Single and combined use of fall-risk-increasing drugs and fracture risk:

A population-based case-control study

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Single and combined use of fall-risk-increasing drugs and fracture risk: A Population-based case-control study

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Zusammenfassung

Hintergrund: Viele Medikamentengruppen sind bei älteren Menschen mit Stürzen assoziiert, jedoch ist wenig darüber bekannt, wie sich das absolute Risiko erhöht und wie diese Risiken bei verschiedenen Medikamentengruppen oder Individuen variieren.

Methodik und Design: Es wurde eine bevölkerungsbasierte Fall-Kontroll-Studie durchgeführt, bei der Menschen im Alter von ≥65 Jahren in den schottischen Regionen Tayside und Fife untersucht wurden. Die Fälle waren Personen, die zwischen 2010 und 2020 mit einer Fraktur ins Krankenhaus eingeliefert wurden. Diesen ordneten wir bis zu 10 Kontrollen zu. Wir untersuchten relative und absolute Risiken von Medikamentengruppen, die als "Fall-risk-increasing drugs" (FRIDs) bekannt sind, allein und in Kombination und bei jüngeren und älteren (≥75 Jahre) Patienten. Unter Berücksichtigung von früheren Krankenhauseinweisungen, Medikamenteneinnahme und Laborwerten verwendeten wir die konditionale logistische Regression, um Assoziationen zwischen Medikamentenexpositionen und Frakturen zu quantifizieren. Wir führten vier Sensitivitätsanalysen durch, um die Stärke unserer Ergebnisse zu testen.

Ergebnisse: Die Kohorte umfasste 246 535 Menschen im Alter von ≥65 Jahren, von denen 18 456 eine Fraktur erlitten. Das Frakturrisiko war für die meisten untersuchten FRIDs signifikant erhöht. Die absoluten Risiken waren bei älteren im Vergleich zu jüngeren Menschen höher, und sowohl die relativen als auch die absoluten Risiken nahmen mit der Anzahl der kombinierten FRIDs zu. Die höchsten absoluten Risikoerhöhungen fanden sich bei Menschen im Alter von ≥75 Jahren, die selektive Serotonin-Wiederaufnahmehemmer (Number needed to harm (NNH) 53), trizyklische Antidepressiva (NNH 81), Antipsychotika (NNH 75) und drei oder mehr FRIDs (NNH ≤66) einnahmen.

Schlussfolgerung: Patienten im Alter von ≥75 Jahren, denen Antidepressiva oder Antipsychotika verschrieben wurden oder die drei oder mehr FRIDs einnehmen, können am meisten von einer Absetzung profitieren.

Schlüsselwörter: Stürze, FRIDs, Fraktur, unerwünschte Arzneimittelwirkung

Abstract

Background. While many drug groups are associated with falls in older people, less is known about absolute increases in risk and how these risks vary across different groups of drugs or individuals.

Method and Design. We conducted a population based nested case control study among people aged ≥65 years in the Scottish regions of Tayside and Fife. Cases were individuals hospitalised with a fracture between 2010 and 2020, to whom we matched up to 10 controls. We examined relative and absolute risks of drug groups known as "Fall-Risk-Increasing Drugs" (FRIDs), alone and in combination, and among younger and older (≥75 years) adults. Adjusting for previous hospitalisations, drug use and laboratory data, we used conditional logistic regression to quantify associations between drug exposures and outcomes. We conducted four sensitivity analyses to test the robustness of our findings.

Results. The cohort comprised 246 535 people aged ≥65 years, of whom 18,456 suffered an incident fracture. Fracture risks were significantly increased for most FRIDs examined. Absolute risks were much larger among older vs younger people and both relative and absolute risks increased with the number of FRIDs combined. Overall, the highest absolute increase in risk were found in people aged ≥75 years for selective serotonin reuptake inhibitors (number needed to harm 53), tricyclic antidepressants (NNH 81), antipsychotics (NNH 75) and use of three or more FRIDs (NNH ≤66).

Conclusion. Patients aged ≥75 years prescribed antidepressants or antipsychotics or taking three or more drugs that increase risk of falls may benefit most from deprescribing interventions.

Keywords: falls, fall risk increasing drugs, fractures, adverse drug events

List of Abbreviations

aOR	adjusted Odds Ratio
BPH	Benign Prostate Hyperplasia
BNF	British National Formulary
CKD	Chronic Kidney Disease
DMARD	Disease Modifying Anti-Rheumatic Drug
eGFR	estimated Glomerular Filtration Rate
EPMS	extrapyramidal syndrome
FRID	Fall-Risk-Increasing Drug
GP	General Practitioner
ICD	International Statistical Classification of Diseases
NHS	National Health Service
NNH	Number Needed to Harm
mARS	modified Anticholinergic Risk Scale
medCDS	medication-based Chronic Disease Score
SD	Standard Deviation
SIMD	Scottish Index of Multiple Deprivation
SSRI	Selective Serotonin Reuptake Inhibitor
STOPPFall	Screening Tool of Older Persons Prescriptions in older adults with high fall-risk
TCA	Tricyclic Antidepressant
U.S.	United States
UK	United Kingdom
WHO	World Health Organization

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1 Introduction

1.1 Background

Today, people have a higher life expectancy than previous generations and can now expect to live well past 60 years. The World Health Organization (WHO) estimates that by 2050, 22 % of the world's population will be over 60 years old, twice as many as today [1]. In general, old age brings a continuous decrease in physical and mental performance, however, the extent is different for each individual. This circumstance increases the susceptibility of the elderly population to suffer various accidents and subsequent injuries [1]. One of these are falls, which are a major source of injuries for elderly people aged 65 and older [2]. Aging populations and the likely increase in the incidence of falls and fall-related injuries have a major impact on the society and the health system on the one hand but also on each individual on the other [3, 4]. Counteracting this rapidly progressive development will be one of the greatest efforts in the near future [5].

1.2 Epidemiology falls

According to the WHO, falls are defined as “inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects” [6]. Today, one out of three community-dwelling elderly people aged 65 or older and 40 % of those aged 80 years or older experience a fall each year. The proportion of people who experience a fall is even higher among nursing home residents, where almost half of the inhabitants experience at least one fall each year. Generally, the incidence of falls in the elderly population increases with age in parallel to the decrease of physical and mental capacities [7]. In addition, studies revealed differences in the susceptibility to suffer a fall between sexes. Women experience falls more frequently and also need to be treated more often after a fall than men. Nevertheless, the rate of fatal falls is higher in men than in women [8, 9]. Out of elderly people who fall, more than 30 % suffer an injury that impairs daily life or requires medical intervention [8]. For instance, in 2018, over eight million elderly citizens in the United States (U.S.) needed medical help after falling [10]. This makes falls one of the most common causes of injury among older people [11]. With a view to demographic changes, it is estimated that the rates of fall-related injuries will increase steadily [12]. In particular, it is predicted that by the end of 2050, annual hip fractures, as an example for fall-related fractures, will reach more than 6.2 million worldwide [13].

1.3 Burden and consequences of falls

1.3.1 Individual

Falls and fall-related injuries frequently result in reduced health and quality of life. One of the most severe consequences elderly people can experience due to a fall are fractures. In particular, the hip and femur are most commonly affected [14, 15] of which up to 90 % are the result of a previous fall [16]. According to the national hip database from the United Kingdom (UK), the incidence of hip fractures is a growing problem. They pointed out that the prevalence of patients suffering from these injuries increases each year in parallel to their medical care expenses [17]. Apart from the hip, the upper limbs, especially humerus and radius, and the head and neck region are also frequently affected [18].

These injuries have a substantial impact on the quality of life of elderly people. In many cases, fall-related fractures are not only associated with a stay in hospital but also with lengthy rehabilitation measures, without any assurance of regaining the original physical resilience. A large proportion of those with fall-related fractures have lasting restrictions in their daily life. This can range from losing the ability to walk without assistance to complete dependency [19, 20]. Furthermore, the risk for being admitted to a long-term care facility after a fall was significantly increased in a study of Donald et al. [21]. A further study also pointed out that for the participants who fell, the risk of death was increased in the following 120 days [22].

Moreover, possible surgical interventions after a fall harbour additional sources of complications, such as nosocomial infections, deep vein thrombosis or bedsores. With hip surgery in particular, there is an increased rate of mortality by up to 36 % in the year after the intervention. It is evident, that patients who had such a surgical treatment generally have a reduced life expectancy than those of the same age who did not [23-25].

In addition to the physical impairments that can result from a fall, there are also psychological ones. Older people who have experienced a fall may limit their daily life to the extent that they develop insecurity about their movement which may lead to unsafe gait and to increasing social isolation [26]. Commonly, this phenomenon is known as post fall syndrome [26]. For instance, Murphy et al. [26] found that almost 30 % of elderly patients developed an unsafe gait and inability to walk alone within four months after a fall despite being physically capable to do so. Also Vellas et al. [27] revealed in their study the impact of a fall and the subsequent fear of the next fall. They pointed out that 32 % of the fallers felt a noticeable fear of the next fall. Among those with fear of falling, a significantly increased impaired balance and ability to walk in general could be determined compared to period before the fall.

Falls are also one of the most important aetiologies of accidental deaths in elderly people [28]. One study revealed that older people with a fracture had a mortality rate of about 11.5 % /14.1 % in women/men within the following 90 days [11]. Moreover, Euro-Safe´s comprehensive injury report, published in 2016, pointed out that almost 52 000 people over the age of 65 died from a fall annually [2]. Further, fall-related deaths increased by nearly 60 % between 1999 and 2019 as data from the U.S. showed [29]. In the U.S., the National Centre of Health Statistics published in 2016 that unintentional injuries are among the leading causes of death in elderly people. The majority of these injuries are caused by falls [30].

The latter in particular shows that falls and subsequent fall-related injuries represent a great danger in old age, especially concerning losing one´s independent life and is even a potential threat to die.

1.3.2 Society and health system

Falls and fall-related injuries are a major socioeconomic problem. However, it is quite difficult to calculate the exact cost of a fall as there is not just the direct immediate medical care but also indirect long-term costs. These arise from rehabilitation, long-term care in the event of total or partial loss of mobility, and the possible loss of income for the person concerned and for relatives who are absent due to the need for care [31]. Nevertheless, there are several studies which quantified the financial burden.

In 2015, health care expenditures in the U.S. were estimated at $50 billion for falls alone [32]. There are also figures from the same year on the differences in the costs of fatal and non-fatal falls. Here, the medical costs of the fatal ones amounted to around $637 million, the non-fatal to $31 billion. Calculated for each individual fall, the cost is approximately $9780 per fall treated. Compared to costs in 2000, there has been an immense increase in the expenditures to the health care system, as, for example, the cost of non-fatal falls has nearly doubled in just 15 years [33]. With the outlook of a rise of the older population and thus the problem of falls, these numbers will continue to rise over the next decades. The Centre of Disease Control and Prevention in the U.S. estimates that by the end of 2030, the fatal falls per year will be over 100 000 and the expenses for falls for the health system will surpass the $100 billion mark [34].

With regard to expanses in Europe, the health care costs are likewise high. In the Netherlands, a study between 2007 and 2009 revealed, that more than €675 million per year were incurred in medical expenditures due to falls. They showed that older patients beyond 80 years were primarily responsible for the main part of the costs, namely for up to 66 %. In figures, the costs of a fall increased from €3900 for people between 65 and 69 to up to 14 600 for people over 85. Furthermore, 80 % of the total costs were estimated for fall-related fractures alone. This study also pointed out that there were differences regarding gender and age since the expenses per fall for women were estimated at €9990 and for men at €7510 [35]. Further, a study published 2015 and carried out in the UK revealed that hip fractures and their immediate medical care cost the National Health Service (NHS) approximately £1 billion annually.

Given that 90 % of all admitted hip fractures are due to falls, it is clear that falls place a substantial financial burden on society [36].

Additionally to the direct hospital costs, there are also indirect expenditures such as for rehabilitation [37]. Elderly people suffered a fall-related injury have to be frequently treated further in long term care facilities. It is estimated that between 6 and 60 % of people with a hip fracture admitted into such a facility after initial hospital treatment. Cost predictions here range from $19 000 to $66 000 [38].

Another factor burdening the health care system is the high bed occupancy rate attributable to falls. In the U.S., over 800 000 people who suffered a fall are hospitalized each year, 300 000 of whom are elderly people with hip fractures requiring intensive care [39]. In the UK, the 2018 published national hip database stated that hip fractures alone accounted for 1,5 million bed days with a mean hospital length of 20 days, amounting to a permanent occupancy of over 3600 NHS beds [17].

Falls are therefore a major burden to individuals, to the health system and to society in general, which is expected to rise substantially with ageing societies [34].

1.4 Causes and risk factors for falling

1.4.1 Causes

Rubenstein et al. [40] published several causes why older people fall. The three most common major causes are accident/environment-related, gait/balance difficulties and muscle weakness and as well as dizziness and vertigo. Regarding the accidental/environmental-related cause it has to be mentioned that a large number of factors play together here. In most cases it is a combination of the environment affecting and the decreasing ability to adapt to it due to aging. Here, risk factors [41], explained in the following, play a major role. According to Rubenstein et al. [40], minor causes of falls were drop attack, confusion, visual disorders and postural hypotension.

1.4.2 Risk factors

Numerous factors influence fall risk directly or indirectly. Various classifications of these risk factors are discussed in the literature. A simplified classification is that of intrinsic and extrinsic factors. Intrinsic ones are generally determined genetically and physiologically. Extrinsic factors originate from the environment [40]. In general, intrinsic factors contribute to fall risk in people aged 80 and older to a higher extent in comparison to the group younger than 75, where extrinsic factors are more important [42]. Furthermore, some factors are modifiable, others not. Important to mention is that there are no clear boundaries and that in most cases, multiple risk factors interact [41] as illustrated in Figure 1.

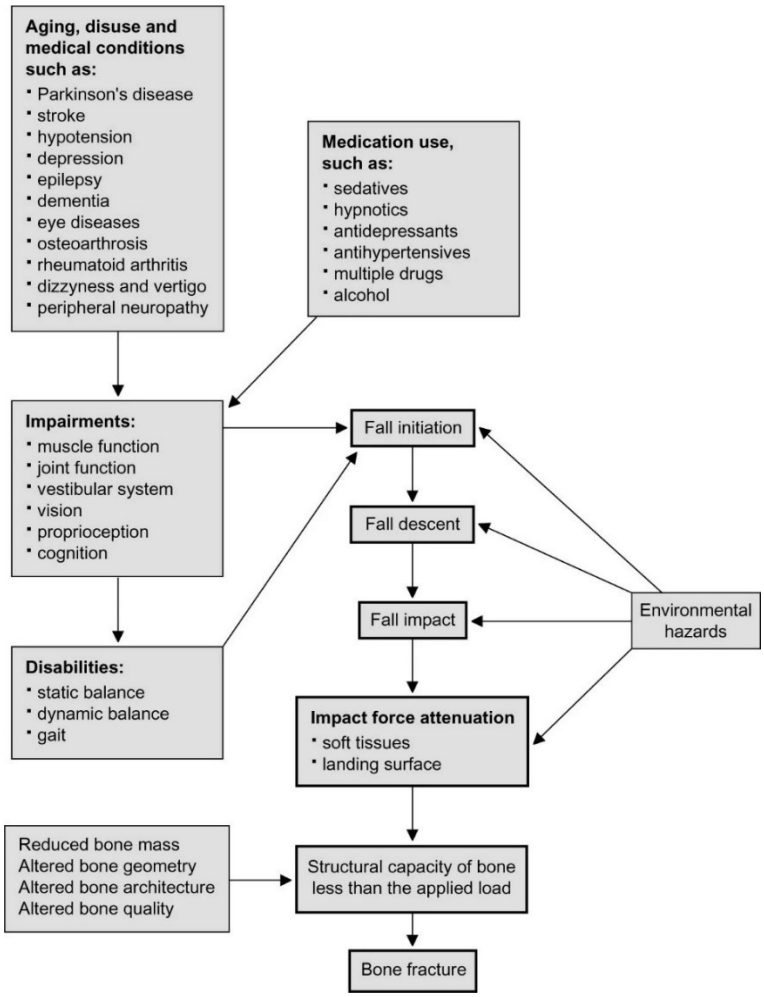

Figure 1: Multifactorial model of risk factors for falls and fall-related fractures [41]

1.4.3 Extrinsic factors

Concerning the environmental factors which contribute to increased fall-risk are for example the lack of adequate aids in everyday life such as proper and safe access to the bathroom or rails at staircases. Further, insufficient lighting and uneven floors belong to extrinsic factors. Generally, environmental hazards and missing strategies to cope with them are an important source of falling [43]. Further factors are a lack of age-appropriate foot wear and also the misuse of walking aids [44].

In addition, the socioeconomic status influences the risk of falling. Especially elderly women living alone and affected by socioeconomic deprivation are the most frequently affected group who fall [45]. Another study found that there was a significant correlation between patients living in deprived areas and increased hospital admissions due to falls [46].

In general, extrinsic factors play a role in 20 % to 50 % of falls [43, 47].

1.4.4 Intrinsic factors

Sociodemographic factors, such as age and gender, have an important prediction regarding the fall-risk. The risk of falling increases significantly with age, as it is the highest above 80 years of age. This circumstance is due to the constant decline in physical and mental abilities, which is an inevitable consequence of aging [45]. Furthermore, women in particular have a higher risk of falling than men of the same age [2].

One of the strongest predictors of a fall is a history of falling [26]. This is attributed to the frequently observed post fall syndrome (see section 1.3.1).

