BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058983
Article Type:	Original research
Date Submitted by the Author:	27-Nov-2021
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Keywords:	INTERNAL MEDICINE, Orthopaedic & trauma surgery < SURGERY, GENERAL MEDICINE (see Internal Medicine)

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Incident falls are strongly associated with subsequent fracture risk in patients attending the FLS after an index fracture: a 3-year prospective cohort study.

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Abstract

Objectives:

Falls are a strong risk factor for fractures, independent of bone mineral density (BMD) and clinical risk factors. The aim of this study was to evaluate the risk of subsequent fractures in patients who attended the Fracture Liaison Service (FLS), with and without incident falls after the index fracture.

Method:

A 3-year prospective observational cohort study was conducted in patients aged 50+ years with a recent clinical fracture, starting at the time they attended the FLS. Patients were treated with anti-osteoporosis medication according to the Dutch osteoporosis guideline. Falls were recorded weekly in fall diaries. Subsequent fractures were recorded in fall diaries and annual questionnaires and were radiologically confirmed. The Cox's proportional hazards model was employed to estimate the association between fall and fracture risk, adjusted for predefined covariates including age, gender, index fracture type, BMD, and prevalent vertebral fractures status.

Results:

The study included 488 patients (71.9% women, mean age 64.6 ± 8.6 years). During the 3-year follow-up, 959 falls had been ascertained in 296 (60.7%) patients (*i.e.,* fallers), and 60 subsequent fractures were ascertained in 53 (10.9%) patients. Of the fractures, 47 (78.3%) were fall-related, of which 25 (53.2%) were sustained at the first fall incident at a median of 34 weeks. An incident fall was associated with an approximately 9-fold (hazard ratio 8.6; 95% CI, 3.1 to 23.8) increase in the risk of subsequent fractures.

Conclusion:

These data suggest that subsequent fractures among patients on treatment prescribed in a FLS setting are common, and an incident falls is a strong predictor of subsequent

fracture risk, and that immediate attention for fall risk could be beneficial in an FLS model of care.

Strengths and limitations

- Although this is one of the largest prospective studies in a FLS population focusing on the incidence of falls after an index fracture, the number of patients is modest, and the number of subsequent fractures relatively small.
- Data on falls were collected prospectively using fall diaries. However, no procedures were in place to validate self-reported falls.
- No information was available on falls between the index fracture and enrollment in the study.
- Relatively healthy patients participated in the study, which may have resulted in an underestimation of incident falls and subsequent fractures.

Introduction

Patients with a recent fracture have a high imminent risk of subsequent fractures as shown after most fractures [1-6], and a high risk of subsequent falls, as shown after a recent hip fracture [7-11]. The Fracture Liaison Service (FLS) is considered the most effective organizational approach for secondary fracture prevention in patients after the age of 50 years with a recent fracture.

Most fractures are caused by a fall, but most falls do not result in a fracture [12,13]. Falls are a major contributing factor to the occurrence of fractures, independent and additive to the risk attributable to age and bone mineral density (BMD) [14-17]. Guidelines on the FLS therefore recommend fall prevention and prescription of anti-osteoporosis medication (AOM) in high risk patients [18-22]. However, it is not well known to what extent the imminent risk of subsequent fractures after an index fracture can be attributed to incident falls. We hypothesized that the risk of subsequent fractures would be substantially higher in patients with falls after a recent fracture than in those without falls. The aim of this study was therefore to evaluate the incidence of falls and subsequent fractures, and the risk of subsequent fractures in those with and without falls after a recent index fracture in patients who attend the FLS.

Methods

Study population and design

A 3-year prospective observational cohort study was conducted including 500 consecutive patients aged between 50 and 90 years with a recent, radiologically confirmed clinical vertebral or non-vertebral low-trauma fracture, and who were willing and able to participate. Patients were recruited at the FLS in VieCuri Medical Center, Venlo, The Netherlands.

Low-trauma fractures were defined as fractures that resulted from a fall from standing height or less. Excluded were non-Caucasian patients, patients with bone metastasis, failure of prosthesis or osteomyelitis, and patients with cognitive impairment.

According to standard care, a nurse specialized in osteoporosis invited all patients aged 50 year and older, who visited the emergency department because of a recent clinical vertebral or non-vertebral fracture, to the FLS. All patients who responded and agreed to be evaluated were scheduled an appointment for fracture risk evaluation. Fracture risk evaluation included a detailed questionnaire for evaluation of risk factors for fractures and falls, including medical history and medication use. Also, height and weight were measured, a bone mineral density (BMD) measurement with dual-energy X-ray absorptiometry (DXA) of the lumbar spine, total hip, and femoral neck, with vertebral fracture assessment (VFA) was performed, and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease [23]. According to the Dutch osteoporosis guideline [24], AOM was started in patients with osteoporosis or having at least one moderate to severe prevalent vertebral fracture according to Genant et al. [25]. Bisphosphonates and denosumab were first-choice treatments. Teriparatide was restricted to patients already on another AOM with at least 3 fractures, of which 2 were vertebral fractures.

The study protocol (registration number NL45707.072.13) was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki. All patients gave written informed consent prior to participation.

Falls and subsequent fractures

During the 3-year follow-up, patients were requested to record falls weekly in a fall diary. Fall registration started at the beginning of the study, mean 3.5 ± 1.0 months after the index fracture. A fall was defined as an unintentional change in position

resulting in coming to rest on the ground or other lower level [26]. Patients were asked to return their fall diaries by mail at 3 and 6 months, and during the study visit at 1, 2 and 3 year of follow-up. They were contacted by telephone if the fall diary was not received or incomplete. Patients were categorized as those with at least one incident fall (*i.e.,* faller) or without an incident fall (*i.e.,* non-faller) during follow-up.

When patients recorded a fall in their diary, they were also asked to record whether or not they sustained a subsequent clinical fracture as a direct result of the fall. Additionally, at 1-, 2-, and 3-year follow-up, patients had to complete a detailed questionnaire, including a question on whether they sustained a fracture due to another trauma than a fall or without an overt trauma. All subsequent fractures were radiologically confirmed according to radiology reports in the electronic patient records. Since no imaging of the spine was performed at the end of the study, all reported vertebral fractures were symptomatic, clinical vertebral fractures. A distinction was made between subsequent fractures that were directly caused by a fall (*i.e.,* fall-related fractures), and those that occurred without an overt trauma or were the result of another trauma than a fall (*i.e.,* non-fall-related fractures).

Data analysis

Baseline characteristics were compared between fallers and non-fallers, and between patients with and without subsequent fractures using the Student's t test or Wilcoxon test for continuous variables, and Chi-squared or Fisher's exact test for categorical variables where appropriate. The incidence rate of falls and subsequent fractures per 100 person-years was estimated at 3 and 6 months and 1, 2 and 3 year follow-up, assuming a Poisson distribution. Kaplan Meier curves were made for incident falls and subsequent fractures, in which patients were included once, and only the first incident fall or subsequent fracture was included. Cox proportional hazards regression was used

to determine the association between incident falls and subsequent fractures, yielding hazard ratios (HR) and 95% confidence intervals (CI). Proportional hazard assumptions were not violated. Follow-up time was determined by the first subsequent fracture, lost-to-follow-up or the end of the study, whatever occurred first. All analyses were adjusted for the predefined covariates, including age, gender, index fracture type (major or hip versus any other fracture), BMD (lowest measured at lumbar spine, total hip, femoral neck), prevalent vertebral fractures (moderate or severe versus mild or no prevalent vertebral fractures). Lowest BMD was measured at the femoral neck in 470 participants, at the total hip in 3 participants, and at the lumber spine in 15 participants. A p-value < 0.05 was considered statistically significant.

Two sensitivity analyses were planned; (i) excluding patients with index and subsequent finger or toe fractures, and (ii) by classifying patients with a non-fall-related subsequent fracture as non-faller, even if they fell at another time during follow-up.

Patient and public involvement

Patients or members of the public were not involved in the design, or conduct, or reporting, or dissemination plans of the research.

Results

Study population

Among 1220 patients approached from the FLS , 1011 patients met the study criteria. Of the 1011 patients, 511 were not willing or able to participate in the study, and after excluding 12 patients with missing fall data, ultimately 488 patients were available for analysis (**Supplementary Figure 1**).

The mean time between the index fracture and FLS visit at which patients were included for this study was 3.9 ± 1.1 months for patients with a hip fracture and 3.5 ± 1.0

months for patients with other fractures. Baseline characteristics of the 488 study participants are presented in **Table 1**. Mean age was 64.6 ± 8.6 year and 71.9% of the patients were women. In 86.5% of patients, the index fracture was caused by a fall, and 28.5% of patients had at least one other fall in the year before the start of the study. At baseline, 21.9% of patients were diagnosed with osteoporosis, 51.1% with osteopenia, and 27.1% had a normal BMD. Moderate to severe (i.e., grade 2-3) prevalent vertebral fractures were present in 14.3% of patients. AOM was prescribed in 34.2% of patients (8 (1.6%) were already using AOM, and 159 (32.6%) started using AOM at baseline visit).

Compared to eligible FLS attenders, who were not willing or able to participate in our study, patients included in our study were younger, had fewer major or hip fractures, had a higher BMD, and a lower proportion had prevalent vertebral fractures (see **Supplementary Table 1**).

Falls

During a median follow-up of 3 years (range 0.1 to 3.0), 296 (60.7%) patients recorded 959 falls, corresponding to 68.6 falls per 100 person-years. The cumulative fall incidences and incidence rates per 100 person-years at 3 and 6 months, and at 1, 2 and 3 year follow-up are presented in **Figure 1**. Of the 296 patients with at least one fall, 115 (38.9%) had one fall and 181 (61.1%) had two or more falls (up to 39 falls in one patient).

A first fall was recorded by 189/488 (38.7%) patients during the first year of follow-up, by 56/299 (18.7%) during the second, and by 51/243 (21.0%) during the third year of follow-up. The median time to the first fall was 34 (range 1-156) weeks. Of the 959 falls, 47 (4.9%) resulted in a subsequent fall-related fracture.

There were no significant differences in baseline characteristics between patients with and without a fall during the 3-year follow-up, except for that a higher proportion

of patients with incident falls reported at least one fall in the year before the start of the study (34.5% vs. 19.3%, p < 0.001) (see **Table 1**). There were no significant differences in baseline characteristics between patients with one fall and those with multiple falls (data not shown).

Subsequent fractures

In total, 53 (10.9%) patients recorded 60 subsequent fractures, corresponding to 4.29 subsequent fractures per 100 person-years. The cumulative subsequent fracture incidences and incidence rates (per 100-person years) at 3 and 6 months, and at 1, 2 and 3 year follow-up are presented in **Figure 2**. Of all subsequent fractures, 47 (78.3%) were fall-related, and 13 (21.7%) were non-fall-related. Fall-related subsequent fracture sites were: radius and ulna (n=9), tibia and fibula (n=8), proximal femur (n=4), metatarsal (n=4), hand phalanx (n=4), symptomatic vertebra (n=3), proximal humerus (n=3), clavicula (n=3), costal bones (n=2), scapula (n=2), pelvic bone (n=1), metacarpal (n=1), tarsal (n=1), patella (n=1), and foot phalanx (n=1), whereas subsequent non-fall-related fractures sites were: symptomatic vertebral (n=5), metatarsal (n=2), foot phalanx (n=5), and hand phalanx (n=1). Half (53.2%) of all fall-related subsequent fractures were sustained at the first fall.

Baseline characteristics for patients with and without subsequent fractures are presented in **Table 1**.

Of the 296 patients with at least one fall, 41 (13.9%) had 46 fall-related subsequent fractures, 7 (2.4%) had 7 non-fall-related subsequent fractures, and 1 (0.3%) had 1 fall- and 1 non-fall-related subsequent fracture. Of the 192 patients without a fall, 4 (2.1%) had 5 non-fall-related subsequent fractures. Of note, the risk of subsequent fractures was higher in patients with at least one fall than in those without a fall (adjusted HR (95% CI): 8.6 (3.1-23.8); cumulative incidence: 16.6%% versus 2.1%) (**Figure 3 and Table 2**).

Results were similar when femoral neck BMD instead of the lowest BMD was used for adjustments (adjusted HR (95% CI): 8.3 (3.0-23.0)). Additionally, subsequent fracture risk was higher in patients with moderate or severe prevalent vertebral fractures than in those with no or mild prevalent vertebral fractures (adjusted HR (95% CI): 3.9 (2.1-7.3); cumulative incidence: 24.3% versus 8.6%) (**Table 2**).

The association between falls and subsequent fractures remained significant in sensitivity analyses (i) excluding patients with index and subsequent finger and toe fractures (adjusted HR (95% CI): 8.2 (2.5-26.6)), and (ii) by classifying patients with a non-fall-related subsequent fracture as non-faller (adjusted HR (95% CI): 2.9 (1.5-5.6)).

Discussion

In this 3-year prospective observational cohort study in patients aged 50+ years with a recent clinical fracture, treated according to current Dutch osteoporosis guidelines at a FLS, 60.7% of patients had at least one fall, and 10.9% had at least one subsequent fracture. The majority (78.3%) of subsequent fractures was caused by a fall, and of all fall-related subsequent fractures, 53.2% occurred at the first fall. Subsequent fracture risk was nine-fold higher in fallers than in non-fallers.

Literature reporting fall incidence in fracture patients is limited. Comparable to our results, Van Helden et al. [27] reported a 3-month fall incidence of 15% in patients with a recent fracture at a FLS, and Matsumoto et al. [28] reported a 1-year fall incidence of 40% in ambulatory patients with a recent fracture. Various other studies included older, hip fracture patients and reported higher one year fall incidences up to 55% [7-11], except for the study from Yeh et al. that reported a lower 1-year fall incidence (31%) [29]. Higher fall incidences in hip fracture studies can partially be explained by the older study population. Unfortunately, other fall risk factors cannot be compared. An explanation for the lower fall incidence in the study by Yeh et al. may be that

information on the occurrence of falls was provided by patients and family caregivers, which may have resulted in under registration of falls.

A comparison between the fall incidence in our study and that in the general population is difficult to make, because population-based studies were conducted in a 65+ aged, community-dwelling population, whereas approximately 50% of our study population was <65 years old. The proportion of community-dwelling people aged 65+ years sustaining at least one fall over a 1-year period ranged from 28 to 35% [30-32], with an increasing incidence with increasing age [33]. The 1-year fall incidence reported is our study is comparable to that in an older (65+ aged) population, and therefore relatively high. However, in contrast to what has been reported in literature, we found no higher 3-year fall incidence with increasing age. An explanation for this could be that, especially in the older age group, relatively more healthy patients participated in our study, resulting in a lower fall incidence in older age group. Another explanation could be that patients aged 50-65 years are more physically active, and therefore fall more often.

Compared to our results, previously published FLS studies reported lower [34,35], similar [27,36,37], and higher [38,39] subsequent fracture rates. Differences can be explained by differences in patient selection. Studies that included older patients [38] and patients with more severe fractures [39] reported higher subsequent fracture rates, whereas studies that excluded hand and foot index and subsequent fractures [34] or frail patients reported lower rates [35].

In 2010, the Dutch population consisted of approximately 6,000,000 people aged 50+ years, of whom 119,419 sustained a fracture that year [40], corresponding to a calculated annual fracture incidence of 2.0% in the general Dutch 50+ population. Compared to the general Dutch 50+ population, the fracture incidence was more than 2 times higher in our study, even in the 3rd year of follow-up. In our study, fracture incidence remained high despite treatment according to the current osteoporosis

guideline, raising the question of what more can be done to prevent subsequent fractures. Even though conflicting results have been published about the effect of fall prevention strategies on subsequent fracture [41], we hypothesize that fall interventions could be effective in patients at highest risk, namely those with a recent fracture at risk of falling. Furthermore, according to literature, recurrent fallers have an almost fourfold increased odds of sustaining a fall-related fracture compared to individuals with a single fall [42]. However, we found that the majority of subsequent fall-related fractures occur at the first fall after the index fracture, with a median time to the first fall of 34 weeks. Moreover, fall incidence was highest in the first year. This implies that the FLS patients with a high fall risk should be identified immediately, because there is a small window of opportunity to prevent falls and fall-related subsequent fractures.

