-31.9)	32.3	(32.1-32.5)	9%
20 - 40 years	30.8	(30.6-30.9)	33.4	(33.3-33.6)	35.1	(35-35.3)	37.1	(36.9-37.2)	20%
40 - 65 years	31.4	(31.2-31.5)	34.4	(34.2-34.5)	36.6	(36.4-36.7)	39.8	(39.7-40.0)	27%
65 - 80 years	96.1	(95.6-96.5)	102.1	(101.-102.)	108.7	(108.-109.)	113.5	(113-114)	18%
>= 80 years	167.2	(166.2-168.2)	178.7	(177.7-179.7)	192.8	(191.7-193.8)	203.6	(202.5-204.7)	22%
90 - 98 years	171.9	(169.1-174.8)	185.7	(182.8-188.6)	204.6	(201.6-207.5)	218.1	(215.1-221.2)	27%
> 99 years	142.0	(126.5-157.6)	145.7	(130.4-161)	139.7	(125.1-154.4)	172.7	(157-188.4)	22%
Fall-related admissions	**2.3**	**(2.3 - 2.4)**	**2.5**	**(2.4 - 2.5)**	**2.6**	**(2.6 - 2.6)**	**2.7**	**(2.7 - 2.7)**	**15.8%**
< 20 years	1.6	(1.6 - 1.6)	1.9	(1.8 - 1.9)	2.0	(1.9 - 2.0)	2.09	(2.0 - 2.1)	30.6%
20 - 40 years	0.7	(0.7 - 0.8)	0.8	(0.8 - 0.8)	0.8	(0.8 - 0.8)	0.85	(0.8 - 0.9)	14.9%
40 - 65 years	1.3	(1.3 - 1.4)	1.4	(1.4 - 1.4)	1.4	(1.4 - 1.5)	1.55	(1.5 - 1.6)	15.7%
65 - 80 years	5.3	(5.2 - 5.4)	5.4	(5.3 - 5.5)	5.5	(5.4 - 5.7)	5.6	(5.5 – 5.7)	5.3%
>= 80 years	22.9	(22.4 - 23.3)	23.2	(22.8 - 23.6)	24.4	(24.0 - 24.8)	24.92	(24.5 - 25.3)	9.1%
90 - 98 years	39.6	(38.1 - 41.1)	41.0	(39.6 - 42.5)	42.7	(41.2 - 44.2)	46.01	(44.5 - 47.5)	16.2%
> 99 years	44.3	(35.1 - 53.4)	48.9	(39.6 - 58.3)	51.7	(42.3 - 61.1)	57.55	(47.9 - 67.2)	30.0%

incidence while the groups aged between 20-40 and 40-65 consistently had the lowest incidence (table 2). The risk as a function of calendar time for 80+ year old persons could be calculated as: risk=0.741*year + 21.995 (R^2 = 0.96). For this group the calculated risk in 2010 would be 29.4 per 1000 persons.

Time trends in risk were similar between women and men although women had a consistently higher risk of fall-related hospital admission. Similar time trends were also seen for areas with a high a well as with a low socio-economical class. With concern to the influence of the environment, persons aged 80 years and older living in a rural area, showed an approximately 20% lower risk of fall-related hospitalisation (p< 0.001).

To evaluate as to whether the observed time-trends were specific for fall-related admissions we also calculated incidence rates of all acute hospital admissions over time. The number of acute hospitalisations rose from 669,279 in 2001 to 821,045 in 2004 resulting in a cumulative incidence of acute hospitalisations in the Netherlands of 41.9 (95% CI 41.8 – 42.0) per 1,000 inhabitants in 2001 and 50.5 (95% CI 50.4 – 50.6) per 1,000 inhabitants in 2004. These findings indicated an overall increase in acute hospitalisation incidence by 20.6% (table 2). The overall and age-specific time trends seemed more pronounced for the complete group of acute admissions than for fall-related admissions except for the youngest and oldest age groups (table 2).

In accordance with the above observed time trends the prevalence of falls as a cause of admission slightly decreased from 5.6% in 2001 to 5.4% in 2004. The mean age at hospital admission decreased from 58.7 years to 57.4 years, but the proportion of 80+ persons and women remained stable at 31.6% and 60% respectively. Compared to other acute admissions, patients with a fall-related hospitalisation were older and included more women.

Mortality among fall-related admissions

The most frequent main diagnoses of fall-related acute admissions implicated ' fracture of neck of femur' (33.9%), ' fracture of radius and ulna' (10.1%), 'fracture of ankle' (7.2%), 'concussion, including commotio cerebri' (6.3%), 'fracture of humerus' (5.9%), 'fracture of tibia and fibula' (4.1%) and 'fracture of vertebral column without mention of spinal cord injury' (3.3%) (table 3). The majority of fatalities occurred in patients admitted with head- or nervous system injury. Among patients admitted with a fracture of the neck of the femur 6.9% died during the stay in the hospital. Institutionalization and long hospital stay occurred especially after admissions involving femur and pelvis fractures and injuries to the central nervous system.

Between 2001 and 2004, the overall proportion of patients with a fall-related admission who died in hospital decreased from 4.2% to 2.9% (table 1). The decrease in in-hospital mortality, corrected for age and gender was independent of the duration of hospital stay, which also decreased over time (p < 0.001).

Table 3 | **Diagnoses accompanying fall-related hospital admissions, in hospital mortality and duration of stay between 2001 and 2004**

Characteristic	ICD-9-CM code	Percentage	Died,%	Discharged not at home, %	Median hospital stay (days)	Interquartile range
Fracture of neck of femur	820	33.9%	6.9%	39.1%	14	(8 - 23)
Fracture of radius and ulna	813	10.1%	0.1%	2.9%	2	(1 - 2)
Fracture of ankle	824	7.2%	0.3%	7.8%	4	(3 - 8)
Concussion (includes: commotio cerebri)	850	6.3%	0.6%	3.4%	2	(1 - 2)
Fracture of humerus	812	5.9%	1.2%	10.4%	2	(2 - 7)
Fracture of tibia and fibula	823	4.1%	0.6%	13.2%	6	(3 - 13)
Fracture of vertebral column without mention of spinal cord injury	805	3.3%	1.7%	15.4%	7	(4 - 14)
Fracture of other and unspecified parts of femur	821	3.1%	4.4%	33.1%	15	(8 - 25)
Fracture of pelvis	808	2.9%	3.8%	31.2%	12	(7 - 21)
Fracture of rib(s), sternum, larynx, and trachea	807	1.8%	3.7%	7.5%	5	(3 - 10)
Contusion of lower limb and of other and unspecified sites	924	1.6%	2.5%	18.0%	6	(3 - 12)
Cerebral laceration and contusion	851	1.4%	6.1%	13.4%	3	(2 - 10)
Fracture of face bones	802	1.4%	0.6%	3.9%	2	(1 - 3)
Contusion of trunk	922	1.3%	1.3%	8.0%	3	(2 - 7)
Intracranial injury of other and unspecified nature	854	1.1%	1.0%	4.9%	2	(1 - 2)
Other diagnoses with high lethality						
Other and unspecified intracranial hemorrhage following injury	853	0.1%	27.5%	31.3%	8	(2 - 21)
Subarachnoid, subdural, and extradural hemorrhage, following injury	852	0.6%	24.7%	40.2%	7	(2 - 15)
Fracture of base of skull	801	0.6%	12.1%	18.7%	5	(2 - 12)
Spinal cord injury without evidence of spinal bone injury	952	0.1%	10.7%	32.2%	8	(3 - 20)
Fracture of vault of skull	800	0.2%	9.7%	14.9%	3	(2 - 7)
Other and unqualified skull fractures	803	0.2%	9.2%	13.2%	3	(2 - 9)
Fracture of vertebral column with spinal cord injury	806	0.2%	6.8%	40.3%	11	(5 - 25)
Traumatic pneumothorax and hemothorax	860	0.5%	4.9%	9.8%	7	(5 - 12)
Other		12.1%	1.4%	7.2%	2	(1 - 6)
Total		100.0%	3.6%	20.2%	6	(2 - 14)

Persons in the age group above 80 years consistently had the highest risk of dying in hospital (table 1).

During the study period there was a strong increase in traumatic head injury as a consequence of a fall, especially in aged persons (> 65 years), with an increase of 34.4% in persons above 80 years (figure 2a). Similar to the overall time trend of a declining in-hospital mortality we found a decrease in in-hospital mortality for patients with head- or nervous system injury (R^2 = 0.95, Figure 2b).

Figure 2a | **Increasing Cumulative Incidence of traumatic head injury**

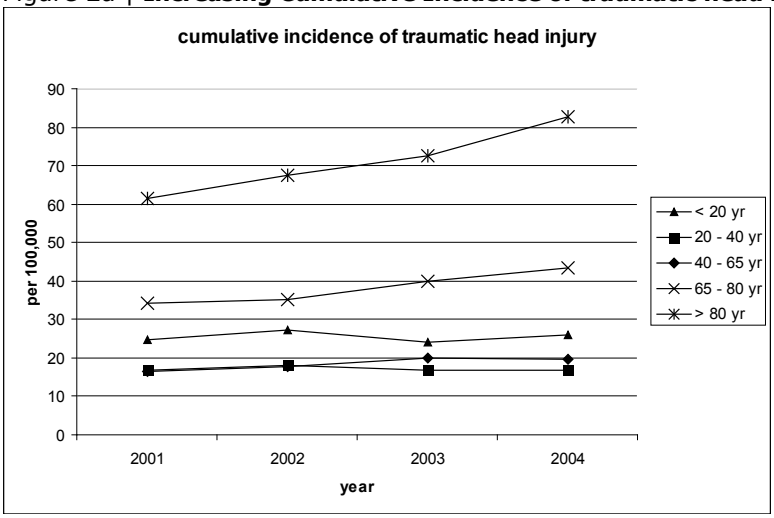
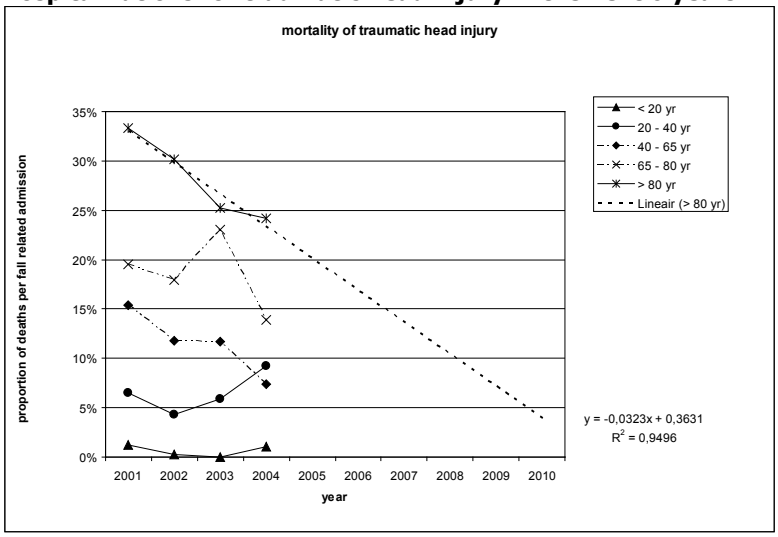


Figure 2b **| Estimate of decrease in lethality of fall related hospitalizations for traumatic head injury in the next 6 years**



DISCUSSION

This nationwide study showed an increasing trend in fall-related hospital admissions rising from 2.3 per 1000 inhabitants in 2001 to 2.7 per 1000 inhabitants in 2004, representing a risk increase of 15.8% or almost 4% per calendar year. If we assume that there will be a continuation of this linear time trend we can expect a risk of fall-related hospital admissions to up to 3.4 per 1000 persons in the year 2010. For 80+ year olds this will even be 29.4 per 1000 persons. The risk of fall-related hospital admissions especially increased in the youngest (below 20 years) and in the very old (above 99 years). Persons above 80 years persistently accounted for 31.6% of fall-related admissions. In addition to the trends in risk increase over time, we observed a decline in hospital deaths from 4.2% to 2.9%.

Age has been recognized as a strong risk factor for falls and fall related morbidity leading to hospital admission[1, 3, 16] . It is generally assumed that the number of people who fall and suffer fall-related morbidity will increase because of the increasing number of elderly people in the population[17-20]. We observed a disproportional increase in fall-related admissions in the very old relative to acute admissions in general, which implies that falls become an increasingly important cause of morbidity and health care resource utilisation with advancing age. Older persons have more fall-related problems, presumably because they are more vulnerable, as a result of decreased physiologic reserve, more comorbidity and disability. A consequence of a greying population is an increase in morbidity, e.g. cardiac and neurological conditions with a subsequent need for more acute hospitalisations partially due to an increased risk of injurious falls in the oldest old.

As in our study, age specific incidence rates have shown to increase substantially in most Western populations in recent decades[13, 17, 19-21]. A Finnish study by Kannus et al. found that the prevalence of fall-related morbidity among older persons is rising at a rate that cannot be explained merely by demographic changes[2]. These observations suggest the influence of changes in risk factors for fall-related hospital admissions other than age. Women, who are at a higher risk of osteoporosis[9], could potentially explain the higher risk of fall-related admissions. However, there was no overt sex-dependent time trend. Other risk factors that may play a role in the growing risk of fall-related hospital admissions, because of their influence on fall risk or frailty, include comedication and comorbidity especially if involving the lower extremities[22].

Our data also suggest that the risk increase is not entirely specific for fall-related problems, except in the very old. Similar trends occurred for other types of acute admissions which comprise a wide range of, probably age dependent, diagnoses. We are not aware of any changes in hospitalisation policy and therefore we can merely conclude that there is a general trend towards more morbidity in the community.

Almost 4% of the fall-related hospitalisations had a fatal outcome, mostly due

to traumatic brain injury. In a recent Finnish study, the number of fall-induced severe head injuries showed an alarming rise at a rate that could not be explained merely by the demographic changes of the population[23]. In our data, we could confirm this trend over a much shorter period especially in aged persons (> 65 years), with an increase of 34.4% in persons above 80 years. In hospital survival following such an injury increased however, but we had no information about late (out of hospital) mortality.

A limitation of this study is that the proportion of fall-related hospitalisations we found is probably an underestimation of the real situation. Although we used a nation-wide registry with complete coverage of all hospital admissions, which is independent of reimbursement in the Netherlands, we have potential misclassification because not all fall-events may be recognized or mentioned in discharge letters and coded accordingly. However, by using the above-described coding system, the assessment of fall-related hospitalisations is unbiased because the code clerks were not coding as part of a study with a pre-defined hypothesis.

In addition, falls resulting in instant death before reaching the hospital, and patients with non-serious injuries who were not hospitalized, will have been missed. These inaccuracies may have led to a slight underestimation of the incidence rate. Furthermore, we were unable to adjust for co-morbidity, use of co-medication or multiple hospitalizations per patient.

In comparison with other studies[24] we may have low estimates because we did not include admissions in which the fall event occurred during the admission but rather focussed on true incident cases.

In conclusion, in the period of 2001 -2004 the increase in fall-related acute hospitalisations exceeds the annual growth of the greying population. Despite a general decrease over the years in duration of hospital stays, this is less the case with fall related hospitalisations. Besides, there are indications of an increase in disabled persons as a result of diminishing mortality, with a greater pressure on available beds and costs. As a consequence, in the future more hospital beds are needed for fall-related admissions. It can be estimated that as a result of decreasing in-hospital mortality there will be increasing need for other institutional care (e.g. nursing homes) for this category of patients.

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03

Chapter 3 | **Determinants and risk factors of falls**

ABSTRACT

Objective:
Falls in elderly are common and often serious. We studied the association between determinants – among which drug use - and falls in elderly.

Design:
Population-based cross-sectional study

Setting:
The Rotterdam Study.

Participants:
6928 individuals aged 55 years and older.

Measurements:
The history of falls in the preceding year in community-dwelling elderly was taken as outcome measure. Medication use was determined with an interviewer-administered questionnaire with verification of use.

Results:
1,144 persons (16.5%) experienced one or more falls in the preceding year. The frequency of falls strongly increased with age. Falls were more common in women than in men. Fall risk increased with increasing disability, presence of locomotor problems, such as joint complaints, use of a walking aid and fracture history, functional restrictions, psychosocial limitations and co-morbid conditions. Falling was also associated with diseases, such as Parkinson's disease or history of stroke. The risk of falling increased significantly with the number of drugs used per day (p for trend < 0.0001).

Conclusions:
Falls in elderly are common and often accompanied with considerable morbidity and mortality. Falling is a multifactorial problem. This study is hypothesis generating and may serve as a starting point for further etiologic research.

INTRODUCTION

Falls are among the most common and serious problems in elderly persons. Falls generally result from an interaction of multiple and diverse risk factors and situations. The incidence of falls as well as the severity of fall-related complications rises steeply beyond the age of 60 years. Among all community dwelling persons of 65 years of age and over, 30-40% have at least one fall each year and the incidence increases with age, affecting women more often than men[1-3]. Over 50% of the cases experience a fall incident more than once a year[4]. Most information on falling in the literature is obtained by means of self-reporting, which implies an underestimation of the real problem. The incidence of falls in nursing homes and hospitals is almost three times as high as in the community[1]. Fall-related morbidity and mortality increases dramatically with advancing age. Unintentional injuries are the fifth leading cause of death in elderly persons, and falls are responsible for two-thirds of the deaths resulting from unintentional injuries[1].

As a result of age-related physiological decline (increased vulnerability and delayed recovery) in combination with a high prevalence of, often pre-existing, co-morbid diseases, the consequences of falling are more serious with advancing age. On a yearly basis, 420 per 100,000 inhabitants are hospitalized as a result of a fall-incident, 140 of them having a femur fracture. It is expected that the number of femur fractures will increase to 400 per 100,000 inhabitants in the year 2030. Half of all admissions to homes for elderly and nursing homes are fall related. Besides physical limitations, falls are associated as well with other negative consequences such as "fear of falling" with a paradoxically increased fall risk and social isolation[5].

Risk factors for falling can be classified as either intrinsic or extrinsic, of which the latter is most accessible to targeted interventions. The association between fall-incidents and the use of medication has been investigated in several studies, but even in large meta-analyses conclusions were drawn with caution[6, 7]. Additionally, previous studies showed a strong relationship between fall-incidents and polypharmacy, i.e. the use of four or more medications[1, 8]. Probably, synergism plays a role in the observed associations with fall risk. Several studies have shown that the risk of falling increases dramatically as the number of risk factors increases[1]. In order to be able to reduce the fall risk in older individuals and in the elderly population as a whole, identification of all modifiable risk factors for falling is necessary. Intervention studies have shown that such an approach leads to a reduction of fall incidents[9].

To gain more insight into the frequency of occurrence of falls in a community based population and into the influence of large variety of potential risk factors, we performed a cross-sectional hypothesis generating survey within the Rotterdam study with a special interest in the risk of drug-associated falling.

METHODS

This cross-sectional analysis was part of the Rotterdam Study, a population-based prospective cohort study of 7,983 people aged ≥ 55 years (mean age 70.6, range 55 – 106.2)[10]. Baseline examination was performed between 1990 and 1993.

The aim of the Rotterdam Study is to investigate determinants of disease occurrence and progression in the elderly. Fields of interest for the Rotterdam Study are conditions which are strongly associated with the morbidity and mortality in the elderly. The aims of the Rotterdam Study are: (1) To investigate, by means of epidemiologic, clinical and basic research, the determinants of diseases in order to assess their etiologic significance. (2) To investigate potentially modifiable determinants in order to be able to develop preventive strategies by providing specific recommendations for intervention studies. The Rotterdam Study focuses on four primary areas of research: neurogeriatric diseases, cardiovascular diseases, locomotor diseases and ophthalmologic diseases.

During baseline interviews and subsequent physical and laboratory examinations, information was gathered on several relevant parameters such as age, gender, functional performance[11, 12] and blood pressure. Also, a full assessment of medical and psychiatric co-morbidity was performed. Systolic and diastolic blood pressures were measured in a recumbent position, followed by subsequent measurements in an upright position after one to five minutes of standing. Orthostatic hypotension was defined as a systolic drop of ≥ 20 mm Hg and a diastolic drop of ≥ 10 mm Hg[13]. The Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands, approved the study.

Study population

The study population comprised all participants of the Rotterdam study with at least one year of medication history. On the basis of questionnaires, we excluded people with dementia (n=482)[14] or unknown mental state (n=455) and those who could not give an adequate fall history at baseline (n=118).

Exposure definition

In the research area, there are 7 fully computerized pharmacies that are linked to one network. During the study, all participants filled their prescriptions in one of these 7 pharmacies. Data on all dispensed drugs were available in computerized format on a day-to-day basis since 1 January 1991. The data include the date of prescribing, the total number of drug units per prescription, the prescribed daily number of units, product name, and the Anatomical Therapeutic Chemical (ATC) code[15]. By doing this, more insight is gained into the prevalence of polypharmacy and possible drug interactions. Besides this, medication use was also determined at baseline by interview and verified by a physician. Although there is no uniform and formally accepted definition of polypharmacy, we defined it, in accordance with the literature, as the use of four or more medications[6, 7, 16, 17].

Outcome definition

As the primary outcome we studied falling. A faller was defined as an individual with a history of one or more falls, without precipitating trauma (e.g. car accident or sports injury), in the 12 months preceding the baseline interview. Falling was assessed by structured personal interviews by trained research nurses.

ANALYSIS

The association between risk factors and falling under everyday circumstances was analysed by performing an age- and gender adjusted logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). All analyses were performed using SPSS version 11.0.1 (SPSS Inc. Chicago, Illinois, 2001).

RESULTS

A total of 6,928 subjects (87%) were eligible for our study, of whom 1,144 (16.5%) experienced one or more falls in the previous year. Characteristics of fallers and non-fallers are shown in table 1. We found a higher fall risk in women and a progressive increase in the frequency of falls with advancing age (figure 1). In all further analyses of factors, which were considered a potential determinant of falls, we adjusted consequently for age and gender.

Table 1 | **Characteristics of fallers and non-fallers**

Description	Without fall (n = 5784)	%	With fall (n = 1144)	%	OR	(95% CI)
Gender						
Male	2522	43.6%	276	24.1%	1.0	Ref.
Female	3262	56.4%	868	75.9%	2.4	(2.1 - 2.8)
Age category (years)						
55-59	1042	18.0%	126	11.0%	1.0	Ref.
60-64	1260	21.8%	154	13.5%	1.0	(0.8 - 1.3)
65-69	1181	20.4%	156	13.6%	1.1	(0.9 - 1.4)
70-74	960	16.6%	209	18.3%	1.8	(1.4 - 2.3)
75-79	673	11.6%	209	18.3%	2.6	(2.0 - 3.3)
80-84	407	7.0%	134	11.7%	2.7	(2.1 - 3.6)
85-89	190	3.3%	104	9.1%	4.5	(3.3 - 6.1)
90-94	63	1.1%	45	3.9%	5.9	(3.9 - 9.0)
> 95	8	0.1%	7	0.6%	7.2	(2.6 - 20.3)

Social factors (appendix table 2)

Persons living alone, or those staying indoors because of poor health showed an increased fall risk. The risk of falling was lower in persons with a positive rating of their general health than in members of the same age and gender who had a negative rating. A lower rating of the own health situation was inversely associated with an increased fall risk. Increasing functional disability was progressively

associated with a higher fall risk. This was also the case in persons with impaired manual skills and those having problems with communication.

Functional factors (appendix table 2 and 3)
Visual impairment was not unequivocally associated with an increased fall risk. The presence, rather than the duration of joint complaints was associated with an increased fall risk. Accordingly, complaints of osteoarthritis and rheumatoid arthritis showed to be associated with falls, as was the use of walking aids, especially the walking frame. A positive fracture history, in particular a fracture of the lower body, as well as a history of hip surgery was associated with falling.

Regarding the functioning of the locomotor apparatus it appeared that impairments with squatting, bending, crossing the legs, standing up and reaching for toes were associated with an increased fall risk. A deviant walking pattern (walking round chair and gait) or postural abnormality were in increasing seriousness progressively associated with an increased fall risk.

Neurological factors (appendix table 4)
The presence of signs of Parkinson's disease, such as hypo- and/or bradykinesia, alterations of facial expression and movement disorders, as well as signs and symptoms of stroke (plantar reflex and hemiparesis, and dysarthria or aphasia) was associated with an increased fall risk. Although the prevalence of these risk factors is low, risk increasing effects are high.

Dizziness, on postural change and episodically, was associated with an increased fall risk, as was the case with symptoms of fits, seizures or epilepsy. Other factors associated with an increased fall risk were tremor, loss of consciousness, serious head trauma, or a concussion, and episodes where contact with the surroundings was lost.

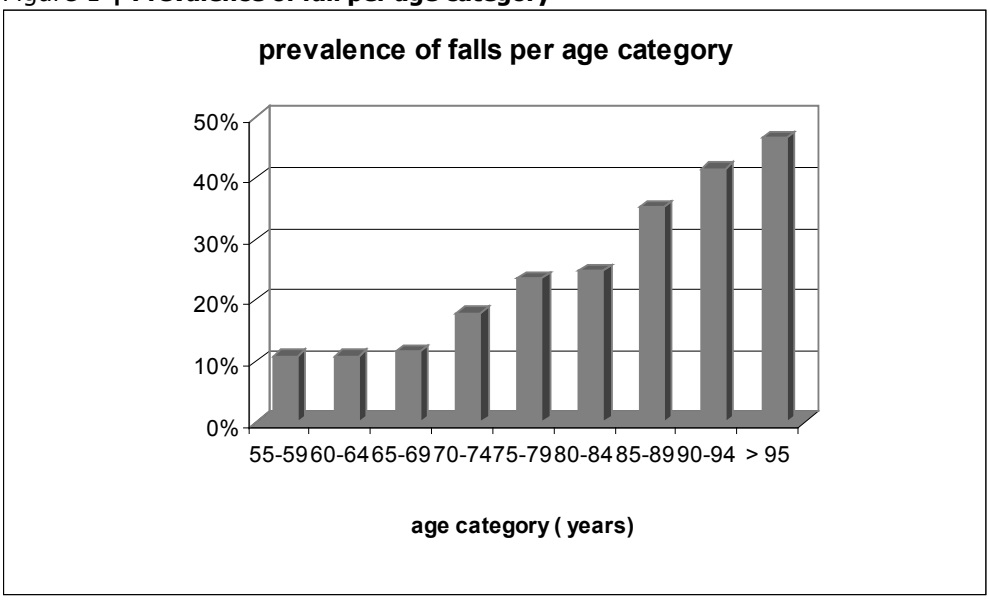
Psychiatric factors (appendix table 4)
Presence, as well as the progression of memory complaints was associated with an increased fall risk. Mood disorders, especially depressive, but also common health complaints, visit to doctors and history of serious life events during the last five years were associated with a higher fall risk.