Moreover, the incidence of living alone and being unmarried revealed to be a risk factor, especially in women. This can be explained by the reduced social and physical abilities linked to old age [48].

Further, factors which influence the balance and mobility contribute to an increased fall risk including impairment of gait or stability when standing. The decrease in physical capacities is due to the normal aging process. Nevertheless, the higher the loss of physical capacities (like increasing muscle weakness), the higher is the risk of falling. Basically, any kind of movement impairments and disabilities in the musculoskeletal system are associated with an increased fall-risk [49].

Additional intrinsic risk factors are reduced visual capacities and the gradual loss in sensory capacities. Difficulties in vision are strongly linked to a higher risk of falling, especially in elderly people [50].

Various deteriorations of health are contributed to intrinsic factors as well, such as arthritis, diabetes mellitus, incontinence, chronic pulmonary diseases, chronic kidney disease and chronic cardiac diseases. Furthermore, patients with diseases that impair cognition like Alzheimer's disease, dementia or depression also have a higher risk of falling [51-55]. In addition, patients with proven cancer diagnosis have a significantly higher fall-risk than peers without this diagnosis [56]. The same applies for patients with terminal diseases as they sooner or later experience a decline in their mental and physical capacities [57]. Diseases that affect bones, such as osteoporosis itself, but also certain liver diseases or vitamin D deficiencies belong to intrinsic factors as well [58-62]. In general, the more mental and physical health deteriorates due to an illness, but also due to the natural aging process, the greater is the risk of falling [63, 64].

One major intrinsic factor in the clinical sense is medication. In general, medication may have a substantial impact on the mental and physical functioning of a patient, and not only for the better. It is estimated that up to 10 % of all admissions of elderly people to the hospital are attributable to adverse drug effects of which almost half are considered avoidable [65, 66]. It is known that polypharmacy (commonly defined as the use of 5 or more medicines concomitantly) can impair coordination and balance, lead to dizziness and difficulties with alertness which subsequently can increase the fall-risk and fall-related injuries, especially in elderly people [40]. Single drugs but also polypharmacy has been shown to be associated with an increased incidence of fall-related fractures [67]. Polypharmacy may amplify fall risk increasing adverse drug effects of single drugs via drug-drug or drug-disease interactions [68].

1.5 Fall-Risk-Increasing Drugs

Various drugs, so called Fall-Risk-Increasing Drugs (FRIDs), belong to one of the most outstanding but also modifiable intrinsic risk factors for falling, as previous studies pointed out [69, 70]. Recently, systematic reviews and meta-analysis [71-73] as well as a panel of experts as part of the STOPPFall study [74] have dealt extensively with these FRIDs. The STOPPFall study is a Delphi study conducted by the European Geriatric Medicine Society Task and Finish Group on FRIDs. The study aimed to develop a screening tool for identifying potentially inappropriate medications that increase the risk of falls in older adults. The study involved a panel of experts who used a structured process to develop and refine the screening tool through multiple rounds of feedback and consensus-building. The final tool, called STOPPFall, consists of a list of medications that should be avoided or used with caution in older adults with a high risk of falls [74]. These are displayed in Table 1.

The prescribing practice of many of these FRIDs, however, is contrary to this background knowledge. The trend clearly shows a continuous increase, which is particularly true for psychotropic drugs, such as antidepressants, and opioids [75-78]. However, other FRIDs are also among the most commonly prescribed medications, especially in the elderly population, such as diuretics [79-82].

Table 1: Fall-Risk-Increasing Drugs [74]

Drug class	FRIDs
Cardiovascular	Alpha-blockers used as antihypertensives
	Central-acting antihypertensive drugs
	Vasodilators in cardiac diseases
	Diuretics
Psychotropics	Antidepressants
	Antipsychotics
	Benzodiazepine-related drugs
	Benzodiazepines
Others	Opioids
	Anticholinergics
	Overactive bladder and urge incontinence medication
	Antiepileptic drugs
	Alpha-blockers used for benign prostate hyperplasia (BPH)
	Antihistamines

Though, the STOPPFall Expert Panel also noted that potential fall-risk may vary within each FRID group and subgroup as showed in Table 2 [74]. For example, subgroups of psychotropic drugs and opioids may differ substantially in their potential to cause adverse effects related to falls. It is therefore assumed that, for example, tricyclic antidepressants (TCAs) and strong opioids each have the highest fall risk in their FRID groups due to their side effect profile, such as sedation, lowered vigilance, dizziness and reduced muscle tone [83, 84].

Table 2: STOPPFall hypotheses [74]

Drugs	Hypotheses
Antipsychotics	Risk difference is related to variation in sedative, anticholinergic and alpha receptor properties
Opioids	Strong opioids are more fall-risk-increasing than weak opioids
Antidepressants	TCAs are more fall-risk-increasing than others; Risk difference is related to variation in sedative effects, propensity to cause orthostatic hypotension and anticholinergic properties
Anticholinergics	Medications with stronger anticholinergic properties are more fall-risk increasing than weak anticholinergics
Antiepileptics	Older generation antiepileptics are more fall-risk-increasing than newer antiepileptics
Diuretics	Loop diuretics are more fall risk increasing than other diuretics
Alpha blockers BPH	Non-selective alpha blockers are more fall-risk-increasing than selective ones
Antihistamines	First-generation antihistamines are more fall risk-increasing than second generation antihistamines; Risk difference is related to variation in sedative effects and anticholinergic activity
Overactive bladder and urge incontinence medication	Risk difference is related to variation in anticholinergic activity
Oral hypoglycaemics	Oral hypoglycaemic agents that can cause hypoglycaemia, sulfonylureas, are more risk-increasing than other agents

1.6 Fall prevention measures

As falls are of multifactorial sources a broad spectrum of factors has to be evaluated and adjusted. It is of great importance to recognize such risk factors described in detail as early as possible and to take precautionary measures. There are numerous strategies and tools for the assessment of possible risk factors in old age patients aiming to prevent individual and socioeconomic consequences of falls and fall-related injuries [85, 86]. Generally, the most important factors are maintaining the physical performance capacity, maintaining bone mass and preventing the loss of bone tissue. This can be combined with the reduction of extrinsic risk factors such as hazards in the home environment. It was pointed out that these interventions belong to the most effective measures preventing falls and subsequent injuries [87]. Concerning the extrinsic risk factors, adapting the environment to physical requirements typical in old age is a possibility that can reduce the fall-risk by almost a third [88, 89].

1.6.1 Drug improvement

Improving medication use (i.e. in compliance with up to date knowledge of the specific properties of each medication) is one of the most important interventions for fall prevention [90]. Due to the high prevalence of many FRIDs in the elderly population, it is of great importance to critically review and adjust the corresponding medication use and consider possible deprescribing [87].

In general, there are many studies indicating the withdrawal of FRIDs leads to a reduction of falls [91]. For instance, Campbell et al. [92] investigated the reduction of psychotropic drugs and the following impact on the risk of falls. They found a decrease in the relative risk of falls, odds ratio (OR) 0.34 (95% Confidence Interval (CI), 0.16-0.74), for this elderly group compared with the patients who continued drug therapy. Similar protective results regarding psychotropic drug deprescribing were shown by Joester et al. and Iyer et al. [93, 94]. However, there are also other studies that have come to opposite conclusions [95].

This circumstance suggests a multifactorial relationship [42], from which it can be concluded that the complete withdrawal of medication, e.g. FRIDs, does not automatically lead to fewer falls and fall-related fractures since many patients depend on their medication due to their diseases [95].

In conclusion, safety measures concerning medication to reduce the risk of falls are generally a difficult undertaking to implement. On the one hand, many elderly patients are dependent on certain medications, and on the other hand, it is known that some of these medications have a broad side-effect profile which can increase the fall-risk. In this context, it is important to assess the risk-benefit balance but also to improve the knowledge about these FRIDs and also about differences regarding the fall-risk within the individual drug groups and subgroups, as there seems to be a high heterogeneity [74].

1.7 Aim of work

This research intends to advance the understanding of the drug groups and subgroups that the STOPPFall expert panel recently defined as FRIDs in terms of their relative fall-risk and subsequent fall-related fractures. The STOPPFall experts make the assumptions that the fall-risk may not be the same within the diverse FRID groups and that the risk of falls and fall-related fractures varies [74]. As described in detail, subgroups of antidepressants, opioids or diuretics seem to differ profoundly in their potential to cause falls and subsequent fractures [83, 84, 96, 97]. Furthermore, since polypharmacy is common practice among the elderly [98], the risk of certain FRIDs may be modified due to the concomitant use of other FRIDs. However, few studies have examined interactions between FRIDs [99, 100]. In addition, most previous studies report the relative increase in fall and fracture-risk associated with FRIDs, but the absolute increase (number needed to harm - NNH) is more relevant to therapeutic decision making. The NNH depends on the detected falls incidence in study populations, which in turn depends on fall detection methods that are often vulnerable to reporting bias. Lastly, although several observational studies have examined the relationship between medications and falls in elderly, there haven't been many studies that have stratified by age but examined older patients as a whole [71-73]. Since the risk of falling and suffering from subsequent fall-related fractures increases with age [45], there might be an alteration of the fall and fracture-risk in different age groups.

The objectives of this observational study are to examine the relative and absolute increase in risk of fall-related fractures associated with drug groups classified by STOPPFall as FRIDs, differences in risk among younger and older people aged ≥65 years, differences in risk between subgroups of drugs classified as FRIDs and differences in risk when FRIDs and FRID subgroups are combined.

2 Methods

2.1 Study design and setting

We conducted case-control analyses nested in a dynamic population-based cohort of individuals aged 65 years and older. The exposures of interest were cardiovascular, psychotropic and other FRIDs included in the STOPPFall list (Table 1) [74] as well as the number of these FRIDs taken concomitantly.

All patients were residents of the Tayside and Fife regions of Scotland. Tayside and Fife have a combined population of approximately 900 000 people and are broadly representative of Scotland in terms of age and socioeconomic status. Access to the NHS Scotland is unrestricted and free of charge. This includes all patient and outpatient services as well as medication. All analyses were conducted using non-identifiable data, so that ethical approval was not required.

2.2 Data set

The data set was provided by the University of Dundee/NHS Tayside Health Informatics Centre and apart from patient demographics (e.g. sex, gender, month of birth, dates of registration/deregistration with a general practice, date of death), contained data on all dispensed prescriptions, inpatient and outpatient laboratory data and hospital admissions. The study period was from January 2010 to December 2020. Data was provided on all Tayside/Fife residents who were registered with a general practitioner (GP) in the region, and who were either 65 years or older at the beginning of the study period or turned 65 years before the end of the study period.

2.3 Study cohort

In order to quantify the fracture risks associated with exposure to each FRID versus no such exposure, we constructed a cohort of people aged 65 years and older with secondary stratification by age (65 to 74 years vs 75 years and older). The study period was 01/01/2010 to 31/12/2020. We required all participants to have been registered with an NHS Tayside/Fife general practitioner for at least 12 months before entering each cohort and we excluded individuals with a fracture during this baseline period. Cohort entry was the first date after the end of the baseline period that patients had reached the age of 65 years. Follow up continued until the first occurrence of the following: deregistration with a NHS Tayside/Fife GP, occurrence of a case defining event, death or end of the study period. Since we were interested in fractures originating in the community, follow up excluded periods of hospital inpatient treatment. For an illustration see Figure 2.

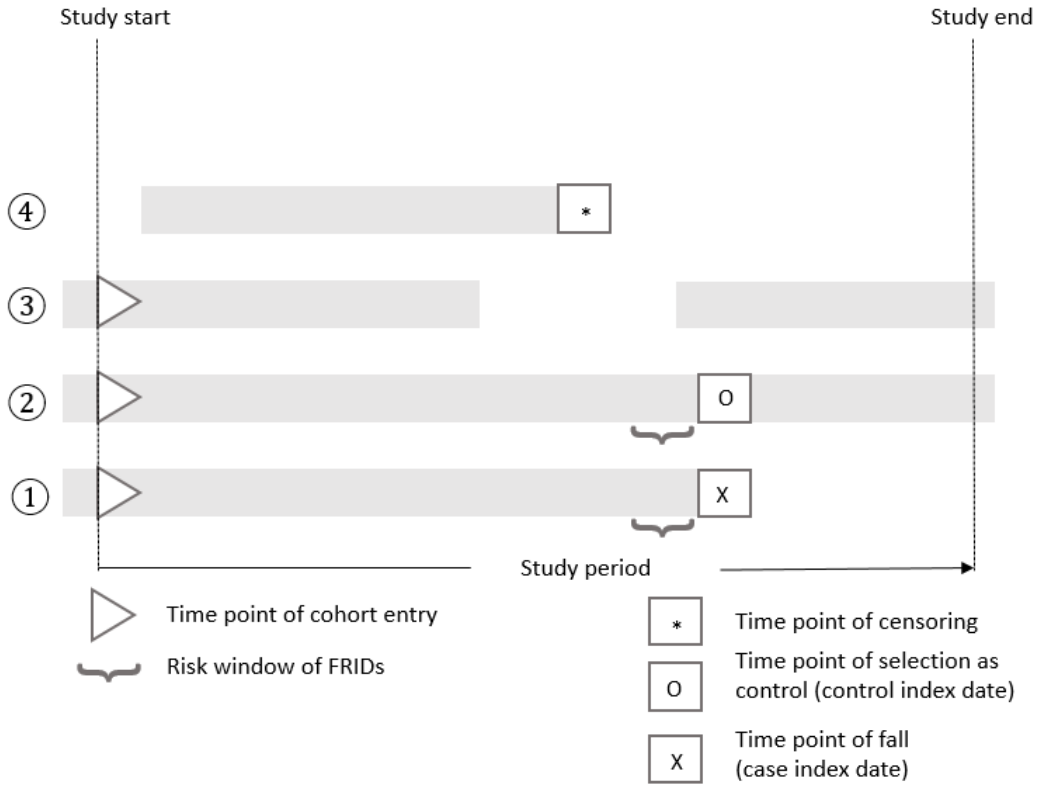

Figure 2: Illustration of the dynamic study cohort

Figure 2 shows four exemplary patients (①-④) who enter the cohort with their 65th birthday or registration with a GP in the Tayside and Fife region during the study period. Patient ④ meets one of the inclusion criteria after the study period was started, whereas the other users did it before. Only patient ② remains a member of the cohort from the study start to end. Patient 1 exits the cohort at the point of suffering a fall, patient ③ at the end point of no longer being registered to a GP and patient ④ is censored at the point of meeting one or more exclusion criteria. Only patient ② is eligible as a control for patient ① because all other patients are not members of the cohort at the time that patient ① became a case.

2.4 Definition of cases

Cases were subjects who experienced an admission with documentation of a fall-related fracture as the main reason for admission. Only the first of such events was considered and the patient was censored afterwards. The index date was the admission date of the respective emergency hospital admission. As fall-related fractures, we defined all fractures via the documented codes of the 10th revision of the International Statistical Classification of Diseases (ICD10th) [101] as displayed in Table 3.

Table 3: ICD10th Codes of fall-related fractures

ICD10th Codes	**Fractures**
S02	Skull and facial bones
S12	Neck
S22	Rib(s), sternum and thoracic spine
S32	Lumbar spine and pelvis
S42	Shoulder and upper arm
S52	Forearm
S62	Wrist and hand level
S72	Femur

ICD^{10th} Codes	Fractures
S82	Lower leg, including ankle
S92	Foot, except ankle
T02	Involving multiple body regions
T08	Spine, level unspecified
T10	Upper limb, level unspecified
T12	Lower limb, level unspecified
T14.2	Unspecified body region

We further identified fractures according to their respective body region, e.g. of the femur, vertebrae, arm, leg and others (including head, neck, thorax, pelvis and fractures not further specified), shown in Table 4.

Table 4: ICD^{10th} Codes of respective body regions

Body regions	ICD^{10th} Codes
Femur	S72
Vertebrae	S12.0, S12.1, S12.2, S12.7, S12.9, S22.0, S22.1, S32.0, S32.1, S32.2, T08
Arm	S42, S52, S62, T10
Leg	S82, S92, T12
Others	S02, S12.8, S22.2, S22.3, S22.4, S22.5, S22.8, S22.9, S32.3, S32.4, S32.5, S32.7, S32.8, T02, T14.2

In addition to the ICD^{10th} Codes, the specific admission type to the hospital was also defined. In our study, we only included admissions which were of emergency type and further excluded road traffic accident, self-inflicted, at work and type not known. We did this to exclude elective admissions and to exclude fractures caused by an accident other than a fall.

2.5 Selection of controls

For each case, we randomly selected up to 10 matched controls from those who were members of the cohort on the calendar date of the case defining event (index date). The specific matching criteria were: gender, age (± 12 months), follow up time since last entry into the cohort (± 1 quarter) and calendar time of the case defining event (same quarter). Each member of the cohort could therefore be selected as a control for more than one case. When matched to a case, controls were therefore alive, registered with an NHS Tayside/Fife general practice, had a similar follow up time and were members of the cohort at the same calendar time of the case defining event.

2.6 Exposure assessment

The exposure window was defined as 90 days prior to the index date. Cases and controls were considered exposed if they were prescribed one of the FRID groups included in the validated STOPPFall list (Table 1) [74] at least once within this time period.