Remarkably, in contrast to previous studies indicating that imminent fracture risk that was highest in the first year after an index fracture [43,44], there was a linear subsequent fracture incidence during 3-year follow-up in this study. An explanation for the linear subsequent fracture incidence may be the relatively healthy patients who agreed to participate in our study. Compared to non-attenders, they were younger, and a lower proportion had a major baseline fracture, a prevalent vertebral fracture, and osteoporosis, and if indicated, were more likely to receive AOM. Importantly, in addition to falls, moderate to severe prevalent vertebral fractures at baseline were associated with subsequent fractures, even though anti-osteoporosis medication had been prescribed to these patients according to the current Dutch osteoporosis guideline.

This study has several limitations. Although, this is one of the largest prospective studies in a FLS population focusing on the incidence of falls after an index fracture, the number of patients is modest, and the number of subsequent fractures relatively low. Therefore, the association between falls and fall-related, and non-fall-related subsequent fractures could not be analyzed separately. A fall 'not-resulting-in-a-

subsequent-fracture' might indicate frailty of patients, and might be different from those falls that directly resulted in a subsequent fracture. Future studies are needed to investigate this difference. Finally, because of small numbers, subgroup analyses should not be performed. Furthermore, data on falls were collected prospectively using fall diaries that had to be returned at 3 and 6 months, and 1, 2, and 3 year. However, no procedures were in place to validate self-reported falls, and it is possible that recall bias, could have led to under registration of falls. Moreover, no information was available on falls between the index fracture and enrollment in the study. Finally, relatively healthy patients participated in the study. Compared to non-attenders, they were younger, a lower proportion had a major baseline fracture, a prevalent vertebral fracture, and osteoporosis. The proportion of patients with a fall and subsequent fractures could be expected to be even higher in the total FLS population.

In conclusion, in this 3-year prospective observational cohort study in FLS patients, subsequent fracture incidence was high despite being prescribed anti-osteoporosis medications according to the current Dutch osteoporosis guideline. Subsequent fracture risk was nine-fold higher in fallers than in non-fallers, and the majority of fall-related subsequent fractures occurred at the first fall at a median time of 34 weeks. These findings emphasize that immediate attention for fall risk reduction could be beneficial in FLS care. Further research is needed to determine predictors for falls to identify patients at highest risk of falling.

Figures and tables

Table 1. Baseline characteristics of 488 participants stratified by incident fall and subsequent fracture status.							
	Total population (n=488)	**Non-fallers** (n=192)	**Fallers** (n=296)	**P-value**	**No subsequent fracture** (n=435)	**Subsequent fracture** (n=53)	**P-value**
Age (years)	64.6 ± 8.6	64.4 ± 8.0	64.8 ± 9.0	0.608	64.5 ± 8.8	65.3 ± 7.1	0.488
Female gender	351 (71.9)	130 (67.7)	221 (74.7)	0.095	308 (70.8)	43 (81.1)	0.114
Baseline fracture							
- Finger or toe	55 (11.3)	30 (15.6)	25 (8.4)	0.060	49 (11.3)	6 (11.3)	0.460
- Minor	303 (62.1)	109 (56.8)	194 (65.5)		270 (62.1)	33 (62.3)	
- Major	104 (21.3)	44 (22.9)	60 (20.3)		95 (21.8)	9 (17.0)	
- Hip	26 (5.3)	9 (4.7)	17 (5.7)		21 (4.8)	5 (9.4)	
- Fall-related *	422 (86.5)	164 (85.4)	258 (87.2)	0.582	378 (86.9)	44 (83.0)	0.436
Fall previous year §							
- 0	349 (71.5)	155 (80.7)	194 (65.5)	<0.001	315 (72.4)	34 (64.2)	0.208
- ≥ 1	139 (28.5)	37 (19.3)	102 (34.5)		120 (27.6)	19 (35.8)	
BMD							
- Normal BMD	132 (27.1)	54 (28.1)	78 (26.4)	0.906	123 (28.3)	9 (17.0)	0.081
- Osteopenia	249 (51.0)	97 (50.5)	152 (51.4)		222 (51.0)	27 (50.9)	
- Osteoporosis	107 (21.9)	41 (21.4)	66 (22.3)		90 (20.7)	17 (32.1)	
Prevalent vertebral fracture #$							
- None	356 (73.0)	139 (72.4)	217 (73.3)	0.572	328 (75.4)	28 (52.8)	<0.001
- Grade 1	62 (12.7)	22 (11.5)	40 (13.5)		54 (12.4)	8 (15.1)	
- Grade 2-3	70 (14.3)	31 (16.1)	39 (13.2)		53 (12.2)	17 (32.1)	
Anti-osteoporosis treatment	167 (34.2)	70 (36.5)	97 (32.8)	0.402	142 (32.6)	25 (47.2)	0.035

Continuous variables are shown in mean ± SD (standard deviation), categorical variables are shown as number of patients (%). * Signifying that fracture was caused by a fall. § Fall resulting in baseline fracture not included. # According to Genant et al. $ According to most severe prevalent vertebral fracture. Abbreviations: BMD, bone mineral density.

Table 2. Predictors of refracture: results of the Cox's proportional hazard model

Predictor	Unit of comparison	Hazard ratio and 95% confidence interval	P-value
Gender	Women vs men	1.39 (0.68 - 2.83)	0.362
Age	+5 years	0.97 (0.82 - 1.13)	0.662
Index fracture	Major or hip vs all other	0.68 (0.35 - 1.33)	0.263
BMD	-0.12 g/cm^2	1.30 (0.95 - 1.78)	0.101
Prevalent vertebral fracture	Yes vs no	3.88 (2.07 – 7.27)	<0.0001
Fall	Yes vs no	8.58 (3.09 - 23.8)	<0.0001

Figure legends

Figure 1. Cumulative incidence of falls stratified by gender.

Figure 2. Cumulative incidence of subsequent fractures stratified by gender.

Figure 3. Cumulative incidence of subsequent fractures stratified by fall status.

Contributors

LV collected data, carried out data analysis and drafted the manuscript. CW and JB developed the study design and wrote the research protocol, collected data, and critically reviewed the manuscript. PG developed the study design and wrote the research protocol, and critically reviewed the manuscript. RV collected data and critically reviewed the manuscript. TN and TT assisted with data analysis and critically reviewed the manuscript. HJ, SK, JD, JA, JC and DB critically reviewed the manuscript. All authors approved the final version of the manuscript.

Competing interest

Dr. Vranken, Dr. Wyers, Dr. Van der Velden, Dr. Janzing, Dr. Kaarsemakers, Dr. Driessen, Dr. Eisman, Dr. Tran, and Dr. Bliuc have nothing to disclose.

Dr. Center reports honoraria for educational talks from Amgen, part support for educational meetings from Amgen, and advisory board participation for Amgen and Bayer, outside the submitted work.

Dr. Nguyen reports honoraria for lectures sponsored from Merck, and participation as executive member Asia Pacific Consortium on Osteoporosis, outside the submitted work.

Dr. Geusens reports grants from Amgen, Pfizer, MSD, UCB, Abbott, Lilly, BMS, Novartis, Roche, and Will Pharma, and honoraria for lectures from Amgen and Lilly, outside the submitted work.

Dr. van den Bergh reports grants for lectures from UCB, and Amgen, outside the submitted work.

Funding

This work was supported by the Weijerhorst Foundation, grand number not applicable. The Weijerhorst Foundation was not involved in conducting the study, analyzing the data or writing the manuscript.

Patient consent for publication

Patient consent for publication was not required.

Ethics approval

This study (protocol ID number NL45707.072.13) has been approved by the Independent Review Board Nijmegen (IRBN).

Data availability statement

No additional data available.

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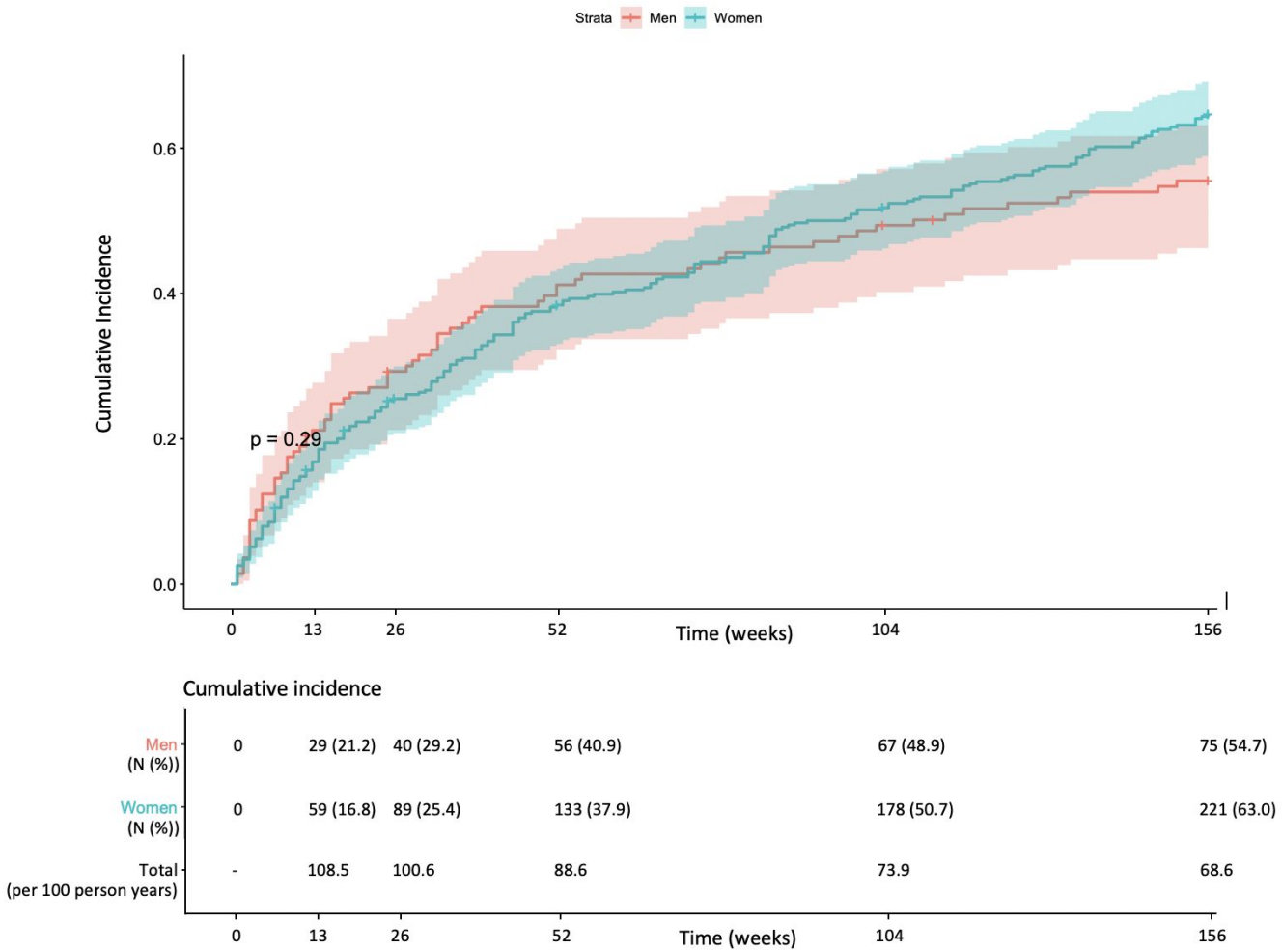


Figure 1. Cumulative incidence of falls stratified by gender.

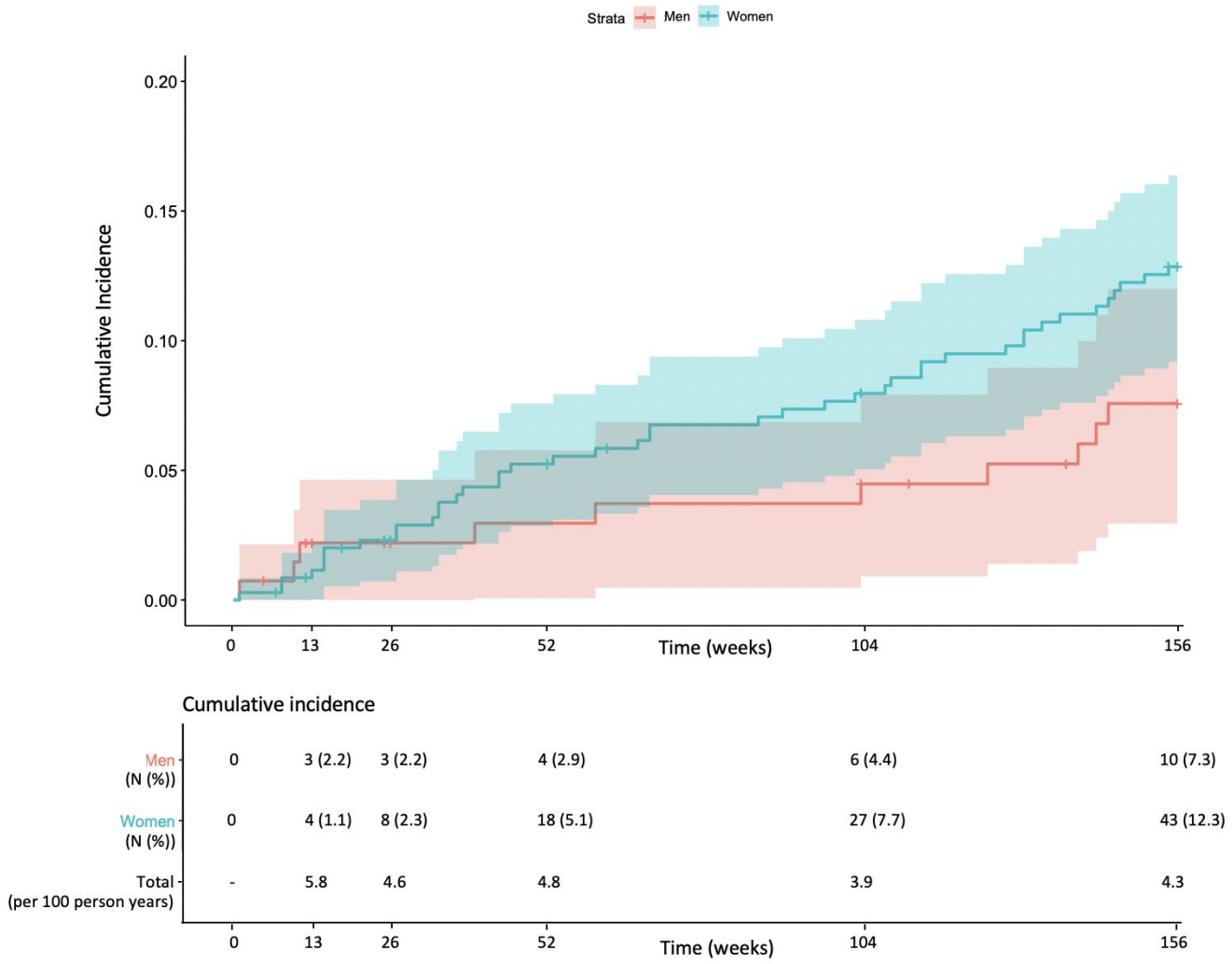


Figure 2. Cumulative incidence of subsequent fractures stratified by gender.