Demographic and life-style factors
Socio-economic factors, such as the level of education, or income were not associated with fall risk. Of the life-style factors low energy intake was associated with a mildly increased fall risk. It concerns large numbers and a marginal effect. No influence on fall risk was found by smoking and use of alcohol.

Other diseases and conditions (appendix table 2)
Diseases, in the past or active at baseline, which were associated with an increased fall risk included diabetes mellitus, hypertension, one or several operations, hyponatremia, hypovolemia, (hypostatic) edema and orthostatic hypotension, occurring after 4 or 5 minutes standing. Heart rhythm disorders, under-, or overweight and radiologic signs of osteoporosis were not associated with an increased fall risk.

In the appendix a summary of the above mentioned risk factors is shown in table 2 to 4.

Figure 1 **| Prevalence of fall per age category**



Pharmacotherapy and falls
The risk of falling increased significantly with the number of drugs used per day (p for trend < 0.0001), which is shown in figure 2. Fall risk increased by 10% per added drug. In the appendix (table 5) a summary is shown of all medications, which have a significant association with falling. In this summary, we used the "Anatomical Therapeutical Chemical (ATC) classification system", at a three-digit level, as well as a five-digit level. For a further elaboration of the influence of drugs on fall risk, a distinction was made between drugs with a considerable effect (i.e. strongly increased risk) and drugs with highly prevalent use (i.e. probably strong population related influence).

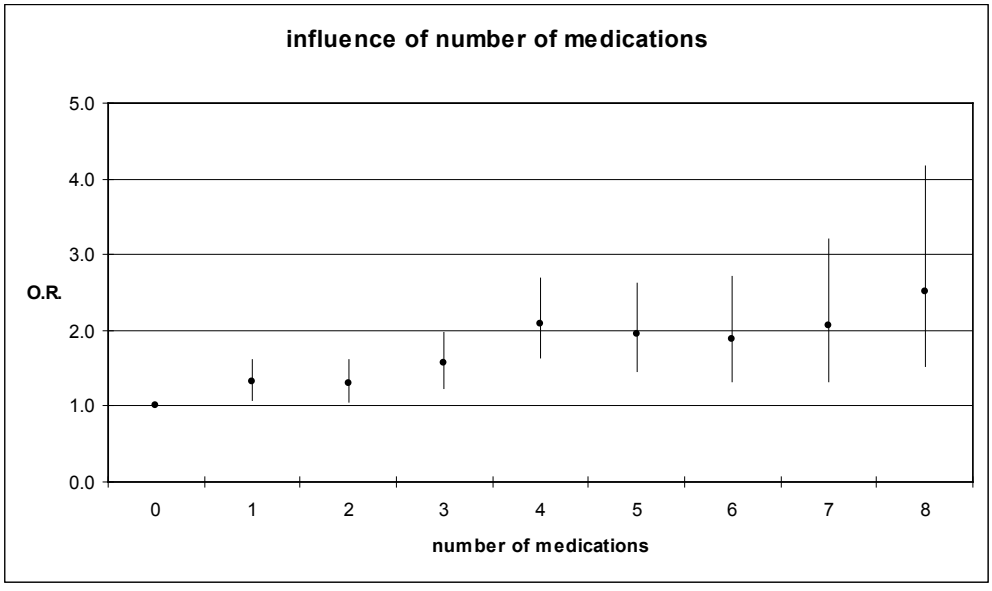
Within the category of drugs for the digestive tract we observed an association between falls and laxatives, orally used and enemas, propulsives and anti-obesity

preparations. The underlying causal factor may be a diminished mobility as an explanation for the use of these drugs. On the other hand, an association was found between falls and the use of antispasmodics and anticholinergic agents. The possible explanation for this finding is twofold. Adverse effects of these drugs are orthostatic hypotension and concentration difficulties. Both explanations are relevant considerations in an elderly population and are associated with an increased fall risk.

Diuretic use was associated with an increased fall risk. In the 5-digit ATC-classification the effect was found in particular with the use of thiazides rather than with loop diuretics. A probable explanation for this effect is the development of dehydration, or hypovolemia, resulting in orthostatic hypotension. Alternatively, the coinciding phenomena of hyponatremia (e.g confusion) may have caused the increase in fall risk.

In the 3-digit ATC-classification an association was found between gynaecologicals and an increased fall risk. It concerned a small number of users (n=10) containing a residual group of drugs. In the 5-digit ATC-classification the association was found with prolactine inhibitors in particular, which have a low prevalence, but a large effect.

Figure 2 **| Risk of falling associated with drug use**



Systemic antibiotics as well as the topical ophthalmologic ones, were associated with an increased fall risk. A possible explanation may be the underlying infectious disease. In geriatric medicine, a fall incident can be the first indication of, for example, an underlying infection. This is known as the so-called "premonitory fall".

Analgesics (anilides and NSAIDs) showed a minor twenty to thirty percent increased fall risk. The prevalence of use of these drugs is high, however, resulting in a considerable influence on the total number of falls. The cause may be related to the underlying co-morbidity, such as, for example, osteoarthritis.

Drugs used for the treatment of Parkinson's disease are not prescribed frequently, but show a serious association with falls in the respective drug-classes. It is likely that the condition itself is associated with an increased fall risk. The influence of the used drugs can be explained by means of orthostatic hypotension (almost all antiparkinsonian drugs) and central cerebral effects (anticholinergics). Comparable mechanisms may play a role with the pharmacologic treatment of seizure disorders.
The fall risk increasing effects of benzodiazepines are extensively dealt with in the literature[1, 7, 18, 19], and were confirmed in our study. Besides the considerable effects on fall risk, the high prevalence of use of these drugs emphasizes their importance in the fall risk in the elderly population.

DISCUSSION

In this cross-sectional analysis, we examined risk factors for falling. Falling occurred in 16.5% of the population. Although high, this frequency is substantially lower than previously reported in the "Longitudinal Aging Study Amsterdam" (LASA) and a study by Stalenhoef et.al, who both reported falls in 33% of the population[20, 21]. The low frequency in our study is probably caused by the younger age of our population (55+ versus 65+ and 70+).

We observed an increasing prevalence with increasing age. This association is probably explained by underlying health problems and functionality disorders which are strongly age dependent and increase fall risk. Other studies showed that after adjustment for other factors, age was no longer associated with falling[22-24].

The risk of falling was higher for women than for men. Similar to age, gender related risk factors for falling probably explain part of this association. However, so far scientific reports have shown conflicting results. After adjustment for confounding factors, risk estimates for women compared to men varied from no risk increase to a strongly elevated risk[22, 23, 25].

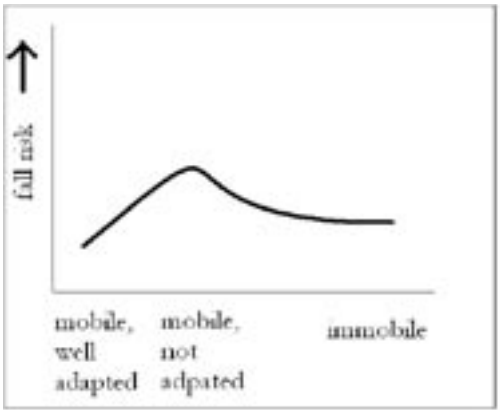
In view of the strong age and sex dependent fall risk these two factors were added to all statistical models to help interpreting the role of other variables as risk factors. After adjustment for age and gender functional impairment and reduced mobility (intrinsic factors) were the most important intrinsic determinants of falling. The observed influence of intrinsic factors is in line with previous studies[18].

Decreased mobility and decreased capacity to adapt, which can be identified by simple physical examination (e.g. squatting, bending, reaching toes and to walk around a seat) have a curvilinear association with fall risk (figure 3). In this, mobility determines the exposure to (external) risk factors for falling. Good

mobility coincides with a relatively high exposure, while in case of immobility there is hardly any exposure to risk factors. For example, persons who use a walking aid fall more frequently than persons in a wheel chair. The capacity to adapt on the other hand determines if the fall risk is indeed increased by risk factors. In case of good mobility the fall risk will be minimal if there is adequate capacity to adapt, while the risk will be increased if the capacity to adapt is poor. An additional problem in the elderly is that they are more susceptible to (severe) injury as a consequence of a fall than younger persons.

Because of the large number of participants in the Rotterdam Study, we could also show associations between falling and exposure to certain rare diseases such as Parkinson's disease or past CVA, which can exert important effects possibly mediated through functional impairment, decreased mobility and decreased capacity to adapt.

Figure 3 **| Fall risk associated level of mobility and capacity to adapt**



As part of external (modifiable) risk factors, we found that polypharmacy was associated with a progressive increase of the fall risk independent of age and gender. It is likely that the involved agent and possibly the underlying co-morbidity is the driving force in determining the fall risk[26].

It is generally acknowledged that falling is a multifactorial problem. The notion that falling has a multifactorial cause is supported by the large number of risk factors revealed in this study. The uniqueness of the Rotterdam study is the extensive and elaborate assessment of health status by physical examination and (health) questionnaires, supplemented with detailed information on drug use from pharmacy dispensing records. Hence our study provides an extensive overview of circumstances which can facilitate falling. Recently, the "American Geriatrics Society, the British Geriatrics Society, and the American Academy of Orthopaedic Surgeons Panel on Falls Prevention" as well as the "Dutch Geriatrics Society" ("De Nederlandse Vereniging voor Klinische Geriatrie (NVKG))" in collaboration

with the Dutch "Kwaliteitsinstituut voor de Gezondheidszorg CBO" published their guidelines on falls prevention[1, 18]. In these guidelines, detailed attention has been given to risk factors for falls. Our findings confirm the suggested influence of multiple risk factors referred to in the guidelines.

Since age and gender are the most relevant confounders in studies on determinants of falling, because of their association with comorbidity, we always adjusted for age and gender. Methodological limitations of our study do not allow us to judge the influence of "confounding by indication", which may play a role in the analyses on the role of pharmaceutical agents. Although we did have data on prevalent morbidity we did not have information on the precise indication for drug prescriptions. Hence, it could be the underlying disease rather than the agent itself which is the causal factor.

Although the cross-sectional design, because of the absence of a time-sequence relationship, is not suitable for identifying causal relationships between risk factors and falls, it can be useful to demonstrate significant associations. Therefore, this study is hypothesis generating and warrants further elaboration of the risk factors in a predictive model.

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APPENDIX

Note: For readability of table reference group is omitted; factors are always compared to normal situation or non presence of impairment or disability

Table 2 | **Influence of multiple determinants on fall risk**

Description	without fall (n = 5784) n	%	with fall (n = 1144) n	%	OR	(95% CI)
General condition / Social factors						
Living not alone	4158	72%	581	51%	0.69	(0.6 - 0.8)
Living in service flat or nursing home	818	14%	345	30%	1.32	(1.1 - 1.6)
General health compared to members of your age group: the same	2144	37%	462	40%	0.67	(0.6 - 0.8)
General health compared to members of your age group: worse	491	8%	173	15%	1.65	(1.3 - 2.0)
Staying indoors, most of time in wheelchair	50	1%	42	4%	3.06	(2.0 - 4.7)
Staying indoors indoors because of health	242	4%	169	15%	2.17	(1.7 - 2.7)
One health complaint	1990	34%	432	38%	1.28	(1.1 - 1.5)
More than one health complaints	665	11%	225	20%	1.91	(1.6 - 2.3)
Visited a specialist last year	445	8%	111	10%	1.41	(1.1 - 1.8)
Functional factors						
Mild functional impairment	815	14%	272	24%	2.00	(1.7 - 2.4)
Moderate functional impairment	254	4%	145	13%	2.94	(2.3 - 3.8)
Severe functional impairment	141	2%	132	12%	4.60	(3.4 - 6.2)
Manual skill impaired (difficulty handling a pencil)	52	1%	34	3%	2.14	(1.3 - 3.4)
Problems with communication	56	1%	25	2%	1.86	(1.1 - 3.1)
Visual acuity, best corrected < 0.64	1039	18%	334	29%	1.20	(1.0 - 1.4)
Psychiatric factors						
Memory complaints	1007	17%	299	26%	1.48	(1.3 - 1.7)
Progressive memory complaints	221	4%	93	8%	1.98	(1.5 - 2.6)
Serious life events during last five years	3830	66%	855	75%	1.47	(1.3 - 1.7)
MMSE score<= 24	307	5%	115	10%	1.29	(1.0 - 1.6)
Periods of depression	1769	31%	435	38%	1.30	(1.1 - 1.5)
Treatment by psychiatrist because of depression	282	5%	81	7%	1.58	(1.2 - 2.1)
Comorbidity						
History of hyperthyroidism	209	4%	65	6%	1.37	(1.0 - 1.8)
History of one or several operations	4605	80%	971	85%	1.32	(1.1 - 1.6)
History of hypertension	804	14%	214	19%	1.26	(1.1 - 1.5)
Diabetes mellitus	328	6%	96	8%	1.29	(1.0 - 1.6)
Hyponatremia Na < 135 mmol	160	3%	55	5%	1.39	(1.0 - 1.9)
Hypovolemia (ureum/creatinin ratio > 0.1)	502	9%	170	15%	1.28	(1.0 - 1.6)
Presence of edema	367	6%	136	12%	1.29	(1.0 - 1.6)
Orthostatic hypotension (RR change > 20/10) after 4'	43	1%	22	2%	2.64	(1.2 - 5.7)
Orthostatic hypotension (RR change > 20/10) after 5'	44	1%	22	2%	3.46	(1.6 - 7.6)

Table 3 | **Influence of mobility factors on fall risk**

Description		without fall (n = 5784) n	%	with fall (n = 1144) n	%	OR	(95% CI)
Slow or stiff movement		1177	20%	419	37%	1.85	(1.6 - 2.1)
Joint complaints last month		2789	48%	701	61%	1.52	(1.3 - 1.7)
Duration present joint complaints							
	Less than 1month	167	3%	40	3%	1.48	(1.0 - 2.1)
	3 to 6 months	161	3%	50	4%	1.85	(1.3 - 2.6)
	6 Months to 1year	229	4%	54	5%	1.42	(1.0 - 2.0)
	1 to 5 years	895	15%	220	19%	1.49	(1.2 - 1.8)
	More than 5years	1098	19%	299	26%	1.70	(1.4 - 2.0)
Osteoarthritis last month		935	16%	260	23%	1.30	(1.1 - 1.5)
Rheumatoid arthritis last 5 years		76	1%	30	3%	1.67	(1.1 - 2.6)
Adaptations in or around the house		378	7%	185	16%	1.77	(1.4 - 2.2)
Morning stiffness		1791	31%	491	43%	1.49	(1.3 - 1.7)
Use of walking stick		280	5%	144	13%	1.97	(1.5 - 2.5)
Use of walking aid without wheels		16	0%	27	2%	5.44	(2.8 - 10.6)
Use of walking aid with wheels		66	1%	53	5%	2.27	(1.5 - 3.4)
Use of crutches		22	0%	13	1%	2.74	(1.3 - 5.6)
History of any fracture		708	12%	251	22%	1.79	(1.5 - 2.1)
Number of hip operations: one or more		144	2%	76	7%	1.76	(1.3 - 2.4)
Bending	Restriction knee	421	7%	131	11%	1.64	(1.3 - 2.1)
	Restriction hip	206	4%	73	6%	1.72	(1.3 - 2.3)
	Muscle weakness	186	3%	77	7%	2.18	(1.6 - 2.9)
	Impossible	69	1%	31	3%	1.97	(1.2 - 3.1)
Squatting	Pain	30	1%	15	1%	2.79	(1.5 - 5.3)
	Impossible	152	3%	67	6%	2.08	(1.5 - 2.9)
	With mild support	424	7%	134	12%	1.56	(1.2 - 2.0)
	Difficult	172	3%	67	6%	1.78	(1.3 - 2.4)
Crossing legs <20% restricted		550	10%	120	10%	1.42	(1.1 - 1.8)
Crossing legs 40 - 60% restricted		382	7%	101	9%	1.47	(1.1 - 1.9)
Unable to cross legs		145	3%	76	7%	2.37	(1.7 - 3.3)
Flexion hip 20 - 60% restricted		351	6%	111	10%	1.34	(1.1 - 1.7)
Flexion hip 60 - 80% restricted		74	1%	33	3%	1.66	(1.1 - 2.6)
Endorotation >80% restricted		54	1%	24	2%	1.89	(1.1 - 3.2)
Exorotation >80% restricted		49	1%	22	2%	1.87	(1.1 - 3.2)
Genua valgus		355	6%	122	11%	1.41	(1.1 - 1.8)
Walk Round Chair 3th Quartile		906	16%	173	15%	1.34	(1.0 - 1.7)
Walk Round Chair 4th Quartile		1018	18%	369	32%	2.03	(1.6 - 2.6)
Standing up with much difficulty		146	3%	81	7%	2.27	(1.7 - 3.1)
Standing up with pain		22	0%	13	1%	2.59	(1.3 - 5.3)
Reach to toes with some difficulty		291	5%	94	8%	1.42	(1.1 - 1.8)
Reach to toes with much difficulty		123	2%	50	4%	1.58	(1.1 - 2.3)
Unable to reach to toes		73	1%	36	3%	1.67	(1.1 - 2.6)
Gait: shuffling, small steps		181	3%	90	8%	1.92	(1.4 - 2.6)
Gait: propulsion & festination		7	0%	6	1%	4.73	(1.5 - 14.9)
Gait: other deviance		132	2%	86	8%	3.16	(2.4 - 4.3)
Posture: head/neck/arms flexed		99	2%	51	4%	1.78	(1.2 - 2.6)
Posture: kyfosis; arms/legs flexed		26	0%	22	2%	2.85	(1.6 - 5.2)
Posture: other deviance		24	0%	14	1%	3.01	(1.5 - 6.0)

Table 4 | **Influence of neurological factors on fall risk**

Description	without fall (n = 5784) n	%	with fall (n = 1144) n	%	OR	(95% CI)
Tremor						
Resting tremor	114	2%	40	3%	1.71	(1.2 - 2.5)
Position tremor doubtful	343	6%	98	9%	1.52	(1.2 - 2.0)
Position tremor present	372	6%	117	10%	1.70	(1.4 - 2.2)
Action tremor doubtful	202	3%	67	6%	1.42	(1.1 - 1.9)
Action tremor present	141	2%	55	5%	1.77	(1.3 - 2.5)
Fingertaps somewhat slowed	242	4%	93	8%	1.54	(1.2 - 2.0)
Fingertaps slowed down	76	1%	46	4%	2.24	(1.5 - 3.3)
Tone_arms raised	209	4%	66	6%	1.51	(1.1 - 2.0)
Cogwheel symptom present	78	1%	28	2%	1.62	(1.0 - 2.6)
Hypo-bradykinesia, less spontaneous movement	71	1%	35	3%	1.80	(1.2 - 2.8)
Hypo-bradykinesia, clear movement poverty /slowness	13	0%	18	2%	6.91	(3.2 - 14.7)
History of Parkinsons disease	22	0%	19	2%	3.37	(1.8 - 6.4)
History of serious head trauma or a concussion						
Once	1295	22%	312	27%	1.63	(1.4 - 1.9)
More than once	344	6%	106	9%	2.06	(1.6 - 2.6)
History of seizures or epilepsy	28	0%	13	1%	2.90	(1.5 - 5.8)
Test of Romberg positive	108	2%	59	5%	2.12	(1.5 - 3.0)
Position reflex slightly disturbed	303	5%	100	9%	1.41	(1.1 - 1.8)
No position reflex	47	1%	33	3%	2.53	(1.6 - 4.1)
Paresis, little pronation	107	2%	37	3%	1.60	(1.1 - 2.4)
Paresis, pronation & prolapse	12	0%	16	1%	7.40	(3.3 - 16.4)
Babinski	145	3%	42	4%	1.45	(1.0 - 2.1)
Dysarthria doubtful	20	0%	12	1%	2.69	(1.3 - 5.7)
Dysarthria present	10	0%	11	1%	7.08	(2.9 - 17.3)
Aphasia	3	0%	5	0%	8.27	(1.9 - 35.8)
Facial mimic, less expression	171	3%	61	5%	1.64	(1.2 - 2.2)
Facial mimic, mask face	7	0%	9	1%	7.88	(2.8 - 22.2)
Dizziness	905	16%	284	25%	1.70	(1.5 - 2.0)
History of stroke	192	3%	83	7%	1.86	(1.4 - 2.5)
History of TIA	482	8%	151	13%	1.59	(1.3 - 1.9)

Table 5a | **Influence of relevant medications on fall risk**

Medication atc - 3 code	without fall (n = 5784) n	%	with fall (n = 1144) n	%	OR	(95% CI)
Antispasmodic and anticholinergic agents and propulsives	122	2.1%	43	3.8%	1.5	(1.0 - 2.2)
Laxatives	183	3.2%	90	7.9%	1.6	(1.2 - 2.1)
Antiobesity preparations	5	0.1%	7	0.6%	7.7	(2.4 - 24.7)
Vitamins	426	7.4%	145	12.7%	1.5	(1.2 - 1.8)
Mineral supplements	95	1.6%	41	3.6%	1.7	(1.2 - 2.5)
Antianemic preparations	89	1.5%	40	3.5%	1.6	(1.1 - 2.3)
Diuretics	787	13.6%	260	22.7%	1.3	(1.1 - 1.5)
Gynaecologicals (other)	3	0.1%	7	0.6%	10.5	(2.6 - 43.3)
Antibacterials for systemic use	56	1.0%	19	1.7%	1.9	(1.1 - 3.3)
Antiinflammatory and antirheumatic products	433	7.5%	124	10.8%	1.3	(1.0 - 1.6)
Analgesics	1369	23.7%	336	29.4%	1.2	(1.1 - 1.4)
Anti-epileptics	52	0.9%	20	1.7%	1.9	(1.1 - 3.3)
Anti-Parkinson drugs	32	0.6%	24	2.1%	2.8	(1.6 - 4.9)
Psycholeptics	786	13.6%	260	22.7%	1.3	(1.1 - 1.5)
Other CNS drugs, including parasysmpathomimetics	123	2.1%	60	5.2%	1.7	(1.2 - 2.4)
Cough and cold preparations	90	1.6%	31	2.7%	1.6	(1.1 - 2.5)

Tabel 5b | **Influence of relevant medications on fall risk**

Medication atc - 5 code	**without fall (n = 5784) n**	**%**	**with fall (n = 1144) n**	**%**	**OR**	**(95% CI)**
Contact laxatives	44	0.8%	26	2.3%	1.8	(1.1 - 3.0)
Enemas	1	0.0%	5	0.4%	23.4	(2.6 - 207.8)
Central acting anti-obesity products	5	0.1%	7	0.6%	7.7	(2.4 - 24.8)
Sulphonamides urea derivatives	169	2.9%	60	5.2%	1.5	(1.1 - 2.0)
Multivitamins	44	0.8%	19	1.7%	2.0	(1.1 - 3.5)
Vitamin b complex	224	3.9%	82	7.2%	1.5	(1.1 - 2.0)
Calcium	71	1.2%	36	3.1%	1.9	(1.3 - 2.9)
Oral ferro- preparations	28	0.5%	24	2.1%	2.8	(1.6 - 5.0)
Bile acid sequestrants	8	0.1%	6	0.5%	3.8	(1.2 - 11.8)
Diuretics - sulfonamides	58	1.0%	26	2.3%	2.1	(1.3 - 3.4)
Diuretics - potassium sparing agents	31	0.5%	18	1.6%	1.9	(1.0 - 3.5)
Ergot alkaloids	7	0.1%	7	0.6%	3.3	(1.1 - 9.7)
Bioflavonoids	5	0.1%	5	0.4%	5.0	(1.4 - 17.9)
Prolactine inhibitors	3	0.1%	7	0.6%	10.5	(2.6 - 43.4)
Oxicams	26	0.4%	18	1.6%	3.1	(1.6 - 5.8)
Quinine and derivatives	65	1.1%	35	3.1%	1.8	(1.2 - 2.8)
Anilides	819	14.2%	214	18.7%	1.4	(1.1 - 1.6)
Hydantoin derivatives	18	0.3%	9	0.8%	3.0	(1.3 - 7.0)
Anticholinergic agents - tertiary amines	2	0.0%	3	0.3%	12.0	(2.0 - 73.6)
Dopa and dopa derivatives	17	0.3%	17	1.5%	3.5	(1.7 - 7.1)
Adamantane derivatives	9	0.2%	7	0.6%	3.2	(1.1 - 9.2)
MAO-inhibitors type b	8	0.1%	8	0.7%	4.6	(1.7 - 12.9)
Anxiolytics, benzodiazepine-derivatives	373	6.4%	132	11.5%	1.5	(1.2 – 1.9)
Hypnotics benzodiazepine derivatives	396	6.8%	147	12.8%	1.3	(1.0 –1.6)
Antivertiginous drugs	121	2.1%	59	5.2%	1.7	(1.2 - 2.4)
Parasympathicolytics	51	0.9%	21	1.8%	2.6	(1.5 - 4.5)
Mucolytics	68	1.2%	25	2.2%	1.8	(1.1 - 2.9)
Ocular antibiotics	5	0.1%	4	0.3%	4.7	(1.2 - 18.1)

04

Chapter 4 | **Hypovolemia as a risk factor for falling in elderly**

ABSTRACT

Background:
Falls in elderly are common, of multifactorial origin, and often serious. Although hypovolemia is a frequent clinical finding in elderly, it has not yet been recognised as an independent risk factor for falling.

Objective:
To investigate the association between hypovolemia and falls.

Design:
Population-based cross sectional study

Setting:
The Rotterdam Study.

Participants:
6928 individuals aged 55 years and older.

Measurements:
The prevalence of falls in the previous year was assessed. Medication use was determined. The presence of hypovolemia was assessed and defined as a serum urea/creatinine ratio of 0.1 or above.

