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The Development of a Personalised Fragility Hip Fracture Risk Calculator

PhD Thesis submitted by

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Abstract

Fragility hip fractures in older adults are a major burden for individuals and society due to increased morbidity, mortality and substantial health care expenditure. The vast majority of hip fractures are caused by falls resulting in an impact on the hip, inducing a force that exceeds the femoral bone strength. At the same time, only 1 - 3% of all falls result in a fracture, suggesting that the fall dynamics defines its severity and, through that, the magnitude of the impact force. Additionally, trochanteric soft tissue thickness is known to play a crucial role in the energy-dissipating mechanism during impact. Thus, the fracture risk depends on the rate of falling, the fall-induced impact force, and the femoral bone strength.

This PhD thesis presents a novel hip fracture risk calculator that is based on a mechanistic stochastic framework that was presented in the literature. The original model uses a Poisson process characterised by the rate parameter λ to describe the occurrence of a fall. A stochastic distribution is then introduced to model the conditional probability that the fall-induced impact force exceeds the femoral bone strength. By combining these, the fall events resulting in a fracture are identified, and a fracture risk can be calculated. The novel model introduced a fall rate model to estimate a personalised λ, and refined the probability distribution representing the chances of the femoral bone to break upon impact with a mechanical impact force model.

The fall rate model to predict a personalised fall rate λ was developed by analysing three independent cohorts that assessed various risk factors of falls. Negative binomial regression models were fitted, and a variable selection algorithm was applied. Thereby, the prior number of falls treated as a categorical variable was the only predictor selected in all cohorts. A meta-analysis and validation of the models confirmed that the number of prior falls is a robust predictor for the prediction of a fall rate among different cohorts.

Furthermore, the personalised impact force model was developed using subject-specific parameters that can be extracted from quantitative computed tomography (QCT) images or substituted with anthropometric data. The model calculates the full range of possible impact forces of an individual, indirectly representing the variability in the dynamics of a fall. By introducing a stochastic distribution that describes the probability of the fall dynamics, a fracture risk can be calculated. With this approach, the stochastic aspects of the mechanism resulting in hip fracture

are concentrated in the Poisson process describing the occurrence of a fall and the fall dynamics. Bone strength was estimated with QCT-based finite element analysis, but it can also be estimated with other densitometric measures. Thus, the required parameters for the model can be extracted from QCT images or substituted with anthropometric and densitometric data.

A sensitivity analysis was conducted using clinical data from the AFFIRM-CT cohort, confirming that the fall rate, the trochanteric soft tissue thickness and the bone strength are the dominating parameters influencing the risk of fragility hip fractures. Furthermore, output variables such as the predicted impact velocity and impact force aligned well with experimental data from the literature.

The work of this thesis resulted in a novel fragility hip fracture risk calculator that models the underlying process of hip fractures by combining the stochastic aspects of a fall with the mechanistic elements of an impact on the hip. Thereby, the model was shown to reflect key observations from empirical data, indicating that it can capture the intrinsic aspects that affect the risk of fragility hip fractures.

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Abbreviations

aBMD areal bone mineral density

AUC area under the curve

BIC Bayesian information criteria

BMD bone mineral density

BMI body mass index

CCI Charlson's comorbidity index

CI confidence interval

CT computed tomography

DAE differential algebraic equations

DXA dual energy X-ray absorptiometry

FEA finite element analysis

FES-I Falls Efficacy Scale - International

FRT Functional Reach Test

FSBT Four Stage Balance Test

FSR force to strength ratio

FTSTS Five Times Sit-to-Stand test

G ground

GERICO Geneva Retirees Cohort

GVIF generalized variance inflation factor

HGS hand grip strength

HP hemi-pelvis

HR-pQCT high-resolution peripheral quantitative computed tomography

IQR interquartile range

IRR Incidence rate ratio

KFPS Kuopio Fall Prevention Study

LASSO least absolute shrinkage and selection operator

MAE mean absolute prediction error

OLST one-legged stance test

OPQOL-35 Older People's Quality of Life Questionnaire

QCT quantitative computed tomography

RMSE root mean squared prediction error

ROC receiver operator characteristic

RR rate ratio

SCT Swiss CHEF Trial

SD standard deviation

SPPB Short Physical Performance Battery

ST soft tissue

TUG Timed Up and Go

vBMD volumetric bone mineral density

VIF variance inflation factor

WHO World Health Organization

Prediction is very difficult, especially if it's about the future.

Niels Bohr

1 Introduction

Humans have always been curious about what the future holds. Knowing what is most likely to come next is extremely valuable, as it allows us to adopt our behaviour according to the upcoming circumstances. In the medical field, insights into the chances of developing a disease under specific conditions or exposures, suffering from an adverse clinical outcome following a chronic disease, or the probability of success for a particular treatment forms an essential foundation of how individuals are treated in healthcare. It lays the foundation for making informed decisions regarding appropriate treatments or interventions and allows us to apply effective preventive measures.

As the title of this doctoral thesis suggests, the work presented here focuses on developing a model to predict the risk of suffering from a fragility hip fracture. Fragility fractures of the hip are a major health concern in the older population, as such an injury leads to increased morbidity and mortality and causes a substantial part of health care costs [1]. With age being a major risk factor for fragility fractures and demographic changes implying an ageing population, the incidence of fragility fractures is expected to rise. Thus, the identification of individuals at risk of such a fracture is of great interest.

In medicine, many prediction models are regression-based and thus belong to the family of statistical models. Examples can be found in cardiovascular disease risk

assessment [2], in stroke risk prediction [3], or in the prediction of fragility fracture risk [4]. Thereby, the model assumes a specific relationship between the variables of the data set and tries to quantify this relationship with its coefficients. Hence, statistical prediction models in medicine depend on the cohorts used to build it, as the model tries to best describe the relationship in the data. The underlying mechanism that produces the data does not necessarily need to be understood. The model coefficients usually inform about the change in relative risk (e.g. as odds or hazard ratios) when exposed or unexposed to a risk factor. To estimate an absolute risk, knowledge about the baseline risk is required.

An alternative approach is provided by mechanistic models, which aim to reflect the mechanism behind an event with the help of mathematical formulations that describe the underlying physical processes. However, it is a prerequisite that the mechanism of the system that produces the data is well understood. Mechanistic models are frequently used in ecology [5], pharmacology [6] or biological processes [7]. In the medical context, mechanistic models are less common. In the case of fragility hip fractures, it is known that most fractures are caused by falls and that the femoral bone breaks if the fall-induced impact force exceeds the femoral bone strength. Thus, a mechanistic modelling approach would be to develop a model that can estimate the fall-induced impact force and a model that can estimate the bone strength and compare these values. However, even if both values can be perfectly modelled, the ratio solely informs about the outcome (fracture or no fracture) given a specific set of input variables. Since we are interested in predicting the probability of the outcome, assigning a probability to the possible range of each input variable in the system is necessary. This can be done using probability distributions and stochastic processes, whereby insight into the stochastic nature describing the occurrence of the input variable is required.

The prediction model presented in this work attempts to demonstrate an alternative framework to regression-based prediction tools. It is based on a mechanistic stochastic model that was presented and introduced in the article "A Poisson process model for hip fracture risk" by Schechner *et al.* in 2010 [8].

The following introduction aims to give an overview of the topic of fragility (hip) fractures and the available tools for prediction. In the first part, the general background and the burden of fragility fractures are discussed, followed by a section about the clinical gold standard in fragility fracture risk prediction. Subsequently, causes of fragility hip fractures are outlined, and mechanistic modelling approaches are presented. In the last part, the framework of the model presented by Schechner *et al.* and aspects that could be developed and refined to make it clinically applicable to the individual are outlined. A short section describes the clinical study conducted to collect data for the development of the calculator. This naturally leads to the aims of the thesis.