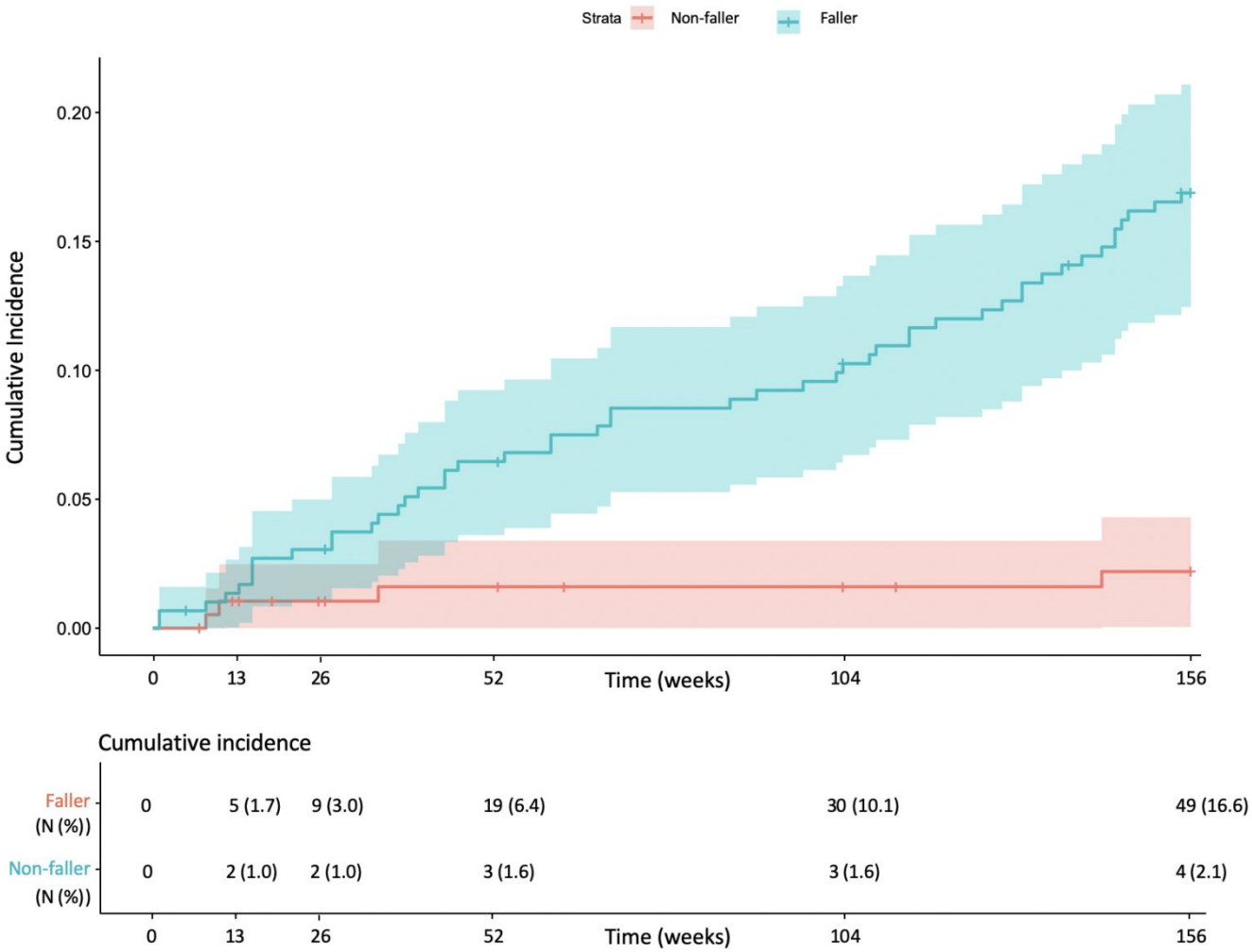
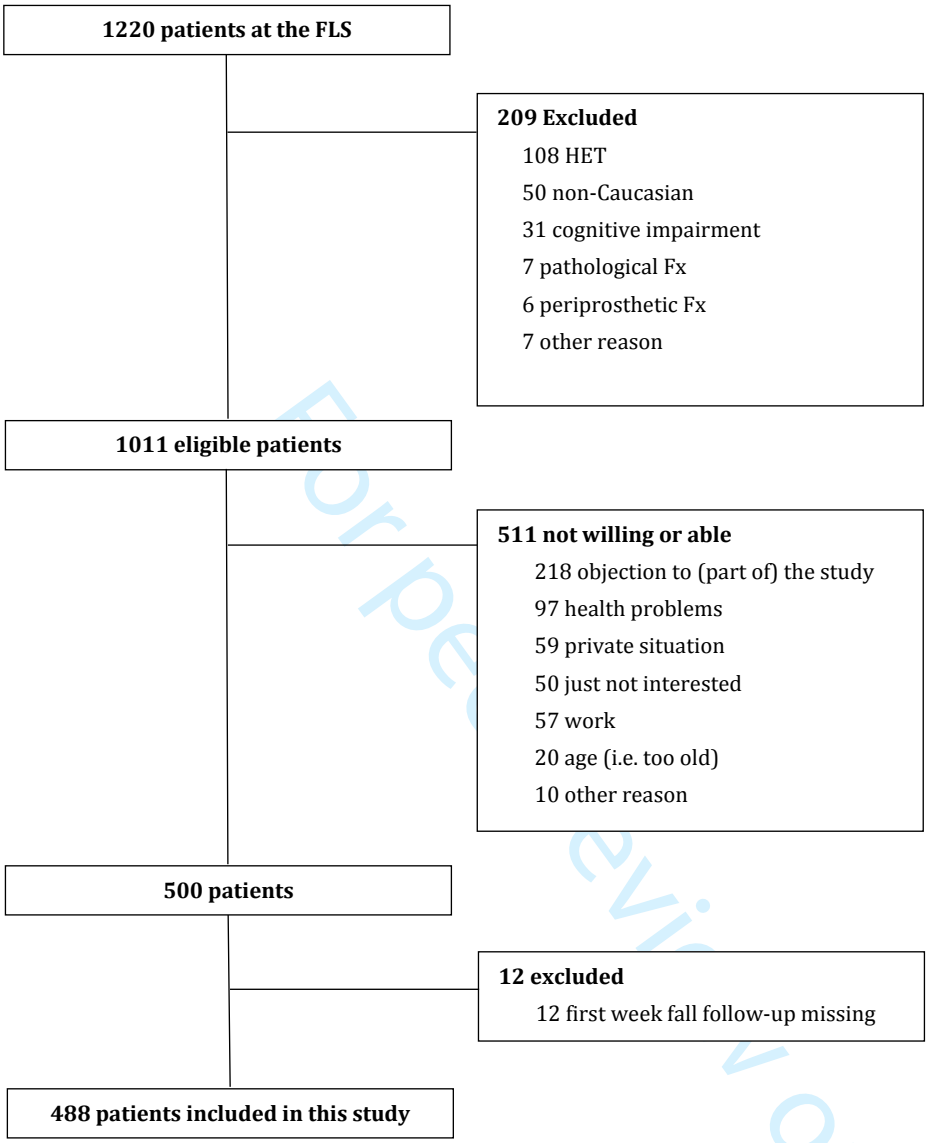


Figure 3. Cumulative incidence of subsequent fractures stratified by fall status.

Supplementary tables and figures



Supplementary Figure 1. Patient selection. Abbreviations: HET, high-energy trauma fractures; Fx, fracture.

Supplementary table 1. Characteristics of 1011 FLS patients that participated and not-participated in this study.			
	Participants (n=500)	**Non-participants** (n=511)	**P-value**
Age in years	64.6 ± 8.6	68.3 ± 9.8	<.001
Female sex	357 (71.4)	396 (77.5)	.026
Baseline fracture			
- Finger or toe	58 (11.6)	53 (10.4)	<.001
- Minor	311 (62.2)	259 (50.7)	
- Major	105 (21.0)	157 (30.7)	
- Hip	26 (5.2)	42 (8.2)	
- Fall-related *	431 (86.2)	441 (86.3)	.963
Fall previous year §			
- 0	356 (71.2)	359 (70.3)	.741
- ≥ 1	144 (28.8)	152 (29.7)	
- ≥ 2	72 (14.4)	87 (17.0)	.252
BMD			
- Normal BMD	135 (27.0)	90 (17.6)	<.001
- Osteopenia	255 (51.0)	258 (50.5)	
- Osteoporosis	110 (22.0)	163 (31.9)	
Prevalent vertebral fracture			
- None	366 (73.2)	349 (68.3)	.010
- Grade 1	63 (12.6)	53 (10.4)	
- Grade 2-3	71 (14.2)	109 (21.3)	
At least one fall past year	143 (29.3)	152 (29.9)	.704

Continues variables are presented as mean ± SD, categorical variables are presented as number of patients (%). § Fall resulting in baseline fracture not included. # According to Genant et al. $ According to most severe prevalent vertebral fracture. Abbreviations: BMD, bone mineral density

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9,10,16,17,18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9,10,11 NA 9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Incident falls are strongly associated with subsequent fracture risk in patients attending the Fracture Liaison Service after an index fracture: a 3-year prospective cohort study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058983.R1
Article Type:	Original research
Date Submitted by the Author:	18-Apr-2022
Complete List of Authors:	Vranken, Lisanne; VieCuri Medical Centre, Department of Internal Medicine; Maastricht University Medical Centre+, Department of Internal Medicine, Research School NUTRIM Wyers, Caroline; VieCuri Medical Centre, Department of Internal Medicine; Maastricht University Medical Centre+, Department of Internal Medicine, Research School NUTRIM Van der Velde, R.Y.; VieCuri Medical Centre, Department of Internal Medicine; Maastricht University Medical Centre+, Department of Internal Medicine, Research School NUTRIM Janzing, Heinrich M. J.; VieCuri Medical Centre, Department of Surgery Kaarsemakers, S.; VieCuri Medical Centre, Department of Orthopedic Surgery Driessen, Johanna; Maastricht University Medical Centre+, Department of Clinical Pharmacy and Toxicology; Maastricht University, Department of Clinical Pharmacy and Toxicology Eisman, John; Garvan Institute of Medical Research, Osteoporosis and bone biology; The University of Notre Dame Australia, School of Medicine Sydney Center, Jacqueline; Garvan Institute of Medical Research, Osteoporosis and bone biology; UNSW, School of Population Health Nguyen, T.V.; Garvan Institute of Medical Research; UNSW, School of Population, Faculty of Medicine Tran, Thach; Garvan Institute of Medical Research, Bone Biology Division Bliuc, Dana; Garvan Institute of Medical Research, Bone and Mineral Research Program Geusens, Piet; Maastricht Universitair Medisch Centrum+, Department of Internal Medicine, Subdivision Reumatology; Maastricht University, CAPHRI School for Public Health and Primary Care van den Bergh, Joop; Maastricht Universitair Medisch Centrum+, Department of Internal Medicine, Research School NUTRIM; VieCuri Medisch Centrum, Department of Internal Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Rheumatology, Geriatric medicine, General practice / Family practice
Keywords:	INTERNAL MEDICINE, Orthopaedic & trauma surgery < SURGERY,

	GENERAL MEDICINE (see Internal Medicine)

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Incident falls are strongly associated with subsequent fracture risk in patients attending the Fracture Liaison Service after an index fracture: a 3-year prospective cohort study.

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Abstract

Objectives:

Falls are a strong risk factor for fractures, independent of bone mineral density (BMD) and clinical risk factors. The aim of this study was to evaluate the risk of subsequent fractures in patients who attended the Fracture Liaison Service (FLS), with and without incident falls after the index fracture.

Method:

A 3-year prospective observational cohort study was conducted in patients aged 50+ years with a recent clinical fracture, starting at the time they attended the FLS. Patients were treated with anti-osteoporosis medication according to the Dutch osteoporosis guideline. Falls were recorded weekly in fall diaries. Subsequent fractures were recorded in fall diaries and annual questionnaires and were radiologically confirmed. The Cox's proportional hazards model was employed to estimate the association between fall and fracture risk, adjusted for predefined covariates including age, gender, index fracture type, BMD, and prevalent vertebral fractures status.

Results:

The study included 488 patients (71.9% women, mean age 64.6 ± 8.6 years). During the 3-year follow-up, 959 falls had been ascertained in 296 (60.7%) patients (*i.e.,* fallers), and 60 subsequent fractures were ascertained in 53 (10.9%) patients. Of the fractures, 47 (78.3%) were fall-related, of which 25 (53.2%) were sustained at the first fall incident at a median of 34 weeks. An incident fall was associated with an approximately 9-fold (hazard ratio 8.6; 95% CI, 3.1 to 23.8) increase in the risk of subsequent fractures.

Conclusion:

These data suggest that subsequent fractures among patients on treatment prescribed in a FLS setting are common, and an incident falls is a strong predictor of subsequent

fracture risk, and that immediate attention for fall risk could be beneficial in an FLS model of care.

Strengths and limitations

- Although this is one of the largest prospective studies in a FLS population focusing on the incidence of falls after an index fracture, the number of patients is modest, and the number of subsequent fractures relatively small.
- Data on falls were collected prospectively using fall diaries. However, no procedures were in place to validate self-reported falls.
- No information was available on falls between the index fracture and enrollment in the study.
- Relatively healthy patients participated in the study, which may have resulted in an underestimation of incident falls and subsequent fractures.

Introduction

Patients with a recent fracture have a high imminent risk of subsequent fractures as shown after most fractures (1-6), and a high risk of subsequent falls, as shown after a recent hip fracture (7-11). The Fracture Liaison Service (FLS) is considered the most effective organizational approach for secondary fracture prevention in patients after the age of 50 years with a recent fracture.

Most fractures are caused by a fall, but most falls do not result in a fracture (12,13). Falls are a major contributing factor to the occurrence of fractures, independent and additive to the risk attributable to age and bone mineral density (BMD) (14-17). Guidelines on the FLS therefore recommend fall prevention and prescription of anti-osteoporosis medication (AOM) in high risk patients (18-22). However, it is not well known to what extent the imminent risk of subsequent fractures after an index fracture can be attributed to incident falls. We hypothesized that the risk of subsequent fractures would be substantially higher in patients with falls after a recent fracture than in those without falls. The aim of this study was therefore to evaluate the incidence of falls and subsequent fractures, and the risk of subsequent fractures in those with and without falls after a recent index fracture in patients who attend the FLS.

Methods

Study population and design

A 3-year prospective observational cohort study was conducted including 500 consecutive patients aged between 50 and 90 years with a recent, radiologically confirmed clinical vertebral or non-vertebral low-trauma fracture, and who were willing and able to participate. Patients were recruited at the FLS in VieCuri Medical Center, Venlo, The Netherlands.

Low-trauma fractures were defined as fractures that resulted from a fall from standing height or less. Excluded were non-Caucasian patients, patients with bone metastasis, failure of prosthesis or osteomyelitis, and patients with cognitive impairment.

According to standard care, a nurse specialized in osteoporosis invited all patients aged 50 year and older, who visited the emergency department because of a recent clinical vertebral or non-vertebral fracture, to the FLS. All patients who responded and agreed to be evaluated were scheduled an appointment for fracture risk evaluation. Fracture risk evaluation included a detailed questionnaire for evaluation of risk factors for fractures and falls, including medical history and medication use. This questionnaire was based on the Dutch guidelines on osteoporosis and fracture prevention, and prevention of falls in the elderly (23,24). Also, height and weight were measured, a bone mineral density (BMD) measurement with dual-energy X-ray absorptiometry (DXA) of the lumbar spine, total hip, and femoral neck, with vertebral fracture assessment (VFA) was performed, and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease (25). According to the Dutch osteoporosis guideline (23), AOM was started in patients with osteoporosis or having at least one moderate to severe prevalent vertebral fracture according to Genant et al. (26). Bisphosphonates and denosumab were first-choice treatments. Teriparatide was restricted to patients already on another AOM with at least 3 fractures, of which 2 were vertebral fractures.