Results:
1,144 persons (16.5%) experienced one or more falls. Hypovolemia was present in almost 672 (10%) and was associated with an increased risk of falling of almost 30%. Fall risk increased to 66% (OR 1.66, 95 CI 1.31 – 2.12) if no concomitant diuretics were used in persons below the age of 85 years.

Conclusions:
Hypovolemia in elderly may be an under-recognized cause of falling. Being a modifiable risk factor, it should be dealt with in programs of patient education.

INTRODUCTION

Falls are a common phenomenon in the elderly and are associated with considerable morbidity and mortality. Falls often lead to reduced functioning and to nursing home admissions. The risk of falling increases dramatically with the number of risk factors[1]. Diuretics have been proposed as a risk factor[2], possibly by hypovolemia or orthostatic hypotension[3]. Hypovolemia is a frequent clinical finding in the elderly, also in persons who do not use diuretics. Hypovolemia has not yet been recognised as an independent risk factor for falling. Therefore, we investigated the association between hypovolemia and falls in a population-based study.

METHODS

This cross-sectional analysis was part of the Rotterdam Study, a population-based prospective cohort study of 7,983 people aged ≥ 55 years[4]. Baseline examination was performed from 1990 to 1993.

Fallers were defined as individuals with a history of one or more falls in the 12 months preceding the baseline interview. We included people without dementia[5] and those who could give an adequate fall history at baseline (n=6,928). During baseline interviews and subsequent physical and laboratory examinations, information was gathered on several relevant parameters such as age, gender, functional performance[6], blood pressure, electrolytes, serum creatinine and urea. Also, a full assessment of medical and psychiatric co-morbidity was performed. Medication use was determined at baseline by interview and verified by a physician. Systolic and diastolic blood pressures were measured in a recumbent position, followed by subsequent measurements in an upright position after one to five minutes of standing. Orthostatic hypotension was defined as a systolic drop of ≥ 20 mm Hg or a diastolic drop of ≥ 10 mm Hg[7]. The presence of hypovolemia was defined as a serum urea/creatinine ratio of 0.1 or above, a generally accepted measure of volume depletion (urea (BUN) in mmol/l, creatinine in µmol/l, which is equivalent to a BUN/creatinine ratio ≥ 25, BUN and creatinine measured in mg/dl)[8, 9].

ANALYSIS

We analysed the association between risk factors and falling by means of logistic regression analysis. Co-variates associated with falls at a $p<0.05$ level adjusted for age and gender, and changing the point estimate of the association between hypovolemia and falls by more than 10%, were kept in the final model. We tested effect-modification by adding an interaction term to the regression model for the following *a priori* defined clinically relevant factors: age, use of diuretics, and presence of orthostatic hypotension. We also performed a fully adjusted multivariate analysis using the following co-factors: age, gender, alcohol use, history of diabetes, history of heart attack, history of hypertension, history of Parkinson's disease, history of stroke, history of thyroid diseases, history of

depressive episodes, disability, dizziness, gait disturbance, staying indoors because of poor health, joint complaints, memory complaints, orthostatic hypotension systolic and diastolic after 5', postural disturbance, use of ACE-inhibitors, use of beta blockers, use of calcium antagonists, use of diuretics, use of psychotropic drugs, and visual acuity.

RESULTS

A total of 6,928 subjects (87%) participated in our study, of whom 1,144 (16.5%) experienced one or more falls in the previous year. We found a substantial increase in the prevalence of falls with age (table 1). Falls were more common in women than in men. Persons living alone, or staying indoors because of poor health had a greater risk of falling. The risk of falling increased with progressive disability.

We found hypovolemia in almost 10% (n = 672) of all individuals. Hypovolemia was associated with an increased risk of falling of almost 30% compared with normovolemic persons. Independent of hypovolemia, we found an association between falls and orthostatic hypotension, but only if the blood pressure-drop occurred 4 or 5 minutes after changing to a supine position. Potential confounders other than age and gender changed the point estimate for the association between hypovolemia and falls by less than 10% and were therefore not included in the final model. We also performed a fully adjusted multivariate analysis, in which we included all known independent risk factors for falling, irrespective of the question whether they changed the point estimate. In this analysis the fall risk was 1.39 (95% CI 1.06 - 1.83).

Age was an effect modifier (p-value for interaction = 0.032). Above the age of 85 years the association between hypovolemia and falling was no longer present. In addition, concomitant use of diuretics significantly modified the association between hypovolemia and risk of falling (p-value for interaction = 0.015). The excess risk of falling in hypovolemic persons increased to 66% (OR 1.66, 95 CI 1.31 – 2.12) if no concomitant diuretics were used in persons below the age of 85 years. (n= 5,614). The combined influence of age and diuretic use is displayed in table 2. There was no statistically significant interaction between orthostatic hypotension and hypovolemia. In the absence of both diuretic use and orthostatic hypotension, the odds ratio of falling with hypovolemia was 1.54 (95% CI 1.20 - 1.98). We checked whether renal insufficiency would dilute the association between hypovolemia and risk of falling and found that the risk of falling was even higher but non-significant (OR 1.91, 95% CI 0.83 – 4.36) for subjects with hypovolemia and no diuretic use.

Table 1 | **Patient Characteristics and Risk of Falling (n= 6,928)**

Characteristic	Without fall (n = 5,784)		With fall (n = 1,144)		univariate Odds Ratio *	univariate (95% CI)	multivariate Odds Ratio $	multivariate (95% CI)
	n	%	n	%				
Age category (year)								
55-64	2,302	39.8%	280	24.5%	**1.00**	Ref	**1.00**	Ref
65-74	2,141	37.0%	365	31.9%	**1.42**	(1.20 - 1.68)	**1.29**	(1.02 - 1.64)
75-84	1,08	18.7%	343	30.0%	**2.52**	(2.11 - 3.00)	**1.82**	(1.35 - 2.45)
> 85	261	4.5%	156	13.6%	**4.31**	(3.40 - 5.46)	**2.27**	(1.06 - 4.83)
Gender								
Female	3,262	56.4%	868	75.9%	**2.43**	(2.10 - 2.81)	**2.00**	(1.55 - 2.57)
Staying indoors Because of poor health		4.2%		14.8%	**2.17**	(1.72 - 2.75)	**1.43**	(0.78 - 2.61)
Disability Index								
Not disabled	4,574	79.1%	595	52.0%	**1.00**	Ref	**1.00**	Ref
Mildly disabled	815	14.1%	272	23.8%	**2.00**	(1.69 - 2.38)	**1.46**	(1.12 - 1.91)
Moderately disabled	254	4.4%	145	12.7%	**2.94**	(2.29 - 3.76)	**1.57**	(0.91 - 2.69)
Severely disabled	141	2.4%	132	11.5%	**4.60**	(3.42 - 6.20)	**0.87**	(0.28 - 2.67)
Cardiovascular medication								
Diuretics #	787	13.6%	260	22.7%	**1.25**	(1.06 - 1.48)	**0.98**	(0.72 - 1.34)
Loop diuretics	251	4.3%	82	7.2%	**1.07**	(0.82 - 1.41)		
Non-loop diuretics	593	10.3%	203	17.7%	**1.31**	(1.09 - 1.58)		
Beta-blocking agents	837	14.5%	172	15.0%	**1.03**	(0.86 - 1.24)	**0.95**	(0.68 - 1.33)
Calcium antagonists	350	6.1%	82	7.2%	**1.06**	(0.82 - 1.37)	**1.03**	(0.67 - 1.60)
Ace-inhibitors	339	5.9%	65	5.7%	**0.98**	(0.74 - 1.30)	**0.84**	(0.51 - 1.38)
Orthostatic Hypotension ‡								
Systolic **and** diastolic drop After 5 minutes		0.8%		1.9%	**2.16**	(1.26 - 3.70)	**1.25**	(0.47 - 3.34)
Systolic **or** diastolic drop at any moment within 5 minutes		20.1%		22.8%	**0.97**	(0.83 - 1.15)		
Hypovolemia	502	8.7%	170	14.9%	**1.28**	(1.05 - 1.57)	**1.39**	(1.06 - 1.83)

* Adjusted for age & gender

\# Numbers do not add up because of overlap of use of loop / non-loop diuretics

‡ Orthostatic hypotension was defined as a systolic drop of ≥ 20 mm Hg, and/or a diastolic drop of ≥ 10 mm Hg

$ Adjusted for age, gender, alcohol use, history of diabetes, history of heart attack, history of hypertension, history of Parkinson's disease, history of stroke, history of thyroid diseases, history of depressive episodes, disability, dizziness, gait disturbance, staying indoors because of poor health, joint complaints, memory complaints, orthostatic hypotension systolic and diastolic after 5', postural disturbance, use of ACE-inhibitors, use of beta blockers, use of calcium antagonists, use of diuretics, use of psychotropic drugs, visual acuity.

DISCUSSION

Falling is a frequent problem among elderly. In several studies, it was shown that approximately 30% of all community dwelling elderly of 65 years of age and older fell at least once a year, and 15% fell at least twice, or more a year[10]. We found a lower prevalence (17%), because we included a younger population of ≥ 55 years of age. Moreover, we excluded all demented persons, who have a much higher fall frequency.

In this population-based study of 6,928 elderly, hypovolemia was an independent risk factor for falls. This association was even more evident after we restricted our analysis to elderly who did not use diuretics and were not older than 85 years. In this group, we found a 66 percent risk increase of falling for subjects with hypovolemia as compared to normovolemic subjects.

Table 2 **| The combined influence of age and diuretic use on fall risk.**

Diuretic Use	Age (years)	OR	(95% CI)
No	55-84	1,66	(1,31 - 2,12)
	≥ 85	0,91	(0,43 - 1,95)
Yes	55-84	1,07	(0,70 - 1,65)
	≥ 85	0,43	(0,18 - 1,03)

Although we can not be certain in this cross-sectional analysis that hypovolemia preceded falling, it is well known that indices of hypovolemia in elderly are stable over time[11]. Older people have a decreased ability to adapt to fluid deprivation. In addition, an age-associated decline in thirst drive has been demonstrated[12]. Because of a decrease in total body water with advancing age, an equal volume of fluid loss in young and old patients represents more severe dehydration in the elderly. In combination with the age-associated decline in thirst drive, fluid intake, and cardiovascular reflexes, hypovolemia may contribute to deficits in hemoperfusion of vital organs[13, 14]. Possibly, this mechanism by itself may lead to an increased risk of falling in hypovolemic persons. Indeed, the association between hypovolemia and falling was stronger in persons with decreased renal function, albeit non-significant. In the oldest age groups (age > 85 years) we did not find an association between hypovolemia and falling. However, in this age group, the urea/creatinine ratio may be invalid as a measure of hypovolemia because of a significant loss of muscle tissue[15].

In conclusion, hypovolemia in elderly may be an under-recognized cause of falling, especially in the absence of orthostatic hypotension and the absence of use of diuretics. Hypovolemia is a modifiable risk factor, if sufficient fluid intake is taken care of. As a prerequisite in the case of adequate patient education[16], we suggest that assessment of hypovolemia should be included in the comprehensive geriatric assessment[17, 18].

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05

Chapter 5 | **Polypharmacy and falls in the middle age and elderly population**

ABSTRACT

Objective:
Falls in elderly are common and often serious. We studied the association between multiple drug use (polypharmacy) and falls in elderly.

Design:
Population-based cross sectional study

Setting:
The Rotterdam Study.

Participants:
6928 individuals aged 55 years and older.

Measurements:
The prevalence of falls in the previous year was assessed. Medication use was determined with an interviewer-administered questionnaire with verification of use. Polypharmacy was defined as the use of 4 or more drugs per day.

Results:
The prevalence of falls strongly increased with age. Falls were more common in women than in men. Fall risk increased with increasing disability, presence of joint complaints, use of a walking aid and fracture history. The risk of falling increased significantly with the number of drugs used per day (p for trend < 0.0001). After adjustment for a large number of comorbid conditions and disability, polypharmacy remained a significant risk factor for falling. Stratification for polypharmacy with or without at least one drug, which is known to increase fall risk (notably CNS-drugs and diuretics) disclosed that only polypharmacy with at least one risk drug was associated with an increased risk of falling.

Conclusions:
Fall risk was associated with the use of polypharmacy, but only when at least one established fall risk increasing drug was part of the daily regimen.

INTRODUCTION

Falls are a common phenomenon in the elderly and are associated with considerable morbidity and mortality[1]. They often lead to reduced functioning and to nursing home admissions[2]. The risk of falling increases dramatically with the number of risk factors, such as musculo-skeletal problems, neurological diseases, psychosocial characteristics, functional dependency and drug use.

Polypharmacy, usually defined as the use of more than three or four medications, is regarded as an important risk factor for falling in the elderly[3-7]. A meta-analysis[6, 7] showed an increased fall risk in users of diuretics, anti-arrhythmics and psychotropics. However, in a large population based study it was concluded that co-morbidity, being a relevant recognized risk factor for falling in the elderly, fully explains the increased risk associated with drug use[8].

Our hypothesis was that drugs can be an independent risk factor for falling but that polypharmacy itself is not a risk factor. In our hypothesis the association between polypharmacy and falling is explained by a higher probability of receiving a risk-increasing drug with the number of drugs taken. To investigate this issue, we assessed the association between polypharmacy and falling.

METHODS

This cross-sectional analysis was part of the Rotterdam Study, a population-based prospective cohort study of 7,983 people aged ≥ 55 years (mean age 70.6, range 55 – 106.2)[9]. Baseline examination was performed between 1990 and 1993.

We excluded people with dementia (n=482)[10] or unknown mental state (n=455) and those who could not give an adequate fall history at baseline (n=118). During baseline interviews and subsequent physical and laboratory examinations, information was gathered on several relevant parameters such as age, gender, functional performance[11, 12] and blood pressure. Also, a full assessment of medical and psychiatric co-morbidity was performed. Systolic and diastolic blood pressures were measured in a recumbent position, followed by subsequent measurements in an upright position after one to five minutes of standing. Orthostatic hypotension was defined as a systolic drop of ≥ 20 mm Hg and a diastolic drop of ≥ 10 mm Hg[13]. As exposure of interest we examined the use of drugs. Medication use was determined at baseline by interview and verified by a physician. Drugs were coded according to the Anatomical Therapeutic Chemical classification (ATC) system[14]. Although there is no uniform definition of polypharmacy, we defined it, in accordance with the literature, as the use of four or more medications[3, 5-7]. Drugs associated with falling in the fully adjusted model were classified as risk drugs. As the primary outcome we studied falling. A faller was defined as an individual with a history of one or more falls, without precipitating trauma (eg. car accident or sports injury), in the 12 months preceding the baseline interview. Falling was assessed by structured personal interviews by trained research nurses.

The Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands,

approved the study.

ANALYSIS

We analysed the association between risk factors and falling by means of multivariate logistic regression analysis. We performed an adjusted multivariate analysis adding all known risk factors for falling: age, gender, alcohol use, history of diabetes mellitus, myocardial infarction, hypertension, Parkinson's disease, stroke, thyroid diseases, depressive episodes, functional performance (described as disability index), dizziness, gait disturbance, home-bound life style, joint complaints, memory complaints, orthostatic hypotension, systolic and diastolic blood pressure after 5', postural disturbance, and visual acuity. All analyses were performed using SPSS version 11.0.1 (SPSS Inc. Chicago, Illinois, 2001).

RESULTS

A total of 6,928 subjects (87%) were eligible for our study, of whom 1,144 (16.5%) experienced one or more falls in the previous year. The prevalence of falls strongly increased with age. Falls were more common in women than in men. In addition, fall risk increased with increasing disability, staying indoors because of health, joint complaints, dizziness, gait – or postural disturbance, orthostatic hypotension, history of diabetes mellitus, hypertension, Parkinson's disease, stroke, depressive episodes and presence of memory complaints (table 1). Almost 72% (n=4983) of the participants were taking at least one drug, and 20.3% (n=1407) were taking four or more drugs. The risk of falling increased significantly with the number of drugs used per day (p for trend < 0. 001) (figure 1). In the univariate analysis, 28 drugs were associated with falling and were therefore considered as potential risk drugs (table 2). After adjustment for age, gender, comorbid conditions and disability, falling remained associated with the use of central acting anti-obesity products, calcium preparations, potassium sparing diuretics, oxicams, quinine and derivatives, anilides, anxiolytics-benzodiazepine-derivatives, hypnotics-benzodiazepine derivatives. (table 2). These drugs were considered as risk drugs.

Figure 1 **| Influence of number of medications on falling**

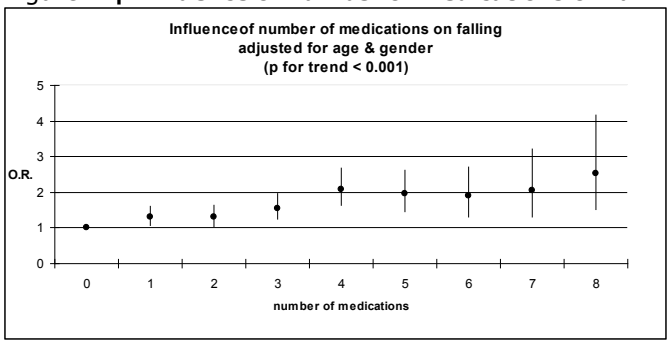


Table 1 | **Patient Characteristics and Risk of Falling (n= 6,928)**

Characteristic	(n = 5,784) without fall		(n = 1,144) with fall		Odds Ratio *	(95% CI)
	n	% (SD)	n	% (SD)		
Age category (year)						
55-64	2,302	39.8%	280	24.5%	1.00	Ref
65-74	2,141	37.0%	365	31.9%	1.42	(1.20 - 1.68)
75-84	1,080	18.7%	343	30.0%	2.52	(2.11 - 3.00)
> 85	261	4.5%	156	13.6%	4.31	(3.40 - 5.46)
Mean age (SD)	68.6	(8.6)	73.2	(9.8)		
Female gender	3,262	56.4%	868	75.9%	2.43	(2.10 - 2.81)
Staying indoors	242	4.2%	169	14.8%	2.19	(1.74 - 2.76)
Disability index						
Not disabled	4,574	79.1%	595	52.0%	1.00	Ref
Mildly disabled	815	14.1%	272	23.8%	2.02	(1.70 - 2.40)
Moderately disabled	254	4.4%	145	12.7%	2.93	(2.29 - 3.74)
Severe disabled	141	2.4%	132	11.5%	4.53	(3.38 - 6.07)
Alcohol use	2,346	40.6%	344	30.1%	0.98	(0.84 - 1.16)
Joint complaints	2,789	48.2%	701	61.3%	1.51	(1.32 - 1.73)
Visual acuity						
Both eyes intact	3,860	66.7%	608	53.1%	1.00	Ref
One eye impaired	884	15.3%	203	17.7%	1.11	(0.92 - 1.34)
Both eyes impaired	633	10.9%	236	20.6%	1.23	(0.99 - 1.52)
Dizziness	1,657	28.6%	557	48.7%	1.98	(1.74 - 2.27)
Gait disturbance	318	5.5%	181	15.8%	2.47	(1.99 - 3.07)
Postural disturbance	149	2.6%	87	7.6%	2.17	(1.62 - 2.91)
Orthostatic hypotension ‡	44	0.8%	22	1.9%	2.10	(1.23 - 3.61)
History of diabetes mellitus	328	5.7%	96	8.4%	1.29	(1.01 - 1.65)
History of heart attack	523	9.0%	101	8.8%	1.01	(0.80 - 1.28)
History of hypertension	804	13.9%	214	18.7%	1.25	(1.05 - 1.50)
History of Parkinson's disease	28	0.5%	24	2.1%	3.27	(1.84 - 5.82)
History of stroke	192	3.3%	83	7.3%	1.89	(1.43 - 2.51)
History of thyroid diseases	477	8.2%	137	12.0%	1.17	(0.95 - 1.45)
History of depressive episodes	1,769	30.6%	435	38.0%	1.30	(1.13 - 1.50)
Memory complaints	1,007	17.4%	299	26.1%	1.49	(1.28 - 1.74)

* Adjusted for age and gender

‡ Orthostatic hypotension was defined as a systolic drop of ≥ 20 mm Hg, and a diastolic drop of ≥ 10 mm Hg

The probability of using a risk drug increased proportionally with the total number of medications taken, from 25% with the use of only one prescription daily, to more than 60% when 6 ore more drugs were prescribed (figure 2). Women were using significantly more risk drugs than men (OR 2.2, 95% CI 1.9-2.4). After adjustment for comorbid conditions and disability, polypharmacy (i.e. the number of drugs) remained a significant risk factor for falling. The odds ratio's increased from 1.4 (95% CI 1.0 – 2.0), using three medications, to 1.6 (95% CI 1.1 – 2.1), using 4 or more medications (p for trend = 0.008). Considering the influence of the number of risk drugs, the odds ratio's increased with 42% per risk drug (p for trend < 0.001), from 1.3 (95% CI 1.0 – 1.6), using one risk drug to 2.5 (95% CI 1.7 – 3.6), using two risk drugs. The analysis has also been done separately for persons under and over age of 75 years, and by introducing an interaction-term in the non-stratified statistical analysis. We found no statistically significant interaction, p = 0.698. In the age group above 75 years old, there remained an association of using more than four drugs and falling although this was no longer significant because of lack of power. Respective odds ratios were 1.58 (95% CI 1.08 – 2.29) for persons 55 – 74 years old, and 1.42 (95% CI .76 – 2.67) for persons above 75 years old.

Stratification for presence or absence of at least one risk-drug, disclosed that polypharmacy is only a risk factor for falling if it includes a risk drug (p for trend =0.004; figure 3). In other words, polypharmacy itself is not a risk factor for falling, unless a risk drug is part of the drug-regimen.

Figure 2 | **Polypharmacy and use of drugs associated with falling**

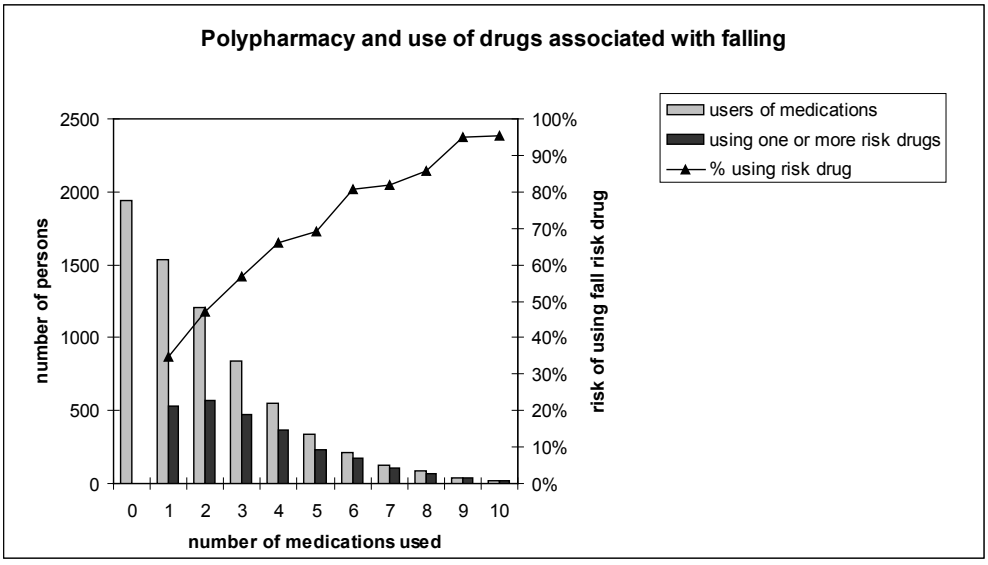


Table 2 | **Drugs associated with falling**

ATC-code	Description	cases	% cases within users	OR*	(95% CI)	OR# (adj.)	(95% CI)
A	**Alimentary tract and metabolism**						
A06AB	Contact laxatives	26	37.1%	1,8	(1,1 - 3,0)	1,3	(0,6 - 2,9)
A06AG	Enemas	5	83.3%	23,4	(2,6 - 207,8)	0,0	(0,0 - ∞)
A08AA	Central acting anti-obesity products	7	58.3%	7,7	(2,4 - 24,8)	4,9	(1,0 - 24,7)
A10BB	Sulphonamides urea derivatives	60	26.2%	1,5	(1,1 - 2,0)	1,4	(0,7 - 3,1)
A11BA	Multivitamins	19	30.2%	2	(1,1 - 3,5)	2,0	(0,9 - 4,2)
A11EA	Vitamin b complex	82	26.8%	1,5	(1,1 - 2,0)	1,2	(0,8 - 1,7)
A12AA	Calcium preparations	36	33.6%	1,9	(1,3 - 2,9)	1,9	(1,0 - 3,3)
B	**Blood and blood forming organs**						
B03AA	Oral ferro- preparations	24	46.2%	2,8	(1,6 - 5,0)	2,3	(0,8 - 6,7)
B04AD	Bile acid sequestrants	6	42.9%	3,8	(1,2 - 11,8)	2,3	(0,4 - 13,5)
C	**Cardiovascular system**						
C03BA	Diuretics - sulphonamides	26	31.0%	2,1	(1,3 - 3,4)	1,4	(0,7 - 2,9)
C03DB	Diuretics - potassium sparing agents	18	36.7%	1,9	(1,0 - 3,5)	3,6	(1,1 - 11,8)
C04AE	Ergot alkaloids	7	50.0%	3,3	(1,1 - 9,7)	2,0	(0,4 - 9,9)
C05CA	Bioflavonoids	5	50.0%	5	(1,4 - 17,9)	3,3	(0,8 - 14,6)
G	**Genito urinary system and sex hormones**						
G02CB	Prolactine inhibitors	7	70.0%	10,5	(2,6 - 43,4)	n.a.	(0,0 - 0,0)
M	**Musculo-skeletal system**						
M01AC	Oxicams	18	40.9%	3,1	(1,6 - 5,8)	3,2	(1,3 - 7,9)
M09AA	Quinine and derivatives	35	35.0%	1,8	(1,2 - 2,8)	2,2	(1,2 - 4,2)
N	**Nervous system**						
N02BE	Anilides	214	20.7%	1,4	(1,1 - 1,6)	1,3	(1,0 - 1,6)
N03AB	Hydantoin derivatives	9	33.3%	3	(1,3 - 7,0)	1,1	(0,2 - 5,8)
N04AA	Anticholinergic agents - tertiary amines	3	60.0%	12	(2,0 - 73,6)	4,2	(0,2 - 80,2)
N04BA	Dopa and dopa derivatives	17	50.0%	3,5	(1,7 - 7,1)	0,8	(0,1 - 6,7)
N04BB	Adamantane derivatives	7	43.8%	3,2	(1,1 - 9,2)	0,3	(0,0 - 4,0)
N04BD	Mao-inhibitors type b	8	50.0%	4,6	(1,7 - 12,9)	1,9	(0,2 - 20,0)
N05BA	Anxiolytics, benzodiazepine-derivatives	132	26.1%	1,5	(1,2 – 1,9)	1,3	(1,0 - 1,9)
N05CD	Hypnotics benzodiazepine derivatives	147	27.1%	1,3	(1,0 –1,6)	1,6	(1,1 - 2,1)
N07CA	Antivertiginous drugs	59	33.0%	1,7	(1,2 - 2,4)	1,0	(0,6 - 1,7)
R	**Respiratory system**						
R03BB	Parasympathicolytics	21	29.2%	2,6	(1,5 - 4,5)	1,1	(0,4 - 2,7)
R05CB	Mucolytics	25	26.9%	1,8	(1,1 - 2,9)	1,0	(0,4 - 2,3)
S	**Sensory organs**						
S01AA	Ocular antibiotics	4	44.4%	4,7	(1,2 - 18,1)	5,9	(0,9 - 37,1)

* corrected for age, gender
\# corrected for age, gender, alcohol use, history of diabetes, history of heart attack, history of hypertension, history of Parkinson's disease, history of stroke, history of thyroid diseases, history of depressive episodes, disability, dizziness, gait disturbance, staying indoors because of poor health, joint complaints, memory complaints, orthostatic hypotension systolic and diastolic after 5 minutes, postural disturbance, and visual acuity.