Specific FRID groups and their respective subgroups were: diuretics (loop diuretics, other diuretics), antihistamines (first generation, second generation), antiepileptic drugs (new, old), alpha blocker used as antihypertensives,alpha blocker used in BPH, oral antidiabetics (oral antidiabetics with hypoglycaemic properties, other oral antidiabetics), overactive bladder and incontinence medication (with anticholinergic properties, others), opioids (low potent, strong potent), typical (butyrophenone,thioxantenes, phenotiazide) and atypical (done, pine, benzamide, partial dopamine agonists) antipsychotics, antidepressants (selective serotonin reuptake inhibitor (SSRI), TCA, Mirtazapine), benzodiazepines, benzodiazepine-related drugs, central antihypertensives, vasodilators in cardiac diseases and anticholinergics (mARS=1, mARS=2, mARS=3) defined by the modified anticholinergic risk scale (mARS) where drugs have been assigned a number 1 to 3 based on their varying potency of anticholinergic potency where 1 means weak and 3 strong potent [102].

Their definitions according to the British National Formulary (BNF) [103] are provided in Table A 2 in the appendix. In addition, we evaluated the number of FRID groups taken concomitantly within the defined exposure window of 90 days prior to the index date.

2.7 Potential confounders

In addition to the matching factors, we considered a number of potential covariates (displayed in Table 5 and in more detail in the Tables A 3 and A 4 in the appendix) that may influence exposure to FRIDs under investigation and/or the incidence of fall injuries. These factors are commonly known as confounders. These are variables that can falsify the result and incorrectly represent a causal relationship between the influencing variable and the target variable. Models in which the confounders are not known and not defined are particularly susceptible for this [104]. For this reason, we defined as many confounders as possible based on the given data we had and included them in our analysis model for adjustment.

First of all, we included hospital admissions for medical conditions reported within 360 days prior the index date. These were *non-terminal cancer* and *terminal disease*. Patients with proven cancer diagnosis have a significantly higher risk of falling than comparable patients without this diagnosis. Patients older than 65 are particularly affected [56]. In addition, we included incurable diseases with a 5-year survival rate less than 50 %. Patients with such a diagnosis sooner or later experience a steady decline in mental and physical capacities to perform and in many cases have to take strong medication due to pain or similar life-impairing symptoms, which in turn can increase the risk of falling [57]. Moreover, we comprised *chronic hepatic diseases* as various studies showed that these diseases can increase the risk of fractures [59, 60]. We defined these three variables via the ICD^{10th} Codes [101], which were documented upon admission to the hospital.

In addition, *chronic kidney disease* (CKD) contributes to a higher risk of bone fractures [54]. A study exposed that the risk of fractures in CKD, defined as estimated glomerular filtration rate (eGFR) less than 60 ml/min/1,73m², was significantly increased [105]. Since it was found that the smaller the eGFR, the higher is the association with falls, we included two variables, CKD1 and CKD2. CKD1 was defined as eGFR between 30 ml/min/1,73m² and 60 ml/min/1,73m², and CKD2 as less than 30 ml/min/1,73m² [106].

Cognitive impairment was defined as either prescription of antidementia drugs or hospital admission due to delirium within 90 days prior the index date. As studies revealed, a decrease in cognitive capacities is an important factor increasing the fall-risk in elderly patients [107].

We further added other drugs prescribed within a 90-day risk window, which are not classified as FRIDs but which can nevertheless increase the risk of falls or fractures, either directly or indirectly. One of these is *Diabetes mellitus* and its medication. It is known that the disease itself increases the risk of falling considerably, as does its medication [55, 108]. Further, we included *antiparkinson drugs.* A prospective multidisciplinary study pointed out that 70 % of the participants diagnosed with Parkinson's fell at least once a year, 50 % at least twice [109]. There is also evidence that Parkinson's medication itself increases the risk of falls in patients [110]. In order to cover chronic diseases of the musculoskeletal system, especially rheumatoid arthritis, which show high risks for falling, we defined the concerning confounder with *disease-modifying antirheumatic drugs* (DMARD) [111]. An increased risk of falls was also found with medications for *neuropathic pain*, such as gabapentin and pregabalin [112]. We further considered drugs that have an anticholinergic effect and were not defined as FRIDs or other confounders. For this reason we determined the *modified anticholinergic risk scale* (mARS) for each patient based on the score developed from Rudolph et al. and modified by Sumukadas et al. [102, 113].

Due to the fact that we defined the cases as admitted fractures, we further defined confounders which not only favours falls itself but also increases the fracture-risk. For this reason we included *antiosteoporosis drugs* to cover patients with osteoporosis, a skeletal disorder with decreased bone mass and stability [114, 115]. Additionally, we also considered *Calcium and Vitamin D* preparations, which can be given in reduced bone density but also in a more protective and prophylactic manner [61, 116]. One of the most common causes of secondary osteoporosis is the treatment with *glucocorticoids* [117, 118]. The criteria for the variables mentioned above were the prescription of them in a 90-day risk window prior the index date. This was recorded using the BNF [103] where each drug and its respective indication has its own special code and can uniquely be identified.

We further considered markers of frailty. In general, frail people have reduced ability to react adequately to stressors and to maintain the homeostasis. As a result of aging, there is a constant decrease in physiological processes and systems with increasing age. To these systems belong the brain, immune system, endocrine system and skeletal muscles. This decline in capacities significantly increases the risk of falling [63, 64]. We evaluated indicators of frailty via *number of emergency admissions* within the year prior the index date [119] and a *medication-based chronic disease score* (medCDS) within 90 days prior the index date. This score is a tool for the prediction of the mortality of elderly people based on the medication for the most prevalent chronic diseases, age and gender [120]. Lastly, we added up all the drugs taken in the exposure period of 90 days prior the index date and defined it as the *mean number of drugs taken* by each individual, as it is proven that frail people are more prone to polypharmacy than non-frail peers [121].

Due to the fact, that there is a prevalence of fractures particularly in *winter*, we added the winter months from December to February [122]. Cases happened within this time period and their matched controls were identified.

As mentioned, a lower socioeconomic environment is another risk factor for falls and fall-related fractures [46]. For this reason, we defined the confounder *deprived* by means of the Scottish index of multiple deprivation (SIMD) [123], which ranks the inhabitants of certain neighbourhoods on a scale of 1 to 10. Here, 1 means most deprived and 10 most affluent. In our case, we recorded all patients with a scale value of 1 to 5 as deprived.

Last but not least we considered the *FRIDs not under investigation* as confounders for each individual model [74].

Table 5: Confounders

Confounder	**Period measured**
mARS	90-day risk window prior Index Date
medCDS	
DMARD	
Antineuropathic-Pain Drugs	
Calcium and Vitamin D	
Glucocorticoids (oral or inhaled)	
Antiosteoporosis Drugs	
Antidiabetic Drugs (Insulin and oral)	
Antiparkinson Drugs	
Mean number of Drugs	
Cognitive Impairment	
FRIDs not under investigation	
Chronic Kidney Disease	Within one year prior Index Date
Liver Diseases	
Malignant Neoplasm, non-terminal	
Terminal Disease (5 year survival rate <50%)	
Number Emergency Admission	
SIMD scale 1-5	
Incident User	
Index date November to February	Index Date

2.8 Statistical analysis

We examined the risks of fall-related fractures associated with exposure to specific FRIDs and relevant FRID subgroups vs no such exposures, for all patients and stratified into younger (aged 65 to 74) and older (75 years or older) people. We further examined the associations between risk of fall-related fractures and exposure to an increasing number of drugs classified as FRIDs vs no such exposure. We also explored the risks of fall-related fractures associated with specific combinations of FRIDs by examining the concomitant use of other FRIDs and FRID subgroups vs no such concomitant exposures in several sensitivity analysis (users of SSRI antidepressants, low potency opioids, loop diuretics).

We used SPSS version 25 for conditional logistic regression analyses, yielding odds ratios that, under the design of this nested case-control study, provided unbiased estimates of the rate ratios and 95% confidence intervals [124]. In addition to the matching variables on which the logistic regression was conditioned, all statistical models were adjusted by backward procedure for the confounders listed in Table 5, yielding adjusted odds ratios (aOR) [104].

We calculated cohort specific incidence rates of fall-related fractures by dividing the number of incident cases by person-years spent as members of the cohort [125]. Time spent by participants in hospital was excluded here. The incidence rates were multiplied by the adjusted rate ratios for the specific subgroups. The absolute difference in falls between the reference subgroup and the subgroup exposed was used to calculate the NNH, i.e. the number of patients needing to be treated for one year, for one additional fracture to occur [126].

Further, we determined the mortality rate by calculating the absolute risk to die in a 90-day window after hospital admission by all fractures. We further stratified by age group, 65-74 and over 74, and compared the mortality rate of hip fractures with other fractures.

The descriptive analysis was displayed by absolute frequency and for metric variables by Mean and Standard Deviation (SD).

2.8.1 Sensitivity analysis

We conducted five sensitivity analysis. First, in order to examine case misclassification (i.e. fractures unrelated to falls), we restricted our case definition to femur fractures. Second, in order to examine confounding by indication, we extended the exposure window to beyond 90 days (i.e. to 91 to 180 days and to 181 to 360 days). Third, to examine changes in prescribing behaviour over time (e.g. due to increasing awareness of FRIDs), we split the study period before and after 01/01/2016. Fourth, we explored whether the fracture-risk associated with FRID combinations differed by background treatment with SSRI antidepressants, low potency opioids and loop diuretics (which were pragmatically chosen as commonly used long term treatments covering a broad spectrum of fracture-risk increasing effects). For this reason, we created three sub-cohorts based on the main cohort, whose members were exposed to the corresponding index medication (SSRI, low potency opioids, loop diuretic) at all times. If the prescription was not filled in the second quarter, the patient dropped out of the cohort, and if the prescription was filled again, the patient was returned to the cohort. Thus, cases and controls had the same background treatment with the respective drug on the index date. Fifth, we explored whether fracture-risk differed between incident and prevalent FRID exposure where incident exposure was defined as FRID use within 90 days but not within 91 to 270 days prior to the index date.

3 Results

3.1 Baseline characteristics of cases and matched controls

The cohort included 246 535 people aged 65 years and older, of whom 18 456 (7.5 %) suffered an incident fracture. 183 723 controls were matched to these cases. Within cohorts, cases and controls were well balanced for matching factors (Table 6). The mean age was just over 80 years and approximately three quarters were women. At their respective index dates, cases were more likely to have comorbidities and drug prescriptions linked to falls or fractures than their matched controls. Moreover, cases had higher values of markers of frailty such as the medCDS score or prior hospital admissions. Cases were also slightly more deprived.

Table 6: Characteristics of cases and matched controls at their respective index dates

Characteristics	**Cases** n= 18 456	**Controls** n= 183 723
Matching factors		
Age, Mean (SD)	81.2 (8.4)	81.8 (8.2)
Female (%)	13 551 (73.4)	13 4878 (73.4)
Known medical conditions within 360 days prior to index date (%)		
Liver Disease	146 (0.8)	276 (0.2)
Chronic kidney disease with eGFR <30 ml/min/1,73m²	702 (3.8)	4 213 (2.3)
Chronic kidney disease with eGFR 30 to 59 ml/min/1,73m²	2 860 (15.5)	25 402 (13.8)
Cancer (non-terminal) [A]	543 (2.9)	2765 (1.5)
Terminal Disease [B]	5 604 (30.4)	12 253 (6.7)
Cognitive Impairment [C]	2 182 (11.8)	8 088 (4.4)
Drug use within 90-day risk window (%)		
Antiparkinson Drugs	496 (2.7)	2 265 (1.2)
Calcium, Vitamin D	4 242 (23.0)	28 236 (15.4)
Glucocorticoids (oral or inhaled)	2 667 (14.5)	18 753 (10.2)
Drugs for osteoporosis	2 155 (11.7)	14 021 (7.6)
Gabapentin or pregabalin	987 (5.3)	5 922 (3.2)
Insulin	629 (3.4)	3 181 (1.7)
DMARD	362 (2)	2 118 (1.2)
No. of drugs, Mean (SD)	7.5 (4.7)	5.6 (4.4)
mARS [102], Mean (SD)	0.3 (0.8)	0.2 (0.6)

Characteristics	Cases n= 18 456	Controls n= 183 723
Markers of frailty		
medCDS [120], Mean (SD)	4.0 (2.3)	3.8 (2.3)
No. of emergency admissions 1y prior index date, Mean (SD)	1.45 (0.97)	0.22(0.65)
Others		
Index date November to February (%)	4 966 (26.9)	49 411 (26.9)
Scottish index of multiple deprivation (SIMD) scale 1-5[D] (%)	8 217 (44.5)	75 860 (41.3)

A: Hospitalisation with a cancer diagnosis (excluding cancers with 5-year survival rate <50%); B: Diseases with 5 year survival rate <50%; C: Use of antidementia drugs or hospitalisation with delirium; D: Scale from 1=most deprived to 10=most affluent

3.2 Incidence of fractures

Figure 3 shows the distribution of fractures by body region. The two most common locations of fractures were those of the arms and femur. It should be noted that in the group of patients over 74 years of age, femur fractures were most common and accounted for more than half of all fractures. This contrasts with the younger patient group, in whom fractures to the arms were most common, accounting for more than one-third. The prevalence of the individual ICD^{10th} codes are provided in the appendix in Table A 1.

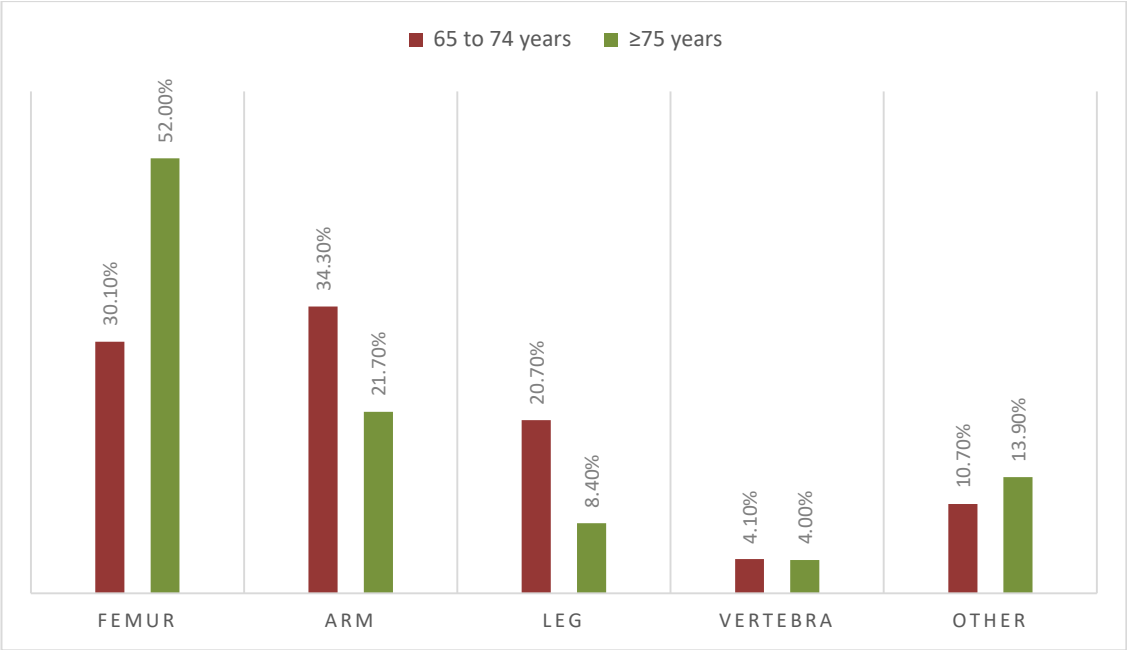

Figure 3: Distribution of fractures by body region in younger (65 to 74) and older (≥75) patients

Table 7 shows the incidence rates of fractures per 10 000 person years (pys). The overall incidence rate of fractures was 111/10 000 pys, where older patients ≥75 years had a 3.7-fold higher incidence rate than younger patients aged 65 to 74 years (184 vs 50/10 000 pys).

Table 7: Incidence of fractures stratified by age

Patient groups according to age	**Follow up time (years)**		**No. of incident fractures**	**Incidence of any fracture per 10 000 pys (95% CI)**
	Total	Mean (SD)		
≥65 years	1 688 825	6,8 (3.7)	18 456	111 (109 to 112)
65 to 74 years	906 476	5.2 (2.9)	4 449	50 (48 to 51)
≥75 years	761 623	5.6 (3.5)	14 007	184 (181 to 187)

3.3 Fracture risk associated with specific FRIDs

Table 8 shows the adjusted relative risks of fractures and numbers needed to harm associated with the use of specific drug classes.

Cardiovascular drugs. Loop diuretics were significantly associated with fractures but only in the older age group (adjusted odds ratio 1.27 [CI 1.19 to 1.35], 1 year number needed to harm 201) while alpha-blockers were significantly associated in the younger age group (1.33 [CI 1.03 to 1.72] 606). There was no evidence of significant associations for other diuretics and vasodilators. Although not statistically significant, the point estimate for central antihypertensive drugs pointed towards an increased risk (1.28 [CI 0.92 to 1.78]).

Overactive bladder drugs. Only anticholinergic drugs were significantly associated with an increased risk among older people aged ≥75 years (1.25 [CI 1.14 to 1.36] 217) but not among younger people. We found no significant associations with fracture risk for other overactive bladder drugs or alpha-blockers used to treat benign prostate hyperplasia.

Anticholinergics. Strong potent anticholinergics (mARS=3) (1.33 [CI 1.26 to 1.42] 273) were significantly associated with increased fracture risk in both age groups whereas weaker anticholinergics (mARS=1 and mARS=2) were only significantly associated in the older age group, mARS=1: 1.08 [CI 1.02 to 1.15] 679); mARS=2: 1.27 [CI 1.19 to 1.34] 201.