1.1 Fragility fractures

Although there is sometimes still debate about how to best define fragility fractures, they are usually referred to as fractures that result from low-energy trauma such as a fall from standing height or lower [1], [9]. In other words, these fractures occur from events that would not typically cause fractures in healthy adults. The most common fracture sites, also referred to as major osteoporotic fractures, are the hip (proximal femur), the forearm (radius), the upper arm (humerus) and the vertebral bodies. However, also other sites of the skeleton are at risk of fragility fractures [9].

In 2019, around 82'000 fragility fractures were reported in Switzerland [1]. Compared to data from 2011, this is an increase of 11%. Due to the demographic shift towards a more aged population, and since ageing is an important risk factor for fragility fractures, the absolute number of fractures is expected to increase by another 37% to more than 113'000 fractures by 2034. In 2018, the crude incidence rate per person year for major osteoporotic fractures was reported to be around 400/100'000 in men and 950/100'000 in women. Among these, the most frequent fracture site was the hip, with an incidence of 180/100'000 in men and 390/100'000 in women [10].

The consequences of fragility fractures are considerable. On the one hand, they represent a significant portion of health care expenditures, ranging from 1.3% up to 6% of the health care costs in the EU27+2 countries [1]. However, when

focusing on a personal level, the effects for the individual are more far-reaching and drastic than just health care costs. Suffering from a fragility fracture results in increased morbidity and mortality and an increased chance of becoming dependent and institutionalised [11], [12]. Thereby, the consequences of hip fractures are the most burdensome of all fracture sites, with a mortality risk of up to 20% in the subsequent 3 - 6 months of fracture [13]. Against this background, identifying individuals at risk of fragility fractures, particularly of the hip, is of great importance. Only then can effective preventive measures be taken.

1.2 Bone strength and its role in fragility fracture prediction

From a biomechanical point of view, a bone breaks if the force acting upon it exceeds its strength. Therefore, bone strength is a critical factor for the prediction of fragility fractures. Bone strength is determined by the total bone mass, its spatial distribution and the intrinsic properties of the tissue [14]. Bone mineral density (BMD) is a representation of structural density that relates the bone mass to its volumetric bone mineral density (vBMD) or its 2D-projected areal bone mineral density (aBMD). In the femoral bone, aBMD can explain up to 80% of its variation in strength [15]. Looking at the development of bone mass with age, an individual's peak bone mass is reached at around 25 - 30 years [16]. After that, it is the natural progression with age that the total bone mass decreases. However, certain genetic and environmental factors can result in profound bone loss and, consequently, an increased susceptibility to fragility fractures [17]. The pathological condition of an abnormally low bone mass is defined as osteoporosis. Therefore, fragility fractures are sometimes referred to as osteoporotic fractures.

The assessment of osteoporosis and bone strength

The clinical standard to diagnose osteoporosis is the measurement of aBMD with a dual energy X-ray absorptiometry (DXA) scan at the lumbar spine and the proximal femur [18]. Since BMD is approximately normally distributed among all age groups,

the definition of osteoporosis introduced by the World Health Organization (WHO) is based on T-scores that describe the standard deviation (SD) when compared to a young healthy reference population[19]. A deviation of -1 SD and higher (T-score > -1) is considered to be normal. A T-score between -1 and -2.5 is referred to as osteopenia, which is a pre-stage of osteoporosis. Values of -2.5 SD and lower are defined as osteoporosis. Severe osteoporosis is referred to as a T-score ≤ -2.5 in the presence of at least one fragility fracture. Numerous experiments have shown that aBMD and experimentally measured bone strength values in the femur correlate well [15]. Hence, bone strength can be indirectly assessed with aBMD. However, as the three-dimensional structure of bone plays an inherent role in its ability to withstand forces, other modalities have been developed to assess its strength.

Finite element analysis (FEA) is a numerical method that allows the calculation of a complex mechanical problem in a three-dimensional structure [20]. Thereby, the structure of interest is divided into a finite number of elements. By assigning material properties to each element and solving equations describing the force equilibrium in the respective elements, mechanical measures such as strength can be calculated.

Computed tomography (CT) images provide a three-dimensional image of the body and, consequently, the skeleton. CT values are measured in Hounsfield units which is a relative number describing the X-ray attenuation [21]. To use CT images for the calculation of bone strength, Hounsfield units need to be transformed into BMD values. This can be done with the help of a calibration phantom. The calibration procedure is referred to as synchronous calibration if the phantom is scanned with the patient, and asynchronous if the phantom is scanned separately. In contrast, phantomless calibration procedures have been proposed that use body tissues for calibration and do not require a phantom to be scanned [22]. Upon calibration, a CT scan is referred to as a quantitative computed tomography (QCT) scan. Consequently, FEA methods to estimate bone strength from QCT images have been developed [20]. This allows the secondary use of routinely performed CT images for osteoporosis screening, which is sometimes also referred to as opportunistic screening [22]. In a comprehensive review, it was shown that both aBMD-based

and FEA-based bone strength estimates compare well with experimentally derived femoral strength values [15].

Predictive ability of aBMD and FEA-based bone strength

Regarding the ability of aBMD to predict fragility fractures, several studies included in meta-analyses have shown that decreased aBMD is associated with an increased risk of fragility fractures at all fracture sites [23], [24]. However, when looking at the predictive ability of the individual, its use is limited. Various studies reported that only a share of all fractures are attributable to an osteoporotic aBMD value as defined by the WHO [25], [26], [27]. This can be explained by its low positive predictive value and low sensitivity [23], [28]. Thus, the distribution of aBMD between individuals who suffer a fracture and those who do not is strongly overlapping.

Moving from aBMD to FEA-based bone strength estimates for fragility fracture prediction, inconclusive results have been found. While few studies have reported a significantly better predictive performance for hip fractures using FEA-based bone strength estimates in comparison to aBMD [29], others found comparable performances or only marginal improvements in fracture prediction when using FEA-based estimates [30], [31], [32], [33]. Contrary, the predictive performance of FEA-based bone strength estimates for vertebral fracture was reported to be superior in comparison to aBMD [20]. Apart from these inconsistencies, FEA-based methods face additional challenges to be integrated into clinical routines, such as the lack of standardised software and calibration protocols [20], [22].

With the aim of improving fracture prediction beyond bone strength alone, other risk factors associated with fragility (hip) fracture risk were sought and integrated into fracture risk prediction models.

1.3 FRAX®: The clinical gold standard to predict the risk of fragility fractures

The clinical gold standard to predict the risk of fragility fractures is the FRAX® calculator. FRAX® was developed by the WHO Collaborating Centre for Metabolic

Bone Diseases at the University of Sheffield (UK) and was presented for the first time in 2007 [4]. It is a regression-based tool and predicts the 10-year probability for major osteoporotic fractures and hip fractures by combining clinical risk factors with aBMD measured at the femoral neck as an optional parameter [34]. These include age, sex, body mass index (BMI), prior osteoporotic fractures, parental hip fractures, alcohol consumption ($\geq$ 3 units a day), current smoking, glucocorticoid exposure ($\geq$ 3 months), rheumatoid arthritis and secondary osteoporosis [35]. The FRAX® calculator is based on nine international prospective population-based cohorts [4]. The association between the clinical risk factors and fracture outcome was analysed separately with a Poisson regression for every cohort, and the resulting coefficients for the risk factors were meta-analysed. Furthermore, FRAX® accounts for competing mortality risk and has been calibrated for different countries. Since the publication of the first version, an updated version called FRAXplus® including additional risk factors such as the history of falls, the hip axis length or type 2 diabetes mellitus has been introduced [36]. FRAX® has been validated with numerous cohorts, whereby the area under the curve (AUC) was reported to lay between 0.61 - 0.78 for major osteoporotic fractures, and between 0.66 - 0.83 for hip fractures [37].