DISCUSSION

In this population-based study, fall risk was associated with the use of multiple drugs, but only when at least one established fall risk increasing drug was part of the daily regimen. Part of the increased risk could be explained by co-morbidity as shown in the fully adjusted model, but some drugs appeared to have a risk increasing effect, independent of co-morbidity. This is in contrast with the findings of Lawlor et al[8]. They did however study composite groups of medications only. Possible explanations for the mechanism of action are numerous, for example diuretics can cause dizziness as a consequence of orthostatic hypotension, with falling as a result. Benzodiazepine derivatives may play a role by effects on the central nervous system. However, after adjustment for comorbid conditions and disability, polypharmacy (i.e. the number of drugs) remained a significant risk factor for falling.

In the "Guideline for the Prevention of Falls in Older Persons" [2], the assessment of persons having experienced a fall focuses on modifiable risk factors. Our results support the recommendation to assess medication use, being a modifiable risk factor for falling. According to our findings, the falls-assessment should focus on identifying risk-increasing drugs rather than polypharmacy per se [1].

Limitations of the study

Being a cross-sectional study, our study may have some limitations. First, 37% of our population was younger than 65 years. This possibly explains the relative low prevalence of falling (16,5%) in comparison with other studies[2], but is consistent with the large study of Lawlor et al [8].

Because of the cross sectional nature of this study we cannot be certain that drug use preceded falling. The magnitude of this problem varies between the different observed associations. Calcium preparations for example may be prescribed as a consequence of falling to prevent fractures. However, in chronic disease situations, medications are generally prescribed on a continuous basis. Therefore it is likely that most of the drugs were already used before the assessment of falls. Third, it was not possible to control for "confounding by indication", which is likely to play a role in the association between e.g. calcium preparations or laxative use and falling. Presumably, there is a clinically relevant association between osteoporosis and falling, or between disabling conditions, causing constipation and falling.

The majority of relevant co-morbid conditions was taken into account in the analysis, however we were, for example, not able to assess the influence of

chronic pulmonary diseases on falling. Hence, some residual confounding may play a role in our study. Finally, there may be misclassification of the outcome, which was based on structured interview. The results are dependent upon recall of events, which might introduce "recall bias", as a consequence of the retrospective character of our study. In an earlier study, falls were recalled with a specificity of 91.4%, and were more likely to be remembered if an injury had occurred. The number of falls was not accurately recalled in more than a third of the persons[15]. In our analysis we therefore dichotomised on falls versus no falls. We have no reason to believe that misclassification of the outcome, if any, was differential. Moreover, the effect of under reporting of falls was minimized by exclusion of persons with an established cognitive disorder, mostly dementia [16].

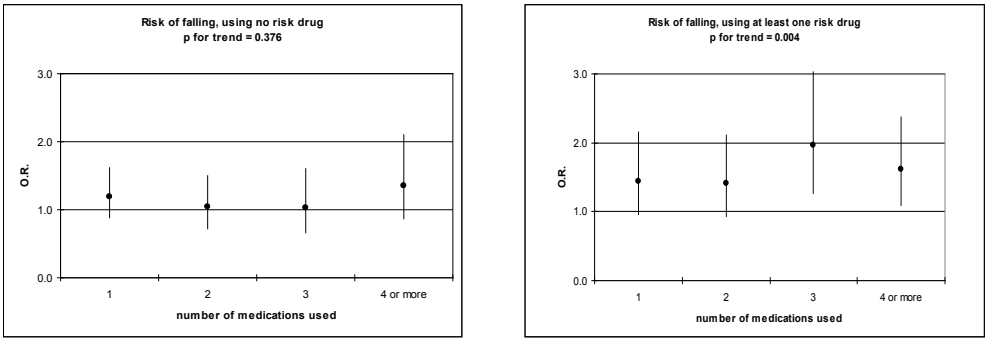
Potentially, drug interactions can play a role in falling, but the methodology of our analysis was not suitable to address that issue.

Implications

In accordance with the meta-analyses by Leipzig et al.[6, 7] we also found an association between diuretics, quinine- and derivatives, and psychotropic drugs (especially anxiolytics-benzodiazepine-derivatives and hypnotics-benzodiazepine derivatives) with falling.

The major finding of our study is that not polypharmacy itself is associated with an increased fall risk, but the contribution of identifiable risk drugs to this polypharmacy. As a consequence, this leads to a better opportunity for risk reducing interventions in a frail elderly population in whom polypharmacy is inevitable in order to control the underlying co-morbidity.

Figure 3 **| Influence of polypharmacy on falling, stratified on use of risk drugs**



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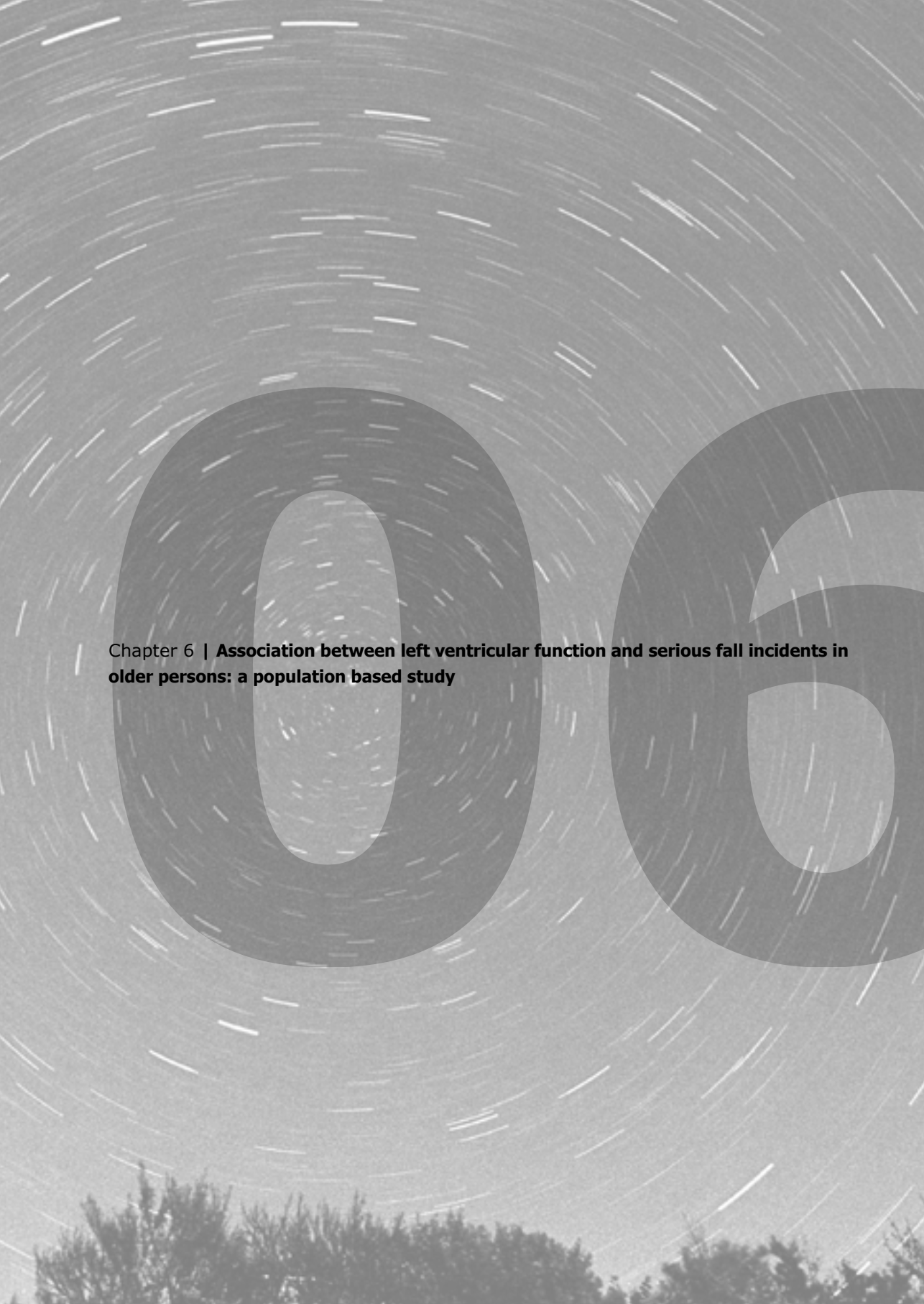

06

Chapter 6 **| Association between left ventricular function and serious fall incidents in older persons: a population based study**

ABSTRACT

Objective:
To investigate the association between left ventricular systolic function and fall incidence in older persons.

Design:
Population-based prospective cohort study

Setting:
The Rotterdam Study consists of inhabitants of 55 years or older of a suburb of Rotterdam in the Netherlands.

Main outcome measures:
The association between left ventricular systolic function and falls with serious consequences in older adults was tested in the Rotterdam Study. In 2266 participants left ventricular ejection fraction (LVEF) was measured with two-dimensional transthoracic echocardiography. Events were defined as a fall leading to hospital admission and/or a fracture during follow-up. Data were recorded between 1991 and 2002. Multivariate adjustment for confounders was performed with a Cox proportional hazards model.

Results:
The risk of a fall with serious consequences was significantly higher if LVEF was impaired. Trend analysis according to degree of LVEF was significant. The adjusted hazard ratio of a fall was 2.70 for LVEF <35% (95% CI 1.11 to 6.58) and 1.71 for LVEF 35-50% (95% CI 1.10 to 2.66).

Conclusions:
These findings suggest that poor systolic function as measured with LVEF is a risk indicator for fall incidents with serious consequences, irrespective of cardiovascular drug use, hypertension and atrial fibrillation. Although for the clinical implications of this finding further research is needed, it can be speculated that clinical benefit might be obtained if systolic function is improved in older fallers.**Introduction**

Falls and fall-induced injuries are common among older people, with often devastating results. The incidence of falls ranges from 30-50% per year depending on the population studied, with a mean injury rate of 20%[1-6]. With advancing age, besides a rising number of fall incidents, the percentage of injurious falls also goes up[7]. Furthermore, the costs per injurious fall incident increase with increasing age[8]. All in all, there is a major need for identification of modifiable fall-risk factors. And although many risk factors have been identified in the last two decades, research regarding cardiovascular risk factors is less abundant[9].

The studies present pertain to vascular risk factors, e.g., orthostatic hypotension, systolic hypertension, carotid sinus hypersensitivity and vasovagal collapse[10]. Besides a recent cohort study by our research group, in which echocardiographic abnormalities as fall-risk factors in geriatric outpatients were addressed, to our knowledge there are no data regarding structural cardiac abnormalities as possible risk factor for falls[11]. This is remarkable, since structural cardiac abnormalities are undisputed risk factors for syncope[12, 13] and older persons suffering from syncope will present with a fall in approximately 50% of cases, mainly because of amnesia for the temporarily loss of consciousness[14]. Syncope, or falls, will occur when circulatory demands outweigh the impaired ability of the heart to increase its output. It is thought that in this situation a transient shortage of cerebral perfusion occurs, resulting in a fall or syncope[12].

Since so little is known about the association between impaired cardiac function and fall incidents, we tested this in a population-based cohort study of persons of 55 years and older, in which we prospectively assessed the association between poor cardiac function and serious fall incidents.

METHODS

Setting

The present study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of and risk factors for chronic diseases in older adults. Objectives and methods of the Rotterdam Study have been described elsewhere[15]. In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older and had lived in the district for at least 1 year, were invited to participate in the study. Of these 10275 eligible persons, 7983 (78%) participated. Participants gave informed consent and permission to retrieve information from treating physicians. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, The Netherlands, approved the study.

Study population

Baseline data were collected from 1990 until 1993. A trained interviewer visited all subjects at home and collected information using a computerized questionnaire. The obtained information included current health status, medical history, history of falls and drug use. Subsequently, participants came to the research centre for several measurements. In addition, a two-dimensional transthoracic echocardiography was performed in a random sample of participants (n=2823). The presented results are based on the 2266 participants of whom data regarding echocardiography were deemed of sufficient quality to reliably measure left ventricular dimensions. Persons in whom M-mode registrations were unsuccessful were more likely to be older, to have a higher body mass index and to use medication for chronic obstructive pulmonary disease. Cardiovascular disease and diabetes were also

more common in participants with an inadequate echocardiographic window[16].

Cofactors

For the current analysis, the following risk factors for falls were assessed as potential confounders: age, gender, body mass index, a history of diabetes mellitus, hypertension and atrial fibrillation, and cardiovascular drug use.

Medication use was gathered via a linked network, including 7 fully computerized pharmacies of the area[17]. Use at the index date was assessed for all antihypertensives (diuretics, beta-blockers, alpha-blockers, centrally acting antihypertensives, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers), anti-arrhythmics, nitrates and other vasodilators, digoxin and beta-blocker eye drops. The data of fall or fracture occurrence was defined as the index date. We defined hypertension as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg, or the use of antihypertensive medication for the indication of hypertension. Diabetes mellitus was defined as the use of blood glucose lowering medication or a random or post-load serum glucose level ≥ 11.1 mmol/l[18]. Height and weight were measured with participants wearing light clothes and without shoes. Body mass index (BMI), was defined as weight divided by height squared (kg/m^2).

Echocardiography interpretation and measurements

Echocardiography was performed with the participant in the partial left decubitus position. A Toshiba SSH-60A was used for all examinations (Nasuworks, Otawara, Japan). Two-dimensional imaging using parasternal long-axis views was performed to aid M-mode studies. Measurements were made according to the recommendations of the American Society of Echocardiography using a leading edge to leading edge convention. Left ventricular internal dimension was measured at end diastole (LVED), as defined by the onset of the QRS complex and at end systole (LVES), as determined at the nadir of septal motion. Left ventricular ejection fraction (LVEF) was calculated using the simplified method of Quinones et al[19].

Follow-up procedure

As the primary outcome we studied a fall leading to hospital admission or diagnosis of a fracture. Follow-up started at the baseline examination and for the present study lasted until January 2002. Information on fatal and non-fatal endpoints for the participants enlisted was obtained from a computerized reporting system for general practitioners (LMR). These data cover approximately 80% of the study sample. For participants who were not covered in this system, research physicians performed annual checks on the complete medical records of all general practitioners in the Rotterdam Study.

Two research physicians independently coded all fractures that occurred during the study period using the International Classification of Diseases, 10^{th} revision

(ICD-10)[20]. This was also done for hospital admissions due to a fall incident. A medical expert in the field who was unaware of the patients' history and medication use reviewed all coded events for a final classification. Definition of an endpoint was either a fall leading to hospital admission or an incident fracture. Vertebral fractures, pathological and post-procedural fractures were excluded from the case definition.

Statistical analysis

Baseline differences between the subgroups with and without impaired LVEF were tested using an independent t-test for continuous variables, and a chi-square test for dichotomous variables.

Cox's proportional hazards analysis was used to estimate the crude and adjusted relative risks of a serious fall incident associated with abnormal left ventricular function. In case of occurrence of death before occurrence of the event the participant was censored in the analysis. Participants with normal left ventricular function, defined as LVEF >50%, were taken as the reference group. Furthermore, abnormal LVEF was divided in participants with an LVEF between 35% and 50% and participants with a LVEF <35%. Both categorical analysis and trend analysis were performed. To adjust for possible confounders, cofactors were included one-by-one in the age- and gender-adjusted model. Cofactors that changed the hazard ratio of a serious fall incident according to LVEF by more than 5% or that were biologically plausible were maintained in the final model. For the assessment of cardiovascular drug use as a potential confounder, a time-varying-exposure analysis was performed, using occurrence of the defined outcome as the index date. All statistical analyses were performed using SPSS software (version 10.1, SPSS Inc., Chicago, IL, USA).

Table 1 **| Baseline characteristics, overall and divided for LVEF >/< 35% (N=2266)**

Characteristic	All (n=2266)	%/SD	LVEF >35% (n=2232)	%/SD	LVEF <35% (n=27)	%/SD	P-value
Age, SD	65.1	7.3	65.1	7.3	67.2	6.1	0.26
Gender, female, %	1219	53.8	1211	54.3	7	25.9	0.002
At least 1 fall, %	249	11	245	11.0	1	3.7	0.22
>1 fall, %	21	0.9	21	0.9	0	0	0.61
BMI, SD	26.9	3.3	25.9	3.3	25.6	2.7	0.79
Systolic BP, mmHg, SD	138.4	22.5	138.3	22.5	144.4	26.1	0.38
Diastolic BP, mmHg, SD	74.6	11.6	74.6	11.5	77.1	13.9	0.19
Diabetes mellitus, %	160	7.1	157	7.0	2	7.4	0.99
Smoking current, %	491	21.7	486	21.8	5	18.5	0.32
Smoking former, %	1021	45.1	998	44.7	16	59.3	0.32
Atrial fibrillation, %	56	2.4%	56	2.5	0%	0	0.41

Abbreviations: LVEF, left ventricular ejection fraction; SD, standard deviation; BMI, body mass index

RESULTS

Table 1 shows baseline characteristics of all participants and of those with a LVEF >35% and < 35%. Mean age of the participants was 65.1 years (SD 7.3) with an approximately equal gender distribution (54% females). An association with LVEF <35% was present for gender only (table 1). Two hundred and forty-nine participants (11%) recalled one or more falls during the previous year. The mean follow-up time was 2996 days (SD 880). During follow-up 251 (11.1%) of participants experienced a fracture and 44 (1.9 %) experienced a hospital admission due to a fall incident. Since for 18 participants the fracture was a reason for admittance to a hospital, the total number of events added up to 267. Table 2 shows the number of events and the incidence rates for the different categories of LVEF.

Table 2 **| Number of events and crude incidence rates per 100 000 person years (with 95% CI), for all participants and according to LVEF**

Description	Total in cohort	Events*	Incidence rate	(95% CI)
All	2266	267	39	35-44
LVEF >50%	2068	238	38	33-43
LVEF <35%	27	6	88	32-192
LVEF 35-50%	171	23	50	32-75

* Fall incident resulting in a hospital admission and/or fracture

Abbreviations: LVEF, left ventricular ejection fraction; CI, confidence interval;

In participants with a LVEF <35%, both the crude and the age- and gender adjusted hazard ratios for a serious falls incident were significantly increased (Tabel 3, model 1 and 2). After further adjusting for body mass index, hypertension, diabetes mellitus, and atrial fibrillation (Tabel 3, model 2) both LVEF <35% and 35-50% showed a significantly increased risk for serious fall incidents (table 3, model 3). Risk of an event increased with worsening of the LVEF. For the assessment of cardiovascular drug use as a possible confounder, a time-varying-exposure analysis was performed with incidence of a serious fall incident as the index date. Since none of the cardiovascular drugs acted as a confounder they were left out of the final analysis. The respective hazard ratios for LVEF adjusted for the cofactors mentioned above and use of cardiovascular drugs were 1.66 for the trend analysis (95% CI 1.19-2.29), 1.69 for LVEF 35-50% (95% CI 1.09-2.63) and 2.61 for LVEF <35% (95% CI 1.04-6.53).

Table 3 | **Relative risk of a fall resulting in hospital admission according to Left ventricular ejection fraction (LVEF) (N=2266)**

LVEF	HR (95% CI) Model 1	HR (95% CI) Model 2	HR (95% CI) Model 3
LVEF categorical	1.42 (1.05-1.93)*	1.47 (1.08-2.01)*	1.68 (1.22-2.31)*
LVEF >50% (ref)	1.00	1.00	1.00
LVEF 35-50%	1.32 (0.86-2.03)	1.35 (0.88-2.08)	1.71 (1.10-2.66)*
LVEF <35%	2.35 (1.04-5.28)*	2.59 (1.15-5.93)*	2.70 (1.11-6.58)*

Abbreviations: LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval
Model 2: adjusted for age and gender
Model 3: adjusted for age, gender, body mass index, diabetes mellitus, hypertension, atrial fibrillation
* $P < 0.05$

DISCUSSION

In our study, poor LVEF was a risk factor for serious fall incidents. Fall risk increased with decreasing LVEF, with an almost tripled risk of a serious fall incident in participants with a LVEF below 35%. Our explanatory hypothesis is that persons with a poor LVEF have a limited spare cardiac output capacity, which can result in cerebral hypoperfusion, and hence falls, in physical demanding situations[12]. Another possible explanation would be that poor LVEF might act as a predictor for frailty, since in the Cardiovascular Health Study, frailty has been shown to predict falls in older persons[21]. However, in that study it was also shown that although the incidence of poor LVEF was higher in frail participants, there was no significant association between LVEF and frailty[22].

As mentioned earlier, falls are a major problem in the healthcare of older persons, because of its high incidence en often devastating consequences. Although in the current guidelines for assessment and treatment of older fallers already many risk factors have been incorporated, the optimal content is still not clear, since studies regarding the multifactorial approach differ regarding the content of the assessment and intervention[23]. The current study suggests that there might be a role for a more thorough cardiovascular assessment, although further research is needed to determine the clinical added value of including echocardiography to the falls assessment. On any account, regarding the results it can be speculated that there might be clinical benefit obtainable if cardiac output is optimalized in older fallers.

In our study, we addressed falls with serious consequences, which is merely a fraction of the total number of fall incidents in older persons; approximately 10% in a Dutch cohort study[24]. As a consequence, we cannot be certain whether our finding is generalizable to overall falls in older persons. However, there is no reason to assume that poor LVEF would only lead to serious fall incidents and not falls with less disastrous consequences. Furthermore, our study group has also assessed

the association between poor LVEF and fall incidents in a small prospective cohort of geriatric outpatients (N=215) and although the incidence of poor LVEF was too small to draw definite conclusions (3%), we found a comparable, though non-significant, fall risk in this group[11].

Due to the size of our study population, left ventricular systolic function was estimated by LVEF, rather than by 2D echocardiographic determination of ejection fraction. In absence of major wall motion abnormalities however, LVEF can be assumed to reliably reflect left ventricular systolic function[19]. Due to a limited availability of echotechnicians, echocardiographic information was only available for 2823 participants. Although no prior rules were set for the performance of echocardiography in certain subgroups, participants who underwent echocardiography tended to be younger and were less likely to have cardiovascular disease as compared to the study group[16]. Furthermore, participants in whom the echocardiographic window was deemed adequate for analysis (N=2266) were also younger and less likely to have cardiovascular disease. Therefore the studied group probably reflects a healthier subgroup of the Rotterdam Study. Nevertheless, one can expect that this only lowered the incidence of poor LVEF and did not affect the relative risk, since there is no reason to expect that with increasing age or presence of cardiovascular disease the relation between fall incidents and poor LVEF alters.

In conclusion, this study suggests that poor LVEF is a risk indicator for fall incidents with serious consequences. This finding was irrespective of cardiovascular drug use, hypertension and atrial fibrillation. Hence, according to our hypothesis, it appears probable that insufficient cardiac spare capacity can lead to periods of cerebral hypoperfusion, which subsequently can result in falls. Although for the clinical implications of our finding further research is needed, this outcome suggests that clinical benefit might be obtained if systolic function is optimalized in older fallers.

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07

Chapter 7 **| Selective Serotonin Reuptake Inhibiting antidepressants are associated with an increased risk of non-vertebral fractures**

ABSTRACT

Background:
Fractures related to osteoporosis and falling constitute a major health problem in the elderly population. Exposure to antidepressants is associated with an increased risk of falls and fractures, but most previous studies incriminate tricyclic antidepressants (TCAs) rather than selective serotonin reuptake inhibitors (SSRIs).

Objective:
To examine the association between antidepressants, including TCAs, SSRIs, and other antidepressants and the risk of non-vertebral fractures in elderly.

Design:
Prospective, population-based cohort study.

Setting:
The Rotterdam Study, consisting of 7983 individuals aged 55 years and older.

Participants:
All persons from the Rotterdam Study.

Results:
1219 persons experienced a non-vertebral fracture, 25 during TCA use and 18 during SSRI use. After adjustment for age, gender, lower limb disability and depression the risk of non-vertebral fracture was 2.35 (95% CI 1.32 to 4.18) for current users of SSRIs compared to non-users of antidepressants. Multiple adjusting for many possible risk factors did not affect the association. To deal with potential confounding by indication, we subsequently restricted the analysis to antidepressant users (n=1217). Compared to past users of TCAs or SSRIs, current users of SSRIs had a 2.21-fold (95% CI 1.33 to 3.67) increased risk of fracture, which increased with prolonged use. In this analysis, depressive state at baseline and during follow-up did not play a role suggesting absence of confounding by indication. The use of TCAs was associated with an increased fracture risk which decreased with longer use.