Oral antidiabetics. Only in the younger age group were oral antidiabetics associated with a significantly increased risk of fractures (1.44 [CI 1.03 to 2.00] 464).

Antiepileptics. Older antiepileptics were significantly associated with fractures in younger (1.41 [CI 1.04 to 1.92] 488) and older (1.28 [CI 1.09 to 1.50] 194) people, whereas newer antiepileptics were not.

Opioids. Both high potency (1.25 [CI 1.18 to 1.34] 360) and low potency (1.42 [CI 1.35 to 1.48] 215) opioids were significantly associated with fractures in all age groups.

Antipsychotics. Both typical (1.73 [CI 1.36 to 2.19] 75) and atypical (1.73 [CI 1.53 to 1.96] 75) antipsychotics were significantly associated with fractures in older people aged ≥ 75 years. In the younger age group, the risk estimates pointed in the same direction but were non-significant (1.99 [CI 0.91 to 4.34] for typical and 1.22 [CI 0.86 to 1.75] for atypical). For the subgroups of typical antipsychotics, significant results in patients over 74 years of age were found for phenotiazides (1.74 [CI 1.05 to 2.88] 74), butyrophenones (1.50 [CI 1.13 to 1.98] 110) and thioxanthenes (2.98 [CI 1.67 to 5.19] 28). The subgroups of atypical antipsychotics that significantly increased the risk of fracture only in patients over 74 were "pine" (1.58 [CI 1.34 to 1.86] 95) and "benzamide" (2.01 [CI 1.32 to 3.08] 54). Antipsychotics of the “done”-type showed significant results in both the younger (2.22 [CI 1.18 to 4.20] 167) and the older (1.83 [CI 1.49 to 2.25] 66) age group.

Antidepressants. TCAs (1.70 [CI 1.58 to 1.82] 129), SSRIs (2.07 [CI 1.95 to 2.21] 84) and Mirtazapine (1.28 [CI 1.16 to 1.41] 322) were associated with fractures in both age groups, although the result for mirtazapine was not significant among those aged 65 to 74 years despite a similar point estimate (1.26 [CI 0.90 to 1.60]).

Hypnotics. Among those aged ≥75 years, both benzodiazepines (1.26 [CI 1.16 to 1.37] 209) and z-drugs (1.13 [CI 1.02 to 1.24] 418) were associated with an increased fracture-risk, but among those aged 65 to 74 years were not despite a similar point estimate for benzodiazepines (1.21 [CI 0.98 to 1.49]).

Antihistamines. Neither first nor second generation antihistamines were significantly associated with fractures in either age group

Table 8: aOR (relative risks) of fractures and 1 year NNH associated with the use of drug groups classified as FRIDs. Bold figures represent statistically significant effects (p<0.05)

Drugs of interest	**Adjusted OR** [95%CI] *NNH*		
	65 years or older	65 to 74 years	75 years or older
Single exposures vs no such exposures			
Central antihypertensives	1.28 [0.92 to 1.78]	1.20 [0.44 to 3.26]	1.27 [0.90 to 1.79]
Vasodilators	1.02 [0.98 to 1.06]	0.96 [0.87 to 1.06]	1.03 [0.98 to 1.07]
Alpha blockers for HTN	1.08 [0.99 to 1.19]	**1.33** [1.03 to 1.72] *606*	1.02 [0.92 to 1.14]
Alpha blockers for BPH	0.93 [0.84 to 1.02]	0.77 [0.59 to 1.01]	0.95 [0.85 to 1.06]
Diuretics			
Loop	**1.19** [1.12 to 1.27] *474*	0.95 [0.78 to 1.16]	**1.27** [1.19 to 1.35] *201*
Other	1.02 [0.97 to 1.07]	0.97 [0.85 to 1.11]	1.01 [0.95 to 1.06]
Overactive bladder drugs			
Anticholinergic	**1.23** [1.13 to 1.33] *392*	1.01 [0.81 to 1.26]	**1.25** [1.14 to 1.36] *217*
Others	0.94 [0.75 to 1.17]	0.98 [0.77 to 1.41]	0.95 [0.75 to 1.21]
Oral antidiabetics			
Hypoglycaemic drugs	**1.28** [1.11 to 1.49] *326*	**1.44** [1.03 to 2.00] *464*	1.11 [0.99 to 1.25]
Others	1.04 [0.96 to 1.13]	**2.51** [1.21 to 5.22] *13*	1.05 [0.96 to 1.15]
Antiepileptics			
Antiepileptics, Old	**1.35** [1.17 to 1.55] *257*	**1.41** [1.04 to 1.92] *488*	**1.28** [1.09 to 1.50] *217*
Antiepileptics, New	1.16 [0.97 to 1.39]	1.43 [0.95 to 2.13]	1.03 [0.83 to 1.27]
Opioids			
Low potency	**1.42** [1.35 to 1.48] *215*	**1.52** [1.42 to 1.62] *385*	**1.36** [1.29 to 1.43] *150*
High potency	**1.25** [1.18 to 1.34] *360*	**1.34** [1.15 to 1.58] *588*	**1.21** [1.13 to 1.30] *259*

Drugs of interest	**Adjusted OR** [95%CI] *NNH*		
	65 years or older	65 to 74 years	75 years or older
Single exposures vs no such exposures			
Antipsychotics			
Typical	**1.77** [1.41 to 2.23] *117*	1.99 [0.91 to 4.34]	**1.73** [1.36 to 2.19] *75*
Phenothiazine	**1.66** [1.08 to 2.53] *138*	1.17 [0.44 to 3.09]	**1.74** [1.05 to 2.88] *74*
Butyrophenone	**1.51** [1.15 to 1.99] *179*	2.33 [0.84 to 6.47]	**1.50** [1.13 to 1.98] *110*
Thioxanthene	**3.01** [1.79 to 5.08] *45*	2.01 [0.42 to 9.61]	**2.95** [1.67 to 5.19] *28*
Atypical	**1.70** [1.52 to 1.91] *129*	1.22 [0.86 to 1.75]	**1.73** [1.53 to 1.96] *75*
Pine	**1.52** [1.31 to 1.77] *175*	0.90 [0.57 to 1.43]	**1.58** [1.34 to 1.86] *95*
Done	**1.94** [1.60 to 2.37] *97*	**2.22** [1.18 to 4.20] *167*	**1.83** [1.49 to 2.25] *66*
Benzamides	**1.89** [1.27 to 2.80] *102*	1.56 [0.53 to 4.61]	**2.01** [1.32 to 3.08] *54*
Partial Agonists	1.53 [0.90 to 2.59]	1.42 [0.30 to 6.80]	0.72 [0.51 to 1.02]
Antidepressants			
TCA	**1.70** [1.58 to 1.82] *129*	**1.65** [1.41 to 1.83] *308*	**1.67** [1.55 to 1.81] *81*
SSRI	**2.07** [1.95 to 2.21] *84*	**1.92** [1.65 to 2.23] *217*	**2.03** [1.89 to 2.18] *53*
Mirtazapine	**1.28** [1.16 to 1.41] *322*	1.26 [0.90 to 1.60]	**1.29** [1.16 to 1.44] *187*
Hypnotics			
Benzodiazepine	**1.27** [1.17 to 1.39] *334*	1.21 [0.98 to 1.49]	**1.26** [1.16 to 1.37] *209*
Z-drugs	**1.11** [1.01 to 1.21] *819*	1.06 [0.83 to 1.36]	**1.13** [1.02 to 1.24] *418*
Antihistamines			
First generation	0.94 [0.80 to 1.11]	0.94 [0.62 to 1.43]	0.98 [0.82 to 1.18]
Second generation	1.02 [0.93 to 1.11]	1.21 [0.99 to 1.28]	1.01 [0.91 to 1.12]

Drugs of interest	**Adjusted OR** [95%CI] *NNH*		
	65 years or older	65 to 74 years	75 years or older
Single exposures vs no such exposures			
Anticholinergics			
Any drug with mARS=1	**1.23** [1.17 to 1.30] 392	1.06 [0.91 to 1.22]	**1.27** [1.19 to 1.34] 201
Any drug with mARS=2	**1.09** [1.04 to 1.16] 1001	1.12 [0.98 to 1.30]	**1.08** [1.02 to 1.15] 679
Any drug with mARS=3	**1.33** [1.26 to 1.42] 273	**1.27** [1.10 to 1.46] 741	**1.33** [1.24 to 1.42] 165

3.4 Cumulative risk of FRIDs

Figure 4 shows the effects found for exposures to an increasing number of drugs classified as FRIDs. Figure 5 illustrates the findings in terms of adjusted ORs (panel I) and NNH (panel II) with use of any number of FRIDs versus use of no FRIDs for younger patients aged 65 to 74 years and older patients aged 75 years and older. Relative fracture-risk increased with an increasing number of FRIDs used with similar relative increases in risk for younger (aged 64 to 75 years) and older (aged ≥75 years) people, respectively. By contrast, the absolute increase in fracture-risk associated with FRIDs (as reflected by lower NNH) was much higher in the older age group. In numbers, for the concomitant use of 5 or more FRIDs, the younger patients had a NNH of 111 whereas the older ones had a NNH of 29.

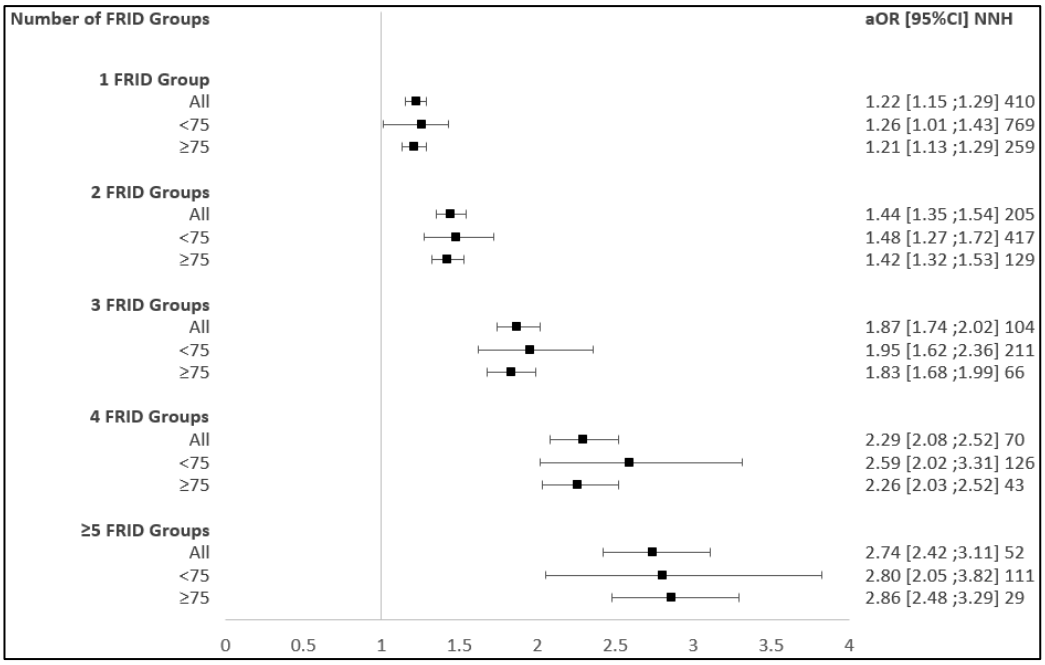

Figure 4: aOR of fractures and NNH associated with the use of an increasing number of drug groups classified as FRIDs

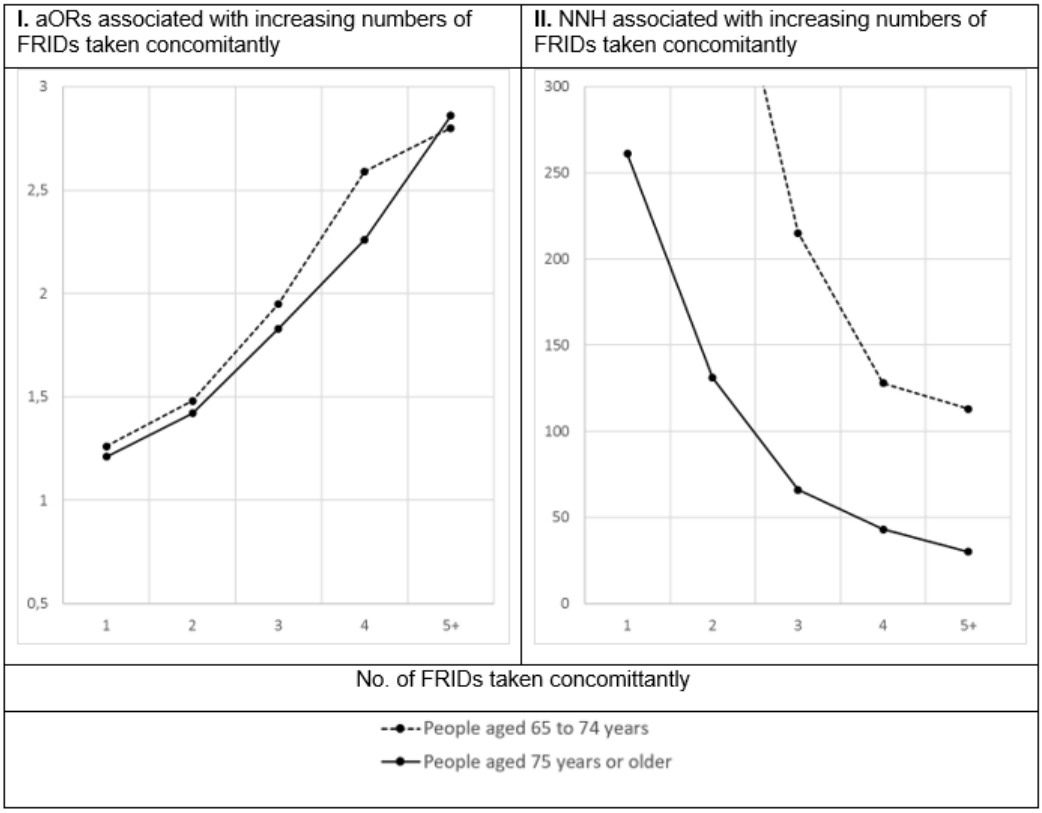

Figure 5: Combined use of FRIDs

3.5 Mortality rate associated with fractures

Figure 6 shows the mortality rate within a 90-day window after hospital admission due to a fracture. Further details are provided Table A 5 in the appendix. The overall mortality rate after hospital admission due to a fracture was 10.3 %. Comparing the two age groups, the older patients had more than 3.2 times the risk of dying than the younger patients. In numbers, 12.4 % among those aged ≥75 years and 3.8 % of the patients between 65 and 74 years admitted due to fractures died within 90 days after the admission. The greatest risk was found for patients older than 74 with a femur fracture. For this patient group, 16 % died in the following of the hospital admission.

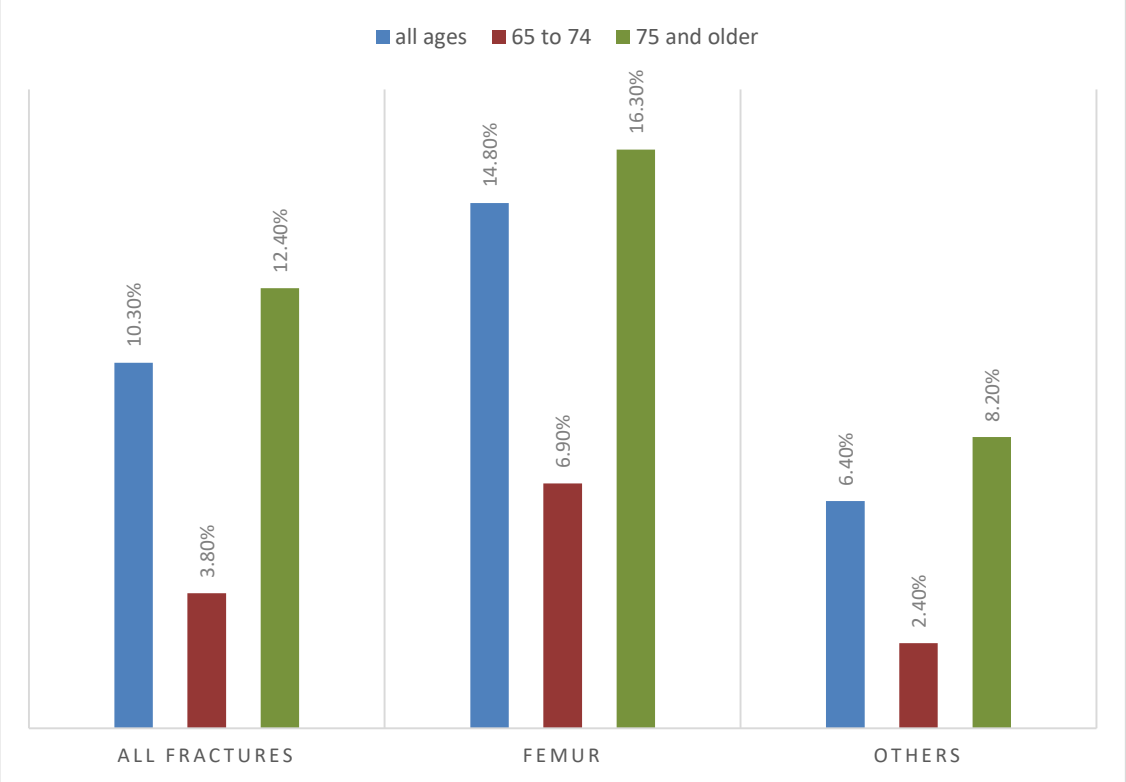

Figure 6: 90-day mortality rate after hospital admission due to a fracture

3.6 Sensitivity analyses

Sensitivity analysis 1 (Table 9), the limitation to femur fractures, yielded central antihypertensive drugs now significantly associated with increased fracture risk (1.83 [CI 1.18 to 2.84] vs 1.28 [CI 0.92 to 1.78] in primary analysis). Extending the risk window in SA2 generally diminished the risk estimates as expected, but increased it for non-hypoglycaemic antidiabetic drugs (1.37 [CI 1.10 to 1.71] vs 1.04 [CI 0.96 to 1.13]).