The study protocol (registration number NL45707.072.13) was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki. All patients gave written informed consent prior to participation.

Falls and subsequent fractures

During the 3-year follow-up, patients were requested to record falls weekly in a fall diary. Fall registration started at the beginning of the study, mean 3.5 ± 1.0 months after the index fracture. A fall was defined as an unintentional change in position resulting in coming to rest on the ground or other lower level (27). Patients were asked to return their fall diaries by mail at 3 and 6 months, and during the study visit at 1, 2 and 3 year of follow-up. They were contacted by telephone if the fall diary was not received or incomplete. Patients were categorized as those with at least one incident fall (*i.e.,* faller) or without an incident fall (*i.e.,* non-faller) during follow-up.

When patients recorded a fall in their diary, they were also asked to record whether or not they sustained a subsequent clinical fracture as a direct result of the fall. Additionally, at 1-, 2-, and 3-year follow-up, patients had to complete a detailed questionnaire, including a question on whether they sustained a fracture due to another trauma than a fall or without an overt trauma. All subsequent fractures were radiologically confirmed according to radiology reports in the electronic patient records. Since no imaging of the spine was performed at the end of the study, all reported vertebral fractures were symptomatic, clinical vertebral fractures. A distinction was made between subsequent fractures that were directly caused by a fall (*i.e.,* fall-related fractures), and those that occurred without an overt trauma or were the result of another trauma than a fall (*i.e.,* non-fall-related fractures).

Data analysis

Baseline characteristics were compared between fallers and non-fallers, and between patients with and without subsequent fractures using the Student's t test or Wilcoxon test for continuous variables, and Chi-squared or Fisher's exact test for categorical variables where appropriate. The incidence rate of falls and subsequent fractures per 100 person-years was estimated at 3 and 6 months and 1, 2 and 3 year follow-up,

assuming a Poisson distribution. Kaplan Meier curves were made for incident falls and subsequent fractures, in which patients were included once, and only the first incident fall or subsequent fracture was included. Cox proportional hazards regression was used to determine the association between incident falls and subsequent fractures, yielding hazard ratios (HR) and 95% confidence intervals (CI). Proportional hazard assumptions were not violated. Follow-up time was determined by the first subsequent fracture, lost-to-follow-up or the end of the study, whatever occurred first. All analyses were adjusted for the predefined covariates, including age, gender, index fracture type (major or hip versus any other fracture), BMD (lowest measured at lumbar spine, total hip, femoral neck), prevalent vertebral fractures (moderate or severe versus mild or no prevalent vertebral fractures). A p-value < 0.05 was considered statistically significant.

Two sensitivity analyses were planned; (i) excluding patients with index and subsequent finger or toe fractures, and (ii) by classifying patients with a non-fall-related subsequent fracture as non-faller, even if they fell at another time during follow-up.

Patient and public involvement

Patients or members of the public were not involved in the design, or conduct, or reporting, or dissemination plans of the research.

Results

Study population

Among 1220 patients approached from the FLS, 1011 patients met the study criteria. Of the 1011 patients, 511 were not willing or able to participate in the study, and after excluding 12 patients with missing fall data, ultimately 488 patients were available for analysis (**Supplementary Figure 1**) of whom 34 (7.0%) patients had

incomplete follow-up data on incident falls (5 patients died, 8 withdrew consent, 21 had incomplete fall registration).

The mean time between the index fracture and FLS visit at which patients were included for this study was 3.9 ± 1.1 months for patients with a hip fracture and 3.5 ± 1.0 months for patients with other fractures. Baseline characteristics of the 488 study participants are presented in **Table 1**. Mean age was 64.6 ± 8.6 year and 71.9% of the patients were women. In 86.5% of patients, the index fracture was caused by a fall, and 28.5% of patients had at least one other fall in the year before the start of the study. At baseline, 21.9% of patients were diagnosed with osteoporosis, 51.1% with osteopenia, and 27.1% had a normal BMD. Lowest BMD was measured at the femoral neck in 470 participants, at the total hip in 3 participants, and at the lumber spine in 15 participants. Moderate to severe (i.e., grade 2-3) prevalent vertebral fractures were present in 14.3% of patients. AOM was prescribed in 34.2% of patients (8 (1.6%) were already using AOM, and 159 (32.6%) started using AOM at baseline visit).

Compared to eligible FLS attenders, who were not willing or able to participate in our study, patients included in our study were younger, had fewer major or hip fractures, had a higher BMD, and a lower proportion had prevalent vertebral fractures (see **Supplementary Table 1**).

Falls

During a median follow-up of 3 years (range 0.1 to 3.0), 296 (60.7%) patients recorded 959 falls, corresponding to 68.6 falls per 100 person-years. The cumulative fall incidences and incidence rates per 100 person-years at 3 and 6 months, and at 1, 2 and 3 year follow-up are presented in **Figure 1**. Of the 296 patients with at least one fall, 115 (38.9%) had one fall and 181 (61.1%) had two or more falls (up to 39 falls in one patient).

A first fall was recorded by 189/488 (38.7%) patients during the first year of follow-up, by 56/299 (18.7%) during the second, and by 51/243 (21.0%) during the third year of follow-up. The median time to the first fall was 34 (range 1-156) weeks. Of the 959 falls, 47 (4.9%) resulted in a subsequent fall-related fracture.

There were no significant differences in baseline characteristics between patients with and without a fall during the 3-year follow-up, except for that a higher proportion of patients with incident falls reported at least one fall in the year before the start of the study (34.5% vs. 19.3%, $p < 0.001$) (see **Table 1**). There were no significant differences in baseline characteristics between patients with one fall and those with multiple falls (data not shown).

Subsequent fractures

In total, 53 (10.9%) patients recorded 60 subsequent fractures, corresponding to 4.29 subsequent fractures per 100 person-years. The cumulative subsequent fracture incidences and incidence rates (per 100-person years) at 3 and 6 months, and at 1, 2 and 3 year follow-up are presented in **Figure 2**. Of all subsequent fractures, 47 (78.3%) were fall-related, and 13 (21.7%) were non-fall-related. Fall-related subsequent fracture sites were: radius and ulna (n=9), tibia and fibula (n=8), proximal femur (n=4), metatarsal (n=4), hand phalanx (n=4), symptomatic vertebra (n=3), proximal humerus (n=3), clavicula (n=3), costal bones (n=2), scapula (n=2), pelvic bone (n=1), metacarpal (n=1), tarsal (n=1), patella (n=1), and foot phalanx (n=1), whereas subsequent non-fall-related fractures sites were: symptomatic vertebral (n=5), metatarsal (n=2), foot phalanx (n=5), and hand phalanx (n=1). Half (53.2%) of all fall-related subsequent fractures were sustained at the first fall.

Baseline characteristics for patients with and without subsequent fractures are presented in **Table 1**.

Of the 296 patients with at least one fall, 41 (13.9%) had 46 fall-related subsequent fractures, 7 (2.4%) had 7 non-fall-related subsequent fractures, and 1 (0.3%) had 1 fall- and 1 non-fall-related subsequent fracture. Of the 192 patients without a fall, 4 (2.1%) had 5 non-fall-related subsequent fractures. Of note, the risk of subsequent fractures was higher in patients with at least one fall than in those without a fall (adjusted HR (95% CI): 8.6 (3.1-23.8); cumulative incidence: 16.6%% versus 2.1%) (**Figure 3 and Table 2**). Results were similar when femoral neck BMD instead of the lowest BMD was used for adjustments (adjusted HR (95% CI): 8.3 (3.0-23.0)). Additionally, subsequent fracture risk was higher in patients with moderate or severe prevalent vertebral fractures than in those with no or mild prevalent vertebral fractures (adjusted HR (95% CI): 3.9 (2.1-7.3); cumulative incidence: 24.3% versus 8.6%) (**Table 2**).

The association between falls and subsequent fractures remained significant in sensitivity analyses (i) excluding patients with index and subsequent finger and toe fractures (adjusted HR (95% CI): 8.2 (2.5-26.6)), and (ii) by classifying patients with a non-fall-related subsequent fracture as non-faller (adjusted HR (95% CI): 2.9 (1.5-5.6)).

Discussion

In this 3-year prospective observational cohort study in patients aged 50+ years with a recent clinical fracture, treated according to current Dutch osteoporosis guidelines at a FLS, 60.7% of patients had at least one fall, and 10.9% had at least one subsequent fracture. The majority (78.3%) of subsequent fractures was caused by a fall, and of all fall-related subsequent fractures, 53.2% occurred at the first fall. Subsequent fracture risk was nine-fold higher in fallers than in non-fallers.

Literature reporting fall incidence in fracture patients is limited. Comparable to our results, Van Helden et al. (28)reported a 3-month fall incidence of 15% in patients with a recent fracture at a FLS, and Matsumoto et al. (29) reported a 1-year fall

incidence of 40% in ambulatory patients with a recent fracture. Various other studies included older, hip fracture patients and reported higher one year fall incidences up to 55% (7-11), except for the study from Yeh et al. that reported a lower 1-year fall incidence (31%) (30). Higher fall incidences in hip fracture studies can partially be explained by the older study population. Unfortunately, other fall risk factors cannot be compared. An explanation for the lower fall incidence in the study by Yeh et al. may be that information on the occurrence of falls was provided by patients and family caregivers, which may have resulted in under registration of falls.

A comparison between the fall incidence in our study and that in the general population is difficult to make, because population-based studies were conducted in a 65+ aged, community-dwelling population, whereas approximately 50% of our study population was <65 years old. The proportion of community-dwelling people aged 65+ years sustaining at least one fall over a 1-year period ranged from 28 to 35% (31-33), with an increasing incidence with increasing age (34). The 1-year fall incidence reported is our study is comparable to that in an older (65+ aged) population, and therefore relatively high. However, in contrast to what has been reported in literature, we found no higher 3-year fall incidence with increasing age. An explanation for this could be that, especially in the older age group, relatively more healthy patients participated in our study, resulting in a lower fall incidence in older age group. Another explanation could be that patients aged 50-65 years are more physically active, and therefore fall more often.

Compared to our results, previously published FLS studies reported lower [34,35], similar (28,37,38), and higher (39,40) subsequent fracture rates. Differences can be explained by differences in patient selection. Studies that included older patients (39) and patients with more severe fractures (40) reported higher subsequent fracture rates,

whereas studies that excluded hand and foot index and subsequent fractures (35) or frail patients reported lower rates (36).

In 2010, the Dutch population consisted of approximately 6,000,000 people aged 50+ years, of whom 119,419 sustained a fracture that year (41), corresponding to a calculated annual fracture incidence of 2.0% in the general Dutch 50+ population. Compared to the general Dutch 50+ population, the fracture incidence was more than 2 times higher in our study, even in the 3rd year of follow-up. In our study, fracture incidence remained high despite treatment according to the current osteoporosis guideline, raising the question of what more can be done to prevent subsequent fractures. Even though conflicting results have been published about the effect of fall prevention strategies on subsequent fracture (42), we hypothesize that fall interventions could be effective in patients at highest risk, namely those with a recent fracture at risk of falling. Furthermore, according to literature, recurrent fallers have an almost fourfold increased odds of sustaining a fall-related fracture compared to individuals with a single fall (43). However, we found that the majority of subsequent fall-related fractures occur at the first fall after the index fracture, with a median time to the first fall of 34 weeks. Interestingly, fall incidence was higher in the first year of follow-up compared to the second and third year. This may indicate an imminent fall risk, which may attribute to the imminent subsequent fracture risk after an index fracture (1-6). This implies that the FLS patients with a high fall risk should be identified immediately, because there is a small window of opportunity to prevent falls and fall-related subsequent fractures.

Remarkably, in contrast to previous studies indicating that imminent fracture risk that was highest in the first year after an index fracture (44,45), there was a linear subsequent fracture incidence during 3-year follow-up in this study. An explanation for the linear subsequent fracture incidence may be the relatively healthy patients who

agreed to participate in our study. Compared to non-attenders, they were younger, and a lower proportion had a major baseline fracture, a prevalent vertebral fracture, and osteoporosis, and if indicated, were more likely to receive AOM. Importantly, in addition to falls, moderate to severe prevalent vertebral fractures at baseline were associated with subsequent fractures, even though anti-osteoporosis medication had been prescribed to these patients according to the current Dutch osteoporosis guideline.

This study has several limitations. Although, this is one of the largest prospective studies in a FLS population focusing on the incidence of falls after an index fracture, the number of patients is modest, and the number of subsequent fractures relatively low. Therefore, the association between falls and fall-related, and non-fall-related subsequent fractures could not be analyzed separately. A fall 'not-resulting-in-a-subsequent-fracture' might indicate frailty of patients, and might be different from those falls that directly resulted in a subsequent fracture. Future studies are needed to investigate this difference. Finally, because of small numbers, subgroup analyses should not be performed. Furthermore, data on falls were collected prospectively using fall diaries that had to be returned at 3 and 6 months, and 1, 2, and 3 year. However, no procedures were in place to validate self-reported falls, and it is possible that recall bias, could have led to underregistration of falls. Moreover, no information was available on falls between the index fracture and enrollment in the study. Finally, relatively healthy patients participated in the study. Compared to non-attenders, they were younger, a lower proportion had a major baseline fracture, a prevalent vertebral fracture, and osteoporosis. The proportion of patients with a fall and subsequent fractures could be expected to be even higher in the total FLS population.

In conclusion, in this 3-year prospective observational cohort study in FLS patients, subsequent fracture incidence was high despite being prescribed anti-osteoporosis medications according to the current Dutch osteoporosis guideline.

Subsequent fracture risk was nine-fold higher in fallers than in non-fallers, and the majority of fall-related subsequent fractures occurred at the first fall at a median time of 34 weeks. These findings emphasize that immediate attention for fall risk reduction could be beneficial in FLS care. Various risk factors, including comorbidities, medication use, polypharmacy and alcohol use among others, contribute to patient's fall risk and further research is needed to determine predictors for falls to identify patients at highest risk of falling.

Figures and tables

Table 1. Baseline characteristics of 488 participants stratified by incident fall and subsequent fracture status.

	Total population (n=488)	**Non-fallers** (n=192)	**Fallers** (n=296)	**P-value**	**No subsequent fracture** (n=435)	**Subsequent fracture** (n=53)	**P-value**
Age (years)	64.6 ± 8.6	64.4 ± 8.0	64.8 ± 9.0	0.608	64.5 ± 8.8	65.3 ± 7.1	0.488
Female gender	351 (71.9)	130 (67.7)	221 (74.7)	0.095	308 (70.8)	43 (81.1)	0.114
Baseline fracture							
- Finger or toe	55 (11.3)	30 (15.6)	25 (8.4)	0.060	49 (11.3)	6 (11.3)	0.460
- Minor	303 (62.1)	109 (56.8)	194 (65.5)		270 (62.1)	33 (62.3)	
- Major	104 (21.3)	44 (22.9)	60 (20.3)		95 (21.8)	9 (17.0)	
- Hip	26 (5.3)	9 (4.7)	17 (5.7)		21 (4.8)	5 (9.4)	
- Fall-related *	422 (86.5)	164 (85.4)	258 (87.2)	0.582	378 (86.9)	44 (83.0)	0.436
Fall previous year §							
- 0	349 (71.5)	155 (80.7)	194 (65.5)	<0.001	315 (72.4)	34 (64.2)	0.208
- ≥ 1	139 (28.5)	37 (19.3)	102 (34.5)		120 (27.6)	19 (35.8)	
BMI (kg/m²)	27.7 ± 4.4	27.7 ± 4.4	27.7 ± 4.4	0.961	27.8 ± 4.4	26.9 ± 4.8	0.154
BMD							
- Normal BMD	132 (27.1)	54 (28.1)	78 (26.4)	0.906	123 (28.3)	9 (17.0)	0.081
- Osteopenia	249 (51.0)	97 (50.5)	152 (51.4)		222 (51.0)	27 (50.9)	
- Osteoporosis	107 (21.9)	41 (21.4)	66 (22.3)		90 (20.7)	17 (32.1)	
Prevalent vertebral fracture #$							
- None	356 (73.0)	139 (72.4)	217 (73.3)	0.572	328 (75.4)	28 (52.8)	<0.001
- Grade 1	62 (12.7)	22 (11.5)	40 (13.5)		54 (12.4)	8 (15.1)	
- Grade 2-3	70 (14.3)	31 (16.1)	39 (13.2)		53 (12.2)	17 (32.1)	
Anti-osteoporosis treatment	167 (34.2)	70 (36.5)	97 (32.8)	0.402	142 (32.6)	25 (47.2)	0.035

Continuous variables are shown in mean ± SD (standard deviation), categorical variables are shown as number of patients (%). * Signifying that fracture was caused by a fall. § Fall resulting in baseline fracture not included. # According to Genant et al. $ According to most severe prevalent vertebral fracture. Abbreviations: BMD, bone mineral density.