Conclusions:
Not only users of TCAs but also of SSRIs have a significantly increased risk of non-vertebral fractures, especially after prolonged use. Despite fewer early adverse effects of SSRIs, physicians treating elderly depressive patients should be aware of the unfavorable long-term consequence of SSRIs on fracture risk.

INTRODUCTION

Fractures related to osteoporosis and falling constitute a major health problem in the elderly population causing high morbidity, mortality and substantial costs[1-5]. Depression has been recognized as an important risk factor for falls[6]. It predicts functional decline and the onset of excess disability, such as poor physical function[7-10], falls[11-15], and low bone density[16, 17], all of which increase susceptibility to osteoporotic and traumatic fractures[18, 19].

Depression in the elderly is treated with tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or other antidepressants. The preferred treatment strategy is to start with an SSRI plus psychotherapy[20], in view of the relatively favorable adverse reaction profile of SSRIs[21]. However, antidepressants themselves may increase fall and therefore fracture risk due to cardiovascular, anticholinergic and antihistaminergic effects[15, 22, 23]. So far, this risk-increasing effect was considered as typical for TCAs, but there is increasing evidence that SSRIs increase the risk of fracture as well possibly through an other pathophysiological mechanism than falling [23]. It has been shown that bone cells possess functional serotonergic pathways for both responding to and regulating the uptake of serotonin (5-HT), suggesting that 5-HT may be involved in bone metabolism[24, 25].Exposure to antidepressants with an effect on the 5-HT system, such as SSRIs may therefore also have an effect on bone. Indeed, a recent study showed that the use of SSRIs was associated with a lower bone mineral density (BMD)[26]. Another study reported an increase in hip bone loss among elderly women using SSRIs[27]. However, other studies presented opposite results and the association between SSRI use and BMD reduction remains controversial to date[28]. A major challenge in studies addressing the influence of SSRIs on fracture risk is to deal with confounding by indication or severity, a factor which was not adequately controlled for in earlier studies.

We conducted a prospective population-based cohort study into the risk of non-vertebral fracture in which we addressed the issue of confounding by indication. Detailed drug-dispensing information as well as extensive information on potential other risk factors was used to examine the association between antidepressants, especially TCAs and SSRIs, and the occurrence of non-vertebral fractures in men and women of 55 years of age and older.

METHODS

Setting

Data came from the Rotterdam Study, a prospective population-based cohort study on the occurrence and determinants of disease and disability in elderly persons[29]. In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older and had lived in the district for at least one year were invited to participate in the study. Of the 10,275 eligible persons, 7983 (78%) participated. Participants gave informed consent and permission to retrieve

information from medical records. At baseline, between 1990 and 1993, trained interviewers administered an extensive questionnaire covering socio-economic background and medical history, among other topics, during a home interview. During subsequent visits to the study center, additional interviewing, laboratory assessments, and clinical examinations were performed. Information on vital status is obtained at regular time intervals from the municipal authorities in Rotterdam. The Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands, approved the study.

The general practitioners of the study participants report all fatal and non-fatal events, such as fractures, through a computerized system. These data cover approximately 80% of the study sample. For participants who were not covered by this system, research physicians of the Rotterdam study perform annual checks on the complete medical records of all general practitioners of the study participants.

All follow-up information is checked in GPs' patient records by research physicians and independently coded according to the International Classification of Diseases, 10th revision (ICD-10)[30]. A medical expert in the field reviews all coded events for a final classification. Data were complete until January 2002.

In the research area, there are seven fully computerized pharmacies that are linked to one network. During the study, almost all participants filled their prescriptions in one of these seven pharmacies. Data on dispensed drugs are available in computerized format on a day-to-day basis as of 1 January 1991. The data include the date of prescribing, the total amount of drug units per prescription, the prescribed daily number of units, product name, and the Anatomical Therapeutic Chemical (ATC) code [31].

Study population

The study population comprised all participants of the Rotterdam study. Study subjects were followed from baseline interview until an incident fracture, death, or the end of the study period (January 2002), whichever came first.

To control for confounding by indication, i.e. the presence of depression, we additionally focused on subjects who had used an antidepressant at any time during the study.

Outcome definition

Our primary endpoint was incident non-vertebral fractures during the follow-up period. Hence, vertebral fractures and pathological and post-procedural fractures were excluded from the case definition. Patients were followed until the first occurrence of a non-vertebral fracture during the study period, which was defined as the index date. For patients with more than one fracture, the follow-up ended on the day of the first non-vertebral fracture. Information on mortality and on incident non-vertebral fractures was collected from baseline until the end of study

on January 1st, 2002. All cases of non-vertebral fracture were reviewed by a medical specialist.

Exposure definition

Data on exposure to antidepressants were gathered from the pharmacy dispensing records and classified as tricyclic antidepressants, SSRIs, or other antidepressants. TCA included imipramine, clomipramine, opipramol, amitriptyline, nortriptyline, doxepine, dosulepine and maprotiline. SSRIs included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram. The group of other antidepressants consisted of tranylcypromine, moclobemide, mianserin, trazodone, nefazodone, mirtazapine and venlafaxin. Antidepressant use was further divided into current and past use of antidepressants as determined on the index date. Current use was defined as use of an antidepressant on the index date and was expressed as the number of consecutive days of use. Past use was defined as a history of use of an antidepressant during the study period and no use on the index date. For this purpose, episodes of use were determined based on the prescription length of the dispensed antidepressants, which was calculated by dividing the total number of tablets/capsules dispensed by the prescribed daily number. Finally, mutually exclusive groups of exposure were defined as 1) no use of antidepressants, 2) past use of TCA and/or SSRI, 3) current use of TCA, 4) current use of SSRI, 5) current use of both TCA and SSRI, 6) current user of TCA and/or SSRI who had switched between TCA and SSRI and 7) current or past use of other antidepressants. For comparisons of dosages, we used the defined daily dose (DDD), i.e. the average dosage of a drug taken by adults for the main indication as indicated by the World Health Organization[31].

To avoid potential misclassification of exposure at baseline, we ensured that all participants had pharmacy data available for at least 5 months before baseline.

Co-factors

Baseline patient characteristics were all determined by interview or during center visit as described elsewhere [29], and included age, sex, any fracture in the five years before baseline, history and frequency of falling, body mass index, current smoking [32], intake of alcohol (g/day), dizziness and visual impairment. For assessment of prevalent dementia at baseline, participants were cognitively screened. Screen-positives underwent further cognitive testing, which has been described in detail elsewhere [33]. Lower-limb disability was assessed by using a modified version of the Stanford Health Assessment Questionnaire [34] and by calculating the mean score of answers to questions about rising, walking, bending, and getting in and out of a car [32]. Bone mineral density (BMD) of the femoral neck was measured by using dual-energy X-ray absorptiometry (DPX-L densitometer, Lunar Corp., Madison, Wisconsin), as described elsewhere [35]. Bone mineral density was divided into high and low, based on the study sample median value (0.82 g/cm^2). Diabetes mellitus

was defined as the use of glucose lowering medication or a random or post load serum glucose level ≥ 11.1 mmol/l at baseline. The presence of Parkinson's disease was ascertained by interview about a previous diagnosis or by the use of antiparkinson drugs.

Hypertension was defined as a systolic blood pressure higher than 160 mm Hg and a diastolic blood pressure higher than 100 mm Hg at baseline, or the use of antihypertensive medication during the study period (time-dependent). Use of other medications, such as antipsychotics, thiazide diuretics, beta-blockers, bisphosphonates, statins, non-narcotic analgesics, glucocorticoids and estrogens within 90 days preceding the index date was also obtained from the pharmacy records and was analyzed as a potential (time-dependent) confounder.

The presence of depression or depressive symptoms was assessed at baseline and during the third round of the Rotterdam study between 1997 and 1999. Baseline presence of depression was added to the model as a proxy of the indication for antidepressant use. In order to adjust for persistence of depression, we also considered depression in a time-dependent manner by including the third round results into the model.

Statistical analysis

We performed a cohort analysis to examine the association between fracture risk and exposure to antidepressants. Since exposure to antidepressants may vary over time, we calculated relative risks of non-vertebral fractures with a time-dependent Cox proportional hazards model [36]. The model compared the prevalence of exposure to antidepressants in cases of incident non-vertebral fracture on the index date with the exposure prevalence in all other participants in the cohort on that date. We used time-dependent categorical variables of exposure to compare various durations of current use with non-use. The dose-effect relationship was studied by categorizing daily dose below and equal to, or above one DDD.

Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. To identify potential confounders, co-factors associated with the occurrence of a fracture were included one-by-one in the age- and sex-adjusted model. Co-factors that changed the HR by more than 5% were maintained in the final model. To explore potential residual confounding, we also tested a second model including all statistical confounders and biologically plausible risk factors for fracture. In an extra analysis, we used missing value indicators for missing values of cofactors to prevent exclusion of cases with incomplete data and to evaluate potential confounding by missing values. Cofactors with missing values were therefore categorized, with a separate category for missing values

We subsequently performed analyses within users of antidepressants, thereby excluding all persons who never used antidepressants during follow-up, in order to control for depression itself as a confounding factor. In this analysis, "past use of any antidepressant (TCA and/or SSRI)" was used as a reference category.

All statistical analyses were performed using SPSS-PC version 11.0 (SPSS Inc., 1989 – 2001).

Table 1 | **Baseline characteristics of the study cohort and hazard ratios for non-vertebral fractures**

Baseline characteristic	Non-vertebral fracture cases (n=1219)		Study cohort (n=7983)		Hazard Ratio (95% CI)
	n	(%)	n	(%)	
Female gender	958	(79%)	4824	(61%)	**2.48 (2.16 - 2.85)**
Mean age, yr (SD)	77.0	(9.5)	77.5	(8.7)	**1.58 (1.49 - 1.68)**
55-64	300	(25%)	2714	(34%)	
65-74	418	(34%)	2692	(34%)	
75-84	348	(29%)	1749	(22%)	
≥ 85	153	(13%)	738	(9%)	
Visual impairment	420	(34%)	2209	(28%)	**1.99 (1.74 - 2.28)**
Any fracture in last 5 years	250	(21%)	1074	(14%)	**1.66 (1.44 - 1.91)**
Lower limb disability	749	(61%)	4054	(51%)	**1.74 (1.54 - 1.97)**
Dizziness	216	(18%)	1263	(16%)	1.01 (0.87 - 1.17)
Recent falling	298	(24%)	1339	(17%)	**1.67 (1.46 - 1.91)**
MMSE score < 25 points	154	(13%)	765	(10%)	**2.04 (1.71 - 2.44)**
Mean BMD of femoral neck, g/cm^2 (SD) [#]	0.78	(0.13)	0.84	(0.14)	**0.02 (0.01 - 0.04)**
Lower (<=0.82 g/cm^2)	586	(48%)	2985	(38%)	
Higher (>0.82 g/cm^2)	279	(23%)	2831	(36%)	**0.51 (0.44 - 0.58)**
Mean Body Mass Index, kg/m^2 (SD)	26.2	(3.7)	26.3	(3.7)	1.00 (1.00 - 1.01)
Alcohol intake. g/day (SD)	8.9	(13.3)	10.4	(15.2)	1.00 (1.00 - 1.01)
Current smoking	247	(20%)	1713	(22%)	0.91 (0.65 - 1.27)
Diabetes mellitus	92	(8%)	500	(6%)	**1.43 (1.16 - 1.78)**
M. Parkinson	18	(1%)	75	(1%)	**2.40 (1.50 - 3.82)**
Depressive state	52	(4%)	320	(4%)	1.13 (0.85 - 1.50)

Values are numbers with percentages or means with standard deviation (SD).
Bold print indicates p<0.05

[#] Bone Mineral Density, available at baseline for 74% of population.

RESULTS

The study cohort included 7983 participants with a mean follow up of 8.4 years and a total follow-up of 66,261 person years. During follow-up 1219 persons experienced an incident non-vertebral fracture yielding an incidence rate of 18.4 cases per 1000 person years (95% CI 17.3 to 19.4). Fractures of the hip were the most frequent (n=352) followed by fractures of the wrist (n=315), humerus (n=120) and pelvis (n=52). The mean age of the population was 77.5 years and 61 % was female (table 1). Female gender, age, visual impairment, history of fracture, lower limb disability, recent falling, cognitive decline, diabetes mellitus, and Parkinson's disease were associated with an increased risk of non-vertebral fracture.

After adjustment for age and gender, there was a 2.25-fold risk increase (95% CI 1.41 to 3.59) of non-vertebral fracture for persons who were current user of SSRIs and a more than threefold risk increase for subjects who had been using SSRIs for at least 6 weeks compared to persons who were not exposed to antidepressants (table 2).

Table 2 **| Hazard ratios and 95% CI for non-vertebral fracture during use of antidepressants compared with non-users (n=7983)**

Exposure status on index date¥	number of cases	crude Hazard Ratio *	(95% CI)	adjusted Hazard Ratio §	(95% CI)
No use of antidepressant	1061	1.00	Ref	1.00	Ref
Current TCA use	25	1.60	(1.08 - 2.38)	1.69	(0.97 - 2.92)
< 6 weeks	10	2.05	(1.10 - 3.82)	2.93	(1.39 - 6.18)
6 weeks to 6 months	12	1.89	(1.07 - 3.35)	0.91	(0.29 - 2.85)
> 6 months	3	0.78	(0.25 - 2.42)	1.47	(0.47 - 4.57)
current SSRI use	18	2.25	(1.41 - 3.59)	2.35	(1.32 - 4.18)
< 6 weeks	5	1.90	(0.79 - 4.57)	2.34	(0.87 - 6.27)
6 weeks to 6 months	8	2.28	(1.14 - 4.58)	2.11	(0.87 - 5.10)
> 6 months	5	3.36	(1.39 - 8.08)	2.94	(0.94 - 9.19)
Past use of TCA and/or SSRI	93	1.12	(0.91 - 1.39)	1.02	(0.76 - 1.35)
Switchers between TCA and SSRI	12	1.54	(0.87 - 2.72)	1.51	(0.71 - 3.19)
Current use of other antidepressants	10	0.79	(0.43 - 1.48)	0.47	(0.15 - 1.45)

TCA= TriCyclic Antidepressant; SSRI= Selective Serotonine Reuptake Inhibitor

¥ no use of antidepressants is used as a reference group for all presented point estimates; exposure groups are mutually exclusive

* Crude figures are adjusted for age and gender

§ adjusted for age, gender, depression during follow-up and lower limb disability

There was a clear duration-effect relationship (p for trend: 0.001). Lower limb disability and the presence of depression were identified as confounding factors. The age, sex, lower limb disability and depression adjusted HR for fracture during SSRI use was 2.35 (95% CI 1.32 to 4.18) but the duration-effect had disappeared.

Further adjustment for clinically plausible potential confounding factors such as visual impairment, a history of fracture, body mass index, MMSE score < 25 points, BMD of the femoral neck, alcohol intake, recent fall history, dizziness, postural hypotension, smoking history, history of heart attack, diabetes mellitus, disease of the thyroid gland and Parkinson's disease, use of thiazide-diuretics, beta-blocking agents, glucocorticoids, hormone replacement therapy, statins, non narcotic analgesics and anti-psychotics did not substantially alter the point estimate for the risk of fracture in persons using SSRIs. The models using indicators for missing values in co-variates yielded similar results as the other models implying that missing data did not play an important role.

Like SSRIs the use of TCAs was associated with an increased fracture risk (HR adjusted: 1.60, 95% CI 1.02 to 2.51). The risk disappeared, however, with use beyond 6 months. The use of antidepressants other than TCAs or SSRIs was not associated with an increased risk of fractures (HR adjusted 0.69; 95% CI 0.36 to 1.32). Patients who had switched between antidepressants seemed to be at an increased risk of fracture but this was not statistically significant (HR adjusted 1.53; 95% CI 0.83 to 2.80). To explore the potential of selective prescribing of SSRIs rather than TCAs to patients with a known increased risk of falling we compared the proportion of patients with a recent fall history in different exposure categories. The proportion of patients with a recent fall history was however similar for users of SSRIs and users of TCAs (p=0.749). Patient numbers did not allow further testing of effect modification or stratification.

To further limit the possibility of residual confounding by indication, we repeated the analysis within antidepressant users only and compared the risk of fracture in current users with the risk in past users (n=1217). In this restricted population, 158 persons experienced an incident non-vertebral fracture at an incidence rate of 15.9 cases per 1000 person years (95% CI 13.6 to 18.6). The results of the restricted analysis were essentially the same as in the main analysis although the risk estimates were slightly lower (table 3). After adjustment for age and gender, the risk of non-vertebral fracture was 2.10 (95% CI 1.26 to 3.49) for current users of SSRIs compared to persons who were past user of TCAs or SSRIs (table 3). This association was present in low-dose as well as in high-dose users and the fracture risk increased with longer duration of use. Depressive state at baseline did no longer act as a confounder in the association. The age, gender and lower limb disability adjusted risk of fracture during current use of SSRIs was 2.21 (95% CI 1.33 to 3.67) compared to past users of TCAs or SSRIs.

Table 3 | **Hazard ratios and 95% CI for non-vertebral fracture during use of antidepressants (n=1217)**

Exposure status on index date¥	Number of cases (n=158)	crude Hazard Ratio *	(95% CI)	adjusted Hazard Ratio §	(95% CI)
Past use of TCA and/or SSRI	93	1.00	Reference	1.00	Reference
Duration of use					
Current use TCA	25	1.60	(1.02 - 2.50)	1.60	(1.02 - 2.51)
≤ 6 weeks	10	1.93	(1.00 - 3.74)	1.97	(1.02 - 3.80)
6 weeks to 6 months	12	1.83	(1.00 - 3.36)	1.83	(1.00 - 3.37)
> 6 months	3	0.77	(0.24 - 2.44)	0.76	(0.24 - 2.40)
Current use SSRI	18	2.10	(1.26 - 3.49)	2.21	(1.33 - 3.67)
≤ 6 weeks	5	1.73	(0.70 - 4.26)	1.80	(0.73 - 4.45)
6 weeks to 6 months	8	2.08	(1.01 - 4.29)	2.19	(1.06 - 4.51)
> 6 months	5	2.73	(1.10 - 6.73)	2.92	(1.18 - 7.22)
Switchers between TCA and SSRI	12	1.43	(0.78 - 2.61)	1.62	(0.87 - 3.00)
Use of other antidepressant	10	0.68	(0.35 - 1.31)	0.72	(0.37 - 1.41)
Daily dosage					
TCA dose <1 ddd	23	1.58	(1.00 - 2.52)	1.59	(1.00 - 2.53)
TCA dose >=1 ddd	2	1.79	(0.44 - 7.36)	1.69	(0.41 - 6.95)
SSRI dose <1 ddd	11	2.10	(1.12 - 3.94)	2.23	(1.19 - 4.18)
SSRI dose >=1 ddd	7	2.09	(0.97 - 4.52)	2.18	(1.01 - 4.71)

TCA= TriCyclic Antidepressant; SSRI= Selective Serotonine Reuptake Inhibitor; DDD= defined daily dose

¥ Past use of TCA and/or SSRI is used as a reference group for all presented point estimates, exposure groups are mutually exclusive

* Crude figures are adjusted for age and gender

§ adjusted for > 5% change point estimate of fracture risk, i.e. age, gender and lower limb disability

To address the issue of confounding by severity of the underlying depression we included depressive state as a time-dependent factor. In doing so we acknowledged the risk of diluting a true association between antidepressant use and fracture risk by including depression occurring after fracture in some cases. Depressive state during follow-up was indeed confirmed as a risk factor for fracture (HR: 1.61, 95% CI 1.02 to 2.56) but it did not confound the association between antidepressant use and fracture risk (HR adjusted: 2.11, 95% CI 1.27 to 3.52 for current SSRI users and HR adjusted: 1.61, 95% CI 1.03 to 2.53 for current TCA users).

DISCUSSION

In this population-based study of community-dwelling elderly, current use of SSRIs was associated with a significantly increased risk of non-vertebral fractures compared to past use of TCAs or SSRIs. The onset of this effect was already visible within the first 6 weeks of treatment and increased with longer duration of use. The fracture risk was independent of other potential risk factors such as age, sex, fall history, low bone mineral density, lower limb disability and most importantly depressive state at baseline and during follow up. An increased fracture risk was also observed during TCA use. Although the risk increase in users of TCA attenuated after more than 6 months of use, the low numbers of exposed cases in this group warrant a cautious interpretation. There was no overt dose-effect relationship between antidepressant use and fracture risk.

Previous studies already demonstrated that the use of TCAs is associated with an increased fracture risk. In line with our results, these studies showed that the increased risk of non-vertebral fractures diminished progressively with the duration of TCA use. This pattern was attributed to a progressive tolerance to the anticholinergic effects rather than a survivor bias[37]. An increased risk of hip and non-vertebral fractures has also been reported for SSRIs[23, 37-41]. Short-term adverse effects of use of SSRIs, for example bradycardia, orthostatic hypotension, syncope, or other central effects, might explain the higher non-vertebral fracture risk seen with short-term use of SSRIs through an increased fall risk[39, 42]. The increased risk of non-vertebral fractures after more than 6 months of use is in line with evidence for a bone mineral density decreasing effect of SSRIs reported in the literature[24, 26, 27, 39].

The validity of observational studies may be limited by selection bias, information bias or confounding. In our study selection bias is unlikely because cases and non-cases were derived from a prospective population-based cohort study, and came from the same study base. However, a positive fall history is associated with an increased fall risk[43] and might hence lead to selective prescribing of SSRIs rather than TCAs to people at an increased risk of falling. This would lead to an overestimation of the impact of SSRIs and an underestimation of the effect of TCAs. Since the proportion of patients with a fall history was similar between SSRI users and TCA users it is however unlikely that selective prescribing played a major role in our study. We minimized the potential influence of selective prescribing by adjusting for fall history and by considering persons who switched between TCAs and SSRIs as a separate exposure group. Information bias is unlikely as data on drug use and outcome data for the Rotterdam study were gathered prospectively and without knowledge of the research question of our study. Because we had access to complete pharmacy-dispensing records from all participating subjects, we had information on daily drug exposure and we could investigate the effect of antidepressants for different periods of use. As a consequence, misclassification of exposure is unlikely to have played a role. Misclassification of fractures is unlikely

and would be non-differential, because the outcome was assessed independently of the exposure. Hence, this could not lead to an overestimation of the risk.

The most challenging issue in this study was dealing with potential confounding by indication, which played a role in our first analysis. In order to control for this confounding, we restricted the analysis to subjects who had used an antidepressant at any time during the study period. Other observational studies that also investigated dose and duration effects of antidepressants on the risk of fracture, almost always used non-users as the reference group[23, 40, 44-46]. As we described[47], in these studies, confounding by indication is a potential problem since the differences in patient characteristics, which are related to exposure and outcome, are probably greater and thus more difficult to adjust for. In our study we further dealt with confounding by indication and severity of the underlying depression by including depressive state into the model both as a baseline characteristic and as a time-dependent factor. It is therefore unlikely that active depression in current users versus resolved depression in past users can explain the observed association.

In conclusion, we demonstrated that not only use of TCAs but also of SSRIs is associated with a significantly increased risk of non-vertebral fractures, which rises with prolonged use. The onset of the effect was already visible within the first 6 weeks of treatment. Consequently, despite fewer initial adverse effects of SSRIs, physicians treating elderly depressive patients should be aware of unfavorable long-term effects associated with these drugs.

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Chapter 8 | **Benzodiazepines, cytochrome P450 3A4, 3A5, 3A7, 2C9 and 2C19 gene polymorphisms and serious fall incidents in older persons: a population based study**

ABSTRACT

Objective:
To investigate the association between benzodiazepine use, cytochrome P450 3A4, 3A5, 3A7, 2C9 and 2C19 gene polymorphisms, and fall incidence in older persons.

Design:
Population-based prospective cohort study

Setting:
The Rotterdam Study consists of inhabitants of 55 years or older of a suburb of Rotterdam in the Netherlands.

Main outcome measures:
The association between benzodiazepine use, the genotypically predicted cytochrome CYP450- polymorphisms and serious fall incidents was investigated in older adults . Events were defined as a fall leading to hospital admission and/ or a fracture during follow-up. Data were recorded between 1991 and 2002. Multivariate adjustment for confounders was performed with a Cox proportional hazards model. Furthermore, we used dominant, recessive, genotype, and allele-effect genetic models to test potential interaction between genetic polymorphisms, benzodiazepines, and fall risk.

Results:
The risk of an injurious fall was significantly higher with benzodiazepine use. Neither CYP3A4, CYP3A5 or CYP3A7, nor CYP2C19 genotype was associated with the risk of a serious incident fall in benzodiazepine users. In the fully adjusted model, stratified on CYP2C9 genotype, however, the risk in current users of hypnotics rose from 1.12 (95% CI 0.84 to 1.49) in the participants with a wild type CYP2C9 genotype, via 1.78 (95% CI 1.19 to 2.67) in carriers of 1 CYP2C9 decreased activity allele (the heterozygote group), to 1.93 (95% CI 1.11 to 3.36) in the persons carrying two CYP2C9 decreased activity alleles (homozygote variant). A significant dose-effect relationship was observed in the age and gender adjusted model as well.

Conclusions:
Benzodiazepine use, especially short-acting hypnotics, have a dose dependent influence on fall risk. CYP2C9 variant alleles influence benzodiazepine induced fall-risk, whereas CYP3A and CYP2C19 genotypes do not. Our results suggest that CYP2C9 plays a more important role in the pharmacokinetics of benzodiazepines than previously assumed.

INTRODUCTION

Falls are among the most common and serious problems in elderly persons. Approximately 30% of the older persons living in the community and more than 50% of those living in geriatric long-stay facilities fall every year[1-3]. Falling is associated with considerable mortality, morbidity, reduced functioning, and premature nursing home admissions[4-6]. Four to 5% of falls in the elderly results in a fracture, and an additional 5% to 11% of falls causes other serious injuries [3, 5, 7]. Ultimately, 23.5% of falls require health services and 17.2% require treatment[8]. The public health impact is considerable as falls account for over 80% of injury-related admissions to hospital of people older than 65 years[9].