Although other calculators such as the Garvan fracture calculator [38], [39] or the QFracture Score [40], [41] exist, FRAX® is probably the best studied and most frequently used tool for fragility fracture risk prediction in the clinical routine. There exist various guidelines on the management of osteoporosis and fragility fractures, of which FRAX® is an integral part [36].

1.4 Causes of fragility hip fractures

As mentioned at the beginning of this introduction, regression-based models try to find associations between predictors and outcomes but do not necessarily reflect the underlying process that leads to or generates the outcome of interest. An alternative is provided by mechanistic models, which try to model this mechanism. However, to develop such a model, knowledge about the underlying causes and mechanism of the outcome of interest is indispensable.

Focusing on fragility hip fractures, it is reported that with more than 95%, the vast majority of those events result from a fall-indcued impact on the hip [42], [43]. At the same time, it is known that approximately one out of three adults aged 65 and older fall every year [44]. However, only 1 - 3% of all fall events result in a hip fracture, indicating that how a fall happens is an important point to consider. As previously mentioned, a bone breaks when the force acting on it exceeds its strength. For hip fractures, this ratio is given by the fall-induced impact force and the femoral bone strength, and is often referred to as the load-to-strength ratio or the factor-of-risk [45], [46]. Looking at the number of falls resulting in a hip fracture, it can be concluded that only a small share of all falls result in an impact force high enough to initiate such an event.

Against this background, it follows that the risk of fragility hip fractures depends on three main factors: the risk of falling, the fall-induced impact force, and the femoral bone strength. The available methods to model and estimate bone strength have already been discussed in Section 1.2. In the following, the two remaining points will be outlined.

1.4.1 Falls

Approximately one out of three older adults aged 65 and older fall every year [44]. When comparing among different age groups, the incidence of falls is increasing with increasing age, reaching up to 40% and more in the age group of 75+ [44], [47], [48]. It is estimated that around one-third of falls result in an injury [49]. The severity of fall-related injuries can vary greatly, ranging from light bruises to severe injuries such as fractures, traumatic brain injuries or even death [49], [50], [51], [52]. Indeed, falls account for the majority of unintentional injuries in adults aged 65 and older. In 2019, falling was the cause of more than 50% of such injuries in the United States [53]. Furthermore, the incidence of injurious falls increases with increasing age, too [51], [54].

Focusing on fragility fractures, it is reported that around 5 - 10% of all falls result in a fracture [54], [55]. Thereby, approximately 1 - 3% of the falls cause a hip

fracture. Flipping the perspective, falls account for up to 87 - 95% of all fractures in older adults [56], [57]. However, this number is fracture site-dependent; while fractures in the hip or radius are almost exclusively caused by falls, fractures in the vertebra and humerus are caused by falls in 60% and 76% of the cases, respectively [57]. Considering these numbers, it might not be surprising that falls have been reported to be predictive of fragility fractures [58]. To summarise, the risk of falling plays a central role in identifying individuals at risk of fragility fractures, as well as fall-related injuries in general.

Many risk factors have been shown to be associated with the risk of falling, which can be divided into intrinsic and extrinsic risk factors. Intrinsic risk factors include age, sex and gender, chronic diseases, physical performance impairment and visual or sensory deficits. Extrinsic risk factors refer to side effects of medications, obstacles in the environment, and footwear. Various reviews and meta-analyses summarised findings about the risk factors of falls for different population groups and settings [59], [60], [61], [62], [63]. Concurrently, many fall risk assessment tools have been developed to identify individuals at risk of falling [60], [64], [65], [66]. These include tests assessing a single risk factor or a combination of these. Most assessment tools have been developed with binary logistic regression models, resulting in individuals being classified as at risk of falling or not at risk of falling [67]. Despite the enormous effort of the research community, the majority of those tools show a moderate performance in discriminating fallers from non-fallers [64], [67].

The risk of fall-related injuries increases directly with the number of experienced falls: The more often someone falls, the higher the risk of injury. Thus, an alternative approach to modelling fall risk would be the estimation of a fall rate. Already in 1990, Cumming *et al.* questioned whether the common approach to model the risk of falling in a binary setting, distinguishing between fallers and non-fallers, is a suitable approach, arguing that a fall rate is more meaningful in identifying individuals at risk of fall-related injuries [68]. In addition, the relationship between risk factors and falls can be biased when recurrent fallers are simply categorised as fallers. By doing so, the weight of risk factors the person was exposed to compared

to single-time fallers or non-fallers is reduced. Count regression is a method that allows the estimation of a fall rate, and that is suitable to analyse recurrent events [69], [70], [71]. However, up to the day, only a minority of studies have used count regression models to analyse fall data [67], [70].

1.4.2 Fall-induced impact force

The fall-induced impact force is a critical factor in determining whether the femoral bone breaks upon impact and directly depends on the velocity with which the body hits the ground. The first models that were developed for estimating the impact velocity and impact force were dynamic models [72], [73], [74]. These models were based on mass-spring-damper systems or rigid-link models. Looking at this in more detail, factors that define the magnitude of the impact force to which the femur is subjected in the event of a fall can be divided into two areas. Once a fall is initiated, there exist countless possibilities of how the body moves during the descent until hitting the ground. This dynamic defines the impact velocity of the hip and, thus, the magnitude of the impact force during the moment the hip touches the ground. Subsequently, the properties of the body and the ground act together in transforming and dissipating the kinetic energy of the fall, and through that, ultimately define the magnitude of the peak impact force in the hip. In the next two paragraphs, these two aspects are elaborated in detail.

Fall dynamics

The initial height of an individual's centre of mass defines the potential energy of a fall. However, movements during the descent of the fall, such as rotations or the outstretching of the hand, can reduce the impact force, as these pre-impact movement strategies decrease the amount of energy available for the impact. Moreover, not only the initial height but also circumstances such as the initiation of a fall event influence the fall dynamics and the resulting impact force.

Experiments conducted with young, healthy volunteers who fell unintentionally revealed that 98% of all falls resulted in an impact on the hip, with the hand used to dampen the impact just as often [75]. In comparison, video-analysis of falls in

older adults showed that impact on the hand occurred only in 81% of the falls [57], indicating that not necessarily the impact site, but pre-impact movement strategies differ among age groups. Taking into consideration that fall-induced hip fractures only start to appear at age 50 and that their frequency increases with age [76], it can be concluded that the fall dynamics changes with age and plays an essential role in whether an individual can dampen the impact force below a critical level. Age-related changes in the sensorimotor and proprioceptive systems, which are crucial for motor control and joint stability, are likely to account for differences in pre-impact movement strategies [77], [78], [79].

Numerous studies have been conducted to investigate the influence of the fall dynamics on the impact force and/or on the hip fracture risk. While some analysed real-life data [43], [80], [81], [82], [83], [84], [85], [86], others assessed different pre-impact movement strategies with experimental data from young healthy volunteers who fell in a controlled environment [75], [87], [88], [89]. The results from those analyses helped identify fall-dynamic-related risk factors for a fracture or gave insight into which circumstances and causes of a fall can result in an impact on the hip. For example, a sideways landing configuration impacting the hip was reported to be a risk factor for hip fracture [43], [81], while an impact on the knee or the hand resulted in a lower impact force and consequently a lower fracture risk [81], [82], [88].

The accurate quantification of the change in magnitude of the impact force due to varying fall dynamics states a challenge with real-life data, as measuring the fall-induced impact force in an uncontrolled environment is not feasible. Instead, the influence on the fracture risk is usually reported as a change in the relative risk for hip fractures using odds or hazard ratios, which can be interpreted as an indirect representation of the change in magnitude of the impact force.