Table 2. Predictors of refracture: results of the Cox's proportional hazard model			
Predictor	**Unit of comparison**	**Hazard ratio and 95% confidence interval**	**P-value**
Gender	Women vs men	1.39 (0.68 - 2.83)	0.362
Age	+5 years	0.97 (0.82 - 1.13)	0.662
Index fracture	Major or hip vs all other	0.68 (0.35 - 1.33)	0.263
BMD	-0.12 g/cm^2	1.30 (0.95 - 1.78)	0.101
Prevalent vertebral fracture	Yes vs no	3.88 (2.07 – 7.27)	<0.0001
Fall	Yes vs no	8.58 (3.09 - 23.8)	<0.0001

Figure legends

Figure 1. Cumulative incidence of falls stratified by gender.

Figure 2. Cumulative incidence of subsequent fractures stratified by gender.

Figure 3. Cumulative incidence of subsequent fractures stratified by fall status.

Contributors

LV collected data, carried out data analysis and drafted the manuscript. CW and JB developed the study design and wrote the research protocol, collected data, and critically reviewed the manuscript. PG developed the study design and wrote the research protocol, and critically reviewed the manuscript. RV collected data and critically reviewed the manuscript. TN and TT assisted with data analysis and critically reviewed the manuscript. HJ, SK, JD, JA, JC and DB critically reviewed the manuscript. All authors approved the final version of the manuscript.

Competing interest

Dr. Vranken, Dr. Wyers, Dr. Van der Velden, Dr. Janzing, Dr. Kaarsemakers, Dr. Driessen, Dr. Eisman, Dr. Tran, and Dr. Bliuc have nothing to disclose.

Dr. Center reports honoraria for educational talks from Amgen, part support for educational meetings from Amgen, and advisory board participation for Amgen and Bayer, outside the submitted work.

Dr. Nguyen reports honoraria for lectures sponsored from Merck, and participation as executive member Asia Pacific Consortium on Osteoporosis, outside the submitted work.

Dr. Geusens reports grants from Amgen, Pfizer, MSD, UCB, Abbott, Lilly, BMS, Novartis, Roche, and Will Pharma, and honoraria for lectures from Amgen and Lilly, outside the submitted work.

Dr. van den Bergh reports grants for lectures from UCB, and Amgen, outside the submitted work.

Funding

This work was supported by the Weijerhorst Foundation, grand number not applicable. The Weijerhorst Foundation was not involved in conducting the study, analyzing the data or writing the manuscript.

Patient consent for publication

Patient consent for publication was not required.

Ethics approval

This study (protocol ID number NL45707.072.13) has been approved by the Independent Review Board Nijmegen (IRBN).

Data availability statement

No additional data available.

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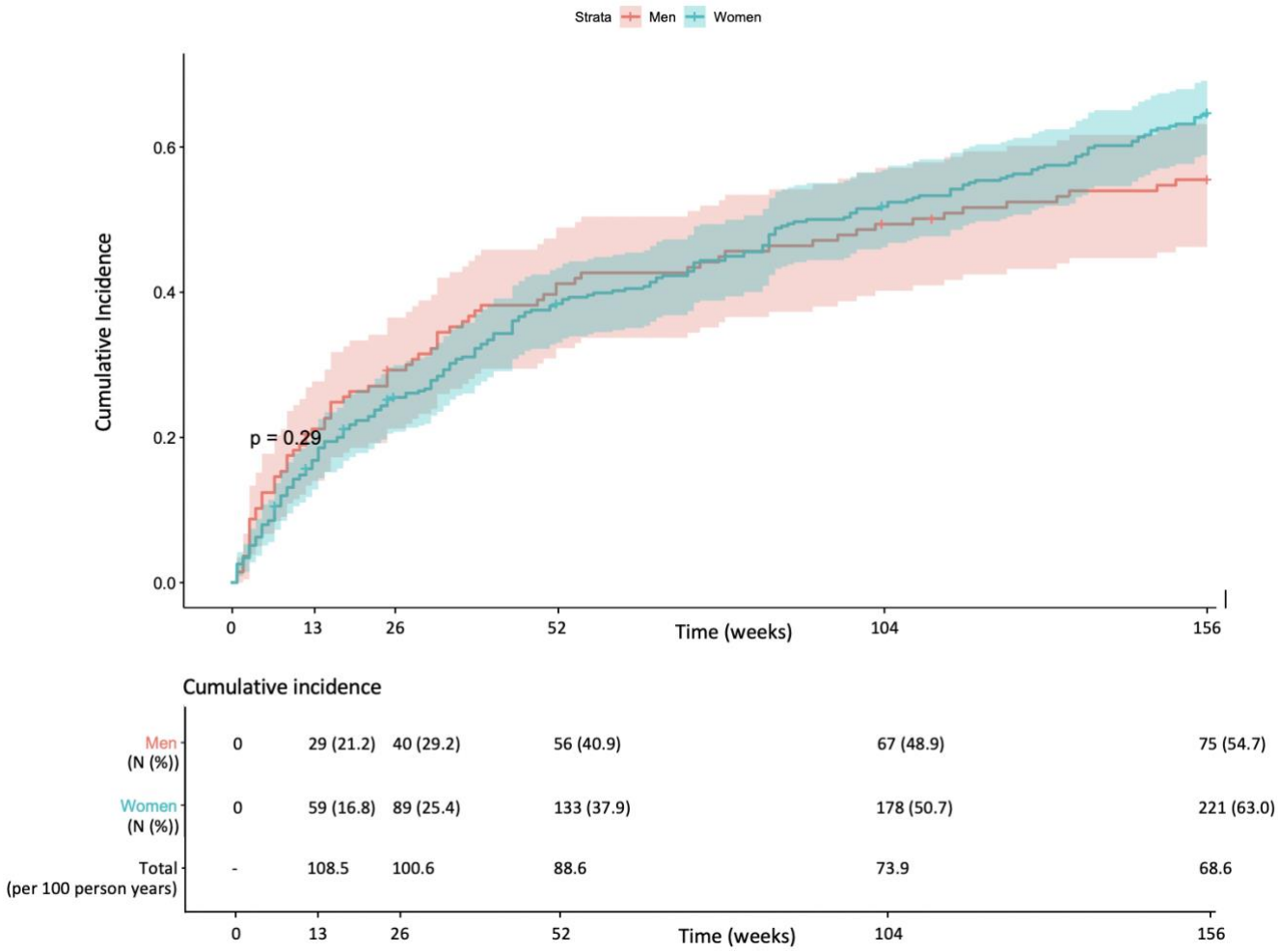


Figure 1. Cumulative incidence of falls stratified by gender.

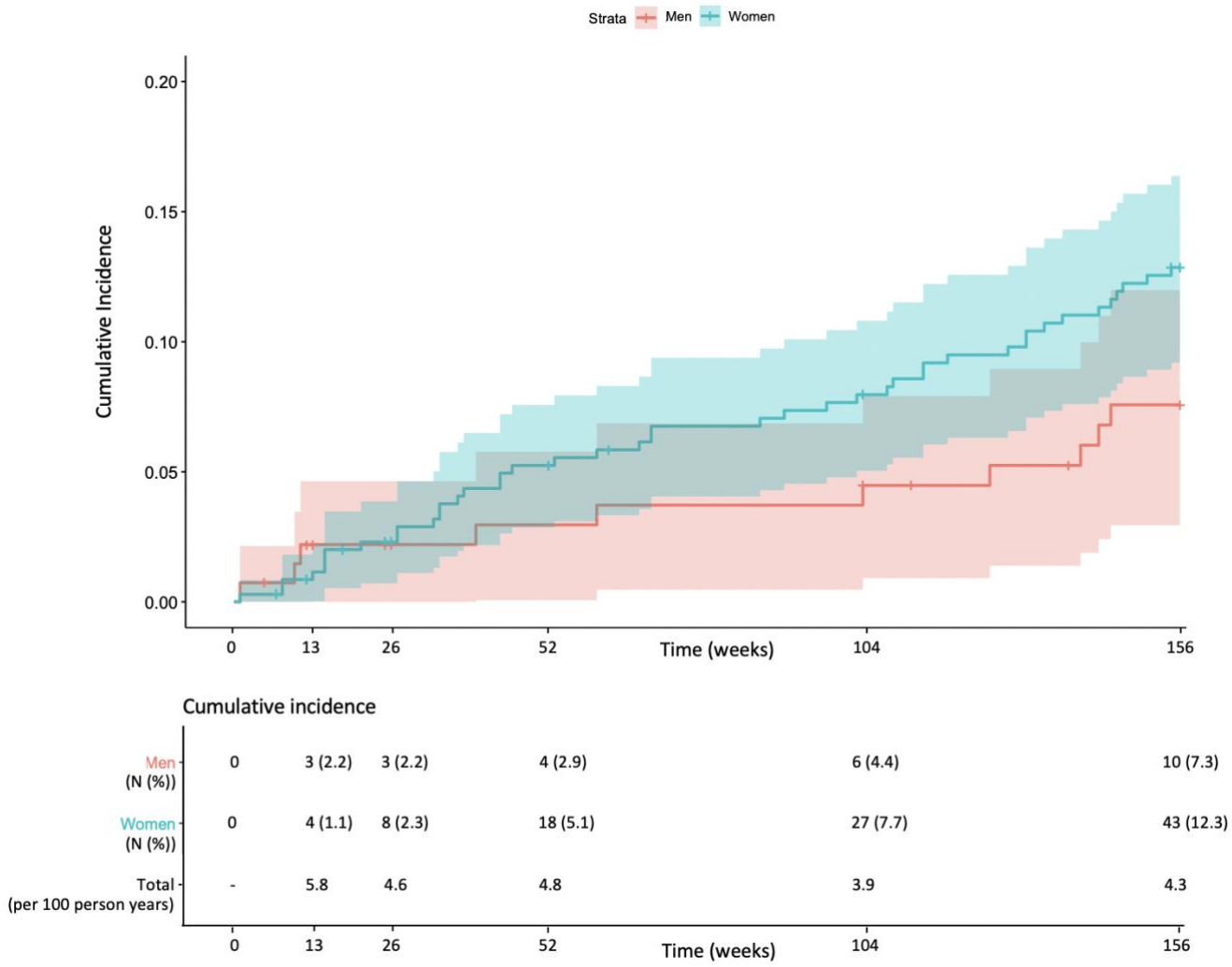


Figure 2. Cumulative incidence of subsequent fractures stratified by gender.

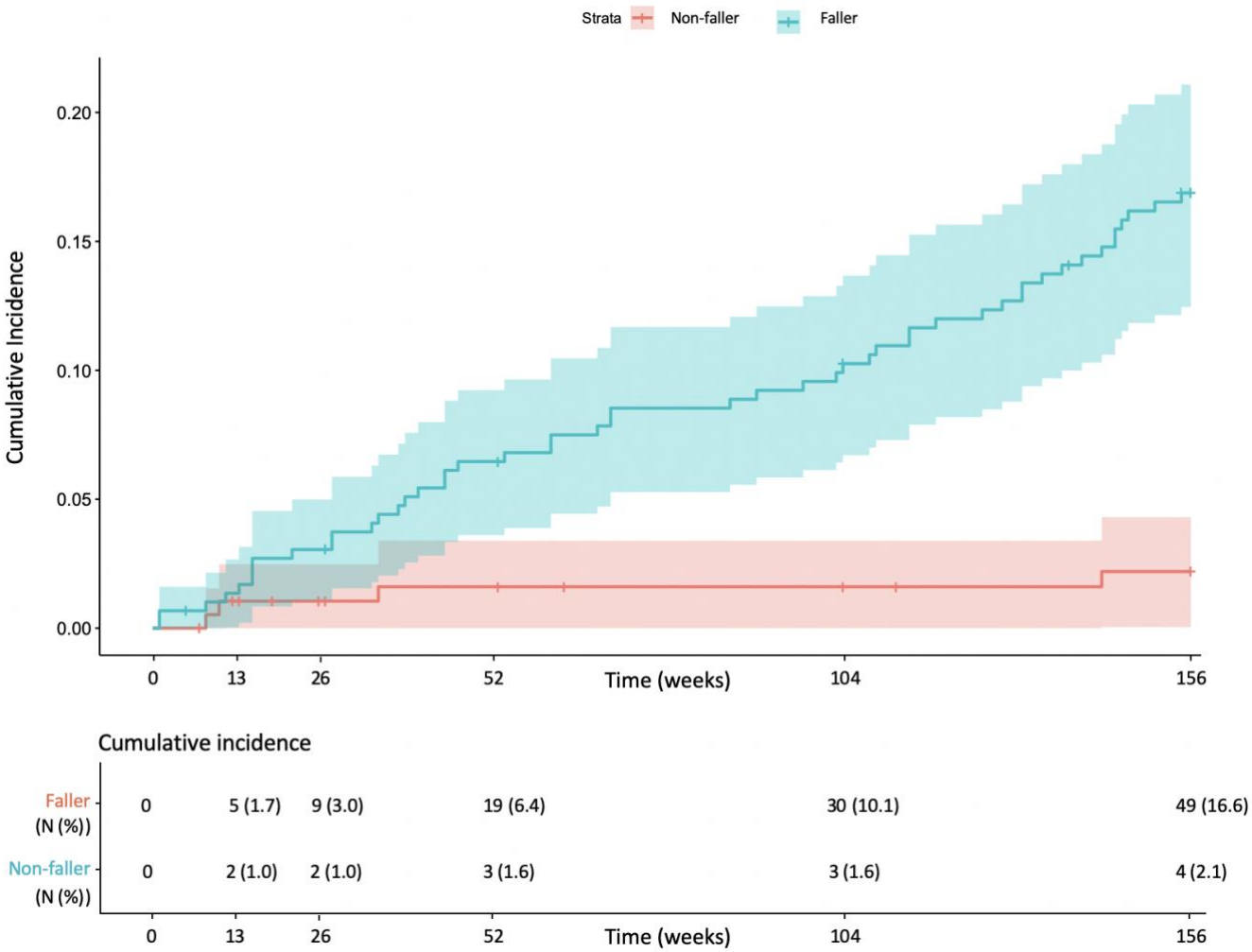
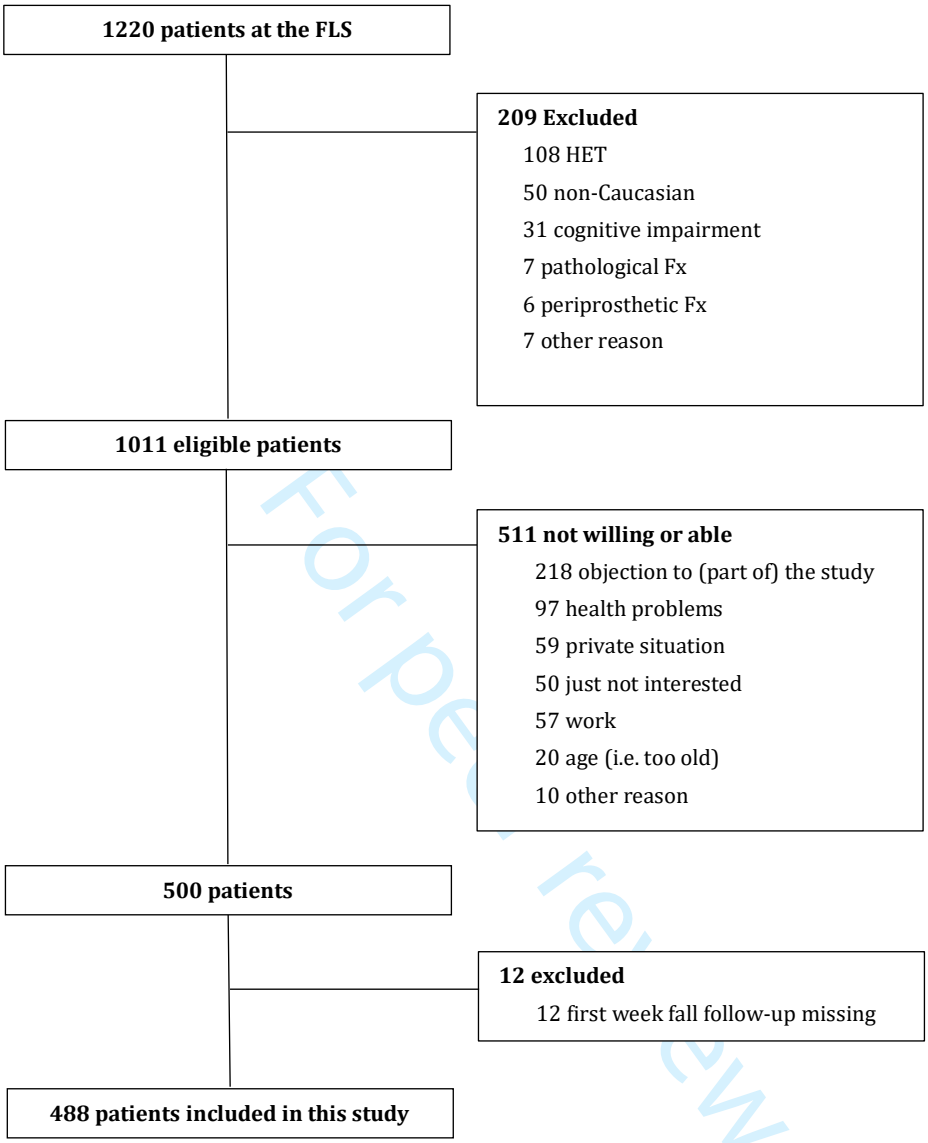