Benzodiazepines are a known modifiable risk factor for falling in the elderly with considerable impact due to the high exposure prevalence in this group [10-13]. The estimated costs of hospitalisations of accidental-fall injuries related to benzodiazepine use in the EU in the period 1985 - 2000 varied between 1.5 and 2.2 billion Euro each year. More than 90% of these costs were in the elderly[14]. The increased risk may probably be explained by prescribing too-high doses to the elderly[15], suggesting that blood concentrations may play a role, rather than the use of long- and short-acting benzodiazepines[11]. The oxidative metabolism of some benzodiazepines includes reactions which are catalyzed by CYP P450 isoenzymes, the most important being the P450 CYP3A sub-family followed by CYP2C19, but the pharmacokinetics are not entirely understood yet. Large differences exist between different types of benzodiazepines although the oxidative metabolism seems to be the primary route of elimination for all. Genetic polymorphisms in the P450 system have shown to affect drug blood concentrations or clinical effects of many drugs. With respect to benzodiazepines polymorphisms in the genes encoding CYP3A, CYP2C19 and CYP2C9 may therefore play a role in benzodiazepine induced fall risk [16, 17]. In the CYP3A family, CYP3A4 is the most important enzyme, but contributions of CYP3A5 and CYP3A7 to total CYP3A metabolism are possible[18]. The most important variant alleles for these genes are CYP3A4*1B (CYP3A4-V: allele frequency in Caucasians 5.3%) [19], encoding a slight increased activity in vitro [20]), CYP3A5*3 (allele frequency 91%) [21], splice variant encoding inactive CYP3A5 [22, 23] ; and CYP3A7*1C (allele frequency in Caucasians 4.2%)[24], encoding persistent CYP3A7 activity after birth in carriers of this allele[25]. For CYP2C9, the most important variant alleles in Caucasians encoding decreased enzymatic activity are the *2 and *3 alleles, while for CYP2C19, CYP2C19*2 is the most frequently encountered deficient allele[26].

To gain more knowledge concerning the influence of metabolic cytochrome-P450 pathways on benzodiazepine induced fall risk [27], we designed a population-based cohort study of persons of 55 years and older, in which we prospectively assessed whether the risk of falling during benzodiazepine use was modified by genetic variation in de genes encoding CYP3A4,CYP3A5, CY3A7, CYP2C19 and CYP2C9.

METHODS

Setting

The present study is part of the Rotterdam Study, a population-based cohort study aimed at assessing the occurrence of, and risk factors for, chronic diseases in older adults. Objectives and methods of the Rotterdam Study have been described elsewhere[28]. In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older and who had lived in the district for at least 1 year, were invited to participate in the study. Of these 10,275 eligible persons, 7983 (78%) participated. Participants gave informed consent and permission to retrieve information from treating physicians. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, The Netherlands, approved the study.

Information on demographics, medical history and medical condition of all participants was obtained through repeated standardized interviews, medical examinations and laboratory assessments. Blood drawn at baseline interview was used for assessment of genotype variations. Information on fatal and non-fatal endpoints for the participants enlisted was obtained from a computerized reporting system for general practitioners within the Rotterdam Study. These data cover approximately 80% of the study sample. For participants who were not covered by this system, research physicians performed annual checks on the complete medical records of all general practitioners in the Rotterdam Study. Additional information on clinical endpoints was obtained from the National Morbidity Registration (LMR), which contains information on all hospital admissions in the Netherlands. For data on co-medication, we used data from all seven regional pharmacies where more than 99% of participants of the Rotterdam Study fill their prescriptions. Complete data on drug use from these pharmacies were available as of 1 January 1991. The pharmacy data include the Anatomical Therapeutical Chemical code[29], the filling date, the total amount of drug units per prescription, the prescribed daily number of units, and product name of the drugs.

Cohort definition

The study cohort consisted of all subjects in the Rotterdam Study, from whom outcome data were available (n = 7976 persons). Subjects were followed until the occurrence of an injurious fall, death or the end of study period, January 2002, whichever came first.

Exposure definition

Data on exposure to benzodiazepines were gathered from the pharmacy dispensing records and classified as anxiolytics or hypnotics. Anxiolytics included diazepam, oxazepam, clorazepate, lorazepam, bromazepam, alprazolam. Hypnotics included flurazepam, nitrazepam, flunitrazepam, lormetazepam, temazepam and midazolam. Benzodiazepine use was further divided into current and past use of

benzodiazepines as determined on the index date as defined below. Current use was defined as use of a benzodiazepine on the index date and was expressed as the number of consecutive days of use. Past use was defined as a history of use of a benzodiazepine during the study period and no use on the index date. For comparison of dosages, we used the defined daily dose (DDD), i.e. the average dosage of a drug taken by adults for the main indication as indicated by the World Health Organization[29].

To avoid potential misclassification of exposure at baseline, we ensured that all participants had pharmacy data available for at least 5 months before baseline.

Outcome definition and follow-up procedure

As the primary outcome we studied a fall leading to hospital admission or leading to a fracture. Two research physicians independently coded all fractures that occurred during the study period using the International Classification of Diseases, 10th revision (ICD-10)[30]. This was also done for hospital admissions due to a fall incident, which were obtained from the National Morbidity Registration (LMR). A medical expert in the field who was unaware of the patients' history and medication use reviewed all coded events for a final classification. Definition of an endpoint was either a fall leading to hospital admission, or an incident fracture ascribed to a fall. The date of first fall or fracture occurrence was defined as the index date. Vertebral fractures, pathological and post-procedural fractures were excluded from the case definition.

Cofactors

For the current analysis, the following risk factors for falls were assessed as potential confounders: age, gender, recent falling, lower limb disability, use of walking aids, dizziness, history of fracture, Parkinson's disease, orthostatic hypotension, visual impairment, cognitive decline, depressive state, alcohol intake, current smoking, body mass index, history of myocardial infarction, diabetes mellitus and any treatment for thyroid disease. Comedication was considered as a potential confounder but also as a potential effect modifier.

Genotyping

Genotyping of the CYP3A4*1B, CYP3A5*3, CYP3A7*1C and CYP2C19*2was performed using TaqMan allelic discrimination assays (Applied Biosystems) on an ABI Prism 9700 HT sequence detection system[31]. Although these polymorphisms are not the only ones in these genes, they were chosen because they were (relatively) frequent and/or well-studied and of potential clinical relevance. Each assay consisted of two allele-specific minor groove binding (MGB) probes, labelled with either the fluorescent dye VIC or FAM. Polymerase chain reactions (PCR) were performed in a reaction volume of 2.0 µl, containing assay-specific primers, allele-specific TaqMan MGB probes, TaqMan Universal PCR Master Mix No AmpErase UNG

(2X) and genomic DNA(1ng). The thermal profile consists of an initial denaturation step at 95°C for 15 minutes, followed by 40 cycles of denaturation at 92°C for 15 seconds, and annealing and extension at 60°C for 1 minute. Genotypes were scored by measuring allelic-specific fluorescence using the SDS 2.2.2 software for allelic discrimination[31].

Genotyping for the CYP2C9*2 and CYP2C9*3 allele variants was performed using a validated polymerase chain reaction restriction enzyme digestion analysis, as previously described[32]. Patients in whom neither CYP2C9*2 nor CYP2C9*3 alleles were identified, were defined as wild-type. Carriers of one variant allele are predicted to be intermediate metabolizers whereas carriers of two variant alleles are defined as poor metabolizers). Because there is ample pharmacological evidence for the genotype-phenotype association regarding CYP2C9, we used allele-effect models for *2 and *3 together, as reported earlier[33].

STATISTICAL ANALYSIS

Allele frequencies were tested for deviations from Hardy–Weinberg equilibrium using a χ^2 –test. Baseline differences between cases and non-cases were tested using an independent t-test for continuous variables, and a chi-square test for dichotomous variables. A time dependent Cox's proportional hazards analysis was used to estimate the crude and adjusted relative risks (RR) with 95% confidence intervals (CI) of a serious fall incident during benzodiazepine use as compared to non-use of benzodiazepines.

To identify potential confounders, co-factors associated with the occurrence of a serious fall incident were included one-by-one in the age- and sex-adjusted model. Co-factors that changed the RR by more than 5% were maintained in the final model. Effect modification by genotype variants and use on the index date of co-medication affecting cytochrome P450 activity, was studied by including an interaction term with benzodiazepine use in the model and by conducting stratified analyses. We investigated the association between CYP3A and CYP2C19 genes and benzodiazepines on fall risk according to four genetic models: a dominant model (e.g. for CYP3A4 GG plus AG versus AA); a recessive model (e.g. for CYP3A4 GG versus AG plus AA); a genotype model (e.g. for CYP3A4 GG versus AA; and AG versus AA), and an allele-effect model (number of G-alleles with zero (AA) as a reference). In an extra analysis, missing value indicators for missing values of cofactors were used to prevent exclusion of cases with incomplete data and to evaluate potential confounding by missing values. Cofactors with missing values were therefore categorized, with a separate category for missing values. All statistical analyses were performed using SPSS software (version 11, SPSS Inc., Chicago, IL, USA).

RESULTS

Data on incident serious falls were available of 7976 persons (99.9%) with a mean follow up of 7.5 years and a total follow-up of 60,198 person years. During follow-up, 1149 persons experienced a serious fall incident, yielding an incidence rate of 19.1 cases per 1000 person years (95% CI 18.0 to 20.2) The mean age of the population was 78.1 years and 61% was female (table 1).

Table 1 **| Baseline characteristics of the study population**

Variable	Number of cases = 1149	% / SD	Number of participants = 7976	% / SD	p-value
Caucasian origin	1149	100.0%	7976	100.0%	
Mean age, yr (SD)	78.3	9.4	78.1	8.7	0.498
55-64	266	23.2%	2717	34.1%	
65-74	392	34.1%	2706	33.9%	
75-84	335	29.2%	1774	22.2%	
≥ 85	156	13.6%	779	9.8%	
Female gender	910	79.2%	4871	61.1%	0.000
Recent falling	285	24.8%	1353	17.0%	0.000
Lower limb disability	726	63.2%	4053	50.8%	0.000
Recent use of walking aids	188	16.4%	844	10.6%	0.000
Dizziness	209	18.2%	1266	15.9%	0.066
any fracture in last 5 years	235	20.5%	1075	13.5%	0.000
Parkinson's disease	21	1.8%	105	1.3%	0.100
Orthostatic hypotension at 4'or 5'	21	1.8%	102	1.3%	0.199
Visual impairment	397	34.6%	2213	27.7%	0.000
MMSE score < 25 points	153	13.3%	809	10.1%	0.000
Depressive state	70	6.1%	363	4.6%	0.000
Alcohol intake. g/day (SD)	3.2	4.0	3.2	4.0	0.125
Current smoking	226	19.7%	1725	21.6%	0.006
Mean Body Mass Index, kg/m2 (SD)	26.2	3.7	26.3	3.7	0.682
History of myocardial infarction	76	6.6%	716	9.0%	0.004
Diabetes mellitus	88	7.7%	514	6.4%	0.070
Any treatment for thyroid disease	119	10.4%	694	8.7%	0.059

All patients were of Caucasian origin. Genotype distributions were all in Hardy-Weinberg equilibrium and frequencies were similar to other studies of Caucasian subjects (table 2) [34].

As expected, persons with an incident serious fall had a more adverse fall risk profile than the total cohort. Advancing age, female gender, lower limb disability, recent falling, use of walking aids, history of fracture, visual impairment, cognitive decline, ,and depressive state were associated with an increased risk of a serious fall incident.

Table 2 | **Genotype characteristics of the study population**

	Genotypes	%
CYP3A4		
Participants available for analysis	6249	
AA	5781	92.5%
AG	461	7.4%
GG	7	0.1%
HWE $\chi 2 = 0.492$, $p = 0.212$		
CYP3A5		
Participants available for analysis	6163	
AA	39	0.6%
AG	837	13.6%
GG	5287	85.8%
HWE $\chi 2 = 0.872$, $p = 0.175$		
CYP3A7		
Participants available for analysis	6004	
TT	5350	89.1%
TG	641	10.7%
GG	13	0.2%
HWE $\chi 2 = 1.847$, $p = 0.087$		
CYP2C9		
Participants available for analysis	6494	
CYP2C9*1/*1	4316	66.5%
CYP2C9*1/*2	1348	20.8%
CYP2C9*1/*3	605	9.3%
CYP2C9*2/*2	105	1.6%
CYP2C9*2/*3	93	1.4%
CYP2C9*3/*3	27	0.4%
HWE allele *2: $p = 1$, HWE allele *3: $p = 0.140$		
CYP2C19		
Participants available for analysis	6248	
CYP2C19*1/*1	4440	71.1%
CYP2C19*1/*2	1644	26.3%
CYP2C19*2/*2	164	2.6%
HWE $\chi 2 = 0.639$, $p = 0.212$		

Benzodiazepine use was associated with an increased risk of serious incident falls. This was especially the case with use of hypnotics, notably with short acting benzodiazepines (table 3). In all classes of benzodiazepine use, but especially in hypnotics, a dose-effect relationship could be observed. Lower limb disability was found to change the point estimate by more than 5% and was therefore maintained in the final model.

Table 3 | **Benzodiazepine use and fall-risk**

Drug		no of cases	Crude* HR	(95% CI)	Adjusted# HR	(95% CI)
Benzodiazepines	no use	576	Ref		Ref	
	past use	385	1.14	(0.99 - 1.31)	1.08	(0.95 - 1.24)
	current use	z188	**1.33**	**(1.10 - 1.60)**	1.18	(0.99 - 1.40)
Anxiolytics	no use	777	Ref		Ref	
	past use	289	1.04	(0.90 - 1.21)	0.98	(0.85 - 1.12)
	current use	83	1.16	(0.91 - 1.49)	1.03	(0.82 - 1.30)
Hypnotics	no use	775	Ref		Ref	
	past use	244	**1.18**	**(1.01 - 1.39)**	1.13	(0.97 - 1.30)
	current use	130	**1.50**	**(1.21 - 1.85)**	**1.33**	**(1.10 - 1.61)**

* Crude analysis, i.e. adjusted for age and gender
\# Adjusted analysis, i.e. adjusted for age, gender and lower limb disability

Cytochrome P450 status itself showed no effect on fall risk, with a RR of 1.08 (95% CI 0.98 to1.20) for the 3A4 genotype variants, RR 1.06 (95% CI 0.91 to 1.23) for the 3A5 genotype variants, RR 0.98 (95% CI 0.90 to 1.07) for the 3A7 genotype variants, RR 1.01 (95% CI 0.96 to 1.07) for the 2C9 genotype variants and RR 0.98 (95% CI 090 to 1.07) for the 2C19 genotype variants.

Neither CYP3A4, CYP3A5 or CYP3A7 genotype modified the association between benzodiazepine use and risk of a serious incident fall (table 4), nor did the CYP2C19*2 genotype (table 5). We did, however, observe an increasing risk of a serious fall incident with benzodiazepine use dependent on CYP2C9 genotype status (table 6). This was especially the case in users of hypnotics. In the fully adjusted model the risk in current users of hypnotics rose from 1.12 (95% CI 0.84 to 1.49) in the CYP2C9 wild type, to 1.78 (95% CI 1.19 to 2.67) in the heterozygote group, and 1.93 (95% CI 1.11 to 3.36) in the homozygote variant group.

To substantiate the results found for CYP2C9 we performed additional stratified analyses according to use or non-use of inhibitors of the CYPC9 enzyme but the numbers were too low to obtain further results. The models using indicators for missing values in co-variates yielded similar results as the other models implying

that missing data did not play an important role. Additionally, haplotype analysis was performed for CYP2C9 *2 and *3 together, in which no substantial differences were found. Apart from the genotype-effect models given in the tables, dominant, recessive, and allele-effect models yielded similar information. The allele-effect model confirmed the presence of an allele dose-effect which was suggested in the genotype model for CYP2C9 (data not shown).

Table 4 | **Influence of CYP3A-genotype on benzodiazepine associated fall-risk**

		Benzodiazpines crude			Adjusted		Anxiolytics adjusted			Hypnotics adjusted		
stratum	**label**	**No of cases**	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**No of cases**	**HR**	**(95% CI)**	**No of cases**	**HR**	**(95% CI)**
variant cyp3a4*1b		N available = 6249										
AA	no use	426	Ref				561	Ref		569	Ref	
	past use	272	1.09	(0.93 - 1.27)	1.04	(0.89 - 1.22)	210	0.99	(0.85 - 1.17)	169	1.06	(0.89 - 1.26)
	current use	130	**1.34**	**(1.10 - 1.64)**	1.17	(0.96 - 1.44)	57	1.02	(0.77 - 1.34)	90	**1.34**	**(1.06 - 1.68)**
AG	no use	25	Ref				39	Ref		37	Ref	
	past use	30	**2.23**	**(1.29 - 3.85)**	**2.23**	**(1.29 - 3.85)**	20	1.34	(0.77 - 2.33)	19	**1.86**	**(1.05 - 3.28)**
	current use	8	1.56	(0.69 - 3.51)	1.61	(0.71 - 3.67)	4	1.04	(0.37 - 2.97)	7	**2.31**	**(1.00 - 5.32)**
GG	no use	1	Ref				1	Ref		1	Ref	
	past use		N.A.		N.A.			N.A.			N.A.	
variant cyp3a5*3c		N available = 6163										
AA	no use	1	Ref				3	Ref		1	Ref	
	past use	2	4.90	(0.44 - 54.68)	4.73	(0.37 - 60.51)		N.A.		2	5.16	(0.41 - 65.26)
	current use		N.A.		N.A.			N.A.			5.29	N.A.
AG	no use	60	Ref				80	Ref		79	Ref	
	past use	40	1.23	(0.82 - 1.85)	1.22	(0.81 - 1.84)	29	1.06	(0.68 - 1.63)	25	1.09	(0.69 - 1.73)
	current use	17	1.25	(0.72 - 2.17)	1.11	(0.64 - 1.94)	8	0.92	(0.44 - 1.94)	13	1.49	(0.81 - 2.72)
GG	no use	385	Ref				506	Ref		522	Ref	
	past use	253	1.11	(0.95 - 1.31)	1.07	(0.91 - 1.26)	198	1.02	(0.87 - 1.21)	154	1.07	(0.89 - 1.28)
	current use	119	**1.35**	**(1.09 - 1.67)**	1.19	(0.96 - 1.47)	53	1.05	(0.78 - 1.39)	81	**1.31**	**(1.03 - 1.67)**
variant cyp3a7		N available = 6004										
TT	no use	399	Ref				527	Ref		535	Ref	
	past use	267	1.12	(0.96 - 1.31)	1.09	(0.93 - 1.27)	205	1.02	(0.86 - 1.20)	167	1.10	(0.92 - 1.32)
	current use	118	**1.27**	**(1.03 - 1.56)**	1.12	(0.91 - 1.39)	52	0.97	(0.73 - 1.29)	82	**1.30**	**(1.02 - 1.65)**
TG	no use	43	Ref				57	Ref		55	Ref	
	past use	18	0.89	(0.51 - 1.56)	0.84	(0.48 - 1.47)	13	0.70	(0.38 - 1.30)	11	0.86	(0.45 - 1.67)
	current use	16	**2.06**	**(1.14 - 3.72)**	1.76	(0.97 - 3.19)	7	1.26	(0.57 - 2.80)	11	**1.99**	**(1.02 - 3.88)**

* Crude analysis, i.e. adjusted for age and gender

\# Adjusted analysis, i.e. adjusted for age, gender and lower limb disability

Table 5 | **Influence of CYP2C19-genotype on benzodiazepine associated fall-risk**

Cyp2c19*2 genotype N available = 6248		**Benzodiazepines Crude***		**Adjusted#**			**Anxiolytics Adjusted#**			**Hypnotics Adjusted#**	
stratum	**No of cases**	**HR**	(95% CI)	**HR**	(95% CI)	**No of cases**	**HR**	(95% CI)	**No of cases**	**HR**	(95% CI)
1 wild type											
no use	338	Ref		Ref		442	Ref		440	Ref	
past use	204	1.08	(0.91 - 1.30)	1.05	(0.88 – 1.26)	158	0.98	(0.81 - 1.18)	136	**1.24**	**(1.02 - 1.51)**
current use	108	**1.54**	**(1.23 - 1.92)**	1.42	(1.13 – 1.77)	50	1.26	(0.94 - 1.69)	74	**1.64**	**(1.28 - 2.12)**
2 heterozygote											
no use	115	Ref		Ref		155	Ref		160	Ref	
past use	92	1.22	(0.92 - 1.62)	1.19	(0.90 – 1.58)	69	1.16	(0.86 - 1.55)	54	1.00	(0.72 - 1.37)
current use	27	0.86	(0.56 - 1.32)	0.83	(0.54 – 1.27)	10	0.61	(0.32 - 1.17)	20	0.98	(0.61 - 1.58)
3 variant allele (poor metab)											
no use	13	Ref		Ref		20	Ref		18	Ref	
past use	9	1.37	(0.58 - 3.23)	1.21	(0.51 – 2.89)	6	0.94	(0.37 - 2.39)	6	1.09	(0.43 - 2.82)
current use	6	1.60	(0.59 - 4.39)	1.57	(0.57 – 4.35)	2	1.19	(0.27 - 5.24)	4	1.44	(0.47 - 4.43)

* Crude analysis, i.e. adjusted for age and gender

\# Adjusted analysis, i.e. adjusted for age, gender and lower limb disability

Table 6 | **Influence of CYP2C9-genotype on benzodiazepine associated fall-risk**

	Benzodiazepines crude			adjusted		Anxiolytics adjusted			Hypnotics adjusted		
Stratum	**No of cases**	**HR**	(95% CI)	**HR**	(95% CI)	**No of cases**	**HR**	(95% CI)	**No of cases**	**HR**	(95% CI)
Cyp2c9 genotype											
N available = 6494											
1 wild type											
no use	322	Ref				431	Ref		427	Ref	
past use	219	1.15	(0.96 - 1.37)	1.09	(0.92 - 1.31)	156	0.95	(0.79 - 1.14)	145	1.18	(0.97 - 1.43)
current use	87	1.16	(0.91 - 1.47)	1.05	(0.82 - 1.34)	41	0.97	(0.70 - 1.34)	56	1.12	(0.84 - 1.49)
2 heterozygote											
no use	117	Ref				154	Ref		158	Ref	
past use	74	1.17	(0.87 - 1.57)	1.14	(0.85 - 1.53)	60	1.08	(0.80 - 1.46)	41	1.10	(0.78 - 1.56)
current use	38	1.56	(1.07 - 2.27)	1.32	(0.90 - 1.93)	15	0.96	(0.56 - 1.63)	**30**	1.78	(1.19 - 2.67)
3 variant allele (poor metab)											
no use	53	Ref				67	Ref		73	Ref	
past use	32	1.02	(0.65 - 1.59)	0.98	(0.63 - 1.53)	31	1.17	(0.76 - 1.81)	19	0.96	(0.58 - 1.60)
current use	24	2.04	(1.25 - 3.34)	1.72	(1.04 - 2.84)	11	1.50	(0.79 - 2.87)	**17**	1.93	(1.11 - 3.36)

* Crude analysis, i.e. adjusted for age and gender

\# Adjusted analysis, i.e. adjusted for age, gender and lower limb disability

DISCUSSION

In this population-based cohort study we confirmed that benzodiazepines are associated with an increased risk of injurious fall incidents. These findings are in line with the medical literature[10-14]. The fall risk appeared especially increased in users of high-doses of short acting hypnotics, as described before[15].

CYP3A genotype status, being the predominant pathway of benzodiazepine metabolism, did not affect benzodiazepine related fall risk. This was not surprising , since the effect of the major variant allele in CYP3A4 is only modest[20], and has been controversial[35]. In fact, it is believed that induction and inhibition by diet, environmental factors or co-medication are more important in causing the observed 40-fold variation of CYP3A4 activity, than genetic polymorphisms in this gene[36]. Also the massive reserve capacity of this metabolizing system may obscure effects of the polymorphisms of this gene [16, 17]. For CYP3A5 and CYP3A7, the effect of the polymorphisms are well described, but the affinity of these enzymes for the drugs investigated is not known. Based upon our findings in this heterogeneous group of aged benzodiazepine users, it can be concluded that CYP3A5 and CYP3A7 contributions are low, and not clinically relevant. However, it cannot be excluded that for some individual benzodiazepines, an effect of CYP3A5 or CYP3A7 polymorphisms exists.

An important finding in this study is that in comparison to persons with the wild-type genotype, individuals heterozygous or homozygous for either CYP2C9*2 or CYP2C9*3, had an additionally increased risk for serious fall incidents associated with benzodiazepine use. We especially found a clear genotype–dose relationship for hypnotic-treated patients when comparing the homozygotic variant allele (CYP2C9*2 or *3) carriers with the homozygotic wild-type allele carriers.

To our knowledge, there is no literature on CYP2C9 status affecting benzodiazepine metabolism, or benzodiazepine blood concentrations, to confirm our findings with the exception of one study with liver microsomes suggesting that CYP2C9 played a role in the metabolism of the active metabolite of diazepam, N-demethyldiazepam to oxazepam[17]. Analogous clinical problems with toxicity and dosage adjustment of both warfarin[33] and phenytoin have been found in CYP2C9 poor metabolizers (PM) , carrying the CYP2C9*3 allele. This allele has a frequency of approximately 6% in Caucasians, whereas the frequency of homozygous CYP2C9*3 individuals is 0.3%)[26].

On the other hand, it has been shown that the in vivo clearance of benzodiazepines is generally underestimated by in vitro data[27, 37].

In our study, we addressed injurious incident falls, which form only a small proportion of the total number of fall incidents in older persons; approximately 10% in a Dutch cohort study[8]. As a consequence, we cannot be certain as to

whether our findings are generalizable to overall falls in older persons. However, there is no reason to assume that benzodiazepine use would only lead to serious fall incidents and not falls with less serious consequences.

Being an observational study, we have to consider the influence of bias and confounding. Selection bias was negligible because our study population comprised all men and women in the Rotterdam study. Furthermore, our study population was in Hardy-Weinberg equilibrium, suggesting that no selection has occurred among genotypes.

Also, information bias is not likely, since all data on CYP3A genotype, CYP2C9 genotype, CYP2C19 genotype, medication use and serious fall incidents were recorded similarly for all participants without prior knowledge of our study hypothesis.