A few studies have tried to fill this gap and conducted experiments with healthy young volunteers that allowed the quantification of the effect of pre-impact movement strategies on the impact force by using force-plates or motion tracking systems [87], [88], [89]. For example, it was demonstrated that impacting with the knee following a sideways fall resulted in a decrease in the hip impact force of more than

30% [88]. A further approach to assess the influence of the fall dynamics on the impact force is kinematic models simulating a sideways fall. As an example, Lo and Ashton-Miller developed an impact force prediction model that integrates a kinematic model to simulate different fall scenarios [90]. Another study did not include the whole fall dynamics but assessed the influence of different impact angles of the hip on the impact force using an FEA model [91], showing that a lateral impact is the most likely configuration to initiate a fracture.

Stiffness and damping properties of the hip

Once the body hits the ground, the whole hip complex and the floor attenuate energy and, through that, reduce the magnitude of the impact force. The hip complex consists of soft tissue (composed of muscle and fat), ligaments, tendons, cartilage, the femur and the pelvis bone. These tissues all display specific visco-elastic material properties that allow energy storage and dissipation upon deflection. To predict the impact force acting on the hip complex, various experiments have been conducted to assess its stiffness and damping properties.

A large number of experiments with living subjects are based on the pelvis release experiment that was developed by Robinovitch *et al.* [72]. In this experiment, subjects were laying laterally on the greater trochanter on a force plate and were lifted with a canvas sling around the hip. Upon release, the force over time was measured. With the experimental data, the parameters of a damped vibrational system modelling the hip complex were fitted. Other studies further developed this experimental setup and evaluated the force-deflection properties of the hip with a motion capture system [92] or assessed the influence of sex and BMI on the impact force and stiffness parameter [93]. The disadvantage of this type of experiment is that the impact forces do not reach the force magnitude following a fall, as this would be ethically not justifiable. However, due to the non-linear nature of the stiffness and damping properties of the pelvis [72], experimental data in the higher force regime are required. Consequently, other studies conducted experiments that allowed the investigation of realistic impact forces upon a fall. For example, Robinovitch *et al.* used an impact pendulum to measure the impact

force in a surrogate pelvis imitating a sideways fall [74]. Fleps *et al.* developed a sideways fall simulator for the human cadaveric pelvis and femur bones [94], [95]. The data collected by Fleps *et al.* were then used to validate an explicit FEA model that models the response of a lateral impact on the hip [96].

In all the research conducted on the stiffness and damping properties of the hip complex, it has been demonstrated that the soft tissues covering the hip play a central role. Several experiments and analyses showed that the peak impact force decreases as the tissue thickness increases [72], [89], [97], [98], [99], [100]. Robinovitch *et al.* found that with every additional millimetre of soft tissue thickness, the peak impact force decreases by 71N [97]. In an analysis of a female cohort with 21 hip fracture cases and 42 age-matched controls, a decreased trochanteric soft tissue thickness was shown to be associated with an increased hip fracture risk [99]. An explanation for this association is that an increase in thickness leads to a larger contact area, which results in more tissue being recruited and deformed [89], and consequently more energy being absorbed during impact [97]. Looking at the formula that relates a material's elastic modulus to its structural stiffness gives another explanation for these findings. The relationship is given by $k = E \cdot A/L$ with A as the contact area, E as the elastic modulus, and L the length. Hence, the stiffness k decreases with increasing thickness L and thus results in a reduced impact force for a given impact energy. These aspects have also been assessed in experimental settings, where the soft tissue stiffness and its influence on the fracture risk have been elaborated [101], [102], [103]. Furthermore, the effect of the tissue's composition (muscle and fat) on its energy-absorbing capacities has been investigated [102], [104], [105]. Other than that, the soft tissue thickness was found to vary depending on factors such as sex, BMI and posture [99], [106], [107]. A further factor that has been shown to influence the stiffness of the hip complex, respectively soft tissue stiffness, is the state of muscle activation, with an activated muscle being stiffer and through that resulting in higher peak impact forces [72], [108]. And last, although not part of the hip itself, the stiffness of the ground on which a subject falls has also been shown to influence the magnitude of the impact force in the hip [109].

In summary, the prediction of the fall-induced impact force is challenging, as it acts in a highly noisy environment. Fall-dynamic-related factors vary from fall to fall, and their effect on the impact force is difficult to quantify. At the same time, the characterisation of the stiffness and damping properties of the hip made it possible to calculate an impact force using mechanical models. Thereby, subject-specific parameters that affect the magnitude of the impact force, such as the soft tissue thickness, can be considered. However, even if the impact force of a specific fall scenario can be calculated accurately, there is still a major obstacle that has not been addressed yet: There exist countless possibilities of how a fall can happen, and it is simply impossible to predict which fall scenario will occur.

1.5 Mechanistic models for the prediction of fragility hip fractures

Most mechanistic models developed for the prediction of fragility hip fractures are based on the evaluation of the factor-of-risk. For example, Dufour *et al.* suggested a model that derived the factor-of-risk by calculating the impact force with a standard formula for a sideways fall using height and weight [73] and accounted for the attenuation of the soft tissue thickness using the relationship found by Robinovitch *et al.* [97]. The femoral strength was estimated using aBMD, and the factor-of-risk was used as a predictor in a Cox proportional hazard model [46]. Other models tried to better reflect the subject-specific dynamics of a fall, as this influences the resulting impact force. Sarvi *et al.* developed a model that integrates this aspect by using a three-link whole-body dynamics model to simulate a standard sideways fall together with a DXA-based 2D-FEA to estimate the bone strength [110]. Thereby, they could show that the prediction of the impact force using subject-specific parameters can improve the prediction of hip fractures. Other approaches tried to develop FEA-models to predict the impact force of a sideways fall [96], [111]

Yet, the factor-of-risk does not describe an actual fracture risk but solely informs about the ratio between the fall-induced impact force and the bone strength. Furthermore, it requires the calculation of an impact force given a specific fall

scenario. However, as mentioned in Section 1.4.2, predicting how a fall will occur is challenging, which is why most mechanistic approaches model a standardised sideways fall. In summary, the majority of research that pursued a mechanistic approach did not predict a fracture risk but investigated factors that influence the impact force and assessed the correct classification of fracture cases [95], [110], [112]. Furthermore, the risk of falling, which is a significant component defining the risk of hip fractures, is often neglected.

A model published by Bhattacharya *et al.* accounts for these aspects [113]. The multi-scale model is based on the factor-of-risk, but integrates the fall dynamics and the risk of falling, allowing the prediction of a fracture risk within a year. It consists of three sub-models: (1) a model that derives the impact force given the varying fall dynamics of a sideways fall; (2) a model that estimates the force attenuation during the impact of the hip; and (3) an FEA model to estimate bone strength given different impact orientations. Subsequently, the fracture outcome of a specific fall using the factor-of-risk is evaluated. In a further step, probability distributions are assigned to the parameters describing the fall dynamics. By integrating this into a probability of different fall scenarios and with the use of a constant fall rate describing the risk of falling, the probability of a fracture during a year can be calculated.

1.6 A novel fragility hip fracture risk prediction model

In 2010, the framework of a novel hip fracture risk calculator addressing the above-mentioned challenges of mechanistic hip fracture risk models was published [8]. To our surprise, it gained only little attention in the fragility fracture research community. The model is based on an alternative approach to what is known in the literature, as it tries to model the complete physical process behind fracture events, allowing a functional understanding of different epidemiological observations of fragility hip fractures. In contrast to regression-based tools like FRAX® or purely mechanistic approaches as the factor-of-risk, the model is based on a mechanistic

stochastic framework, integrating the random aspects of a fall and the fall-induced impact force together with bone strength. In the next section, the framework of the model that was published by Schechner *et al.* in *Medical and Biological Engineering and Computing* is explained, its uniqueness is outlined, and aspects for further development are pointed out.