Table 9: Findings of sensitivity analyses 1 and 2

Exposure of interest	**Adjusted OR** [95%CI]			
	Primary analysis: 65 years or older	**Sensitivity analysis 1:** Femur Fractures	**Sensitivity analysis 2a**: risk window 91 to 180 days prior index	**Sensitivity analysis 2b:** risk window 181 to 360 days
Central antihypertensives	1.28 [0.92-1.78]	**1.83** [1.18-2.84]	1.30 [0.95-1.78]	1.12 [0.82-1.54]
Vasodilators	1.02 [0.98-1.06]	1.01 [0.95-1.07]	0.98 [0.94-1.02]	**0.91** [0.87-0.95]
Alpha blockers for HTN	1.08 [0.99-1.19]	1.02[0.89-1.18]	1.04 [0.94-1.14)	0.96 [0.87-1.05]
Alpha blockers for BPH	0.93 [0.84-1.02]	0.90 [0.78-1.03]	**0.90** [0.82-0.99)	**0.56** [0.78-0.94]
Diuretics				
Loop	**1.19**[1.12-1.27]	**1.20** [1.10-1.30]	1.05 [1.00-1.12]	**0.91** [0.86-0.96]
Other	1.02 [0.97-1.07]	**0.91** [0.85-0.98]	0.97 [0.92-1.02]	**0.87** [0.82-0.91]
Overactive bladder drugs				
Anticholinergic	**1.23** [1.13-1.33]	**1.21** [1.07-1.36]	**1.14** [1.05-1.23]	0.99 [0.91-1.07]
Others	0.94 [0.75-1.17]	1.04 [0.76-1.42]	1.02 [0.82-1.27]	1.01 [0.81-1.24]

Exposure of interest	**Adjusted OR** [95%CI]			
	Primary analysis: 65 years or older	**Sensitivity analysis 1:** Femur Fractures	**Sensitivity analysis 2a**: risk window 91 to 180 days prior index	**Sensitivity analysis 2b:** risk window 181 to 360 days
Antiepileptics				
Old	**1.35** [1.17-1.55]	**1.36** [1.11-1.66]	**1.29** [1.12-1.48]	**1.26** [1.10-1.45]
New	1.16 [0.97-1.39]	1.19 [0.92-1.54]	**0.84** [0.77-0.92]	**0.81** [0.75-0.88]
Opioids				
Low potency	**1.25** [1.18-1.34]	**1.37** [1.28-1.47]	**1.10** [1.05-1.16]	0.98 [0.94-1.03]
High potency	**1.42** [1.35-1.48]	1.19 [1.08-1.30]	0.98 [0.91-1.04]	**0.89** [0.83-0.95]
Antipsychotics				
Typical	**1.77** [1.41-2.23)	**2.22** [1.68-2.93]	**1.70** [1.33-2.17)	**1.93** [1.55-2.40]
Atypical	**1.70** [1.52-1.91]	**2.35** [2.03-2.72]	1.75 [1.55-1.96]	**1.68** [1.49-1.89]
Antidepressants				
TCA	**1.70** [1.58-1.82]	**1.69** [1.52-1.87]	**1.43** [1.34-1.54]	**1.28** [1.20-1.37]
SSRI	**2.07** [1.95-2.21]	**1.92** [1.75-2.10]	**1.82** [1.71-1.94]	**1.54** [1.45-1.64]
Mirtazapine	**1.28** [1.16-1.41]	**1.50** [1.32-1.71]	**1.18** [1.07-1.31]	**1.12** [1.01-1.24)
Hypnotics				
Benzodiazepine	**1.27** [1.17-1.39]	**1.15** [1.01-1.30]	**1.13** [1.05-1.22]	**1.10** [1.02-1.18]
Z-drugs	**1.11** [1.01-1.21]	**1.37** [1.24-1.52]	1.09 [0.99-1.19]	0.94 [0.86-1.03]
Antihistamines				
First generation	0.94 [0.80-1.11]	1.04 [0.83-1.32]	0.97 [0.82-1.14]	0.89 [0.85-0.93]
Second generation	1.02 [0.93-1.11]	1.07 [0.94-1.22]	1.02 [0.93-1.11]	1.95 [0.88-1.03]

Stratification by study period in SA3 (Table 10) now yielded significantly increased fracture risk in the earlier study period for alpha-blockers used in hypertension (1.20 [1.06 to 1.36] vs 1.04 [0.96 to 1.13]).

Table 10: Findings of sensitivity analysis 3

Exposure of interest	**Adjusted OR** [95%CI]		
	Primary analysis: 65 years or older	**Sensitivity analysis 3a:** before 01/01/2016	**Sensitivity analysis 3b**: after 01/01/2016
Central antihypertensives	1.28 [0.92 -1.78]	1.33 [0.88 -2.01]	1.18 [0.69 -2.02]
Vasodilators	1.02 [0.98 -1.06]	0.97 [0.91 -1.02]	**1.08** [1.02 -1.15]
Alpha blockers for HTN	1.08 [0.99 -1.19]	**1.20** [1.06 -1.36]	0.91 [0.78 -1.06]
Alpha blockers for BPH	0.93 [0.84 -1.02]	**0.83** [0.71 -0.96]	1.02 [0.89 -1.16]
Diuretics			
Loop	**1.19** [1.12 - 1.27]	**1.24** [1.15 -1.35]	**1.14** [1.04 -1.25]
Other	1.02 [0.97 -1.07]	1.01 [0.94 -1.07]	1.01 [0.93 -1.09]
Overactive bladder drugs			
Anticholinergic	**1.23** [1.13 -1.33]	**1.18** [1.06 -1.31]	**1.30** [1.15 -1.48]
Others	0.94 [0.75 -1.17]	0.79 [0.48 -1.29]	0.80 [0.45 -1.25]
Antiepileptics			
Old	**1.35** [1.17 -1.55]	**1.45** [1.22 -1.72]	1.22 [0.97 -1.55]
New	1.16 [0.97 -1.39]	1.04 [0.79 -1.36]	**1.30** [1.02 -1.65]
Opioids			
Low potency	**1.25** [1.18 -1.34]	**1.39** [1.30 -1.47]	**1.44** [1.34 -1.55]
High potency	1.42 [1.35-1.48]	**1.24** [1.14 -1.35]	**1.30** [1.19 -1.44]

Exposure of interest	**Adjusted OR** [95%CI]		
	Primary analysis: 65 years or older	**Sensitivity analysis 3a:** before 01/01/2016	**Sensitivity analysis 3b**: after 01/01/2016
Antipsychotics			
Typical	**1.77** [1.41 -2.23]	**2.05** [1.55 -2.71)	1.39 [0.94 -2.07]
Atypical	1.70 [1.52 -1.91]	**1.82** [1.56 -2.13]	**1.61** [1.36 -1.92]
Antidepressants			
TCA	**1.70** [1.58 -1.82]	**1.73** [1.58 -1.90]	**1.66** [1.49 -1.84]
SSRI	**2.07** [1.95 -2.21]	**2.07** [1.90 -2.25]	**2.11** [1.93 -2.31]
Mirtazapine	**1.28** [1.16 -1.41]	**1.32** [1.14 -1.53]	**1.24** [1.08 -1.41]
Hypnotics			
Benzodiazepine	**1.27** [1.17 -1.39]	**1.30** [1.18 -1.43]	**1.24** [1.10 -1.41]
Z-drugs	1.11 [1.01 -1.21]	**1.24** [1.11 to 1.39]	0.93 [0.81 -1.08]
Antihistamines			
First generation	0.94 [0.80 -1.11]	1.13 [0.93 -1.39]	**0.71** [0.54 -0.94]
Second generation	1.02 [0.93 -1.11]	0.96 [0.85 -1.09]	1.13 [1.00 -1.48]

In SA4 (table 11) we found that among FRIDs found to significantly increase fracture-risk in primary analysis, the following drug groups were found to also increase fracture-risk when used in addition to background treatment with SSRIs, low potency opioids or loop diuretics (compared to use of these background treatments alone): anticholinergic overactive bladder drugs, opioids, antidepressants, and atypical antipsychotics. In contrast, the following drug groups were found not to increase fracture-risk when used in addition to either background treatment: older antiepileptics and benzodiazepines. For z-drugs, typical antipsychotics and hypoglycaemic drugs, observed increases in fracture-risk differed by background treatment. Z-drugs were significantly associated with an increased fracture-risk in case of the background treatment with SSRIs and loop diuretics but not with low potency opioids. Hypoglycaemic oral antidiabetics were only associated with an increased fracture-risk with the background treatment of loop diuretics. Typical antipsychotics showed an increased fracture risk only with the background treatment of low potency opioids.

Table 11: Findings of sensitivity analysis 4

Drugs of interest used in addition to background treatment with	**Adjusted OR** [95%CI] *NNH*		
	SSRIs	**low potency opioids**	**loop diuretics**
Single additive exposures vs no such additive exposures			
Diuretics			
Loop	1.02 [0.88 -1.17]	0.95 [0.87-1.04]	*Not applicable*
Overactive bladder drugs			
Anticholinergic	**1.29** [1.09 -1.53] *153*	**1.15** [1.02-1.29] *321*	**1.22** [1.02-1.45]
Antiepileptics			
Old	1.17 [0.87 - 1.57]	1.16 [0.94-1.44]	1.25 [0.93-1.67]

Drugs of interest used in addition to background treatment with	**Adjusted OR** [95%CI] *NNH*		
	SSRIs	**low potency opioids**	**loop diuretics**
Single additive exposures vs no such additive exposures			
Opioids			
Low potency	**1.19** [1.04 - 1.37] *234*	*Not applicable*	**1.41** [1.28-1.56]
High potency	**1.30** [1.17 - 1.46] *148*	*Not applicable*	**1.24** [1.09-1.40]
Antipsychotics			
Typical	1.38 [0.89 - 2.13]	**2.07** [1.41-3.02] *45*	1.20 [0.71-2.01]
Atypical	**1.33** [1.08 - 1.64] *135*	**1.67** [1.22-2.29] *70*	**1.53** [1.20-1.95] 89
Antidepressants			
TCA	*Not examined*	**1.30** [1.19-1.42] *160*	**1.25** [1.08-1.49]
SSRI	*Not applicable*	**1.53** [1.39-1.68] *91*	**1.53** [1.34-1.74] *89*
Hypnotics			
Benzodiazepines	1.03 [0.90 - 1.19]	1.07 [0.96-1.19]	0.95 [0.81-1.11]
Z-drugs	**1.23** [1.05 - 1.44] *193*	1.11 [0.98-1.25]	**1.44** [1.22-1.71]

For SA5 displayed in Table 12, incident users of opioids were found to be at significantly higher risk of fractures than prevalent users, 1.81 [1.68 to 1.95] vs 1.18 [1.13 to 1.24].

Table 12: Findings of sensitivity analysis 5

Exposure of interest	**Adjusted OR** [95%CI]	
	Prevalent User	**Incident User**
Diuretics	**1.12** [1.07-1.17] 751	**0.89** [0.77-1.02] 751
Central antihypertensives	1.37 [0.92-1.90]	0.06 [0.00-0.90]
Vasodilators	**1.04** [1.00-1.09] 2252	0.77 [0.66-0.90]
Alpha blockers for HTN	**1.13** [1.02-1.24] 693	0.51 [0.32-0.81]
Alpha blockers for BPH	0.93 [0.84-1.03]	0.87 [0.62-1.22]
Overactive bladder drugs	1.23 [1.15-1.30]	0.93 [0.84-1.03]
Antiepileptics	**1.20** [1.08-1.34] 451	**1.13** [0.91-1.41] 693
Opioids	**1.18** [1.13-1.24] 501	**1.81** [1.68-1.95] 111
Antipsychotics	**1.83** [1.64-2.04] 109	0.86 [0.67-1.10]
Antidepressants	**1.85** [1.76-1.95] 106	**1.56** [1.40-1.75] 161
Benzodiazepine	**1.31** [1.20-1.42] 291	**1.09** [0.93-1.28] 451
Z-drugs	**1.11** [1.01-1.23] 819	1.05 [0.87-1.28]
Antihistamines	**1.11** [1.01-1.22] 819	0.83 [0.71-0.98]
Anticholinergics	0.94 [0.86-1.03]	**1.12** [1.03-1.23] 751

4 Discussion

4.1 Summary of findings

The purpose of this population-based nested case-control study was to examine whether and to which extent there are differences in the relative and absolute increase in the risk of fall-related fractures associated with individual groups and subgroups of FRIDs, and whether and to which extent fracture-risk varies by age and by co-medication with one or more other FRIDs. This should be helpful in weighing the prescribing and deprescribing of FRIDS in patients who are nonetheless dependent on these medications.

In this study of patients aged 65 years or older, we found that some but not all drug groups previously classified as FRIDs were associated with an increased risk of fall-related fractures. More specifically, we found no evidence in any of the subgroups (defined by age or concomitant drug exposure) that centrally acting antihypertensive drugs, vasodilators used in cardiac disease, alpha blockers used for BPH or antihistamines increased the risk of fall-related fractures. In addition, the risk of fall-related fractures was restricted to the older age group ≥75 years for loop diuretics, antipsychotics and hypnotics. Furthermore, even where the risk of fall-related fractures was significantly increased among younger people, we found much larger increases in absolute risk among older people aged ≥75, owing to an almost four-fold increased incidence of fall-related fractures (184/10 000 pys vs 50/10 000 pys). This is particularly important in view of our finding that the 90-day mortality rate was increased more than three-fold (12.4 vs 3.8) among older vs younger people. Among patients aged ≥75 years, the largest increases in absolute risk (NNH <100) were found for SSRI antidepressants (NNH 53), TCAs (NNH 83), atypical and typical antipsychotics (both with a NNH 75) and for the concomitant use of three or more FRIDs vs no FRIDs (NNH ≤ 66). Similarly high increases in fall-related fracture risk were found among users of low potency opioid users for the additional use of antipsychotics (NNH 70 for atypical and NNH 45 for typical antipsychotics) and SSRI antidepressants (NNH 91).

Likewise, patients on loop diuretic background therapy had high absolute risks for fall-related fractures in case of additional use of atypical antipsychotics (NNH 89) and SSRI antidepressants (NNH 89). There was empirical evidence for some but not all presumptions around the differential risk of FRID subgroups (Table 2). In particular, our finding that SSRI antidepressants were associated with a larger increase in fall-related fracture risk than TCAs or mirtazapine is not consistent with the presumption of the STOPPFall authors (assuming that TCAs are the most risk increasing subgroup of antidepressants and that the increase in risk is related to sedating or anticholinergic properties). We further found empirical evidence that the risk of fall-related fractures increases with the number of FRIDs prescribed in both younger and older age groups in a linear manner, which generally supports the classification of the examined drug groups as fall-risk increasing drugs and suggests that the risk of combining FRIDs is additive rather than over-additive (e.g. exponential). However, our findings suggest that some combinations of FRIDs may be associated with a higher risk of fall-related fractures than others. For example, we found no association between fall-related fractures and the additional use of loop diuretics, mirtazapine, benzodiazepines and antiepileptics among users of SSRI antidepressants, low potency opioids or loop diuretics.

4.2 Comparison to literature

In contrast to previous meta-analyses [71-73] and subsequent expert consensus [74], we found no evidence that centrally acting antihypertensive drugs, vasodilators used in cardiac disease, alpha-blockers used for BPH or antihistamines increased the risk of fall-related fractures. Possible explanations for a lower risk are that relevant adverse effects for the former drug groups, such as orthostatic hypertension, are susceptible to preventive interventions and/or that falls associated with these drugs are less frequent or less frequently lead to fractures because they tend to have of a lower impact [127, 128].

4.2.1 Diuretics

Our finding that loop diuretics but not other diuretics were associated with an increased risk of fall-related fractures are consistent with earlier randomised trials. The meta-analysis of Vries et al. [71] reported the relative risk of falling at OR 1.36 (CI 1.17, 1.57) whereas we found a relative risk for all age groups of OR 1.19 (CI 1.12; 1.27) which increased to OR 1.27 (CI 1.19; 1.35) for patients aged 75 and older. Similar results were found by Marcum et al. [97]. They revealed the increased fall-risk with patients only under the regiment of loop diuretics, not for other antihypertensive drugs. On the other hand, diuretics other than loop diuretics did not show an increase in the fall-risk when using them [129]. For instance, it was demonstrated that thiazide diuretics didn´t show differences in comparison to other antihypertensive drugs in terms of their potential to cause orthostatic hypotension [130]. Further, Rejnmark et al. [131] found, that users of loop diuretics were more susceptible to fractures, especially of the hip. In general, loop diuretics are well known to cause orthostatic hypotension due to their profound impact on the water household, which can favour falls. The increased fracture-risk for loop diuretics may also be biologically explained by the calcium depleting properties of these drugs, which subsequently can lead to bone loss and a stronger vulnerability to fractures [132, 133]. These effects seem to specially have an impact on older, frailer patients as the younger age group appear to cope these side effects in a better way [134, 135].