Figure 3. Cumulative incidence of subsequent fractures stratified by fall status.



Supplementary Figure 1. Patient selection. Abbreviations: HET, high-energy trauma fractures; Fx, fracture.

Supplementary table 1. Characteristics of 1011 FLS patients that participated and not-participated in this study.

	Participants (n=500)	**Non-participants** (n=511)	**P-value**
Age in years	64.6 ± 8.6	68.3 ± 9.8	<.001
Female sex	357 (71.4)	396 (77.5)	.026
Baseline fracture			
- Finger or toe	58 (11.6)	53 (10.4)	<.001
- Minor	311 (62.2)	259 (50.7)	
- Major	105 (21.0)	157 (30.7)	
- Hip	26 (5.2)	42 (8.2)	
- Fall-related [*]	431 (86.2)	441 (86.3)	.963
Fall previous year [§]			
- 0	356 (71.2)	359 (70.3)	.741
- ≥ 1	144 (28.8)	152 (29.7)	
- ≥ 2	72 (14.4)	87 (17.0)	.252
BMD			
- Normal BMD	135 (27.0)	90 (17.6)	<.001
- Osteopenia	255 (51.0)	258 (50.5)	
- Osteoporosis	110 (22.0)	163 (31.9)	
Prevalent vertebral fracture			
- None	366 (73.2)	349 (68.3)	.010
- Grade 1	63 (12.6)	53 (10.4)	
- Grade 2-3	71 (14.2)	109 (21.3)	
At least one fall past year	143 (29.3)	152 (29.9)	.704

Continues variables are presented as mean ± SD, categorical variables are presented as number of patients (%). [§] Fall resulting in baseline fracture not included. [#] According to Genant et al. [$] According to most severe prevalent vertebral fracture. Abbreviations: BMD, bone mineral density

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9,10,16,17,18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9,10,11 NA 9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Association between incident falls and subsequent fractures in patients attending the Fracture Liaison Service after an index fracture: a 3-year prospective observational cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058983.R2
Article Type:	Original research
Date Submitted by the Author:	23-Jun-2022
Complete List of Authors:	Vranken, Lisanne; VieCuri Medical Centre, Department of Internal Medicine; Maastricht University Medical Centre+, Department of Internal Medicine, Research School NUTRIM Wyers, Caroline; VieCuri Medical Centre, Department of Internal Medicine; Maastricht University Medical Centre+, Department of Internal Medicine, Research School NUTRIM Van der Velde, R.Y.; VieCuri Medical Centre, Department of Internal Medicine; Maastricht University Medical Centre+, Department of Internal Medicine, Research School NUTRIM Janzing, Heinrich M. J.; VieCuri Medical Centre, Department of Surgery Kaarsemakers, S.; VieCuri Medical Centre, Department of Orthopedic Surgery Driessen, Johanna; Maastricht University Medical Centre+, Department of Clinical Pharmacy and Toxicology; Maastricht University, Department of Clinical Pharmacy and Toxicology Eisman, John; Garvan Institute of Medical Research, Osteoporosis and bone biology; The University of Notre Dame Australia, School of Medicine Sydney Center, Jacqueline; Garvan Institute of Medical Research, Osteoporosis and bone biology; UNSW, School of Population Health Nguyen, T.V.; Garvan Institute of Medical Research; UNSW, School of Population, Faculty of Medicine Tran, Thach; Garvan Institute of Medical Research, Bone Biology Division Bliuc, Dana; Garvan Institute of Medical Research, Bone and Mineral Research Program Geusens, Piet; Maastricht Universitair Medisch Centrum+, Department of Internal Medicine, Subdivision Reumatology; Maastricht University, CAPHRI School for Public Health and Primary Care van den Bergh, Joop; VieCuri Medical Centre, Department of Internal Medicine; Maastricht University Medical Centre+, Department of Internal Medicine, Research School NUTRIM
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Rheumatology, Geriatric medicine, General practice / Family practice
Keywords:	INTERNAL MEDICINE, Orthopaedic & trauma surgery < SURGERY,

	GENERAL MEDICINE (see Internal Medicine)

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Association between incident falls and subsequent fractures in patients attending the Fracture Liaison Service after an index fracture: a 3-year prospective observational cohort study.

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Abstract

Objectives: To evaluate the risk of subsequent fractures in patients who attended the Fracture Liaison Service (FLS), with and without incident falls after the index fracture.

Design: A 3-year prospective observational cohort study.

Setting: An outpatient FLS in The Netherlands.

Participants: Patients aged 50+ years with a recent clinical fracture.

Outcome measures: Incident falls and subsequent fractures.

Results: The study included 488 patients (71.9% women, mean age 64.6 ± 8.6 years). During the 3-year follow-up, 959 falls had been ascertained in 296 (60.7%) patients (*i.e.,* fallers), and 60 subsequent fractures were ascertained in 53 (10.9%) patients. Of the fractures, 47 (78.3%) were fall-related, of which 25 (53.2%) were sustained at the first fall incident at a median of 34 weeks. An incident fall was associated with an approximately 9-fold (hazard ratio 8.6, 95% confidence interval 3.1 to 23.8) increase in the risk of subsequent fractures.

Conclusion: These data suggest that subsequent fractures among patients on treatment prescribed in a FLS setting are common, and that an incident fall is a strong predictor of subsequent fracture risk. Immediate attention for fall risk could be beneficial in an FLS model of care.

Trial registration: Registration number NL45707.072.13

Strengths and limitations

- Although this is one of the largest prospective studies in a FLS population focusing on the incidence of falls after an index fracture, the number of patients is modest, and the number of subsequent fractures relatively small.

- Data on falls were collected prospectively using fall diaries, but no procedures were in place to validate self-reported falls.
- No information was available on falls between the index fracture and enrollment in the study.
- Relatively healthy patients participated in the study, which may have resulted in an underestimation of incident falls and subsequent fractures.

Introduction

Patients with a recent fracture have a high imminent risk of subsequent fractures as shown after most fractures (1-6), and a high risk of subsequent falls, as shown after a recent hip fracture (7-11). The Fracture Liaison Service (FLS) is considered the most effective organizational approach for secondary fracture prevention in patients after the age of 50 years with a recent fracture.

Most fractures are caused by a fall, but most falls do not result in a fracture (12,13). Falls are a major contributing factor to the occurrence of fractures, independent and additive to the risk attributable to age and bone mineral density (BMD) (14-17). Guidelines on the FLS therefore recommend fall prevention and prescription of anti-osteoporosis medication (AOM) in high risk patients (18-22). However, it is not well known to what extent the imminent risk of subsequent fractures after an index fracture can be attributed to incident falls. We hypothesized that the risk of subsequent fractures would be substantially higher in patients with falls after a recent fracture than in those without falls. The aim of this study was therefore to evaluate the incidence of falls and subsequent fractures, and the risk of subsequent fractures in those with and without falls after a recent index fracture in patients who attend the FLS.

Methods

Study population and design

A 3-year prospective observational cohort study was conducted including 500 consecutive patients aged between 50 and 90 years with a recent, radiologically confirmed clinical vertebral or non-vertebral low-trauma fracture, and who were willing and able to participate. Patients were recruited at the FLS in VieCuri Medical Center, Venlo, The Netherlands.

Low-trauma fractures were defined as fractures that resulted from a fall from standing height or less. Excluded were non-Caucasian patients, patients with bone metastasis, failure of prosthesis or osteomyelitis, and patients with cognitive impairment.

According to standard care, a nurse specialized in osteoporosis invited all patients aged 50 year and older, who visited the emergency department because of a recent clinical vertebral or non-vertebral fracture, to the FLS. All patients who responded and agreed to be evaluated were scheduled an appointment for fracture risk evaluation. Fracture risk evaluation included a detailed questionnaire for evaluation of risk factors for fractures and falls, including medical history and medication use. This questionnaire was based on the Dutch guidelines on osteoporosis and fracture prevention, and prevention of falls in the elderly (23,24). Also, height and weight were measured, a bone mineral density (BMD) measurement with dual-energy X-ray absorptiometry (DXA) of the lumbar spine, total hip, and femoral neck, with vertebral fracture assessment (VFA) was performed, and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease (25). According to the Dutch osteoporosis guideline (23), AOM was started in patients with osteoporosis or having at least one moderate to severe prevalent vertebral fracture according to Genant et al. (26). Bisphosphonates and denosumab were first-choice treatments. Teriparatide was restricted to patients already on another AOM with at least 3 fractures, of which 2 were vertebral fractures.

The study protocol (registration number NL45707.072.13) was approved by an independent Medical Ethics Committee and complied with the Declaration of Helsinki. All patients gave written informed consent prior to participation.

Falls and subsequent fractures

During the 3-year follow-up, patients were requested to record falls weekly in a fall diary. Fall registration started at the beginning of the study, mean 3.5 ± 1.0 months after the index fracture. A fall was defined as an unintentional change in position resulting in coming to rest on the ground or other lower level (27). Patients were asked to return their fall diaries by mail at 3 and 6 months, and during the study visit at 1, 2 and 3 year of follow-up. They were contacted by telephone if the fall diary was not received or incomplete. Patients were categorized as those with at least one incident fall (*i.e.,* faller) or without an incident fall (*i.e.,* non-faller) during follow-up.

When patients recorded a fall in their diary, they were also asked to record whether or not they sustained a subsequent clinical fracture as a direct result of the fall. Additionally, at 1-, 2-, and 3-year follow-up, patients had to complete a detailed questionnaire, including a question on whether they sustained a fracture due to another trauma than a fall or without an overt trauma. All subsequent fractures were radiologically confirmed according to radiology reports in the electronic patient records. Since no imaging of the spine was performed at the end of the study, all reported vertebral fractures were symptomatic, clinical vertebral fractures. A distinction was made between subsequent fractures that were directly caused by a fall (*i.e.,* fall-related fractures), and those that occurred without an overt trauma or were the result of another trauma than a fall (*i.e.,* non-fall-related fractures).

Data analysis

Baseline characteristics were compared between fallers and non-fallers, and between patients with and without subsequent fractures using the Student's t test or Wilcoxon test for continuous variables, and Chi-squared or Fisher's exact test for categorical variables where appropriate. The incidence rate of falls and subsequent fractures per 100 person-years was estimated at 3 and 6 months and 1, 2 and 3 year follow-up,

assuming a Poisson distribution. Kaplan Meier curves were made for incident falls and subsequent fractures, in which patients were included once, and only the first incident fall or subsequent fracture was included. Cox proportional hazards regression was used to determine the association between incident falls and subsequent fractures, yielding hazard ratios (HR) and 95% confidence intervals (CI). Proportional hazard assumptions were not violated. Follow-up time was determined by the first subsequent fracture, lost-to-follow-up or the end of the study, whatever occurred first. All analyses were adjusted for the predefined covariates, including age, gender, index fracture type (major or hip versus any other fracture), BMD (lowest measured at lumbar spine, total hip, femoral neck), prevalent vertebral fractures (moderate or severe versus mild or no prevalent vertebral fractures). A p-value < 0.05 was considered statistically significant.

Two sensitivity analyses were planned; (i) excluding patients with index and subsequent finger or toe fractures, and (ii) by classifying patients with a non-fall-related subsequent fracture as non-faller, even if they fell at another time during follow-up.

Patient and public involvement

Patients or members of the public were not involved in the design, or conduct, or reporting, or dissemination plans of the research.

Results

Study population

Among 1220 patients approached from the FLS, 1011 patients met the study criteria. Of the 1011 patients, 511 were not willing or able to participate in the study, and after excluding 12 patients with missing fall data, ultimately 488 patients were available for analysis (**Supplementary Figure 1**) of whom 34 (7.0%) patients had

incomplete follow-up data on incident falls (5 patients died, 8 withdrew consent, 21 had incomplete fall registration).

The mean time between the index fracture and FLS visit at which patients were included for this study was 3.9 ± 1.1 months for patients with a hip fracture and 3.5 ± 1.0 months for patients with other fractures. Baseline characteristics of the 488 study participants are presented in **Table 1**. Mean age was 64.6 ± 8.6 year and 71.9% of the patients were women. In 86.5% of patients, the index fracture was caused by a fall, and 28.5% of patients had at least one other fall in the year before the start of the study. At baseline, 21.9% of patients were diagnosed with osteoporosis, 51.1% with osteopenia, and 27.1% had a normal BMD. Lowest BMD was measured at the femoral neck in 470 participants, at the total hip in 3 participants, and at the lumber spine in 15 participants. Moderate to severe (i.e., grade 2-3) prevalent vertebral fractures were present in 14.3% of patients. AOM was prescribed in 34.2% of patients (8 (1.6%) were already using AOM, and 159 (32.6%) started using AOM at baseline visit).

Compared to eligible FLS attenders, who were not willing or able to participate in our study, patients included in our study were younger, had fewer major or hip fractures, had a higher BMD, and a lower proportion had prevalent vertebral fractures (see **Supplementary Table 1**).