1.6.1 The Schechner model

The model presented by Schechner *et al.* is based on a Poisson process that describes the occurrence of a fall. A Poisson process is a stochastic process that models the arrival of an event in a finite time interval with a random variable following the Poisson distribution. It is defined as

$$P(k \text{ falls in } (0,T]) = \frac{(\lambda t)^k}{k!} e^{-\lambda t} \qquad k = 0, 1, 2, ... \tag{1.1}$$

with k as the number of falls, λ as the annual fall rate parameter, and t defining the finite time interval $(0, T]$. Hence, the probability of no fall reduces Equation (1.1) to

$$P(\text{no falls in } (0,T]) = e^{-\lambda T} \tag{1.2}$$

and the probability of at least one fall to

$$P(k \geq 1 \text{ fall in } (0,T]) = 1 - e^{-\lambda T} \tag{1.3}$$

In a second step, a random variable is introduced to model the conditional probability of the fall-induced impact force exceeding the femoral strength, so that

$$p_S = P(\text{Fracture}|\text{Fall}) = P(\text{Force}>\text{Strength}) \tag{1.4}$$

By combining the rate parameter λ and p_S, a thinned Poisson process characterised by $\lambda_{thinned} = \lambda \cdot p_S$ retains only the falls that result in a fracture. The thinned Poisson process is a Poisson process itself, and thus the probability of at least one fracture in the time period $(0, T]$ is given by

$$P(\geq 1 \text{ fracture in } (0,T]) = 1 - e^{-\lambda p_S T} \tag{1.5}$$

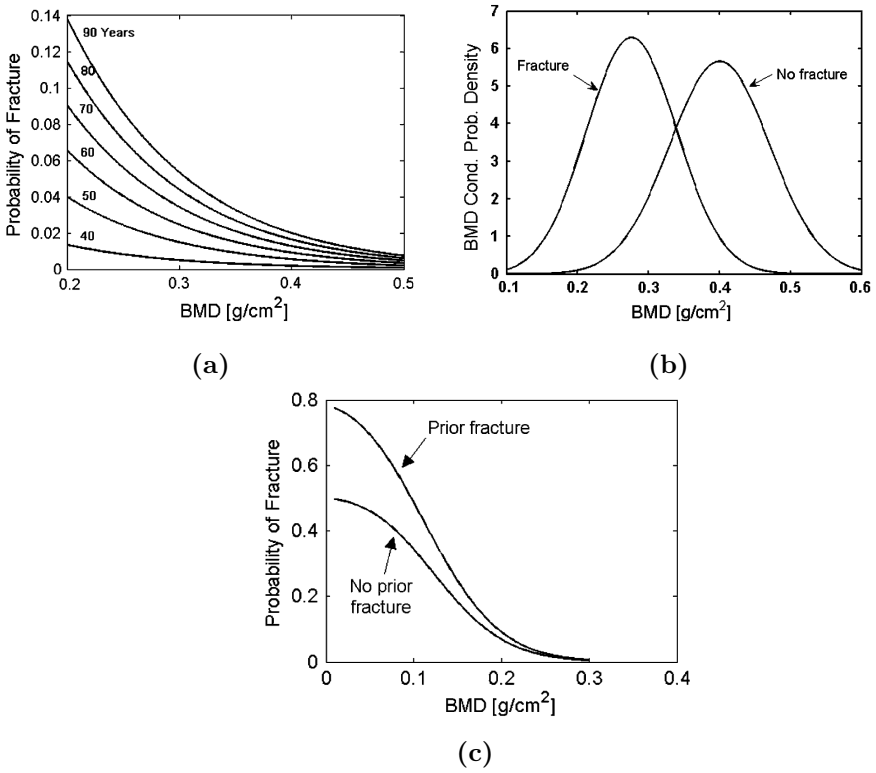

Figure 1.1: Figures from the original publication by Schechner *et al.* [8], showing different features of the model. (a) Fracture probability given age and BMD. (b) BMD distribution of fracture and non-fracture individuals. (c) The probability of a fracture given the state of a prior fracture. Reprinted with permission from the publisher.

The model is based on three additional assumptions. First, it assumes that p_S follows a Weibull distribution. Then, the fall rate λ is defined to be linearly increasing with age. And last, BMD is used as a bone strength surrogate. Without the use of any data, the model is able to describe several key observations about hip fractures from empirical data. It shows clearly that the risk of fracture is synergistically increasing with increasing age and decreasing BMD (FFigure 1.1a). Furthermore, by using a Bayesian modelling approach, it can be shown that the BMD distribution between individuals who fracture and individuals who do not fracture is strongly overlapping (Figure 1.1b). And last, by using the information about a fracture event in a previous time period as prior information, the model shows that the presence of such an event results in a higher risk of fracturing again when compared to no prior fracture (Figure 1.1c).

1.6.2 Further development of the Schechner model

The mechanistic stochastic framework for the prediction of hip fracture risk presented by Schechner *et al.* is a promising modelling approach. It reflects the whole mechanism involved in causing hip fractures by combining mechanistic and stochastic principles: It models the occurrence of falls and thus the risk of falling with a Poisson process; it assesses the lack of knowledge about how a fall will occur by modelling the probability of the impact force to exceed the femoral strength with a random variable; and it uses BMD as bone strength surrogate. Thereby, the model is able to reflect various key observations of hip fractures in empirical data and captures the intrinsic aspects of the risk of such a fracture.

To make the model clinically applicable to the individual, some aspects need to be further developed and refined. First, a model to estimate a personalised fall rate could be developed. Although the risk of falling is clearly dependent on age, numerous other risk factors exist that could improve the estimation of a fall rate, taking into account the personal circumstances and physical abilities of an individual. Then, instead of modelling the probability of the fall-induced impact force exceeding the femoral bone strength with a random variable, this aspect could be refined by integrating a mechanical impact force model that estimates a personalised impact force using subject-specific parameters. Instead, a stochastic distribution could be introduced to describe the fall dynamics that defines the magnitude of the impact force. Furthermore, bone strength could be estimated using QCT-based FEA instead of being derived from BMD. Lastly, insights into the stochastic distribution modelling the fall dynamics are required, as the Weibull distribution proposed by Schechner *et al.* was mainly chosen due to its simplicity and ability to model various shapes with the use of only two parameters.