Random misclassification of the outcome may have occurred due to measurement error. False positive falls are unlikely as only fall incidents that led to a hospital visit or fracture were considered.
Moreover, random misclassification would tend to underestimate rather than overestimate the true risk. Potential confounding factors were dealt with in the analyses. Although residual confounding may still be present, its influence is probably limited as our findings are in line with literature.

In conclusion, this population-based cohort study shows that benzodiazepine use, especially short-acting hypnotics, have a dose dependent influence on fall risk. CYP2C9 variant alleles influence benzodiazepine induced fall-risk, whereas CYP3A and CYP2C19 genotype variants do not. This finding suggests that CYP2C9 plays a more important role in the pharmacokinetics and pharmacodynamics of benzodiazepines than previously assumed. The underlying mechanism however needs to be clarified.

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09

Chapter 9 **| General discussion**

GENERAL DISCUSSION

As described in the 'International Classification of Diseases, 9th revision', falling is a symptom[1], not a diagnosis. A fall is defined[2] as "An unexpected event when the person "falls" to the ground from any level, this also includes falling on the stairs and onto a piece of furniture". Falls result from an interaction of multiple and diverse risk factors and situations, many of which can be corrected[3].

In 1965, Bernard Isaacs described the "giants" of geriatrics, incontinence, immobility, impaired intellect and instability, asserting that all common problems with older people relate back to one of these giants[4].

In the conceptualization of models in geriatric medicine, the variable patterns of illness presentation have given rise to the development of so-called "geriatric syndromes".

The "geriatric syndromes", such as delirium, falls and syncope, incontinence, dizziness and frailty are "multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render (an older) person vulnerable to situational challenges''[5] The usage of the term ''syndrome'' emphasizes multiple causation of a unified manifestation[6]. This is schematically represented in Figure 1.

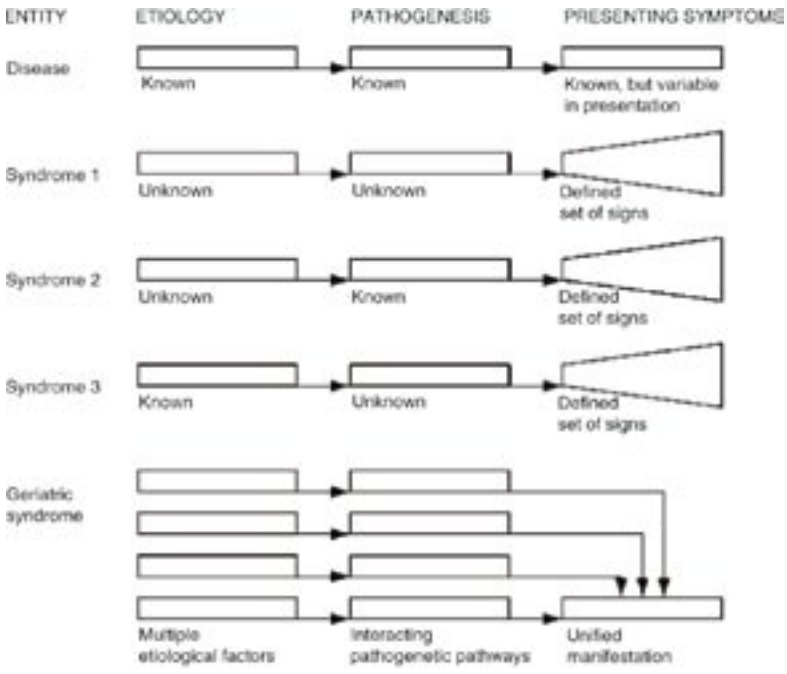

Figure 1 | Schematic conceptual representation of clinical conditions defined by the terms ''disease,'' ''syndrome,'' and ''geriatric syndrome,'' illustrating differences in numbers and complexity of relevant factors, including etiological risk factors, pathophysiological mechanisms, and presenting symptoms. Source: Olde Rikkert et al[6].

In their search for the "holy grail" of a unifying conceptual model for geriatric pathophysiology, the assumption has been made recently by Inouye et al[7] that some geriatric syndromes might share underlying risk factors[5]. In their study, the following risk factors for falls were identified: "older age, prior history of falls, functional impairment, use of a walking aid or assistive device, cognitive impairment or dementia, impaired mobility or low activity level, and balance abnormality". In a further analysis, four shared risk factors (i.e. older age, functional impairment, cognitive impairment, and impaired mobility) were identified consistently across all geriatric syndromes. It is postulated that these findings could raise the possibility of shared pathophysiological mechanisms across these syndromes, making them amenable to targeted interventions. Therefore, a new "Interactive Concentric" model addressing the pathophysiology of multifactorial complex geriatric syndromes has been proposed, supplementary to the "traditional linear model" (figure 2).

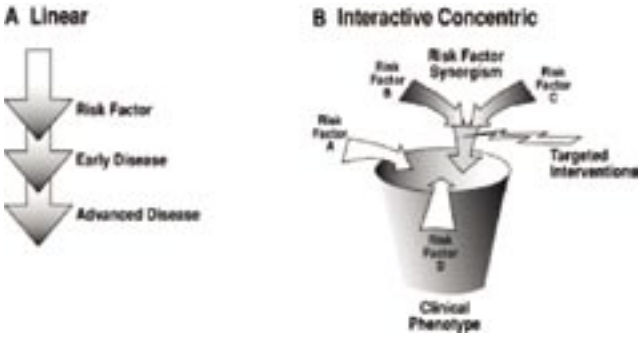

Figure 2 | The traditional linear model (A) does not adequately capture the multifactorial nature of geriatric syndromes. An interactive concentric model (B) is proposed as a means of reconciling the need for mechanistic research with the conditions' multifactorial complexity by focusing on pathways associated with risk factor synergisms, thus offering a locus for the design of targeted interventions. Modified from Inouy et al[7].

The interactive concentric model is attractive, as it offers opportunities for interventions targeted at identified "risk factors". However, the "shared risk factors", used in this model may themselves be composite endpoints of various multifactorial causes, which complicates targeting interventions.

In the "epidemiologic method of conceptualization", the multifactorial process can be explained by a theory on disease risks, described in 1976 (8). Many different risk factors have been identified for falls and in this theory these are called component causes. A combination of these causes (the so-called sufficient cause) results in a fall incident. Nevertheless, different combinations of component causes may lead to the same outcome, e.g. a fall. Therefore, for the individual patient, different component causes might be present that contribute to the total risk of falling (figure 3). *Mutatis mutandis*, "shared risk factors" are presumably

a composite endpoint of various underlying risk factors, of which at least one can be addressed as "necessary cause". In this way, the epidemiologic method contributes more properly to the etiologic analysis of complex geriatric syndromes.

Figure 3 | As can be seen in Figure 3, component cause A is present in all sufficient causes. This component is therefore a necessary cause, since without this factor, the syndrome of interest will not become manifest. (Source Rothman, 1976[8])

The challenge of geriatric medicine is the management of geriatric syndromes. This requires special consideration of three major issues. First, multiple risk factors and multiple organ systems are involved. Second, in applying diagnostic strategies to identify the underlying cause geriatricians have to continuously weigh the expected benefits and possible harm of the necessary investigations, as well as factors dealing with cost effectiveness. Finally, therapeutic management should be evidence -based as much as possible, while evidence in geriatric medicine is sparse.

A commonly used classification for falls distinguishes intrinsic risk factors (e.g., lower extremity weakness, poor grip strength, balance disorders, functional and cognitive impairment, visual deficits)[9, 10] and extrinsic risk factors (e.g., polypharmacy) and environmental factors[11, 12] such as poor lighting, loose carpets, and lack of bathroom safety equipment). The focus of health care services concerning falls is usually on people who are prone to fall[13] (i.e. presence of intrinsic risk factors). For a thorough analysis of falls, however, it is pivotal to perform a comprehensive geriatric multidisciplinary assessment in which each of these contributing factors are identified and valued [3].

Main findings

In the previous chapters, each specific study was described in detail, including the limitations and benefits. In this chapter, the main findings are discussed and placed in the broader context of clinical practice.

Epidemiology of falls

The dimension of falls in the Netherlands

To gain more insight into the burden of illness due to falls over time on a population level we analysed time-trends in the occurrence and characteristics of fall-related hospitalisations in the Netherlands in the period 2001–2004. For this, we used a database containing all hospital discharge records from the Netherlands, the LMR (Landelijke Medische Registratie). We showed a steady age dependent increase in cumulative incidence of fall-related hospital admissions over time from 2.34 (95% CI 2.31-2.36) per 1,000 inhabitants in 2001 to 2.71 (95% CI 2.68-2.73) in 2004, a siginificant increase of almost 20 pecent. A general decline in in-hospital mortality was observed, which was independent of the observed trend towards shorter hospitalisations. As in our study, age specific incidence rates have shown to increase substantially in most Western populations in recent decades[10, 14-17]. This increase in falls cannot be explained merely by demographic changes[18]. We observed a steady increase in fall-related hospitalisations which exceeded the annual growth of the ageing population. Changing demographics worldwide, including the aging of the baby boomers, will be responsible for an increasing need for hospital beds[19]. Additionally, the development of new technologies will lead to an increasing number of patients in the coming years. Possible solutions to decrease the presssure for hospital beds in the future may reside in a progressive decrease in mean duration of hospital stay and a change towards even more day-care treatment[20]. However, net trade-off will lead to a greater pressure on available beds and costs. In this discussion, choices will have to be made as to whether and, if so, where to treat the increasing number of frail elderly patients.

Risk factors for falling.

We presented investigations in the baseline cohort of the Rotterdam Study to determine the risk factors for falls in this population, and to study the possible relationship with drug use. For the study described in chapter 3, we assessed the prevalence of a fall history in the previous year and studied the association between multiple drug use (polypharmacy) and falls in elderly. After excluding subjects with cognitive impairment, 6982 persons from the baseline cohort of the Rotterdam Study were included in the analyses. In this population of whom 1144 persons (16.5%) experienced one or more falls.

After adjustment for age and gender functional impairment and reduced mobility (intrinsic factors) were identified as the most important risk factors for falling. The observed influence of intrinsic factors is in line with previous studies[21-24]. Decreased mobility and decreased capacity to adapt, which can be identified by simple physical examination have a curvilinear association with fall risk. In this, mobility determines the degree of exposure to (external) risk factors for falling. Good mobility coincides with a relatively high exposure, while in case of immobility

there is hardly any exposure to risk factors. As is recently stated in the BGS policy paper[13], anyone can fall given a difficult enough activity. Likewise, anyone can fall doing something quite ordinary if their functional ability is severely hampered, which points at effect modification by the capacity to adapt. Apart from mobility and functionality parameters we were also able to show associations between prevalent falling and exposure to certain rare diseases such as Parkinson's disease or past CVA. Given the large number of subjects with detailed and objective exposure assessment this study provides an extensive overview of circumstances which can facilitate falling.

Hypovolemia

The presence of hypovolemia was assessed using the urea/creatinine ratio as a surrogate parameter. It appeared that hypovolemia, defined as a serum urea/creatinine ratio of 0.1 or above, was present in almost 10% of the study population and was associated with an increased risk of falling of almost 30%. Fall risk increased to 66% (OR 1.66, 95 CI 1.31 – 2.12) if no concomitant diuretics were used in persons below the age of 85 years. The detection of hypovolemia in elderly patients, although a common phenomenon, is difficult. The used measurement methods should ideally be correlated with standardized tests, applying deuterium- and bromide-dilution techniques. In a hospital based study[25], the internal validity of the definition of hypovolemia, using the Ureum/Creatinin Ratio was subject of discussion, however the authors did not define a specific cut-off value. It was further argued that population-based reference ranges would be of limited value in monitoring fluid balance. Correlated with age-related changes in body composition, subject specific reference ranges would be more reliable. Another study, using the same standardized test, found remarkable differences between elderly people living at home and volunteers living in institutional care[26]. According to our definition, derived from a simple laboratory test, hypovolemia in the elderly may be an under-recognized cause of falling. Being a modifiable risk factor, it could be dealt with in assessment programs.

Polypharmacy in the elderly

To study the association between polypharmacy and falls in elderly, we performed a population-based cross sectional study in the baseline cohort of the Rotterdam Study. Polypharmacy was defined as the use of 4 or more drugs per day. Our hypothesis was that the association between polypharmacy and falling could be explained by a higher probability of receiving a risk-increasing drug with the number of drugs taken. We found the risk of falling increasing significantly with the number of drugs used per day (p for trend < 0.0001). After adjustment for a large number of comorbid conditions and disability, polypharmacy remained a significant risk factor for falling. Stratification for polypharmacy with or without at least one drug, which is known to increase fall risk (notably CNS-drugs and

diuretics) disclosed that only polypharmacy with at least one risk drug was associated with an increased risk of falling. Hence we concluded that the major finding of our study is that not polypharmacy itself is associated with an increased fall risk, but the contribution of identifiable risk drugs to this polypharmacy. This is important to emphasize because policy makers tend to treat polypharmacy as one specific homogeneous risk factor whereas in fact the term polypharmacy reflects a heterogeneous cluster of various risk factors for falling. Consequently, this leads to a better opportunity for risk reducing interventions in a frail elderly population in whom polypharmacy is inevitable in order to control the underlying co-morbidity. There are different definitions of polypharmacy in the literature. Within geriatric medicine, usually the definition of 4 or more drugs is used. Polypharmacy (defined as the use of four or more drugs) is associated with an increase in fall risk in older persons[27, 28]. Another possible definition is the use of unnecessary drugs or drugs with the same mode of action[29]. A retrospective study from 1994 until 1997 showed that polypharmacy increased with age and mainly occurred in patients with cardiovascular disease, diabetes mellitus or stomach complaints[29]. For example, evidence-based guidelines for the management of heart failure recommend that a range of medications be considered for patient with heart failure. These may include ACE inhibitors (or, if not tolerated, angiotensin II receptor antagonists), beta blockers, spironolactone, digoxin, and diuretics, depending on the severity of heart failure[30, 31]. All of these medications have been shown to be beneficial: for example, ACE inhibitors and beta blockers have both been shown to improve survival and reduce hospitalisations in patients with heart failure[32, 33]. Consequently, because they suffer from age-related illnesses,elderly people are likely to gain most. However, they are also more likely to experience adverse drug reactions (ADRs). The reasons for the increased frequency of ADRs are complex[34]. In a nationwide study of all hospital admissions, the prevalence of ADRs increased with age from 0.8% (95% CI 0.75, 0.85) in the <18 years group to 3.2% in the >/=80 years group (95% CI 3.08, 3.32)[35]. In addition to polypharmacy, there is also an increased sensitivity for drugs in the elderly caused by age dependent changes in pharmacodynamics and pharmacokinetics[36].

As is stated by Routledge et al : "*Rational* or *obligatory* polypharmacy is becoming a legitimate practice as increasing numbers of individuals live longer and the range of available therapeutic options for many medical conditions increases. The clear risk of ADRs in this situation should be considered in the context that dose-related failure of existing therapy to manage the condition adequately may be one of the most important reasons for admission of elderly to a hospital. Thus, age itself should not be used as a reason for withholding adequate doses of effective therapies" [37]. Finally, in a large population based study on falling in the elderly, it was concluded that co-morbidity, being a relevant recognized risk factor, fully explains the increased risk associated with drug use[22].

Left Ventricular functioning and falls

Chapter 6 contains a prospective, population-based cohort study regarding the association between left ventricular systolic function and falls with serious consequences (e.g. fractures and/or hospital admission) in older adults. In total 2266 participants underwent two-dimensional transthoracic echocardiography. In this study, the risk of a fall with serious consequences was significantly higher if left ventricular ejection fraction (LVEF) was impaired. Trend analysis according to the degree of LVEF was also significant. These findings suggest that poor systolic function as measured with LVEF is a risk indicator for fall incidents with serious consequences. Our hypothesis behind these findings is that persons with a poor cardiac function have a limited reserve cardiac output capacity, which can result in cerebral hypoperfusion, and hence falls, in physically demanding situations[38]. Another possible explanation would be that poor cardiac function might act as a predictor for frailty, since frailty has been shown to predict falls in older persons[39]. However, although the incidence of clinical cardiovascular disease was higher in the frail participants, the Cardiovascular Health Study showed no significant association between frailty and LVEF or mitral valve abnormalities[40]. Data on other valvular abnormalities were not available.

Psychotropic drug use and falls and resulting fractures

Psychotropic drugs have often been implicated in the fall risk in the elderly. Especially tricyclic antidepressants and benzodiazepines are recognized risk factors for falls.

Antidepressants

The traditional treatment of depression with tricyclic antidepressants (TCAs) showed major adverse effects, such as cardiac conduction problems and lethality in overdose. The risk of falls, as a result of the cardiac adverse effects, and consequently fractures, was esteemed as serious. Selective Serotonin Reuptake Inhibitors (SSRIs) were considered safe in comparison with TCAs[41] After their introduction SSRIs were rapidly considered a safe advantage in the treatment of depression in the elderly[42]. As a consequence SSRIs were recommended as the first choice of treatment of depression in elderly. However, increasing data emerged on side effects of SSRI's, such as gastrointestinal effects, hyponatremia[43] as a result of the syndrome of inappropriate antidiuretic hormone (SIADH) and bleeding complications, especially in combination with antithrombotics [44, 45]. New insights into bone metabolism suggest that exposure to SSRIs could also have an effect on bone through the 5-HT receptor[46, 47]. However, studies appeared with conflicting results[48-50]. As depression itself may affect fall risk and even bone strength[51], confounding by indication is an important issue to be dealt with in observational studies. Therefore, we performed a study described in chapter 6, in which we examined the association between antidepressant use and the risk of

non-vertebral fracture while we controlled for the indication. In the first analysis with all participants, we found that, compared to past users, current users of SSRIs had a 2.21-fold (95%CI 1.33 to 3.67) increased risk of fracture, which increased with prolonged use. In the second analysis study, we used a case-control design nested in a cohort of people with a history of treatment of antidepressants. In this way, there was a lower chance of confounding by indication although, admittedly, the time-varying aspect of this indication makes it difficult to exclude residual confounding completely. The use of TCAs was associated with an increased fracture risk which decreased with prolonged use. Prolonged use of SSRI was associated with an increased risk of fracture. At variance with recent studies suggesting an increased risk of bone-loss with SSRI [52,53], we did not observe an effect on BMD. Nevertheless, our study suggests that the safety of SSRIs, initially advocated (and marketed) to be advantageous compared with the "gold standard" of treatment with TCA, should be reconsidered in the light of these long term adverse effects.

Benzodiazepines

The gold standard in the research on drug effects is the randomized controlled clinical trial. Risk estimates obtained in clinical trials will be unbiased by baseline prognosis and confounding by indication will be absent[52]. However, randomized trials are very expensive and pharmaceutical companies have no commercial interest in such studies because patents of benzodiazepines have expired. Therefore, observational studies on benzodiazepine effects on fall risk are of additional value. Benzodiazepines are a known modifiable risk factor for falling in the elderly with considerable impact due to the high exposure prevalence in this group [27, 53-56]. Once prescribed, these drugs are difficult to stop[56]. The increased risk may probably be explained by prescribing too-high doses to the elderly[57], suggesting that blood concentrations may play a role, rather than the use of long- and short-acting benzodiazepines[27]. Although differences exist between different types of benzodiazepines, the oxidative metabolism seems to be the primary route of elimination for all. Genetic polymorphisms in the P450 system have shown to affect drug blood concentrations or clinical effects of many drugs. With respect to benzodiazepines, polymorphisms in this system may therefore play a role in benzodiazepine induced fall risk. In the study described in chapter 8, we could demonstrate that drug response can be modified by the genotype, especially the CYP450 2C9 subfamily. Genotype variations in the gene encoding CYP3A isoenzyme, being the predominant element in benzodiazepine metabolism, did not affect benzodiazepine related fall risk. This was not totally unexpected, since the effect of the major variant allele in CYP3A4 is only modest[58], and has been controversial[59]. In fact, it is believed that induction and inhibition by diet, environmental factors or co-medication are more important in influencing CYP3A4 activity, than the most frequent genetic polymorphisms in this gene[60]. A limitation of our findings is that we studied only one polymorphism for CYP3A4, 3A5 and 3A7

whereas many other known or unkown ones might play a role. The new technique of Genome-wide association studies might contribute further information on this point. Another limitation is that efforts to study gene-environment interactions are complicated by the difficulty in obtaining adequate sample size[61-63]. As a consequence, we were not able to perform in-depth analyses on individual drugs. In our study on gene-environment interaction we used the genotype-model and classified drug exposure in different strata, although we also investigated other models with more or less similar results. To our knowledge, this is the first study to the association of cytochrome P450 gene polymorphisms and fall risk. Our finding suggests that CYP2C9 may play a more important role in the pharmacokinetics of benzodiazepines than previously assumed. Because of the limited number of observational pharmacogenetic studies on the role of CYP2C9 in benzodiazepine action, however, our findings warrant replication by others.

Methodological considerations

Pharmaco-epidemiological studies have an important role in studying unintended (adverse) effects of drugs. The methodological considerations of the presented studies have been discussed in the individual chapters. In the current paragraph, we review general methodological issues such as study setting and design, the use of time-dependent exposure variables and the important epidemiological issue of confounding by indication.

Study setting

All studies described in this thesis used data from 2 population-based data sources: 1) the Rotterdam Study, a prospective population-based cohort study among 7983 older adults living in Ommoord, a suburb of Rotterdam[64] and 2) the National Morbidity Registration (LMR) , a nationwide computer database for all hospital discharge records, the LMR (Landelijke Medische Registratie) database. In the Rotterdam Study a large population of older adults is included in a follow-up program. Its strengths are the relatively long follow-up period and the extensive information available on all participants. In addition to follow-up surveys, the total cohort is continuously being monitored for major morbidity and mortality through linkage of general practitioner and municipal mortality records. Furthermore, all participants fill their prescriptions in automated pharmacies linked to one computer network. Data on all dispensed drugs since 1 January 1991 are available in computerized format on a day-to-day basis. AII information is gathered before, and irrespective of, the outcome under study for the large majority of the study participants. This limits the chance of selection bias and information bias.

Study design

Cross-sectional design

The first studies were performed with a cross-sectional design. The reason for this was the baseline assessment of fall history. Although multiple risk factors could be analysed together in one model the cross-sectional nature has obvious disadvantages. The most important shortcoming is the uncertainty of a temporal relationship. The results of these studies should therefore rather be regarded as hypothesis generating. In order to substantiate the findings of the cross-sectional studies, further prospective studies are needed.

Methodology of time-varying exposure to medication

Information about medication use until 1991 was reported by the participants during the interview at the start of their inclusion in The Rotterdam Study. Information about medication use since 1991 was available for all participants on a day-to-day basis by using computerized pharmacy data. This allowed us to calculate the duration of use per drug for each participant at each time point, which results in a higher precision of information about medication use and a considerable increase of the total number of exposed participants with less misclassification of exposure. In order to adjust for changing risks over time due to changes in medication use we choose a time-dependent Cox-proportional hazards model in our analyses of drugs use and fall risk. Although compiling a dataset with time-dependent exposure is complicated and puts high demands on the computer hardware the model has several advantages[65]. The model allowed us to compare different types of exposure: current and past exposure, low dose and high dose, short duration long duration.

Bias and confounding

In observational studies, selection bias, information bias and/or confounding may jeopardize the validity. In the population-based Rotterdam Study, selection bias is probably limited although non-participants may be sicker. It is likely, however, that this would tend to underestimate our findings rather than inflate our risk estimates. Because all information in the Rotterdam Study is prospectively gathered, information bias is unlikely. In our studies where an intervention with medication potentially played a role in the etiology of falling, confounding by indication was the most challenging issue to be dealt with. The indication depression has been recognized as an important risk factor for falls[51, 66]. It predicts functional decline and the onset of excess disability[67], such as poor physical function, falls, and low bone density, all of which increase susceptibility to osteoporotic and traumatic fractures[68].In most observational studies[69-71] that investigated dose and duration effects of antidepressants on the risk of fracture, almost always non-users were chosen as the reference group[72]. It was argued that previous studies

analyzing the relationship between depression and fractures that controlled for falls found no association between depression and fractures. In these studies, confounding by indication remains a potential problem since the differences in patient characteristics, which are related to exposure and outcome, are probably large and difficult to adjust for. To control for potential confounding by indication in our study described in chapter 7, we adjusted for the indication of the therapy, i.e. depression at baseline and we performed an analysis in a nested case-control model. Residual confounding in such a model, however, cannot be excluded.

Future implications

The studies in this thesis point at areas in geriatric medicine regarding falling, which have room for improvement. These concern research related and policy related issues.

Research issues

First, further research is needed analysing incident falls in a prospective setting. Such a study could be used to build a predictive model of falls on independent risk factors. In order to adequately deal with confounding by indication in this study it would be useful to assess the indications for drug prescriptions. Second, given the association with cardiovascular risk factors it may be worthwhile to perform an intervention study on cardiovascular treatment and fall risk. Finally, effect modification of drug induced fall risk by genetic variations is an intriguing issue, especially in this elderly population in whom genetic effects (i.e. expression and phenotype) may be different from a younger population. More knowledge about the effect of (known) genetic variations in the elderly in general and regarding fall risk in specific will help developing preventive control measures in geriatric medicine.

Policy issues

Including more elderly patients in clinical trials before the marketing of new drugs might be a good initiative to increase the knowledge about the subtle balance between optimum drug dosages, drug-drug, or drug-co-morbidity interactions and adverse reactions in the elderly. Since falls are not registered as an official ADR, they are often not recognized as such[73] and up to now, trials were not specifically designed with concern to fall risk. Therefore, in new research projects, falls have to be included as a potential serious adverse drug reaction, especially when it concerns high-risk pharmacotherapy such as cardiovascular and psychotropic drugs. Research in daily clinical practice might be even more important, because the setting in the real world of medical practice is different from the setting in randomised clinical trials. Clinical trials are performed in a highly controlled clinical setting, which may not mimic the setting in which the drug will ultimately be used. Therefore, it is of utmost importance that elderly patients are included

in "phase-IV trials", or other types of post-marketing studies, as long as they are well-designed and not meant as a form of seeding to enhance prescribing. New fields of research appear. For research in geriatric medicine, the concept of "mendelian-randomization" [74-76]offers attractive opportunities. Many adverse effects have a genetic basis. As the prescriber is not aware of such genetic risk factors an observational study with incident users of a drug can be regarded as a randomised clinical trial. Although, of course, no randomisation takes place prescribing will take place in such a way that it is largely unaffected by genetic factors. It should be emphasized, however, that this is only true when the genetic risk factor is not associated with prognosis itself. Under favourable circumstances, however, 'mendelian randomisation' may help to gain more insight into potentially harmful genotype - drug interactions. Hereto, prospective studies can be performed in a "single-blinded" setting, in which controlled prescribing of drugs (e.g. psychotropics) can be done, relatively simply, in an out-patient clinic setting, performing outcome analysis on different endpoints (e.g. falls, fractures, mortality). Obviously, genotype analysis results should not be reported to the prescriber to maintain the single blinded status. The introduction of "electronic medical dossiers" (EMD) will provide an outstanding opportunity to analyse medical data by linking them to general pharmacy records, conditional on the adherence to current privacy legislation. The recent introduction of the "Diagnose Behandel Combinatie" (DBC) however, bears the threat of misclassification of diagnoses. It is an ominous example that, as a result of these regulations, the Dutch health care authorities recently decided to stop the formerly obligatory registration of hospitalisation-related diagnoses[77].