4.2.2 Oral Antidiabetics

The only subgroup of the oral antidiabetic drugs with significant findings in patients aged 65 and older were the ones causing hypoglycaemia. Only in younger patients aged 65 to 74 years, both subgroups, hypoglycaemic drugs and non-hypoglycaemic drugs, showed a significantly increased risk of fall-related fractures. However, the point estimate was higher for non-hypoglycaemic drugs, but the confidence-intervals overlapped. Hypoglycaemic oral antidiabetics are known to increase the fall-risk in elderly people.

Contrary, non-hypoglycaemic oral antidiabetics were not associated with an increased fall-risk [136]. However, several studies linked non-hypoglycaemic oral antidiabetics to an increased susceptibility for fractures. It was shown that patients under the regiment of these drugs were at an up to three-fold increase risk for suffering hip fractures [137, 138]. This can explain the results of our studies as we defined falls as fractures subsequent to a fall. However, bias of indication can´t be ruled out as patients diagnosed with Diabetes mellitus are generally prone to falls and fractures due to the illness itself [55, 139]. Further, residual confounding [140] can play a role here, as prescribers could avoid hypoglycaemic drugs in patients with high fracture-risk. Nevertheless, our findings highlight that non-hypoglycaemic oral antidiabetics are not risk free.

4.2.3 Anticholinergics

Strong potent anticholinergics (mARS=3) were associated with fractures in both the younger and older patient groups. Weak (mARS=1) and moderate (mARS=2) potent ones only in the older patient group. This is consistent with the findings of a systemic-review by Reinold et al. [141] as they stated an increased fracture risk with the increase of the anticholinergic burden. Anticholinergics are a class of drugs that block the action of acetylcholine, which results in a number of side effects, including drowsiness, confusion and reduced coordination. Additionally, it can also cause changes in blood pressure and blurred vision, all of which can increase the risk of falls and subsequent fractures [142]. These effects particularly seem to have an impact on elderly patients as the less potent anticholinergics (mARS=1 and mARS=2) were only significant in this group but not in the younger group. This is consistent with the findings of several other studies, which stated the fall and fracture-risk is highest in older, frail patients [143, 144].

4.2.4 Overactive bladder and incontinence

Among drugs used for overactive bladder and incontinence, only those with anticholinergic properties were significantly associated with fall-related fractures, and only in the older age group (NNH 117). This is in line with a previous published study as they showed an increased fracture and fall-risk for anticholinergic overactive bladder medication [145]. The risk of falling with anticholinergics and in particular with the mentioned specific subgroup can mainly be attributed to the anticholinergic side-effects, mentioned in section 4.2.3 [142]. Whereby younger and non-frail patients seem to compensate these side-effects in terms of fall and fracture-risk better than the older and possible frailer patient group. Similar results were obtained by Naharci, M.I. and I. Tasci et al. [143] , as they found an increased fall-risk of anticholinergics on frail older patients but not in hearty ones.

4.2.5 Alpha Blocker

Only alpha blockers used in hypertension but not those used for prostate hyperplasia were significantly associated with fall related fractures. However, significant associations were only found in the younger age group. Similar results were revealed by Souverin et al. [146], who showed a positive association between falls and the use of antihypertensive alpha blockers in a younger population. Alpha blockers used in the treatment of hypertension can cause severe hypotension which subsequently can lead to falls and fall-related fractures as a previous study found [147]. On the other side, in contrast to our findings, a study stated that alpha blockers used in the treatment for prostate hyperplasia increased the fall-risk, especially in the initiation period [148]. However, selective alpha-blockers used in the treatment of BPH have generally a lower cardiovascular side-effect profile than non-selective ones, which can explain our results [149].

4.2.6 Antiepileptic drugs

Several studies are in line with our findings of the overall fall and fracture-risk and antiepileptic use [73, 150]. Nevertheless, there is scarce literature comparing old and new antiepileptic drugs regarding their differences in the risk for falls and fall-related fractures. We found that older generation antiepileptic drugs had significantly associations with fall-related fractures with a NNH of 261 whereas new ones didn´t. This is in line with the findings of Kreys et al. [151] as they demonstrated in their nested case-control study an increased fall-risk for patients under the regiment of old antiepileptic drugs compared to patients using new antiepileptics. Old antiepileptic drugs have well known side-effects, such as fatigue or dizziness which favours falls and subsequent fractures [152]. However, a bias of indication cannot be ruled out as patients with epilepsy are inherently prone to falls and fractures because of their illness itself [153]. It is therefore difficult to differentiate whether the fall and subsequent fracture was caused by a seizure or the medication. Nonetheless, our results indicate a difference in the fracture-risk between old and new antiepileptic drugs.

4.2.7 Antipsychotics

We found in our study that typical antipsychotics and atypical antipsychotics seem to have a comparable risk to suffer from fall-related fractures. Similar results were obtained in the studies of Mehta et al. [154] and Landi et al. [155] as well as the meta-analysis by Seppala et al. [72]. They found no significant differences in the risk of falls between typical and atypical antipsychotics [72, 154, 155]. In general, patients taking antipsychotics are more susceptible to falls and subsequent fractures either due to the underlying conditions, such as schizophrenia [156], or the broad side-effect profile of the medication [157].

In terms of the side-effect profile, typical antipsychotics have a high affinity to dopamine receptors which in turn favours side-effects such as tardive dyskinesia or extrapyramidal syndrome (EPMS) as well as increased prolactin levels. This subsequently can lead to falls and fall-related fractures [158]. With a closer look at the typical antipsychotics we found that especially thioxanthenes (e.g. chlorprothixen, flupenthixol), increased the risk of fractures particularly in the elderly patient group. One explanation can be the increase in prolactin levels of these drugs, which seems to have a strong influence on the possible fracture-risk in older, more frail patients who already have a poorer bone substance in comparison to the younger patient group [159].

On the other side, atypical antipsychotics are rather less known to cause these mentioned side-effects. However, one study revealed that they are not less associated with EPMS than low potent typical ones [160]. Furthermore, atypical antipsychotics have a high affinity for histamine receptors and also alpha receptors, which can cause sedative side-effects and orthostatic hypotension, respectively [161]. This in turn may explain the susceptibility to falls. A closer look at the subgroups showed the highest relative and absolute risk of fall-related fractures for elderly patients aged 75 and older for “benzamides” (e.g. amisulprid), followed by “done” (e.g. risperidon), and “pine” (e.g. olanzapine, quetiapine). As “benzamides” can increase the prolactin levels to a great extent which subsequently favours bone mass loss and osteoporosis, this can be an explanation for their high risk to cause fractures. “Done” are likewise characterized by the possibility to increase the prolactin level [162]. Additionally, they have a strong alpha receptor affinity, which can lead to orthostatic hypotension and subsequently to falls and fall-related fractures. This circumstance may explain why the younger and usually more mobile patient group of those under 75 years of age is exposed to an increased risk of fall-related fractures when taking "done" [163]. Most of the “pine” have a great histaminergic effect which cause sedation and drowsiness and in the case of clozapine a strong anticholinergic effect which are in sum well known risk factors for falls and subsequent fractures [164, 165].

4.2.8 Opioids

We found that low potent opioids had a significantly higher relative and absolute fracture-risk than strong potent opioids. This was even more evident in the older age group, where the NNH was significantly lower than the users of strong opioids, 150 vs 259 respectively. This is in contrast to a previous published review, which postulates an increased risk the higher the dosage and the more potent the opioid is [84]. The results of our study can be explained by the circumstance that patients receiving low potent opioids are generally in a better health condition than patients under the regiment of strong opioids [166]. Therefore, these users are more exposed to possibilities to falls and fractures as they are more mobile and the side-effects of low potent opioids have a greater impact on them compared to users of strong potent opioids who are probably less active and more at rest [166, 167]. Nevertheless, the point estimates were lower for stronger opioids, but confidence intervals overlapped, what makes an exact distinction difficult. What can be said with certainty is that opioids have a strong association with falls-related fractures and this is especially true for patients over 74 as the absolute risk was doubled in comparison to the patients aged 65 to 74.

4.2.9 Antidepressants

Previous published studies from Tamblyn et al. [168] and Pisa et al. [169] are consistent with our findings concerning the subgroups of antidepressants. They showed that SSRIs had a greater association with falls and fall-related fractures compared to other subgroups of antidepressants. In addition, further studies confirmed that there are no significant differences in fall or fracture-risk between SSRIs and TCAs [72, 170, 171]. One possibility which can play a role here is residual confounding as prescribers may avoid TCAs in patients at higher risk of falls [171]. Concerning mirtazapine, it may be predominantly be given at night time and unless the patient gets up during the night, which might more frequently be the case in older people, its sedating effects may not affect fall and fracture-risk [172].

However, our data highlight that even non-sedating antidepressants may increase the risk of fractures. This could be due to activating effects that can lead to higher mobility levels and also sleep disturbances, which subsequently contribute to an increased risk of falls and fall-related fractures [173]. In addition, there are suggestions that the use of SSRIs may affect bone density and matrix. This in turn increases the fracture-risk, which could explain why in our study the SSRIs achieved a higher relative and absolute risk in comparison to other subgroups of antidepressants [174, 175].

4.2.10 Cumulative risk of FRID use

We found an increased fracture-risk for the concomitant use of FRIDs which is consistent with findings of several other studies [176-179]. Considering that diuretics, antidepressants and opioids were the most commonly prescribed drugs in our study, drug interactions among them with other FRID groups apparently possess a great risk of increasing the susceptibility to falls and fall-related fractures. The result of a study by Krak et al. [180] is particularly noteworthy. They found an increased mortality after a fall especially for patients who were exposed to four or more FRIDs prior to the incidence. This highlights the fundamental impact of polypharmacy on elderly patients and in particular the potential danger of the concomitant use of FRIDs.

4.2.11 Interaction between FRIDs

Furthermore, we found that patients under exposure to opioids had a particularly increased risk of fall-related fractures if they also took psychotropic medications such as antidepressants or antipsychotics at the same time. This is in line with a study by Leach et al. [99], who found that concomitant use of opioids, especially with antidepressants, significantly increases the risk of falling.

With regard to the simultaneous intake of antipsychotics, it was found that the risk of an amplified effect of the medication and the resulting possible overdose is increased. This in turn favours falling and suffering subsequent fractures significantly [181].

The results of our study concerning the concomitant use of especially opioids in patients on SSRI antidepressant regiment are consistent with other studies. For instance, it was shown that taking centrally acting medication at the same time can exacerbate the effect of the drugs and lead to severe drowsiness, which eventually favours falling [182-184].

Concerning our results of patients with loop diuretics background therapy we could show that especially the additional use of centrally acting drugs (antidepressants, opioids, antipsychotics) and anticholinergics increased the risk of falls and fractures. With regard to the concurrent use of the centrally acting drugs, the combination of side-effects such as hypotension, dizziness and drowsiness may explain the increased risk [133]. Especially the concomitant use of diuretics and anticholinergic incontinence medication is a special point to consider as it is frequently an example of competitive therapy [185]. It is evident that up to half of all heart failure patients develop incontinence, certainly also due to the use of diuretics which is supposed to increase the diuresis frequency [186].

In summary, we showed that despite changing background treatment (SSRI, loop diuretics, low potent opioids), the risk of falls and fractures remained high for certain medications. These were anticholinergic overactive bladder and incontinence medication, TCAs and SSRIs, atypical antipsychotics and low and high potent opioids. This suggests that the above subgroups, independent of other factors e.g. concomitant drug use, represent a consistent risk of increasing the risk of falls and fall-related fractures in different types of patients.

4.2.12 Age

A particular risk factor in our study was age. Across all analyses, both the relative and absolute risk of falling and subsequent fractures was higher for nearly all FRIDs studied in the over 75 patient group compared to the 65 to 74 year old patient group. While the relative risk did not show in most of the cases any decisive differences at first glance, the absolute risk in form of the NNH displayed that age had an immense influence on potential falls and the susceptibility to suffer fall-related fractures. This is consistent with various previous studies which have likewise identified age as one of the greatest risk factors for falls and fall-related fractures [52, 187, 188]. The impact of a fall and fall-related fracture on the older patient group becomes particularly clear with regard to the mortality rate (Figure 6), which was constantly more than twice as high as that of the younger group.

4.3 Summary of hypotheses

In summary, we were able to confirm some of the hypotheses of the STOPPFall expert round [74], but some were not consistent with our results, displayed in Table 14. The hypothesis that medications with stronger anticholinergic properties are more fracture-risk increasing than weak anticholinergics was supported by our findings. Further, according to our findings, loop diuretics are more fracture-risk increasing than other diuretics. The hypothesis that older antiepileptic drugs increase the risk of falls and fall-related fractures more than newer drugs was also supported by our study. Particularly older people were at higher risk than younger people. In addition, non-selective alpha blockers are more fracture-risk increasing than selective ones. However, significant associations were only found in the younger age group. We also confirmed that the more FRID groups are being taken concomitantly, the higher is the risk of fall-related fractures.

Our findings partially support the hypothesis concerning the interaction between the background treatments of FRIDs (SSRI, low potent opioids, loop diuretics) with other FRIDs taken concomitantly. Lastly, the FRID associated risk of fall-related fractures was higher in the older than in the younger patient group.

Our findings do not support the hypothesis that antihistamines increase the fracture-risk in either age group. Moreover, the hypothesis about oral hypoglycaemic drugs was not consistent with our findings. Residual confounding [140] may play a role as prescribers may avoid hypoglycaemic drugs in people at higher fracture-risk but the findings highlight that non-hypoglycaemic antidiabetics are not risk-free. Our finding that increased fracture-risk associated with oral antidiabetic drugs is limited to younger patients is most likely explained by the fact that prescribing physicians use these drugs more cautiously in the elderly (i.e. confounding by contraindication [189]). Regarding opioids, our findings do not support the assumption, but likewise residual confounding may play a role as patients on stronger opioids may be less mobile and avoid fall hazards [166]. The suggestion dealing with the subgroups of antidepressants were not consistent with our findings. In comparison to sedating TCAs and mirtazapine, SSRIs are more arousing [173] and have been linked to higher hazards in our findings. This could contribute to residual confounding as prescribers may refrain from giving TCAs to patients who are more likely to fall and suffer subsequent fractures [171]. In addition, used mostly at night, mirtazapine may not have a sedative effect on fall and fracture-risk until the patient awakens during the night, which may happen more frequently in older adults [172]. The hypothesis of the differences of the subgroups of antipsychotics based on sedative, anticholinergic and alpha receptor effects could in our analysis not to be simply confirmed. We found no general differences in the potential to cause falls across all common atypical and typical antipsychotics. The highest relative and absolute risks were with subgroups with strong prolactin increasing effects suggesting that this has a high influence on fracture-risk [162]. Nevertheless, there are major differences in the mechanisms responsible and the atypical antipsychotics in particular are a very heterogeneous subgroup [190].

Table 13: Summary of Hypotheses

Hypotheses		**Interpretation**
Antipsychotics	Risk difference is related to variation in sedative, anticholinergic and alpha receptor properties	Our findings **do not to support** the hypothesis.
Opioids	Strong opioids are more fall-risk increasing than weak opioids	Our findings **do not support** the hypothesis
Antidepressants	TCAs are more fall-risk increasing than others; Risk difference is related to variation in sedative effects, propensity to cause orthostatic hypotension and anticholinergic properties	Our findings **do not support** the hypothesis.
Anticholinergics	Medications with stronger anticholinergic properties are more fall-risk increasing than weak anticholinergics	Our findings **support** the hypothesis.
Overactive bladder and urge incontinence	Risk difference is related to variation in anticholinergic activity	Our findings **support** the hypothesis.
Antiepileptics	Older generation antiepileptics are more fall-risk increasing than newer antiepileptics	Our findings **support** the hypothesis.
Diuretics	Loop diuretics are more fall-risk increasing than other diuretics	Our findings **support** the hypothesis.
Alpha blockers BPH	Non-selective alpha blockers are more fall-risk increasing than selective ones	Our findings **support** the hypothesis.
Antihistamines	First-generation antihistamines are more fall-risk increasing than second generation antihistamines; Risk difference is related to variation in sedative effects and anticholinergic activity	Our findings **do not support** the hypothesis.
Oral hypoglycaemics	Oral hypoglycaemic agents that can cause hypoglycaemia, sulfonylureas, are more risk-increasing than other agents	Our findings **do not support** the hypothesis.

Hypotheses		Interpretation
Cumulative risk of FRIDs	The more FRID groups are being taken concomitantly, the higher the risk of fall-related fractures	Our findings **support** the hypothesis
Age	The FRID associated risk of fall-related fractures is higher in older than in younger people	Our findings **support** the hypothesis
Interactions between FRIDs: SSRI, loop diuretic, low potent opioids + other FRIDs versus SSRI, loop diuretic, low potent opioids alone	The use of FRIDs among users of SSRI, loop diuretics, low potent opioids further increases the risk of fall-related fractures	Our findings **support** the hypothesis for some FRIDs but not others.