1.7 AFFIRM-CT

The AFFIRM-CT (A Fragility Fracture Integrative Risk Method with CT-Recycling) project is a collaboration between the University of Bern and the University of Geneva with the overall goal of developing a mechanistic fragility fracture risk

calculator for the prediction of non-vertebral fragility fractures, specifically of the hip, with CT recycling. Other aspects of interest were the comparison of aBMD, QCT-FEA and high-resolution peripheral quantitative computed tomography (HR-pQCT) derived bone strength estimates, as well as the comparison between the synchronous and asynchronous calibration of CT images. With the aim of obtaining a data set that contains all required variables for testing the developed methods and the resulting fracture risk calculator, a prospective observational study was conducted starting in 2021. Individuals aged 65 and older who underwent a CT scan of the upper body or abdomen with the hip visible at the University Hospitals of Bern or Geneva were eligible for study participation. Exclusion criteria were a life expectancy of less than a year, a prior hip fracture, being bedridden or in a wheelchair, cognitive impairment, living in a nursing home or institution, and bone diseases. Eligible participants were contacted by phone call or letter for enrolment. Subsequently, participants were invited for a single visit to the respective medical centre. During the visit, the participants underwent a DXA scan to assess the BMD of the lumbar spine and the hip. A subgroup of the participants in Bern underwent an HR-pQCT scan of the radius and tibia. At the same time, many variables and tests were assessed and recorded. The medical history, including comorbidities, medication, the number of falls in the previous 12 months and the history of fractures, were assessed. The 10-year probability of major osteoporotic fractures and hip fractures was calculated with FRAX®. Furthermore, various physical performance tests were carried out, such as gait speed, Five Times Sit-to-Stand test (FTSTS), Short Physical Performance Battery (SPPB), hand grip strength (HGS) or visual acuity. Falls Efficacy Scale - International (FES-I) was used to evaluate the fear of falling. Cognitive impairment was assessed with the Mini Mental State Examination. The soft tissue stiffness in the area of the greater trochanter was measured using a handheld soft tissue indentation device (MyotonPro). Furthermore, the participants were encouraged to wear an activity tracker for 7 days, measuring the movement of the wrist with an accelerometer (Axivity AX3). After the examination, individuals were followed up with phone

calls for at least 18 months to assess incident falls, incident fractures, and start of osteoporosis treatment in case of an osteoporosis diagnosis.

2
Thesis Aims

The overall aim of this thesis was to personalise and further develop the fragility hip fracture risk model presented by Schechner *et al.* [8]. To this end, the objectives are three-fold.

Various fall risk assessment tools exist to identify individuals at risk of falling. However, most of these are based on binary logistic regressions, classifying individuals as at risk of falling or not at risk of falling. However, as mentioned in Section 1.4.1, estimating a rate might be more appropriate to identify fallers. Furthermore, the Poisson process describing the occurrence of a fall requires a rate parameter. Since the rate parameter solely included an age dependency, although many other risk factors for falling exist, the first aim was to develop a model for the estimation of a personalised fall rate considering additional risk factors beyond age.

The model assumes a Weibull distribution that describes the probability of the fall-induced impact force exceeding the femoral bone strength derived with BMD. With this approach, the mechanical aspects of the fall-induced impact on the hip are modelled together with the stochastic aspects of the fall dynamics. However, as described in Section 1.4.2, various methods exist to calculate the fall-induced impact force using subject-specific parameters. Consequently, the second aim was to refine this aspect by introducing a mechanistic model that calculates a personalised impact force. Thereby, the model should be able to derive the full

range of possible impact forces given the fall dynamics. Furthermore, bone strength estimates from QCT-based FEA instead of BMD will be used. This refinement allows for the assessment of whether the impact force exceeds the femoral bone strength in a mechanical context. The stochastic aspects of a fall will then be modelled by introducing a probability distribution that describes the probability of different fall scenarios and the fall dynamics.

The third aim of this thesis is the integration of the personalised fall rate and impact force model into a novel fragility hip fracture risk calculator. For proof of concept and with the aim to demonstrate how the model functions, the calculator will be applied to clinical data from the AFFIRM-CT study, and the sensitivity of the parameters on various output values will be assessed.

The next four Chapters present work conducted to fulfil the above-presented aims. Thereby, Chapter 3 - Chapter 5 are about the development of the personalised fall rate model, and Chapter 6 introduces the personalised impact force model together with the novel fragility hip fracture risk calculator.

3

The development of a personalized fall rate prediction model in community-dwelling older adults: a negative binomial regression modelling approach

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Abstract

Background Around a third of adults aged 65 and older fall every year, resulting in unintentional injuries in 30% of the cases. Fractures are a frequent consequence of falls, primarily caused in individuals with decreased bone strength who are unable to cushion their falls. Accordingly, an individual's number of experienced falls has a direct influence on fracture risk. The aim of this study was the development of a statistical model to predict future fall rates using personalized risk predictors.

Methods In the prospective cohort GERICO, several fall risk factor variables were collected in community-dwelling older adults at two time-points four years apart (T1 and T2). Participants were asked how many falls they experienced during 12 months prior to the examinations. Rate ratios for the number of reported falls at T2 were computed for age, sex, reported fall number at T1, physical performance tests, physical activity level, comorbidity and medication number with negative binomial regression models.

Results The analysis included 604 participants (male: 122, female: 482) with a median age of 67.90 years at T1. The mean number of falls per person was 1.04 and 0.70 at T1 and T2. The number of reported falls at T1 as a factor variable was the strongest risk factor with an unadjusted rate ratio [RR] of 2.60 for 3 falls (95% confidence interval [CI] 1.54 to 4.37), RR of 2.63 (95% CI 1.06 to 6.54) for 4 falls, and RR of 10.19 (95% CI 6.25 to 16.60) for 5 and more falls, when compared to 0 falls. The cross-validated prediction error was comparable for the global model including all candidate variables and the univariable model including prior fall numbers at T1 as the only predictor.

Conclusion In the GERICO cohort, the prior fall number as single predictor information for a personalized fall rate is as good as when including further available fall risk factors. Specifically, individuals who have experienced three and more falls are expected to fall multiple times again.

Trial registration ISRCTN11865958, 13/07/2016, retrospectively registered.

Keywords Falls, Fall rate, History of falls, Prediction, Count data

3.1 Background

Falls contribute substantially to increased morbidity and mortality in older people. Around 25—30% of persons aged 65 and older fall every year, and this number is increasing with advancing age [44], [115]. Approximately a third of all falls result in an injury [48], ranking falls as the leading cause of unintentional injuries and injury-related deaths [44], [52], [53], [54], [116]. Thereby, fractures account for the most frequent consequence leading to disability [51]. While 5—15% of falls result in a fracture, the share of non-vertebral fractures caused by falls ranges between 59 – 96% and is site dependent [117]. Individuals who suffer from a fracture after falling are likely affected by decreased bone strength and are unable to cushion the fall [55]. Accordingly, the number of falls occurring to an individual influences the fracture risk [118]. In a meta-analysis including three cohorts, it was shown that the number of prior falls is improving fracture prediction over current used fracture risk assessment tools such as FRAX [58]. Accordingly, predicting not only the risk of falling but how many times an individual is expected to fall could improve fracture prediction in older adults.

Risk factors that have been associated with falling include increasing age, female gender, musculoskeletal deficits, gait and balance problems, a history of falls, fear of falling, vision impairment, cognitive deficits, urinary incontinence, medication, and comorbidities amongst many others [59], [60], [61], [62], [119]. To examine the risk of falling, various fall risk assessment tools and screening methods have been developed. A detailed overview of existing tools is provided in several reviews and meta-analyses [60], [64], [65], [66], [120], [121], [122], [123]. In summary, the assessments usually consist of performance tests and/or questionnaires that are designed to identify individuals at risk for falling. Thereby, when exceeding a defined threshold score value, individuals are considered as at risk of falling. So far, no single tool has been sufficient to successfully discriminate between fallers and non-fallers.

The association between fall risk factors and falling is often reported in the form of odds ratios derived with binary logistic regression. An alternative to measure the association are rate ratios. For this statistical method, not only

the information whether a fall occurred or not is needed but the number of falls per individual is required. An expected fall rate can then be calculated. Count regression models belong to the family of generalized linear models and are used to estimate rates and rate ratios.

To our knowledge, only few studies have been conducted analysing the association between fall number and risk factors in terms of rate ratios [124], [125], [126]. Accordingly, the aim of this study was to develop a statistical model using a count regression approach for fall rate prediction and to investigate associations between the fall number and different fall risk factors for community-dwelling older adults.

3.2 Methods

3.2.1 Reporting guidelines

This publication followed the Transparent Reporting of a multivariable prediction model for individual Prognosis Or Diagnosis (TRIPOD) [127]. The completed checklist is available in the supplementary materials.