Guideline implementation

The policy regarding fall risk reduction will have to be set out by the health care professionals, with or without the authorities. Professional organisations have already undertaken action by generating 'Fall- prevention guidelines in geriatric patients'[3, 13, 21], in which both diagnostic and interventional strategies are discussed. The health authorities could start from this guidelines, after which implementation could take place according to the model of the European Foundation for Quality Management (EFQM)[78]. The model goals will be met conditional on leadership, employees, strategy and policy, tools and processes. In this process several barriers have been identified which have to be overcome. These can be divided into knowledge (e.g. lack of awareness that falls are preventable), attitudinal (e.g. lack of importance assigned to falls by providers), and organizational barriers (e.g. the uncoordinated nature of the healthcare system or health care providers focusing on diseases, rather than multifactorial geriatric syndromes)[7].

In the Netherlands, guideline implementation has been initiated under the auspices of the "Dutch Institute for Healthcare Improvement (CBO)". As is stated on the website[79]: "The highest priority for medical professionals is to be able to

offer their patients an ever better quality of care. After all, it is management that creates the requisite conditions for innovation and improvement. In this way it fulfils an important function, by setting an example. The integration of professional and organizational quality improvement forms the basis for optimal care. Both parties always put the patient's interests first".

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Chapter 10 **| Summary**

SUMMARY

Falls are among the most common and serious problems facing older persons and are associated with considerable morbidity and mortality. They often lead to reduced functioning and nursing home admissions. The incidence of falls as well as the severity of fall-related complications rises steeply beyond the age of 60 years. Among all community dwelling persons of 65 years and over, 30-40% have at least one fall each year. The incidence of falls in nursing homes and hospitals is almost 3 times as high as in the community. Not all falls of older adults result in injury, but 4% to 5% of the falls cause a fracture, and an additional 5% to 11% of falls cause other serious injuries, e.g., serious soft tissue contusions, joint distortions and dislocations, severe wounds and lacerations, and head injuries. Unintentional injuries are the fifth leading cause of death in older adults, and falls are responsible for two-thirds of the deaths resulting from unintentional injuries.
A number of studies have identified risk factors for falling. A commonly used classification for falls distinguishes between intrinsic, extrinsic and environmental factors. The risk of falling, i.e., the chance to experience one or more falls per year, increases dramatically if the number of risk factors increases. Polypharmacy (defined as the use of four or more medications) is regarded as an important risk factor for falling in the elderly. To reduce the fall risk within the older population all risk factors need to be assessed. Special efforts should be made to identify modifiable risk factors which can be useful for undertaking effective interventions.

In this thesis, investigations are described concerning the occurrence and consequences of falls in the Netherlands, to address risk factors for falls and to explore the association of drug use with falls and fall related fractures in more depth. Main analyses were performed in the Rotterdam Study, a prospective population-based cohort study. Additionally, the 'Landelijke Medische Registratie' (LMR) database was used, a registry that stores discharge information from all hospitalizations in the Netherlands. Both data sources could be combined by record linkage.

Chapter 1 gives a general introduction to falls in the elderly, in which we outlined the problem and formulated the main research objective of this thesis on drugs as a potential risk factor for falling. In **chapter 2**, we studied the incidence and characteristics of fall-related acute hospitalisations in the Netherlands in the period 2001-2004 using a nationwide computer database for all hospital discharge records, the LMR (Landelijke Medische Registratie) database. We found an increase in the cumulative incidence of fall-related hospitalisations, which exceeded the annual growth of the ageing population. The most frequent main diagnosis implicated 'fracture of neck of femur' (33.9%). In **chapter 3**, a cross-sectional study is described on the prevalence of falls in the baseline cohort of the Rotterdam Study, with an emphasis on the association with drug use. We found that 16.5% of persons aged 55 years and older experienced one or more

falls per year. The prevalence of falls strongly increased with age. Falls were more common in women than in men. Fall risk increased with increasing disability, presence of locomotor problems, functional restrictions, psychosocial limitations and comorbid conditions. Because of the large number of participants in this study, associations were also shown between prevalent falling and exposure to certain rare diseases such as Parkinson's disease or history of stroke. The risk of falling increased significantly with the number of drugs used per day (p for trend < 0.0001). In **chapter 4**, we focused on the association of falls and hypovolemia, defined as a serum Urea/Creatinin ratio of 0.1 or above. Hypovolemia was present in almost 10% of the participants and was associated with an increased risk of falling of almost 30%. Fall risk increased to 66% if no concomitant diuretics were used in persons below the age of 85 years. The results seem to indicate that hypovolemia, being a modifiable risk factor, may be an under-recognized cause of falling. In **chapter 5**, we examined the influence of polypharmacy on fall risk. It was demonstrated that the risk of falling increased significantly with the number of drugs used per day (p for trend < 0.0001), even after adjustment for a large number of comorbid conditions and disability. This was, however, only the case when at least one established fall risk increasing drug (notably CNS-drugs and diuretics) was part of the daily regimen. **Chapter 6** focuses on cardiovascular determinants of falls, notably left ventricular systolic function, measured with echocardiography. The risk of a serious incident fall during follow-up was significantly higher if left ventricular ejection fraction was impaired. Fractures related to osteoporosis and falling constitute a major health problem in the elderly population. Exposure to antidepressants is associated with an increased risk of falls and fractures, but most previous studies incriminate tricyclic antidepressants (TCAs) rather than selective serotonin reuptake inhibitors (SSRIs). In **chapter 7**, a prospective population-based cohort study is described concerning the risk of non-vertebral fracture in which we addressed the issue of confounding by indication. We could demonstrate that not only users of TCAs but also of SSRIs have a significantly increased risk of non-vertebral fractures, especially after prolonged use. The association between benzodiazepine use, cytochrome P450 gene polymorphisms, and fall incidence was studied in **chapter 8**. Benzodiazepines are a known modifiable risk factor for falling in the elderly with considerable impact due to the high exposure prevalence in this group. In a population-based cohort study we showed that CYP2C9 variant alleles influenced benzodiazepine induced fall-risk, whereas CYP3A and CYP2C19 genotype variants did not. This finding suggests that CYP2C9 plays a more important role in the pharmacokinetics and pharmacodynamics of benzodiazepines than previously assumed.

In the general discussion in **chapter 9**, the main findings are summarized and some methodological issues are discussed. In addition, recommendations for future research and implications for falls-prevention strategies in elderly, by means of 'guideline-implementation' are discussed.

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Chapter 11 **| Samenvatting**

SAMENVATTING

Vallen vormt een groot gezondheidsprobleem bij ouderen, omdat het veel voorkomt en ernstige gevolgen kan hebben. Vallen leidt vaak tot een afname van de zelfredzaamheid en tot verpleeghuisopname. De incidentie van vallen, maar ook de ernst van valgerelateerde complicaties stijgt fors na het zestigste levensjaar. Ongeveer 30 - 40% van de zelfstandig wonende ouderen van 65 jaar en ouder valt ten minste een keer per jaar. Bij verpleeg- en verzorgingshuisbewoners is de incidentie bijna 3 maal zo hoog. Niet elke val bij ouderen leidt tot letsel, maar in 4 à 5% treedt een fractuur op en in nog eens 5 tot 11% is er sprake van ernstige gevolgen, zoals kneuzingen, verstuikingen en dislocaties, ernstige wonden en rupturen, en hersenletsel. Bij ouderen is onintentioneel letsel de vijfde doodsoorzaak. Tweederde hiervan is ontstaan door een val.

In een aantal studies is onderzoek gedaan naar risicofactoren voor vallen. Een vaak gebruikte indeling voor vallen maakt onderscheid tussen intrinsieke, extrinsieke en omgevingsfactoren. De kans om te vallen, dat wil zeggen het risico om eens of vaker per jaar te vallen, stijgt dramatisch met het aantal aanwezige risicofactoren voor een val.

Om reductie van het valrisico bij ouderen te kunnen bewerkstelligen dient onderzoek naar alle aanwezige risicofactoren plaats te vinden. Ten behoeve van potentieel effectieve interventies dient hierbij speciaal aandacht geschonken te worden aan modificeerbare risicofactoren. Polyfarmacie, gedefinieerd als het (gelijktijdig) gebruik van vier of meer geneesmiddelen, wordt bij ouderen als een belangrijke modificeerbare risicofactor voor vallen beschouwd.

In dit proefschrift wordt onderzoek beschreven naar het voorkomen en de gevolgen van vallen in Nederland. Daarnaast wordt dieper ingegaan op onderzoek naar risicofactoren van vallen en de associatie tussen het gebruik van geneesmiddelen en vallen, dan wel valgerelateerde fracturen. Alle studies, die hier worden beschreven, zijn uitgevoerd binnen het Rotterdamse ERGO – onderzoek (Erasmus Rotterdam Gezondheid en Ouderen), internationaal bekend als "The Rotterdam Study". Dit is een prospectief bevolkingsonderzoek naar de frequentie en oorzaken van chronische ziekten bij ouderen. Aanvullend werd gebruik gemaakt van de gegevens van de "Landelijke Medische Registratie" (LMR), een bestand, waarin ontslaggegevens van alle ziekenhuisopnames in Nederland zijn opgeslagen. Deze beide gegevensbestanden konden met elkaar worden verbonden door probabilistische koppeling.

Na een algemene introductie over vallen bij ouderen wordt in **hoofdstuk 1** ingegaan op het belangrijkste onderzoeksdoel van dit proefschrift, namelijk geneesmiddelgebruik als een mogelijke risicofactor voor vallen. In **hoofdstuk 2** onderzochten we de incidentie en de karakteristieken van valgerelateerde ziekenhuisopnames in Nederland in de periode 2001 – 2004. Hierbij werd gebruik gemaakt van het bovengenoemde geautomatiseerde gegevensbestand met alle ontslaggegevens, de LMR. We vonden een stijging van de cumulatieve incidentie van

valgerelateerde ziekenhuisopnames, die uitsteeg boven de jaarlijkse groei van de vergrijzende bevolking. De meest gestelde diagnose betrof een collumfractuur van het femur (33.9%). In **hoofdstuk 3** wordt een *cross-sectionele* studie beschreven naar de prevalentie van vallen in het *baseline* - cohort van het ERGO-onderzoek ("the Rotterdam Study"). Hierin werd nadrukkelijk gekeken naar de associatie tussen geneesmiddelgebruik en vallen. We vonden dat 16.5% van alle deelnemers, die 55 jaar of ouder waren, tenminste een keer per jaar viel. De valfrequentie steeg fors met toenemende leeftijd. Vallen kwam vaker voor bij vrouwen dan bij mannen. Het valrisico nam toe met een toenemende afhankelijkheid, de aanwezigheid van locomotore problemen, functionele beperkingen, psychosociale belemmeringen en bijkomende ziekten. Vanwege het grote aantal participanten in deze studie konden ook associaties worden beschreven tussen vallen en de aanwezigheid van zeldzame ziekten, zoals de Ziekte van Parkinson, of een beroerte. De kans om te vallen nam significant toe met het aantal gelijktijdig gebruikte geneesmiddelen (p-waarde voor trend <0.0001). De relatie tussen vallen en hypovolemie, gedefinieerd als een Ureum/Kreatinine ratio van 0.1 of hoger wordt beschreven in **hoofdstuk 4**. Hypovolemie was bij 10% van de deelnemers aanwezig en bleek geassocieerd met een verhoogd valrisico tot bijna 30%. In ouderen tot 85 jaar steeg het valrisco tot 66% als zij niet gelijktijdig diuretica gebruikten. Deze resultaten wijzen erop dat hypovolemie, als een beïnvloedbare risicofactor, een onderschatte oorzaak zou kunnen zijn van vallen. In **hoofdstuk 5** onderzochten we de invloed van polyfarmacie op de kans om te vallen. We konden aantonen dat de kans om te vallen significant toe nam met het aantal gelijktijdig gebruikte geneesmiddelen (p-waarde voor trend <0.0001), zelfs na correctie voor een groot aantal bijkomende ziekten en beperkingen. Deze associatie bleek echter alleen aanwezig als tenminste één geneesmiddel met een aangetoond valrisico deel uitmaakte van het dagelijks gebruikte geneesmiddelenregime. **Hoofdstuk 6** gaat in op cardiovasculaire determinanten van vallen, met name de linker ventrikelfunctie, gemeten met echocardiografie. De kans op een ernstige incidente val in het cohort-onderzoek bleek significant hoger als sprake was van een verminderde linker-ventrikel ejectie fractie.

Fracturen als gevolg van osteoporose en vallen vormen een belangrijk gezondheidsprobleem voor de verouderende bevolking. Het gebruik van antidepressiva is geassocieerd met een verhoogde kans op vallen en fracturen, maar in de meeste beschreven studies wordt meer gewezen op het schadelijke effect van tricyclische antidepressiva (TCA's) dan dat van selectieve serotonine heropname remmers (SSRI's). In **hoofdstuk 7** wordt een prospectief cohort onderzoek beschreven naar de kans op een niet-vertebrale fractuur bij gebruik van antidepressiva, waarbij gelijktijdig werd gecorrigeerd voor het effect van de onderliggende depressie. We konden aantonen dat niet alleen gebruikers van TCA's een verhoogde kans hadden op niet-vertebrale fracturen, maar dat dit ook gold voor gebruikers van SSRI's, vooral bij langdurig gebruik. De associatie

tussen benzodiazepine gebruik, een aantal cytochroom P450 polymorfismen en vallen wordt beschreven in **hoofdstuk 8**. Benzodiazepines zijn een bekende en belangrijke, beïnvloedbare risicofactor voor vallen bij ouderen. In een prospectieve cohort studie konden we aantonen dat CYP2C9 variant allelen het valrisico door benzodiazepines beïnvloeden, terwijl dat niet het geval was bij CYP3A en CYP2C19 varianten. Deze bevindingen wijzen erop dat CYP2C9 wellicht een belangrijkere rol speelt in de farmacokinetiek en farmacodynamiek van benzodiazepines dan voorheen werd aangenomen. In de algemene discussie in **hoofdstuk 9** worden de belangrijkste bevindingen uit dit proefschrift samengevat en in een bredere context geplaatst. Tevens worden enkele methodologische zaken besproken en worden aanbevelingen gedaan voor toekomstig onderzoek en de incorporatie hiervan in richtlijn ontwikkeling ten behoeve van strategieën voor valpreventie bij ouderen.

D

| Dankwoord

DANKWOORD

Nu het boekje klaar is wordt nog eens duidelijk hoe zeer je bij een project als dit afhankelijk bent van de bereidwilligheid en hulp van velen. Graag wil ik hier de gelegenheid nemen om een aantal van hen te noemen.

Allereerst mijn promotor, Prof.dr. B.H.Ch. Stricker. Bruno, ik ben je zeer dankbaar voor je enorm stimulerende no-nonsense begeleiding in de afgelopen jaren. Jij leerde me de juiste onderzoeksvragen te stellen, wat erg helpt wanneer je als "hemelbestormende clinicus" begint met epidemiologisch onderzoek. Soms leidden onze discussies tot zeer interessante omtrekkende bewegingen, maar ik heb nooit het gevoel gehad dat we daarmee verder van het uiteindelijk doel afkwamen. Ik heb daarnaast zeer genoten van onze gesprekken tussendoor, ook over onderwerpen die helemaal niets met wetenschap te maken hadden. Het aanvankelijke gevoel van verwondering en vreugde dat jij mijn promotor wilde zijn is in de loop van deze periode uitgegroeid tot groot respect voor jouw kwaliteiten.

Mijn co-promotor, Dr. J.P. Dieleman. Beste Jeanne, een beetje vreemd moet het aanvankelijk wel zijn geweest, dat zo'n "ouwere jongere", die al lang had moeten genieten van zijn klinische taken bij jou in de leer mocht komen om de beginselen van het farmaco-epidemiologisch onderzoek onder de knie te krijgen. Naast al je andere taken was je altijd bereid weer bij te springen als een analyse, vooral de syntax, weer eens vastliep en het vaak uiteindelijk alleen maar om het verkeerd plaatsen van een punt ging. Ik ben je zeer erkentelijk voor de nauwgezetheid waarmee je telkens weer mijn manuscripten hebt beoordeeld, maar nog meer voor de wijze waarop we hebben samen gewerkt.

Mijn tweede co-promotor Dr. T.J.M. van der Cammen, hoofd van de sector geriatrie. Beste Tischa, hopelijk heeft mijn werk ook een bijdrage geleverd aan de realisatie van jouw ideaal om Rotterdam als kliniek geriatrie meer "body" te geven. Ik ben dankbaar voor de ruimte die ik heb gekregen om naast mijn klinisch taken dit promotie-onderzoek te mogen doen. Gelukkig heeft de klinische productie er niet onder hoeven lijden.

Prof.dr. H.A.P. Pols wil ik danken voor het in mij gestelde vertrouwen om zo'n perifere jongen een dienstverband in de academie te geven. Beste Huib, ik heb veel geleerd van jouw soms wat temptatieve wijze van bevragen als ik weer dacht dat ik wel snapte wat de inhoud van mijn manuscript was. Het dwong me telkens weer even terug naar de basis te gaan om van daaruit weer verder te komen. Dat heeft mijn ontwikkeling gestimuleerd. Twee uitspraken die je bij mijn aanstelling deed hebben grote indruk op me gemaakt: "maak er geen olifantsdracht van" en "ik wil één mijl met je meelopen". Het eerste is gelukt, voor het tweede ben ik je dankbaar.

Prof. J.H.P. Wilson en Prof.dr. M.G.M. Olde Rikkert dank ik voor hun bereidheid om zitting te nemen in de kleine commissie en voor de inhoudelijke beoordeling van dit proefschrift. Maar de loop van de dingen heeft er voor gezorgd dat jullie beiden voor mij meer betekenen dan toevallige commissie leden. Beste Paul, waarschijnlijk zonder het te weten heb jij voor mij al vanaf het begin van mijn studie geneeskunde een onvergetelijke rol gespeeld. Jouw eerste-jaars colleges bevestigden mijn gevoel de juiste studie te hebben gekozen. Ik mocht aan het eind artsexamen, voor wat betreft de interne geneeskunde, bij jou doen. Je speelde een rol bij het verwerven van mijn eerste baan en later, na mijn terugkeer in Rotterdam werden we collega's en mocht ik enkele van jouw patiënten verder begeleiden. En tenslotte wilde je secretaris zijn van de kleine commissie.

Beste Marcel, nu collega en opponent, al meer dan 15 jaar geleden beiden een deel van onze opleiding gedaan in Arnhem, ik denk met plezier terug aan een "winter meeting" in Oostende, toen je al bijna echt Vlaams begon te spreken.

Prof.dr. A. Hofman wil ik danken voor de gelegenheid die hij mij bood om met ERGO-data onderzoek te mogen doen. Beste Bert, ik heb daarnaast erg genoten van jouw enthousiasmerende wijze van doceren binnen het NIHES onderwijs. Dat laatste geldt ook Prof.dr. Th. Stijnen, die statistiek zo inzichtelijk wist te maken dat je het wel leuk moest vinden. En als je het dan onverhoopt toch niet snapte met een geweldige oplossing kwam: "just believe it".

Ron van Schaik ben ik bijzonder erkentelijk voor het bepalen van de CYP polymorfismen, vooral CYP2C19. Ron, dat je tussen alle verplichtingen door ook nog dit wilde doen en inhoudelijk wilde meedenken over de invloed van benzo-metabolisme op het valrisico heb ik zeer gewaardeerd.

De deelnemers, huisartsen, apothekers en medewerkers op het centrum van het ERGO onderzoek ben ik zeer erkentelijk voor hun deelname en medewerking.

Mijn kamergenoten Jan Heeringa en Henning Tiemeier wil ik bijzonder danken voor de verbale en non-verbale steun die ik in de afgelopen jaren heb ervaren. Samen met Bruno op één kamer is toch wel een interessante mix van "oudere - jongeren en jongere - ouderen". Behalve dat er op onze kamer altijd keihard wordt gewerkt is het toch ook wel jammer dat er zo weinig beleidsmakers op de hoogte zijn van de uitkomsten van onze beschouwingen over het wereldleed, die we naast al dat harde werken gratuit voeren. Ik denk stellig dat als we hierin weten te volharden het ongetwijfeld weer goed komt met alles, en de wereld in het bijzonder.

Alle collega's van de sectie farmaco-epidemiologie Albert-Jan, Ana, Bettie, Charlotte, Claire, Cornelis, Dika, Eva, Geert, Georgio, Gianluca, Gysèle, Ingo,

Katia, Laura, Loes, Mariëtte, Marissa, Mark, Martina, Matthijs, Mendel, Miriam, Monique, Roelof, Sabine, Sarah, Yannick dank ik voor de plezierige sfeer, het soms even willen meekijken, -denken en -doen, en de inspirerende discussies tijdens de staf.

Graag wil ik Nano danken voor alle hulp bij computerproblemen, Frank voor de hulp bij database en SPSS perikelen en Yolande voor alle hulp bij het opsnorren van de "incidente vallers".

In de kliniek gaat mijn dank uit naar Arend, Diana, Francesco en Jaap voor de hulp, waarneming tijdens weer eens een cursus en het verdragen van mijn soms wat wisselend humeur, vooral in deze laatste fase. Ik waardeer de goede onderlinge samenwerking en het plezier dat we met elkaar hebben. Nathalie, het tweede boekje over vallen uit onze groep binnen een jaar. Dank voor de samenwerking en co-auteurschap. Ik prijs me bijzonder gelukkig in het Havenziekenhuis te mogen samenwerken met een groot aantal directe collega's binnen polikliniek, het DCG en afdeling geriatrie en daarnaast alle collega's in de medische staf. Hanneke, Anneke, Anne, Wil, Josien en Edwien dank ik voor hun secretariële ondersteuning.

Ook wil ik graag collega Dr. P.J. Barendregt, reumatoloog, bedanken. Beste Erna, zonder jouw hulp had ik de helft van dit boekje misschien wel moeten laten typen.

Mijn opleiders, Dr. P.G. Gerlag, internist en Dr. E. Bruijns, klinisch geriater ben ik erkentelijk voor hun bijdrage aan mijn vorming tot specialist. Overigens wil ik daarbij de inspanningen van Marja Jellesma en Prof. Dr. S.A. Duursma, beiden klinisch geriater, niet onvermeld laten.

Jorrit van der Velden ben ik zeer erkentelijk voor de prachtige opmaak van dit boekje. Wat een werk, Jorrit en alles toch nog 'just in time'.

Voor de foto op de omslag, een verbeelding van sterren en de invloed van de zwaartekracht, dank ik Jan Koeman, medewerker van Volkssterrenwacht Philippus Lansbergen, te Middelburg. Het is een leuke coïncidentie dat precies daar 400 jaar geleden de telescoop werd uitgevonden.

Vrienden wil ik bedanken voor hun steun, belangstelling en gezelschap de afgelopen jaren. Deze dank geldt ook mijn zus Arianne en haar gezin.

Mijn paranimfen en goede vrienden, Frans le Fèvre en Chris Laarman. Ik ben heel erg blij dat jullie me terzijde willen staan. Het symboliseert een gevoel wat aanwezig is vanaf het eerste moment dat wij elkaar leerden kennen. Chris en Ida,

heel hartelijk dank voor wat jullie voor ons betekenen! Frans en Adriana, het is heel bijzonder deze dag samen te mogen beleven. Dank voor al jullie liefde en vriendschap!

Moeder Laarman, hartelijk dank voor uw liefde en hulp in al die jaren!

Mijn ouders ben ik zeer dankbaar voor hun liefde en betrokkenheid. Ik ben dankbaar met alle kansen die u mij heeft geboden om me te kunnen ontwikkelen tot wie ik nu ben. Maar evenzeer dank voor alle praktische hulp in al die jaren. Ik hoop dat u kunt genieten van dit resultaat.

Tenslotte, mijn thuisbasis. Lieve Ageeth, Gijs en Johanneke. Promoveren naast een baan is redelijk tijdrovend. Daardoor kwam de tijd die we samen konden doorbrengen nog wel eens onder druk te staan. Ik ben jullie heel dankbaar voor het telkens weer royaal bieden van alle ruimte en begrip.

Liefste Schat, jouw onvoorwaardelijke liefde en steun heeft mij in staat gesteld om ook dit project tot een goed einde te brengen. Er liggen weer voldoende bezigheden in het verschiet, “never a dull moment”.

C

| Curriculium vitae

CURRICULUM VITAE

Curriculum vitae van de auteur van dit proefschrift.

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1978	Start studie Geneeskunde, Erasmus Universiteit Rotterdam
1985	Artsexamen, Erasmus Universiteit, Rotterdam
1985- 1986	Arts-assistent Interne Geneeskunde, St.Jozef Ziekenhuis, Heemskerk
1986 – 1987	Foreign Medical Graduate Examination in the Medical Sciences
1986	Start opleiding voor het specialisme klinische geriatrie
1986 – 1988	Interne geneeskunde, St. Joseph Ziekenhuis Eindhoven, Dr. P.G. Gerlag
1989 – 1991	Klinische geriatrie, Rijnstate Ziekenhuis Arnhem, Dr. E. Bruijns
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De auteur is gehuwd met Ageeth Laarman, zij hebben twee kinderen, Gijs & Johanneke.

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