4.4 Strengths and limitations

Our study has certain strengths. Due to the fact that we had a broad spectrum of data, starting with laboratory values, hospital diagnoses and detailed demographic information, we could take into account a great amount of confounders other studies haven't. Beyond that, major strengths of our study are also its population-based design which implies a high level of external validity and our examination of subgroups of FRID exposure, stratification by age and co-exposure with commonly prescribed FRIDs. Further, we could report of stratum specific NNH, all of which contribute to the relevance of our findings for clinical decision making in primary care. This should improve the communication about possible risks taking and prescribing FRIDs regarding general practitioners and their patients [191].

There are some limitations in our study. A limitation is that we cannot know whether the included fractures were actually fall-related implying the risk for case misclassification, which would bias relative risk estimates towards the null.

Consistent with this, we found central antihypertensives to be associated with increased fracture-risk when we restricted the case definition to femur fractures only (SA1). However, all other findings were consistent with the primary analysis. A further limitation of our data set is that it did not include ambulatory care diagnosis such as cognitive impairment. However, we compensated for this using medication (e.g. prior use of antidementia drugs) and/or hospital diagnoses (e.g. prior admissions due to delirium). Nevertheless, residual confounding, such as confounding by indication or contraindication (i.e. prescribers avoiding specific FRIDs in patients at highest fracture-risk), cannot be excluded in any observational study. Stratifying the study period in SA3 did not substantively change risk estimates suggesting no substantive changes in prescribing behaviour over the study period. However, regardless of confounding by contraindication, comparison of risk estimates for fractures may highlight priorities for improvement in current practice.

5 Conclusion

FRIDs are a significant concern for older adults and can lead to serious injuries and even death. It is essential for healthcare providers to identify and manage the use of these medications in older patients [5]. The observed dose response relationship of this study, with increasing risk associated with increasing numbers of FRIDs taken in combination strongly suggests a causal link between drug groups previously classified as FRIDs [74] and fractures in older people. Despite the limitations of observational studies, this work reinforces the need for more cautious use of loop diuretics, anticholinergic drugs and psychotropics, especially among patients aged 75 years or older. Among the latter group, the risk was highest (one year NNH < 100) for most subgroups of antipsychotics, both TCAs and SSRI antidepressants and the use of three or more FRIDs. It is known that antidepressants and antipsychotics are often prescribed inappropriately or for longer durations than necessary in older people [192-195]. They are therefore plausible priorities for deprescribing interventions. Such high absolute increases in risk were also consistently found among users of loop diuretics when antipsychotics or SSRI antidepressants were added. In addition, the practice of co-prescribing analgesics and psychotropic drugs is common and often unavoidable [196], however, this interaction resulted in a significant increase in the risk of falls and fall-related fractures. Considering the high 90-day mortality risk (>10%), these combinations should be reconsidered whenever possible. Consistent with this the world guidelines for falls prevention and management of older adults [5] recommend that falls risk should be assessed before prescribing FRIDs and deprescribing of FRIDs should be part of multidimensional fall prevention interventions.

In summary, most attempts to reduce risk of falls and subsequent fall-related fractures by deprescribing FRIDs as a single action have shown disappointing results [95], but it has been shown to be an effective element of multicomponent interventions [5]. This study found that most groups and subgroups of drugs classified as FRIDs are significantly associated with an increased risk of fractures. Our findings suggest that patients aged ≥75 years who are prescribed antidepressants or antipsychotics or taking three or more FRIDs may especially benefit from this multicomponent intervention.

Although our findings suggest that certain combinations of FRIDs are riskier than others, we did not investigate all possible combinations and the mechanisms underlying such differences require further research. In addition, subsequent studies should examine differences at the individual drug level within the FRID subgroups. From our results it can be concluded that there are also large heterogeneities with regard to the risk of falling and suffering subsequent fall-related fractures. For further studies, it would be also important to include secondary prevention, since we focused exclusively on primary prevention. It can be assumed that patients who have suffered from a fall-related fracture more than once and are frail, the absolute risk is certainly lower than in our analysis.

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7 Appendix

Table A 1: Prevalence of Fractures

ICD^{10th} Code	Number (%)	Definition
Skull and facial bones		
S 02.0	22 (0.1)	Fracture of vault of skull
S 02.1	54 (0.3)	Fracture of base of skull
S 02.2	57 (0.3)	Fracture of nasal bones
S 02.3	42 (0.2)	Fractur of orbital floor
S 02.4	68 (0.4)	Fracture of malar and maxillary bones
S 02.5	4 (0)	Fracture of tooth
S 02.6	25 (0.1)	Fracture of mandible
S 02.7	11 (0.1)	Multiple fractures involving skull and facial bones
S 02.8	21 (0.1)	Fractures of other skull and facial bones
S 02.9	6 (0)	Fracture of skull and facial bones, part unspecified
Neck		
S 12.0	27 (0.1)	Fracture of first cervical vertebra
S 12.1	83 (0.4)	Fracture of second cervical vertebra
S 12.2	43 (0.2)	Fracture of other specified cervical vertebra
S 12.7	49 (0.3)	Multiple fractures of cervical spine
S 12.8	1 (0)	Fracture of other parts of neck
S 12.9	22 (0.1)	Fracture of neck, part unspecified
Rib(s), sternum and thoracic spine		
S 22.0	169 (0.9)	Fracture of thoracic vertebra
S 22.1	29 (0.2)	Multiple fractures of thoracic spine
S 22.2	42 (0.2)	Fracture of sternum
S 22.3	215 (1.2)	Fracture of rib
S 22.4	336 (1.8)	Multiple fractures of ribs
S 22.5	15 (0.1)	Flail chest
S 22.8	2 (0)	Fracture of other parts of bony thorax
S 22.9	2 (0)	Fracture of bony thorax, part unspecified

ICD[10th] Code	Number (%)	Definition
Lumbar spine and pelvis		
S 32.0	244 (1.3)	Fracture of lumbar vertebra
S 32.1	56 (0.3)	Fracture of sacrum
S 32.2	3 (0)	Fracture of coccyx
S 32.3	32 (0.2)	Fracture of ilium
S 32.4	136 (0.7)	Fracture of acetabulum
S 32.5	1257 (6.8)	Fracture of pubis
S 32.7	37 (0.2)	Multiple fractures of lumbar spine and pelvis
S 32.8	26 (0.1)	Fracture of other and unspecified parts of lumbar spine and pelvis
Shoulder and upper arm		
S 42.0	247 (1.3)	Fracture of clavicle
S 42.1	45 (0.2)	Fracture of scapula
S 42.2	1192 (6.5)	Fracture of upper end of humerus
S 42.3	217 (1.2)	Fracture of shaft of humerus
S 42.4	142 (0.8)	Fracture of lower end of humerus
S 42.7	6 (0)	Multiple fractures of clavicle, scapula and humerus
S 42.8	11 (0.1)	Fracture of other parts of shoulder and upper arm
S 42.9	62 (0.3)	Fracture of shoulder girdle, part unspecified
Forearm		
S 52.0	213 (1.2)	Fracture of upper end of ulna
S 52.1	35 (0.2)	Fracture of upper end of radius
S 52.2	7 (0)	Fracture of shaft of ulna
S 52.3	7 (0)	Fracture of shaft of radius
S 52.4	15 (0.1)	Fracture of shafts of both ulna and radius
S 52.5	1576 (8.5)	Fracture of lower end of radius
S 52.6	306 (1.7)	Fracture of lower end of both ulna and radius
S 52.7	35 (0.2)	Multiple fractures of forearm
S 52.8	27 (0.1)	Fracture of other parts of forearm
S 52.9	0	Fracture of forearm, part unspecified

ICD[10th] Code	Number (%)	Definition
Wrist and hand level		
S 62.0	21 (0.1)	Fracture of navicular [scaphoid] bone of hand
S 62.1	7 (0)	Fracture of other carpal bone(s
S 62.2	11 (0.1)	Fracture of first metacarpal bone
S 62.3	57 (0.3)	Fracture of other metacarpal bone
S 62.4	21 (0.1)	Multiple fractures of metacarpal bones
S 62.5	41 (0.2)	Fracture of thumb
S 62.6	172 (0.9)	Fracture of other finger
S 62.7	27 (0.1)	Multiple fractures of fingers
S 62.8	68 (0.4)	Fracture of other and unspecified parts of wrist and hand
Femur		
S 72.0	5958 (32.3)	Fracture of neck of femur
S 72.1	1977 (10.7)	Pertrochanteric fracture
S 72.2	230 (1.2)	Subtrochanteric fracture
S 72.3	180 (1)	Fracture of shaft of femur
S 72.4	201 (1.1)	Fracture of lower end of femur
S 72.7	1 (0)	Multiple fractures of femur
S 72.8	34 (0)	Fractures of other parts of femur
S 72.9	47 (0.3)	Fracture of femur, part unspecified
Lower leg, including ankle		
S 82.0	133 (0.7)	Fracture of patella
S 82.1	227 (1.2)	Fracture of upper end of tibia
S 82.2	103 (0.6)	Fracture of shaft of tibia
S 82.3	140 (0.8)	Fracture of lower end of tibia
S 82.4	154 (0.8)	Fracture of fibula alone
S 82.5	62 (0.3)	Fracture of medial malleolus
S 82.6	199 (1.1)	Fracture of lateral malleolus
S 82.7	17 (0.1)	Multiple fractures of lower leg
S 82.8	838 (4.5)	Fractures of other parts of lower leg
S 82.9	1 (0)	Fracture of lower leg, part unspecified

ICD^{10th} Code	Number (%)	Definition
Foot, except ankle		
S 92.0	62 (0.3)	Fracture of calcaneus
S 92.1	10 (0.1)	Fracture of talus
S 92.2	16 (0.1)	Fracture of other tarsal bone(s)
S 92.3	83 (0.4)	Fracture of metatarsal bone
S 92.4	11 (0.1)	Fracture of great toe
S 92.5	14 (0.1)	Fracture of other toe
S 92.7	22 (0.1)	Multiple fractures of foot
S 92.9	4 (0)	Fracture of foot, unspecified
Multiple body regions		
T 02.1	4 (0)	Fractures involving thorax with lower back and pelvis
T 02.2	1 (0)	Fractures involving multiple regions of one upper limb
T 02.4	2 (0)	Fractures involving multiple regions of both upper limbs
T 02.8	3 (0)	Fractures involving other combinations of body regions
Spine, level unspecified		
T 08	18 (0.1)	Fracture of spine, level unspecified
Total	18,456	

Table A 2: Specification of exposure to fall-risk-increasing-drugs (FRIDs)

FRID exposure			Drugs included (BNF codes)
Group	Subgroup		
Antipsychotics	Atypical	Done	Paliperidone (0402010AE 0402020AB) Ziprasidone (0402010AG) Risperidone (040201030 0402020AA)
		Benzamide	Amisulpride (0402010A0) Sulpiride (0402010U0)
		Pine	Clozapine (0402010C0)

FRID exposure			Drugs included (BNF codes)
Group	Subgroup		
			Olanzapine (040201060 0402020AC) Quetiapine (0402010AB) Asenapine (0402030R0) Zotepine (0402010AC)
		Partial dopamine agonist	Aripiprazole (0402010AD) Aripiprazole (0402020AD) Cariprazine (0402010AJ)
	Typical	Phenothiazine	Chlorpromazine (0402010D0) Fluphenazine (0402010I0 0402020L0) Perphenazine (0402010Q0) Thioridazine (0402010W0) Pipotiazine (0402020V0)
		Butyrophenone	Haloperidol (0402020T0 0402010J0) Benperidol (0402010B0) Melperone (0402010AF) Pimozide (0402010R0)
		Thioxanthene	Flupentixol (0402020G0 0402010H0) Chlorprothixene (0402010F0) Zuclopenthixol (040201010 0402010T0 0402020Z0)
Alpha blocker, antihypertensives			Doxazosin (0205040D0) Indoramin (0205040I0) Phenoxybenzamine (0205040M0) Phentolamine (0205040P0) Prazosin (0205040S0) Terazosin (0205040V0)
Alpha blocker, prostate hyperplasia			Alfuzosin (0704010A0) Indoramin (0704010M0) Solifenacin/tamsulosin (0704010W0) Tamsulosin and dutasteride (0704010V0)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Tamsulosin (0704010U0) Terazosin (0704010T0)
Antihistamines	First generation	Diphenhydramine (0304010N0) Promethazine (0304010W0) Clemastine (0304010H0) Brompheniramine (0304010F0) Hydroxyzine (0304010J0) Chlorphenamine (0304010G0) Cyproheptadine (0304010K0) Azatadine (0304010C0) Alimemazine (0304010Y0)
	Second generation	Loratadine (0304010D0) Cetirizine (030401OI0) Levocetirizine (0304010AC) Acrivastine (0304010A0) Fexofenadine (0304010E0) Ketotifen (0304010AG) Mizolastine (0304010AA) Rupatadine (0304010AE) Terfenadine (0304010X0) Bilastine (0304010AF)
Overactive Bladder and Incontinence	Anticholinerg	Trospium (0704020Z0) Oxybutynin (0704020J0) Fesoterodine (0704020AD) Flavoxate (0704020G0) Tolterodine (0704020N0) Darifenacin (0704020AC) Solifenacin (0704020AB) Solifenacin/Tamsulosin (0704020AF) Propiverine (0704020P0)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
	Others	Mirabegron (0704020AE) Duloxetine (0704020AA)
Benzodiazepine		Midazolam (0401010Q0) Nitrazepam (0401010R0) Temazepam (0401010T0) Flurazepam (0401010L0) Loprazolam (0401010N0) Lormetazepam (0401010P0) Alprazolam (0401020A0) Bromazepam (0401020G0) Diazepam (0401020K0) Lorazepam (0401020P0) Oxazepam (0401020T0)
Z-Drugs		Zaleplon (0401010W0) Zolpidem (0401010Y0) Zopiclone (0401010Z0)
Vasodilators in cardiac disease		Ambrisentan (0205010X0) Bosentan (0205010U0) Diazoxide (0205010E0) Hydralazine (0205010J0) Iloprost (0205010V0) Macitentan (0205010AA) Minoxidil (0205010N0) Riociguat (0205010AB) Sildenafil (0205010Y0) Sitaxentan (0205010W0) Tadalafil(0205010Z0) Vericiguat (0205010AC) Amyl nitrite (0206010A0) Glyceryl trinitrate (0206010F0)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Isosorbide (0206010I0 0206010K0) Amlodipine (0206020A0) Diltiazem (0206020C0) Felodipine (0206020F0) Isradipine (0206020I0) Lacidipine (0206020K0) Lercanidipine (0206020L0) Nicardipine (0206020Q0) Nifedipine (0206020R0) Nimodipine (0206020M0) Nisoldipine (0206020W0) Trimetazidine (0206020B0) Valsartan/Amlodipine (0206020Z0) Verapamil (0206020T0) Aliskiren (0205053A0) Azilsartan (0205052AD) Candesartan (0205052C0) Captopril (0205051F0) Cilazapril (0205051E0) Co-Zidocapt (0205051G0) Enalapril (0205051I0 0205051H0) Eprosartan (0205052W0) Fosinopril (0205051J0) Imidapril (0205051W0) Irbesartan (0205052I0 0205052A0) Lisinopril (0205051L0 0205051K0) Losartan (0205052N0 0205052P0) Moexipril (0205051C0) Olmesartan (0205052B0 0205052Y0 0205052AC 0205052AB)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Perindopril (0205051AA 0205051AC 0205051AB 0205051N0 0205051M0 0205051Z0 0205051Y0) Quinapril (0205051Q0 0205051P0) Ramipril (0205051R0 0205051S0) Sacubitril/Valsartan (0205052AE) Telmisartan (0205052Q0 0205052R0) Trandolapril (0205051U0 0205051V0) Valsartan (0205052V0 0205052X0)
Centrally acting antihypertensives		Clonidine (0205020E0) Guanfacine (0205020G0) Methyldopa (0205020H0) Moxonidine (0205020M0)
Oral antidiabetics	Hypoglycaemic properties	Glibenclamide (0601021H0) Tolbutamide (0601021X0) Gliclazide (0601021M0) Glimepiride (0601021A0) Glipizide (0601021P0) Nateglinide (0601023U0) Repaglinide (0601023R0)
	Others	Acarbose (0601023A0) Albiglutide (0601023AS) Alogliptin (0601023AK 0601023AJ) Canagliflozin (0601023AM 0601023AP) Chlorpropamide (0601021E0) Dapagliflozin (0601023AG 0601023AL) Dulaglutide (0601023AQ) Empagliflozin (0601023AN 0601023AR 0601023AY) Ertugliflozin (0601023AX) Exenatide (0601023Y0)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Linagliptin (0601023AE 0601023AF) Liraglutide (0601023AB) Lixisenatide (0601023AI) Metformin (0601022B0 0601023W0 0601023Z0 0601023V0 0601023AD) Nateglinide (0601023U0) Pioglitazone (0601023B0) Saxagliptin (0601023AV 0601023AH 0601023AC) Semaglutide (0601023AW) Sitagliptin (0601023X0) Vildagliptin (0601023AA)
Antiepileptics	Old	Valproic acid (040801020) Phenytoin (0408010Z0 0408010Q0) Carbamazepine (0408010C0) Ethosuximide (0408010I0) Mesuximide (0408010K0) Phenobarbital (0408010N0 0408010P0) Primidone (0408010U0)
	New	Gabapentin (0408010G0) Lamotrigine (0408010H0) Topiramate (040801050) Tiagabine (0408010AB) Levetiracetam (0408010A0) Zonisamide (0408010AD) Oxcarbazepine (0408010D0) Pregabalin (0408010AE) Felbamate (0408010AA) Eslicarbazepine (0408010AI) Lacosamide (0408010AH) Rufinamide (0408010AF)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Vigabatrin (0408010X0) Stiripentol (0408010AG) Perampanel (0408010AK) Lacosamide (0408010AH) Cenobamate (0408010AN)
Diuretics	Loop	Bumetanide (0202020D0 0202080C0 0202080D0) Furosemide (0202020L0 0202080K0) Torasemide (0202020U0)
	Others	Bendroflumethiazide (0202010B0 0202080B0) Chlorothiazide (0202010D0) Chlortalidone (0202010F0) Cyclopenthiazide (0202010J0) Hydrochlorothiazide (0202010L0) Indapamide (0202010P0) Metolazone (0202010V0) Polythiazide (0202010X0) Xipamide (0202010Y0) Eplerenone (0202030X0) Finerenone (0202030Y0) Amiloride (0202040D0 0202040A0 0202030C0) Co-amilofruse (0202040B0) Co-amilozide (0202040C0) Co-flumactone(0202040G0) Co-triamterzide (0202040H0) Spironolactone (0202040S0 0202040T0 0202030S0) Triamterene (0202040U0 0202040V0 0202030W0)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Mannitol (0202050M0)
Antidepressants	SSRI	Citalopram (0403030D0 0403030Z0) Duloxetine (0403030Y0) Escitalopram (0403030X0) Fluoxetine (0403030E0) Fluvoxamine (0403030L0) Paroxetine (0403030P0) Sertraline (0403030Q0)
	TCA	Amitriptyline (0403010B0) Amoxapine (0403010C0) Clomipramine (0403010F0) Dosulepin (0403010J0) Doxepin (0403010L0) Imipramine (0403010N0) Lofepramine (0403010R0) Maprotiline(0403010S0) Mianserin(0403010T0) Nortriptyline (0403010V0) Trazodone (0403010X0) Trimipramine (0403010Y0)
	Mirtazapine	Mirtazapine (0403040X0)
	Others	Nefazodone (0403040T0) Oxitriptan (0403040R0) Reboxetine (0403040U0) Tryptophan (0403040S0) Venlafaxine (0403040W0) Vortioxetine (0403040AB) Agomelatine (0403040Z0) Duloxetine (0403040Y0) Flupentixol (0403040F0)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Isocarboxazid (0403020H0) Moclobemide (0403020K0) Phenelzine (0403020M0) Tranylcypromine (0403020Q0)
Opioids	Low potent	Codeine (0407020C0) Dihydrocodeine (0407020G0) Tramadol (040702040)
	Strong potent	Dipipanone (0407020H0) Fentanyl (0407020A0) Hydromorphone (040702050) Meptazinol (0407020L0) Methadone (0407020M0) Morphine (0407020P0 0407020W0 0407020Q0 040702020) Nalbuphine (0407020Y0) Oxycodone (0407020Z0 (0407020AD 0407020AF) Papaveretum (0407020AB) Pentazocine (0407020T0 0407020U0) Pethidine (0407020V0) Tapentadol (0407020AG 0407020AH) Dextromoramide (0407020D0) Dextropropoxyphene (0407020E0) Diamorphine(0407020K0) Buprenorphine (0407020B0)
Modified Anti-cholinergic risk score (mARS 1) = “weakly anti-cholinergic”		Lofepramine (0403010R0) Metoclopramide (0406000P0) Mirtazapine (0403040X0) Paroxetine (0403030P0) Quetiapine (0402010AB) Ranitidine (0103010S0 0103010T0)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Selegiline (0409010T0) Co-Careldopa (0409010N0) Levodopa (0409010X0) Entacapone (0409010V0) Haloperidol (0402010J0 0402020T0) Methocarbamol (1002020S0) Pramipexole (0409010W0) Reboxetine (0403040U0) Risperidone (040201030 0402020AA) Tiotropium (0301020Q0 0301020X0) Trazodone (0403010X0)
Modified Anti-cholinergic risk score (mARS 2) = “moderately anticholinergic”		Cetirizine (0304010I0) Levocetirizine (0304010AC) Cimetidine (0103010D0) Dosulepin (0403010J0) Loperamide (0104020L0) Desloratadine (0304010AB) Loratadine (0304010D0) Prochlorperazine (0406000T0 0406000U0) Pseudoephedrine (0310000N0 0310000M0) Solifenacin (0704020AB 0704020AF) Tolterodine (0704020N0) Amantadine (0409010B0 0503040C0) Baclofen (10002020C0) Clomipramine (0403010F0) Clozapine (0402010C0) Darifenacin (0704020AC) Doxepin (0403010L0) Fesoterodine (0704020AD) Flavoxate (0704020G0)