Falls

During a median follow-up of 3 years (range 0.1 to 3.0), 296 (60.7%) patients recorded 959 falls, corresponding to 68.6 falls per 100 person-years. The cumulative fall incidences and incidence rates per 100 person-years at 3 and 6 months, and at 1, 2 and 3 year follow-up are presented in **Figure 1**. Of the 296 patients with at least one fall, 115 (38.9%) had one fall and 181 (61.1%) had two or more falls (up to 39 falls in one patient).

A first fall was recorded by 189/488 (38.7%) patients during the first year of follow-up, by 56/299 (18.7%) during the second, and by 51/243 (21.0%) during the third year of follow-up. The median time to the first fall was 34 (range 1-156) weeks. Of the 959 falls, 47 (4.9%) resulted in a subsequent fall-related fracture.

There were no significant differences in baseline characteristics between patients with and without a fall during the 3-year follow-up, except for that a higher proportion of patients with incident falls reported at least one fall in the year before the start of the study (34.5% vs. 19.3%, $p < 0.001$) (see **Table 1**). There were no significant differences in baseline characteristics between patients with one fall and those with multiple falls (data not shown).

Subsequent fractures

In total, 53 (10.9%) patients recorded 60 subsequent fractures, corresponding to 4.29 subsequent fractures per 100 person-years. The cumulative subsequent fracture incidences and incidence rates (per 100-person years) at 3 and 6 months, and at 1, 2 and 3 year follow-up are presented in **Figure 2**. Of all subsequent fractures, 47 (78.3%) were fall-related, and 13 (21.7%) were non-fall-related. Fall-related subsequent fracture sites were: radius and ulna (n=9), tibia and fibula (n=8), proximal femur (n=4), metatarsal (n=4), hand phalanx (n=4), symptomatic vertebra (n=3), proximal humerus (n=3), clavicula (n=3), costal bones (n=2), scapula (n=2), pelvic bone (n=1), metacarpal (n=1), tarsal (n=1), patella (n=1), and foot phalanx (n=1), whereas subsequent non-fall-related fractures sites were: symptomatic vertebral (n=5), metatarsal (n=2), foot phalanx (n=5), and hand phalanx (n=1). Half (53.2%) of all fall-related subsequent fractures were sustained at the first fall.

Baseline characteristics for patients with and without subsequent fractures are presented in **Table 1**.

Of the 296 patients with at least one fall, 41 (13.9%) had 46 fall-related subsequent fractures, 7 (2.4%) had 7 non-fall-related subsequent fractures, and 1 (0.3%) had 1 fall- and 1 non-fall-related subsequent fracture. Of the 192 patients without a fall, 4 (2.1%) had 5 non-fall-related subsequent fractures. Of note, the risk of subsequent fractures was higher in patients with at least one fall than in those without a fall (adjusted HR (95% CI): 8.6 (3.1-23.8); cumulative incidence: 16.6%% versus 2.1%) (**Figure 3 and Table 2**). Results were similar when femoral neck BMD instead of the lowest BMD was used for adjustments (adjusted HR (95% CI): 8.3 (3.0-23.0)). Additionally, subsequent fracture risk was higher in patients with moderate or severe prevalent vertebral fractures than in those with no or mild prevalent vertebral fractures (adjusted HR (95% CI): 3.9 (2.1-7.3); cumulative incidence: 24.3% versus 8.6%) (**Table 2**).

The association between falls and subsequent fractures remained significant in sensitivity analyses (i) excluding patients with index and subsequent finger and toe fractures (adjusted HR (95% CI): 8.2 (2.5-26.6)), and (ii) by classifying patients with a non-fall-related subsequent fracture as non-faller (adjusted HR (95% CI): 2.9 (1.5-5.6)).

Discussion

In this 3-year prospective observational cohort study in patients aged 50+ years with a recent clinical fracture, treated according to current Dutch osteoporosis guidelines at a FLS, 60.7% of patients had at least one fall, and 10.9% had at least one subsequent fracture. The majority (78.3%) of subsequent fractures was caused by a fall, and of all fall-related subsequent fractures, 53.2% occurred at the first fall. Subsequent fracture risk was nine-fold higher in fallers than in non-fallers.

Literature reporting fall incidence in fracture patients is limited. Comparable to our results, Van Helden et al. (28) reported a 3-month fall incidence of 15% in patients with a recent fracture at a FLS, and Matsumoto et al. (29) reported a 1-year fall

incidence of 40% in ambulatory patients with a recent fracture. Various other studies included older, hip fracture patients and reported higher one year fall incidences up to 55% (7-11), except for the study from Yeh et al. that reported a lower 1-year fall incidence (31%) (30). Higher fall incidences in hip fracture studies can partially be explained by the older study population. Unfortunately, other fall risk factors cannot be compared. An explanation for the lower fall incidence in the study by Yeh et al. may be that information on the occurrence of falls was provided by patients and family caregivers, which may have resulted in under registration of falls.

A comparison between the fall incidence in our study and that in the general population is difficult to make, because population-based studies were conducted in a 65+ aged, community-dwelling population, whereas approximately 50% of our study population was <65 years old. The proportion of community-dwelling people aged 65+ years sustaining at least one fall over a 1-year period ranged from 28 to 35% (31-33), with an increasing incidence with increasing age (34). The 1-year fall incidence reported is our study is comparable to that in an older (65+ aged) population, and therefore relatively high. However, in contrast to what has been reported in literature, we found no higher 3-year fall incidence with increasing age. An explanation for this could be that, especially in the older age group, relatively more healthy patients participated in our study, resulting in a lower fall incidence in older age group. Another explanation could be that patients aged 50-65 years are more physically active, and therefore fall more often.

Compared to our results, previously published FLS studies reported lower (35,36), similar (28,37,38), and higher (39,40) subsequent fracture rates. Differences can be explained by differences in patient selection. Studies that included older patients (39) and patients with more severe fractures (40) reported higher subsequent fracture

rates, whereas studies that excluded hand and foot index and subsequent fractures (35) or frail patients reported lower rates (36).

In 2010, the Dutch population consisted of approximately 6,000,000 people aged 50+ years, of whom 119,419 sustained a fracture that year (41), corresponding to a calculated annual fracture incidence of 2.0% in the general Dutch 50+ population. Compared to the general Dutch 50+ population, the fracture incidence was more than 2 times higher in our study, even in the 3rd year of follow-up. In our study, fracture incidence remained high despite treatment according to the current osteoporosis guideline, raising the question of what more can be done to prevent subsequent fractures. Even though conflicting results have been published about the effect of fall prevention strategies on subsequent fracture (42), we hypothesize that fall interventions could be effective in patients at highest risk, namely those with a recent fracture at risk of falling. Furthermore, according to literature, recurrent fallers have an almost fourfold increased odds of sustaining a fall-related fracture compared to individuals with a single fall (43). However, we found that the majority of subsequent fall-related fractures occur at the first fall after the index fracture, with a median time to the first fall of 34 weeks. Interestingly, fall incidence was higher in the first year of follow-up compared to the second and third year. This may indicate an imminent fall risk, which may attribute to the imminent subsequent fracture risk after an index fracture (1-6). This implies that the FLS patients with a high fall risk should be identified immediately, because there is a small window of opportunity to prevent falls and fall-related subsequent fractures.

Remarkably, in contrast to previous studies indicating that imminent fracture risk that was highest in the first year after an index fracture (44,45), there was a linear subsequent fracture incidence during 3-year follow-up in this study. An explanation for the linear subsequent fracture incidence may be the relatively healthy patients who

agreed to participate in our study. Compared to non-attenders, they were younger, and a lower proportion had a major baseline fracture, a prevalent vertebral fracture, and osteoporosis, and if indicated, were more likely to receive AOM. Importantly, in addition to falls, moderate to severe prevalent vertebral fractures at baseline were associated with subsequent fractures, even though anti-osteoporosis medication had been prescribed to these patients according to the current Dutch osteoporosis guideline.

This study has several limitations. Although, this is one of the largest prospective studies in a FLS population focusing on the incidence of falls after an index fracture, the number of patients is modest, and the number of subsequent fractures relatively low. Therefore, the association between falls and fall-related, and non-fall-related subsequent fractures could not be analyzed separately. A fall 'not-resulting-in-a-subsequent-fracture' might indicate frailty of patients, and might be different from those falls that directly resulted in a subsequent fracture. Future studies are needed to investigate this difference. Finally, because of small numbers, subgroup analyses should not be performed. Furthermore, data on falls were collected prospectively using fall diaries that had to be returned at 3 and 6 months, and 1, 2, and 3 year. However, no procedures were in place to validate self-reported falls, and it is possible that recall bias, could have led to underregistration of falls. Moreover, no information was available on falls between the index fracture and enrollment in the study. Finally, relatively healthy patients participated in the study. Compared to non-attenders, they were younger, a lower proportion had a major baseline fracture, a prevalent vertebral fracture, and osteoporosis. The proportion of patients with a fall and subsequent fractures could be expected to be even higher in the total FLS population.

In conclusion, in this 3-year prospective observational cohort study in FLS patients, subsequent fracture incidence was high despite being prescribed anti-osteoporosis medications according to the current Dutch osteoporosis guideline.

Subsequent fracture risk was nine-fold higher in fallers than in non-fallers, and the majority of fall-related subsequent fractures occurred at the first fall at a median time of 34 weeks. These findings emphasize that immediate attention for fall risk reduction could be beneficial in FLS care. Various risk factors, including comorbidities, medication use, polypharmacy and alcohol use among others, contribute to patient's fall risk and further research is needed to determine predictors for falls to identify patients at highest risk of falling.

Figures and tables

Table 1. Baseline characteristics of 488 participants stratified by incident fall and subsequent fracture status.

	Total population (n=488)	**Non-fallers** (n=192)	**Fallers** (n=296)	**P-value**	**No subsequent fracture** (n=435)	**Subsequent fracture** (n=53)	**P-value**
Age (years)	64.6 ± 8.6	64.4 ± 8.0	64.8 ± 9.0	0.608	64.5 ± 8.8	65.3 ± 7.1	0.488
Female gender	351 (71.9)	130 (67.7)	221 (74.7)	0.095	308 (70.8)	43 (81.1)	0.114
Baseline fracture							
- Finger or toe	55 (11.3)	30 (15.6)	25 (8.4)	0.060	49 (11.3)	6 (11.3)	0.460
- Minor	303 (62.1)	109 (56.8)	194 (65.5)		270 (62.1)	33 (62.3)	
- Major	104 (21.3)	44 (22.9)	60 (20.3)		95 (21.8)	9 (17.0)	
- Hip	26 (5.3)	9 (4.7)	17 (5.7)		21 (4.8)	5 (9.4)	
- Fall-related *	422 (86.5)	164 (85.4)	258 (87.2)	0.582	378 (86.9)	44 (83.0)	0.436
Fall previous year §							
- 0	349 (71.5)	155 (80.7)	194 (65.5)	<0.001	315 (72.4)	34 (64.2)	0.208
- ≥ 1	139 (28.5)	37 (19.3)	102 (34.5)		120 (27.6)	19 (35.8)	
BMI (kg/m²)	27.7 ± 4.4	27.7 ± 4.4	27.7 ± 4.4	0.961	27.8 ± 4.4	26.9 ± 4.8	0.154
BMD							
- Normal BMD	132 (27.1)	54 (28.1)	78 (26.4)	0.906	123 (28.3)	9 (17.0)	0.081
- Osteopenia	249 (51.0)	97 (50.5)	152 (51.4)		222 (51.0)	27 (50.9)	
- Osteoporosis	107 (21.9)	41 (21.4)	66 (22.3)		90 (20.7)	17 (32.1)	
Prevalent vertebral fracture #$							
- None	356 (73.0)	139 (72.4)	217 (73.3)	0.572	328 (75.4)	28 (52.8)	<0.001
- Grade 1	62 (12.7)	22 (11.5)	40 (13.5)		54 (12.4)	8 (15.1)	
- Grade 2-3	70 (14.3)	31 (16.1)	39 (13.2)		53 (12.2)	17 (32.1)	
Anti-osteoporosis treatment	167 (34.2)	70 (36.5)	97 (32.8)	0.402	142 (32.6)	25 (47.2)	0.035

Continuous variables are shown in mean ± SD (standard deviation), categorical variables are shown as number of patients (%). * Signifying that fracture was caused by a fall. § Fall resulting in baseline fracture not included. # According to Genant et al. $ According to most severe prevalent vertebral fracture. Abbreviations: BMD, bone mineral density.

Table 2. Predictors of refracture: results of the Cox's proportional hazard model			
Predictor	**Unit of comparison**	**Hazard ratio and 95% confidence interval**	**P-value**
Gender	Women vs men	1.39 (0.68 - 2.83)	0.362
Age	+5 years	0.97 (0.82 - 1.13)	0.662
Index fracture	Major or hip vs all other	0.68 (0.35 - 1.33)	0.263
BMD	-0.12 g/cm^2	1.30 (0.95 - 1.78)	0.101
Prevalent vertebral fracture	Yes vs no	3.88 (2.07 – 7.27)	<0.0001
Fall	Yes vs no	8.58 (3.09 - 23.8)	<0.0001

Figure legends

Figure 1. Cumulative incidence of falls stratified by gender.

Figure 2. Cumulative incidence of subsequent fractures stratified by gender.

Figure 3. Cumulative incidence of subsequent fractures stratified by fall status.

Contributors

LV collected data, carried out data analysis and drafted the manuscript. CW and JB developed the study design and wrote the research protocol, collected data, and critically reviewed the manuscript. PG developed the study design and wrote the research protocol, and critically reviewed the manuscript. RV collected data and critically reviewed the manuscript. TN and TT assisted with data analysis and critically reviewed the manuscript. HJ, SK, JD, JA, JC and DB critically reviewed the manuscript. All authors approved the final version of the manuscript.

Competing interest

Dr. Vranken, Dr. Wyers, Dr. Van der Velden, Dr. Janzing, Dr. Kaarsemakers, Dr. Driessen, Dr. Eisman, Dr. Tran, and Dr. Bliuc have nothing to disclose.

Dr. Center reports honoraria for educational talks from Amgen, part support for educational meetings from Amgen, and advisory board participation for Amgen and Bayer, outside the submitted work.

Dr. Nguyen reports honoraria for lectures sponsored from Merck, and participation as executive member Asia Pacific Consortium on Osteoporosis, outside the submitted work.

Dr. Geusens reports grants from Amgen, Pfizer, MSD, UCB, Abbott, Lilly, BMS, Novartis, Roche, and Will Pharma, and honoraria for lectures from Amgen and Lilly, outside the submitted work.

Dr. van den Bergh reports grants for lectures from UCB, and Amgen, outside the submitted work.

Funding

This work was supported by the Weijerhorst Foundation, grand number not applicable. The Weijerhorst Foundation was not involved in conducting the study, analyzing the data or writing the manuscript.

Patient consent for publication

Patient consent for publication was not required.

Ethics approval

This study (protocol ID number NL45707.072.13) has been approved by the Independent Review Board Nijmegen (IRBN).

Data availability statement

No additional data available.