Study participants

The Geneva Retirees Cohort (GERICO) is a prospective cohort study conducted between 2008 and 2018 to identify risk factors for fall and fracture risk prediction in retired workers in the Geneva area (`www.isrctn.com/ISRCTN11865958`). From 2008 to 2011, healthy community-dwelling older adults were recruited using different strategies such as local newspaper advertisement, targeted mass mailing and advertisement at large local companies. After baseline examination (T0), participants were followed up the first time after 4 years (T1), and a second time after another 4 years (T2). Participants included in this study were of both sexes, aged between 63 and 67, around the time of their retirement, and living in the rural or urban Geneva area. Exclusion criteria were major comorbidities, in particular cancer treated within the last 5 years, chronic renal failure, liver or lung disease, corticosteroid therapy, primary hyperparathyroidism, Paget disease of bone, malabsorption or any neurological or musculoskeletal condition affecting

bone health. The complete study design has been described previously [128], [129]. The present analysis included all participants that completed the two follow-up examinations at T1 and T2. The flow of participants in the study is presented in Figure 3.1. The study protocol was approved by the University Hospitals Research Ethics Commission and written informed consent was provided by all participants.

3.2.2 Sample size

Sample size calculation for the GERICO cohort was based on the primary outcome of the study, the number of incident fractures. No specific sample size calculation for the present analysis was conducted. All participants that completed the two follow-up visits at T1 and T2 were included in the current analysis (see Figure 3.1).

3.2.3 Variable selection

All covariates recorded in the GERICO cohort that have been associated with the risk of falling in literature and that are easily measurable (e.g., not requiring special equipment) and applicable in a clinical setting were included in the present analysis.

3.2.4 Outcome

The number of falls was the outcome of interest. Participants were asked whether they had experienced any falls during the 12 months prior to the examination at T1 and T2 (also referred to as prior falls). The number of prior falls, the consequences (fracture, injurious fall requiring medical attention, injurious fall not requiring medical attention, uninjurious fall), and the activity during the fall (locomotion, transfer, run, sport, height/ladder, other) were recorded. A fall was defined as an event resulting in a person coming unintentionally to rest on the ground, floor, or any lower level. Extreme observations such as an individual falling five times and more, for example during sports or recreational activities, were not excluded since every single fall has the potential to result in an injurious outcome such as a fracture. The prior fall number reported at T2 was the dependent variable.

3.2.5 Predictors

History of falls

The number of experienced falls prior to T1 was included as predictor for the history of falls.

Demographic and anthropometric variables

Age, sex, standing height and body weight were recorded at follow-up examinations T1 and T2, and body mass index (BMI) was calculated accordingly.

Physical performance tests

The Short Physical Performance Battery (SPPB) is a test to assess lower extremity function in older adults [130]. Shortly, SPPB includes a balance test, the measurement of normal gait speed over 4m distance, and the Five Times Sit-to-Stand test. Every subtest scores 4 points, reaching maximum 12 points. Hand grip strength (HGS) was measured with the JAMAR® Hand Dynamometer device. Participants were sitting on a chair with the elbow at a 90° flexion position. Three measurements were performed for each hand and the maximum value of the dominant or non-dominant hand was chosen. The one-legged stance test (OLST), also known as single-legged stance test, is a test assessing balance. Participants had to stand on one leg with crossed arms and eyes open. The test was stopped when reaching 45s. If the maximum time was not reached, a second measurement was obtained. Both legs were tested, and the best performance of the dominant leg was used for analysis. No distinction between participants requiring one or two attempts to reach the maximum time was made. All physical performance tests were obtained both at T1 and T2.

Physical activity

Physical activity was evaluated both at T1 and T2 by a face-to-face questionnaire that uses an inventory of 45 activities to estimate the time spent on usual walking, cycling, stair climbing, organized sports, and recreational activity over the past 12 months. The collected data were converted to physical activity energy

expenditure (kilocalories (kcal) per day) using validated formulas developed by Ainsworth *et al.* [131].

Comorbidities and medication

Age unadjusted Charlson's comorbidity index (CCI) [132], the number of comorbidities and the number of medications were recorded at T2 only.

3.2.6 Statistical analysis

Handling of predictors

Age and BMI were included from follow-up T1. Physical performance tests (SPPB, HGS and OLST) were also included from follow-up T1 to avoid retrodiction. Physical activity was included from follow-up visit T2 since it covers the same period of observation as the outcome variable. CCI, comorbidity and medication number were included from follow-up T2. The continuous variables (age, BMI, HGS, physical activity, comorbidity and medication number) were standardized to a mean of zero and a standard deviation of one, resulting in the rate ratio estimates corresponding to a standard deviation increase. HGS was standardised separately for sex due to a big difference in the corresponding mean. The number of prior falls at T1 was treated as a factor variable with levels 1, 2, 3, 4 and ≥ 5. SPPB, OLST and CCI were dichotomized because of their irregular and unbalanced distribution. SPPB score was dichotomized into the intervals [0, 9] and [10, 12]. The time score reached in the OLST was dichotomized into the three intervals [1, 20], [21, 40] and [41, 45]. CCI was dichotomized into the intervals [0, 1] and [2, 8].

Missing data

We conducted a complete case analysis but report the number of missing values for all variables as well as the number of participants with missing values.

Descriptive statistics

All variables were summarized with the median and the interquartile range (IQR). Additionally, the range and the mean number of prior falls at T1 and T2 were

derived. For factor variables, the number of participants and the percentage per category respectively intervals were calculated.

Model fit

The Poisson regression is the best-known count regression model and assumes equidispersion of the count data (the mean equals the variance). However, most count data is overdispersed (the variance exceeding the mean). An alternative distribution that can model the overdispersion is the negative binomial distribution. It is described with an additional dispersion parameter that allows the variance to exceed the mean. Additionally, the negative binomial distribution is suitable to model recurrent events such as multiple falls per person by modelling the Poisson mean with a gamma distribution, accounting for population heterogeneity [69], [71]. In a study analysing fall count data from four cohorts, the negative binomial distribution performed best to model such data [71].

Accordingly, rate ratios (RRs) were computed with negative binomial regression models using the log link and corresponding 95% Wald confidence interval (CI) were calculated. Three different model types were fit: (1) 11 univariable models including every predictor separately, (2) a global model, including all available predictors described above, and (3) a subset model including age, sex, fall number reported at T1, SPPB, physical activity level and CCI. The covariates of the subset model were selected so that risk factors from different domains were represented while requiring as little time as possible when applied in a clinical setting. The number of falls reported at T2 was defined as the dependent variable. The generalized variance inflation factor (GVIF) was calculated for the global and subset model to detect the presence of multicollinearity among predictors [133]. GVIF is comparable to the variance inflation factor (VIF) when transformed by $()^{-\frac{1}{2}(n-p)}$. A transformed GVIF of ≤ 2.5 is acceptable [134]. Dispersion statistics was calculated with Pearson's Chi2 dispersion statistic given as $\frac{1}{(n-p)} \sum_{i=1}^{n} \frac{e_i}{Var(y_i)}$ with n as the number of observations, p as the number of parameters included in the model [135]. A dispersion statistic greater than one indicates overdispersion, resulting

in underestimation of standard errors of coefficient estimates and subsequently in too narrow confidence intervals [136].

To ensure that observations with high fall numbers do not bias the coefficient estimates, all models were re-fitted excluding observations with 5 or more falls either at T1 or T2.