FRID exposure		Drugs included (BNF codes)
Group	Subgroup	
		Levomepromazine(0402010L0 0402010K0) Nortriptyline (0403010V0) Olanzapine (040201060 0402020AC) Pericyazine (0402010P0) Propiverine (0704020P0) Trimipramine (0403010Y0) Trospium (0704020Z0)
Modified Anti-cholinergic risk score (mARS 3) “strongly anti-cholinergic”		Amitriptyline (0403010B0) Chlorphenamine (0304010G0) Oxybutynin (0704020J0 0704040G0) Thioridazine (0402010W0) Atropine (0102000AC) Cyproheptadine (0304010K0) Clemastine (0304010H0) Chlorpromazine (0402010D0) Benzatropine (0409020E0) Ipratropium (0301020I0) Dicycloverine (0102000K0 0102000J0) luphenazine (0402020L0 0402010I0) Perphenazine (0402010Q0) Procyclidine (0409020S0) Promethazine (0304010W0 0406000V0) Tizanidine (1002020T0) Trifluoperazine (0402010X0 0402010X0) Chlorpheniramine (0304010G0) Hydroxyzine (0304010J0) Imipramine(0403010N0 0403010Y0) Tizanidine (1002020T0) Orphenadrine (0409020N0)

Table A 3: Specification of confounder variables I

Confounder	Drugs included (BNF codes)
Antiosteoporosis drugs	Alendronic acid (0606020A0 (0606020Y0) Denosumab (0606020Z0) Etidronate disodium (0606020C0) Ibandronic acid (0606020W0) Other bisphosphonate and other preparations (060602000) Pamidronate disodium (0606020P0) Risedronate sodium (0606020R0) Sodium clodronate (0606020T0) Strontium ranelate (0606020X0) Tiludronic acid (0606020U0) Zoledronic acid (0606020V0) Raloxifene (0604011X0) Teriparatide (0606010U0) Calcitonin (0606010T0)
Antiparkinson drugs	Amantadine (0409010B0) Apomorphine (0409010A0 0409010AC) Cabergoline (0409010U0) Carbidopa (0409010D0) Co-beneldopa (Benserazide/levodopa) (0409010K0) Co-careldopa (Carbidopa/levodopa) (0409010N0) Entacapone (0409010V0) Levodopa (0409010I0) Levodopa/carbidopa/entacapone (0409010X0) Memantine (0409010M0) Opicapone (0409010AB) Pergolide (0409010P0) Pramipexole (0409010W0) Rasagiline (0409010Y0) Ropinirole (0409010H0) Rotigotine (0409010Z0)

Confounder	Drugs included (BNF codes)
	Safinamide (0409010AA) Selegiline (0409010T0) Tolcapone (0409010S0) Benzatropine (0409020E0) Biperiden (0409020G0) Orphenadrine (0409020N0) Procyclidine (0409020S0) Trihexyphenidyl (0409020C0) Botulinum toxin type A (0409030B0) Botulinum toxin type B (0409030A0) Piracetam (0409030P0) Riluzole (0409030R0) Tetrabenazine (0409030C0)
Disease-modifying antirheumatic drugs (DMARDs)	Abatacept (1001030V0) Adalimumab (1001030S0) Anakinra (1001030R0) Apremilast (1001030AA) Auranofin (1001030A0) Baricitinib (1001030AC) Certolizumab pegol (1001030Y0) Etanercept (1001030D0) Filgotinib (1001030AG) Golimumab (1001030X0) Hydroxychloroquine (1001030C0) Infliximab (1001030T0) Leflunomide (1001030L0) Methotrexate (1001030U0) Penicillamine (1001030F0) Sarilumab (1001030AD) Secukinumab (1001030AF) Sodium aurothiomalate (1001030J0)

Confounder	Drugs included (BNF codes)
	Tiopronin (1001030Q0) Tocilizumab (1001030W0) Tofacitinib (1001030AB) Upadacitinib (1001030AE)
Glucocorticoids	Betamethasone (0603020B0 0603020C0 1104010D0) Cortisone (0603020F0) Deflazacort (0603020I0) Dexamethasone (0603020G0 0603020AA 0603020H0 1104010X0) Hydrocortisone (0603020J0 0603020L0 0603020M0 0105020C0 0105020B0 1001022G0 1104010M0) Methylprednisolone (0603020S0 0603020AC 0603020K0 1001022K0) Prednisolone (0603020T0 0603020X0 0105020F0 0105020D0 0105020E0 1001022N0 1104010R0 1104010S0) Triamcinolone (0603020Z0 1001022U0 1001022Y0) Beclometasone (0302000C0 0105020G0) Budesonide (0302000K0 0302000Y0 0105020A0) Ciclesonide (0302000U0) Fluticasone (0302000V0 0302000N0) Mometasone (0302000X0 0302000R0) Clobetasone butyrate (1104010F0) Dexamethasone (1104010I0) Fluorometholone (1104010K0) Loteprednol (1104010W0) Rimexolone (1104010V0)
Neuropathic Pain drugs	Capsaicin (0407030AE) Gabapentin (0407030AD) Pregabalin (0408010AE)
Insulin	Biphasic insulin aspart (0601012W0) Biphasic insulin lispro (0601012F0) Biphasic isophane insulin (0601012D0) Insulin aspart (0601011A0)

Confounder	Drugs included (BNF codes)
	Insulin degludec (0601012Z0) Insulin detemir (0601012X0) Insulin glargine (0601012V0) Insulin glargine/lixisenatide (0601012AB) Insulin glulisine (0601011P0) Insulin human (0601011R0) Insulin Lispro (0601011L0) Insulin zinc suspension (0601012G0) Isophane insulin (0601012S0) Protamine zinc insulin (0601012U0) Soluble insulin(0601011N0)
Vitamin D and Calcium	Alfacalcidol (0906040B0) Calcitriol (0906040C0) Colecalciferol (0906040G0) Dihydrotachysterol (0906040K0) Ergocalciferol (0906040N0) Other vitamin D preparations (090604800) Paricalcitol (0906040P0) Calcium (0905011D0 0905011B0 0905011K0 0905011R0)
Antidementia drugs	Donepezil (0411000D0) Galantamine (0411000F0) Idebenone (0411000H0) Memantine (0411000G0) Rivastigmine (0411000E0)

Table A 4: Specification of confounder variables II

Confounder	Definition (medication coded by BNF)	Period measured
mARS {Sumukadas, 2014}	Score to assess anticholinergic exposure (drugs defined as FRID or other confounder excluded)	90-day risk window
medCDS {Quinzler, 2019}	Prediction of frailty/mortality of patients according to prescribed medication for most prevalent chronic diseases ,age and gender <u>Chronic Diseases:</u> Chronic gastritis, gastroesophegeal reflux disease Cardiac arrhythmias Asthma, COPD Cancer (colorectal, mamma, prostate carcinoma) including aniemetic therapy Cardiovascular disease category 2 (heart failure) Psychiatric diseases (depression, schizophrenia, anxiety)	90-day risk window
FRIDs not under investigation	STOPPFall (Seppala, 2020} Antipsychotics Opioids Antidepressants Diuretics Alpha blocker, antihypertensives Alpha blocker, prostate hyperplasia Antihistamines Overactive Bladder and Incontinence Z-Drugs Benzodiazepines Vasodilators in cardiac disease Centrally acting antihypertensives Oral antidiabetics Antiepileptics	90-day risk window

Confounder	Definition (medication coded by BNF)	Period measured
Mean number of Drugs	Sum of all drugs taken concomitantly	90-day risk window
Cognitive Impairment	ICD10th Delirium: F05 OR Antidementia Drugs: Donepezil, Galantamine, Idebenone, Memantine, Rivastigmine	90-day risk window
Chronic Kidney Disease	CKD1= eGFR<=30 ml/min/1,73m² CKD2= eGFR>30 ml/min/1,73m² and eGFR<=60 ml/min/1,73m²	Within one year prior Index Date
Liver Diseases	ICD10th Alcoholic liver disease: K70 Toxic liver disease: K71 Hepatic failure: K72 Chronic Hepatitis: K73 Fibrosis an Cirrhosis: K74 other inflammatory liver diseases: K75 Other diseases of liver: K76 K77	Within one year prior Index Date
Malignant Neoplasm, non-terminal	ICD10th C00 – C97 (terminal diseases excluded)	Within one year prior Index Date
Terminal Disease (5 year survival rate <50%)	ICD10th Neoplasms: C3,4,5,6,10,11,12,13,15,16,17,23,24,25,33,34,38,40,41,45,47,52,56,57,66,70,71,72,84,90,91 Dementia: F00 F01 Alzheimer disease: G30 Cardiomyopathy: I42 Heart failure: I50 Intracerebral hemorrhage: I61 Cerebral Infarction: I63 COPD: J44 Diseases of liver: K70 K72 Renal Failure: N17 N18	Within one year prior Index Date

Confounder	Definition (medication coded by BNF)	Period measured
Number Emergency Admission	Sum of all emergency admissions within one year prior to index date	Within one year prior Index Date
SIMD scale 1-5	Scottish index of multiple deprivation (SIMD) {Scottish Government, 2020} Scale 1-10, 1=most deprived, 10=most affluent Deprivation defined as scale=1-5	Within one year prior Index Date
Incident User	no prescription of Index drug SSRI (B), low potency opioids (C), loop diuretics (D) within one year before cohort entry	within one year before cohort entry
Index date November to February	If index date happened in winter time November- February	Index date

Table A 5: 90-day mortality rate of cases overall (A) and stratified by fracture type and by exposure to SSRIs (B), low potency opioids (C) and loop diuretics (D)

A. All cases aged 65 years or older			
Patient group according to age	**No. of cases/fractures**	**No. of deaths within 90 days after fracture**	**Case fatality rate**
All fractures			
≥65 years	18,456	1,906	**10.3**
65 to 74 years	4,449	168	**3.8**
≥75 years	14,007	1,738	**12.4**
Fractures of femur			
≥65 years	8,628	1,280	**14.8**
65 to 74 years	1,339	93	**6.9**
≥75 years	7,289	1,187	**16.3**
Other fractures			
≥65 years	9,828	626	**6.4**
65 to 74 years	3,110	75	**2.4**
≥75 years	6,718	551	**8.2**

B. All cases aged 65 years or older and exposed to SSRIs			
Patient group according to age	**No. of cases/fractures**	**No. of deaths within 90 days after fracture**	**Case fatality rate**
All fractures			
≥65 years	2535	285	**11.2**
65 to 74 years	717	37	**5.2**
≥75 years	1818	248	**13.6**
Fractures of femur			
≥65 years	1144	194	**17.0**
65 to 74 years	204	25	**12.3**
≥75 years	940	169	**18.0**
Other fractures			
≥65 years	1391	91	**6.5**
65 to 74 years	513	12	**2.3**
≥75 years	878	79	**9**

C. All cases aged 65 years or older and exposed to low potency opioids			
Patient group according to age	**No. of cases/fractures**	**No. of deaths within 90 days after fracture**	**Case fatality rate**
All fractures			
≥65 years	5878	588	**10**
65 to 74 years	1527	83	**5.4**
≥75 years	4351	505	**11.6**
Fractures of femur			
≥65 years	2625	354	**13.5**
65 to 74 years	491	43	**8.8**
≥75 years	2134	311	**14.6**
Other fractures			
≥65 years	3253	234	**7.2**
65 to 74 years	1036	40	**1.8**
≥75 years	2217	194	**8.8**

D. All cases aged 65 years or older and exposed to loop diuretics			
Patient group according to age	**No. of cases/fractures**	**No. of deaths within 90 days after fracture**	**Case fatality rate**
All fractures			
≥65 years	3689	629	**17.5**
65 to 74 years	494	39	**7.9**
≥75 years	3194	590	**18.5**
Fractures of femur			
≥65 years	1848	404	**21.9**
65 to 74 years	181	21	**11.6**
≥75 years	1667	383	**23.0**
Other fractures			
≥65 years	1841	225	**12.2**
65 to 74 years	313	18	**5.8**
≥75 years	1527	207	**13.6**

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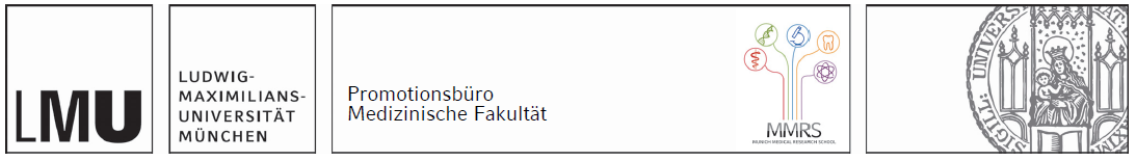
Affidavit



Affidavit

I hereby declare, that the submitted thesis entitled

Single and combined use of fall-risk-increasing drugs and fracture risk:

A population-based case-control study

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

Wiesbaden, 31.12.2023 — Jonathan Hauff

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List of publications

Age and Ageing:

Single and combined use of fall-risk-increasing drugs and fracture risk:

A population based case-control study