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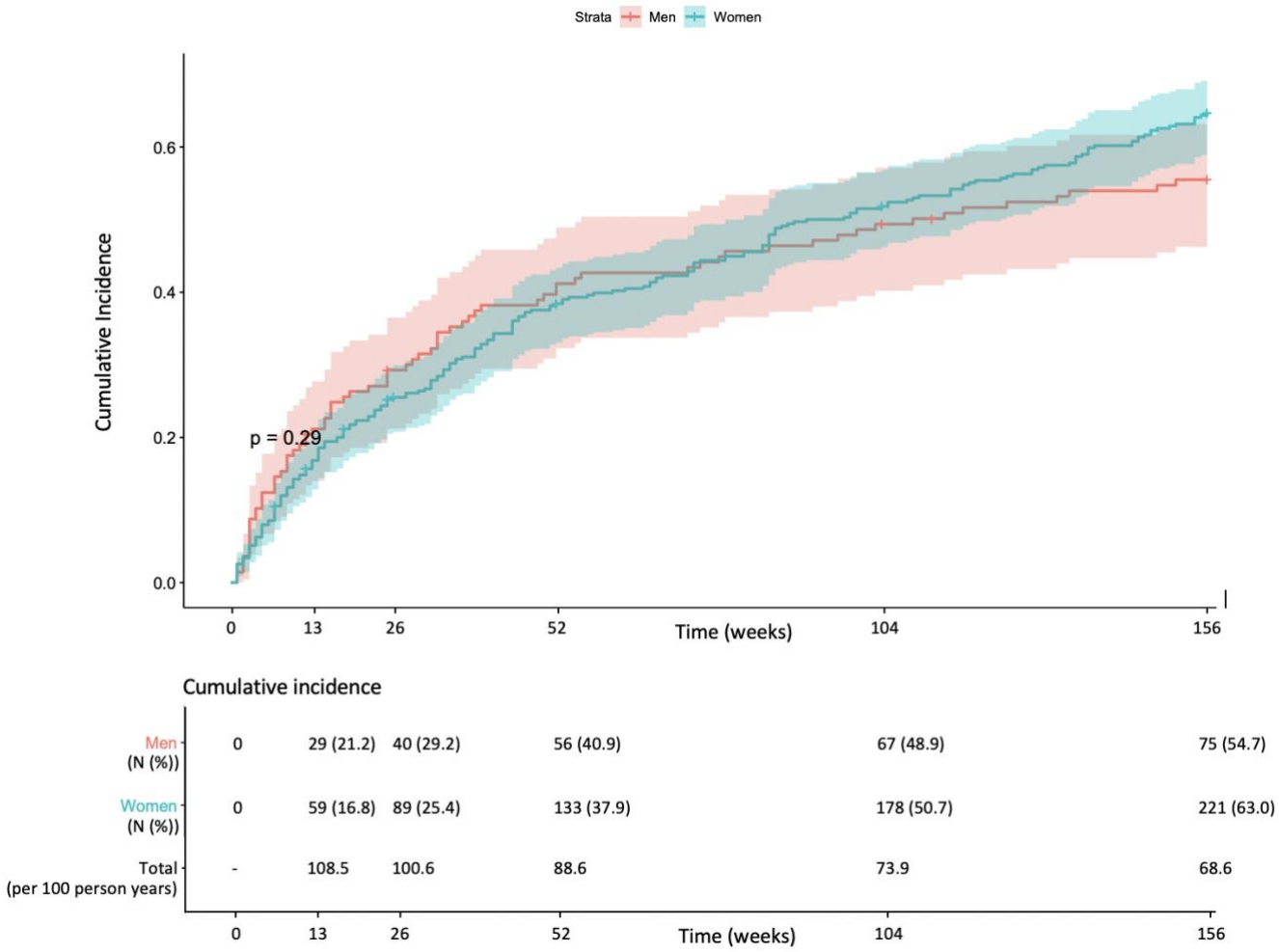


Figure 1. Cumulative incidence of falls stratified by gender.

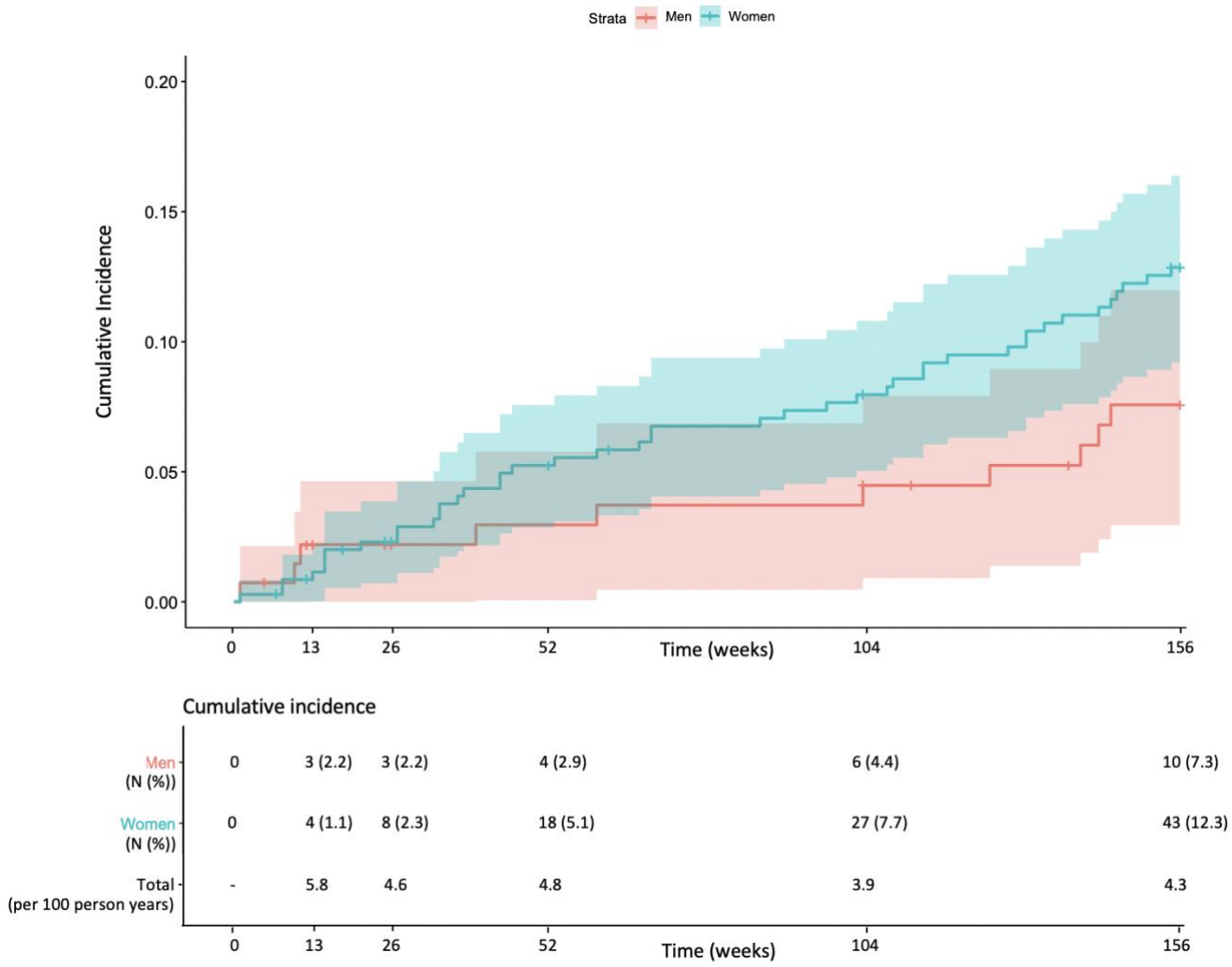


Figure 2. Cumulative incidence of subsequent fractures stratified by gender.

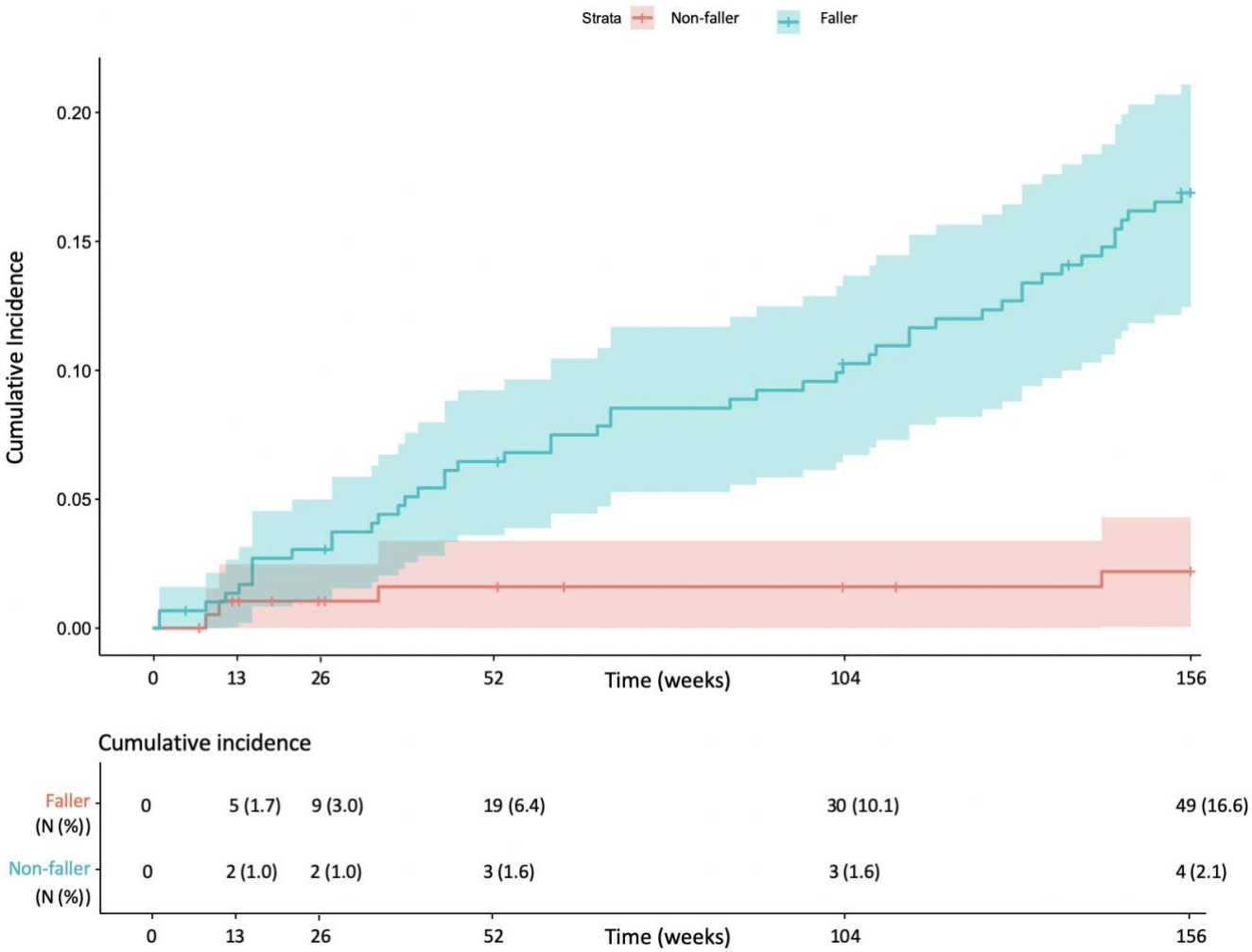
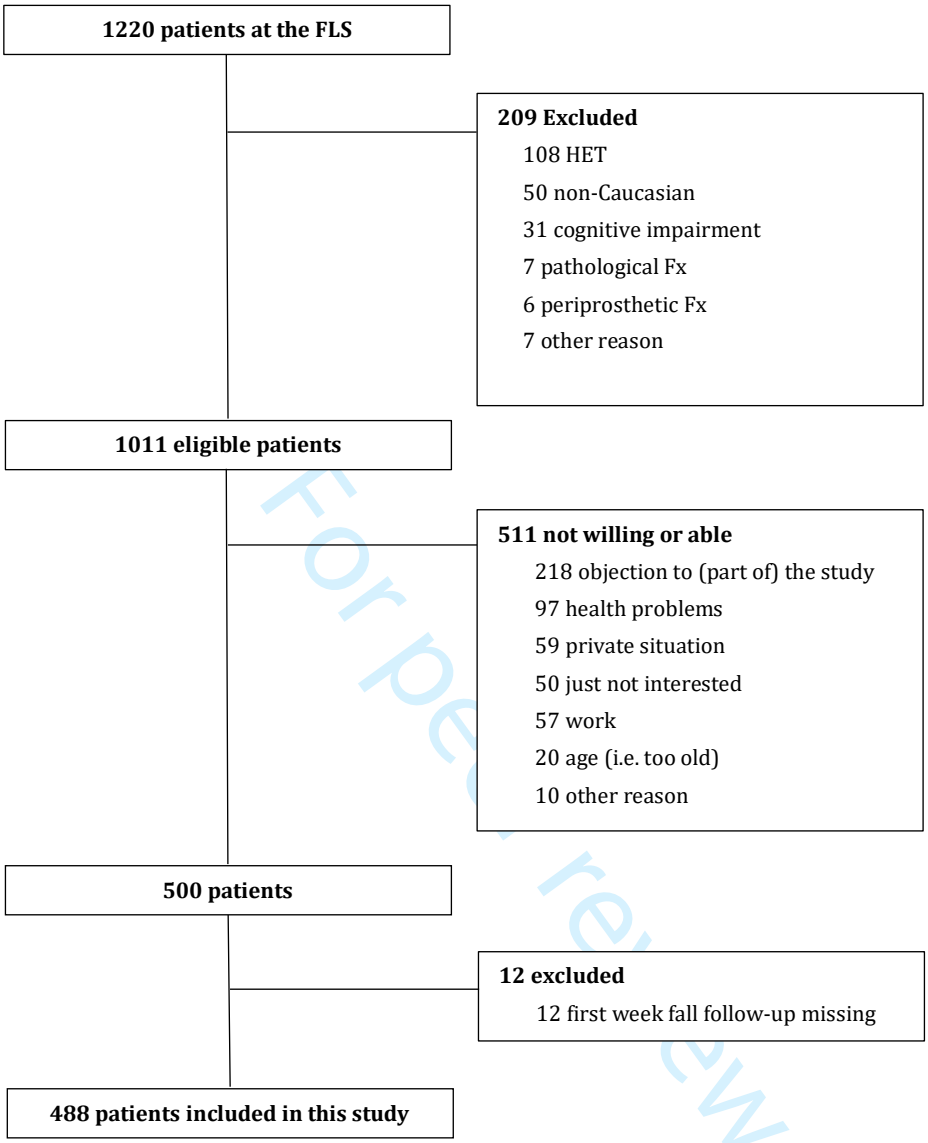


Figure 3. Cumulative incidence of subsequent fractures stratified by fall status.



Supplementary Figure 1. Patient selection. Abbreviations: HET, high-energy trauma fractures; Fx, fracture.

Supplementary table 1. Characteristics of 1011 FLS patients that participated and not-participated in this study.

	Participants (n=500)	**Non-participants** (n=511)	**P-value**
Age in years	64.6 ± 8.6	68.3 ± 9.8	<.001
Female sex	357 (71.4)	396 (77.5)	.026
Baseline fracture			
- Finger or toe	58 (11.6)	53 (10.4)	<.001
- Minor	311 (62.2)	259 (50.7)	
- Major	105 (21.0)	157 (30.7)	
- Hip	26 (5.2)	42 (8.2)	
- Fall-related [*]	431 (86.2)	441 (86.3)	.963
Fall previous year [§]			
- 0	356 (71.2)	359 (70.3)	.741
- ≥ 1	144 (28.8)	152 (29.7)	
- ≥ 2	72 (14.4)	87 (17.0)	.252
BMD			
- Normal BMD	135 (27.0)	90 (17.6)	<.001
- Osteopenia	255 (51.0)	258 (50.5)	
- Osteoporosis	110 (22.0)	163 (31.9)	
Prevalent vertebral fracture			
- None	366 (73.2)	349 (68.3)	.010
- Grade 1	63 (12.6)	53 (10.4)	
- Grade 2-3	71 (14.2)	109 (21.3)	
At least one fall past year	143 (29.3)	152 (29.9)	.704

Continues variables are presented as mean ± SD, categorical variables are presented as number of patients (%). [§] Fall resulting in baseline fracture not included. [#] According to Genant et al. [$] According to most severe prevalent vertebral fracture. Abbreviations: BMD, bone mineral density

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	20
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9,10,16,17,18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9,10,11 NA 9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.