Model comparison and prediction accuracy

Models were compared with the log-likelihood and the Bayesian information criteria (BIC). The error in a regression model is defined as $e_i = y_i - \hat{y}_i$ with y_i as the reported number of falls and $\hat{y}_i$ as the models predicted number of falls for the ith individual. Predictive performance was measured with the logarithmic score, the Brier score and the mean absolute error [137]. Internal model validation was conducted by calculating the mean absolute error for the test data with leave-one-out cross-validation. In count regression models with a small expected mean, residuals are usually not normally distributed [138]. Therefore, we also report the median and the interquartile range of the cross-validated residuals. Additionally, a marginal calibration diagram was derived to compare the actual number of individuals per fall number category at T2 to the predicted number of persons per fall number category based on the leave-one-out-prediction distribution in form of a hanging rootogram [137], [139].

Software

All statistical analysis was computed with R version 4.2.2.

3.3 Results

Nine hundred fifty-four participants were included and participated in the baseline examination at T0. Thereof, 644 participants completed the two follow-up examinations at T1 and T2. 40 (6.2%) participants were excluded due to missing data, resulting in 604 observations included in the analysis (Figure 3.1). Examination of excluded observations revealed no difference to the data used for analysis.

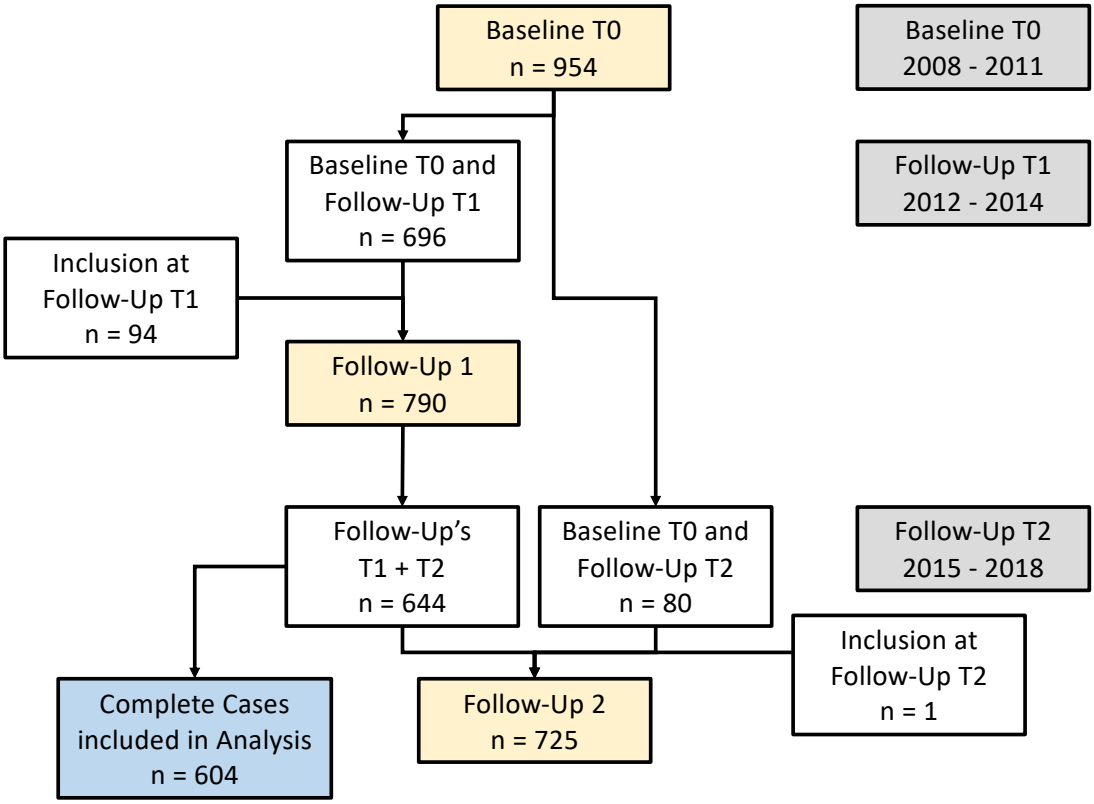

Figure 3.1: Flow of study participants in the GERICO study.

With a percentage of 79.8, most of the participants were female. Median (IQR) age was 67.90 (66.50, 69.03) years at T1, and median (IQR) BMI was 24.79 (22.26, 27.70) kg/m2. The median (IQR) SPPB score was 12.00 (12.00, 12.00) with 94.0% of observations reaching 10—12 points. Median (IQR) HGS was 28.60 (25.10, 33.70) kg. The difference in sex was 17.70 kg, resulting in a median (IQR) of 27.05 (24.33, 29.98) kg for female and 44.75 (40.20, 50.68) kg for male participants. Median (IQR) OLST time was 35.45 (17.22, 45.00) seconds. Median (IQR) kcal/day as a measure of physical activity was 291.29 (196.54, 434.27). The majority of CCI were observed in the interval 0.00 – 1.00 (94.9%). Median comorbidity and medication number were 2.00 with an IQR of (1.00, 3.00) and (1.00, 4.00), respectively. Table 3.1 presents the summary of all variables included in the analysis in detail.

Table 3.1: Summary of predictor variables and the outcome variable, the fall number at T2.

Variable	**Level and measure**	**Value**	**NA's**
Sex	Female, n (%)	482 (79.8)	0
	Male, n (%)	122 (20.2)	
Assessed at T1			
Fall number	mean	1.04	4
	median (IQR)	0.00 (0.00, 1.00)	
	min - max	0 - 20	
	0 falls, n (%)	310 (51.3)	
	1 falls, n (%)	174 (28.8)	
	2 falls, n (%)	57 (9.4)	
	3 falls, n (%)	31 (5.1)	
	4 falls, n (%)	9 (1.5)	
	$\geq$ 5 falls, n (%)	23 (3.8)	
Age [years]	median (IQR)	67.90 (66.50, 69.03)	0
BMI [kg/m^2]	median (IQR)	24.79 (22.26, 27.70)	1
SPPB (score 0 - 12)	median (IQR)	12.00(12.00, 12.00)	16
	[0 - 9], n (%)	36 (6.0)	
	[10 - 12], n (%)	568 (94.0)	
HGS [kg]	median (IQR)	28.60 (25.10, 33.70)	16
OLST [s]	median (IQR)	35.45 (17.22, 45.00)	17
	[1 - 20], n (%)	177 (29.3)	
	[21 - 40], n (%)	149 (24.7)	
	[41 - 45], n (%)	278 (46.0)	
Assessed at T2			
Fall number	mean	0.70	8
	median (IQR)	0.00 (0.00, 1.00)	
	min - max	0 - 24	
	0 falls, n (%)	370 (61.3)	
	1 falls, n (%)	152 (25.2)	
	2 falls, n (%)	55 (9.1)	
	3 falls, n (%)	11 (1.8)	
	4 falls, n (%)	8 (1.3)	
	$\geq$ 5 falls, n (%)	8 (1.3)	
Physical activity [kcal/-day]	median (IQR)	291.29 (196.54, 434.27)	2
CCI (score)	median (IQR)	0.00 (0.00, 0.00)	1
	[0 - 1], n (%)	573 (94.9)	
	[2 - 8], n (%)	31 (5.1)	
Comorbidity (number)	median (IQR)	2.00 (1.00, 3.00)	0
Medication (number)	median (IQR)	2.00 (1.00, 4.00)	0

Abbreviations: NA's Missing data; *IQR* Interquartile range; *n* Number; *%* Percentage; *BMI* Body mass index; *SPPB* Short physical performance battery; *HGS* Hand grip strength; *OLST* One-legged stance test; *CCI* Charlson's comorbidity index

The mean fall number at T1 was 1.04 and decreased to 0.70 falls at T2. At T1, 48.7% of participants reported to have fallen at least once in the previous 12 months,

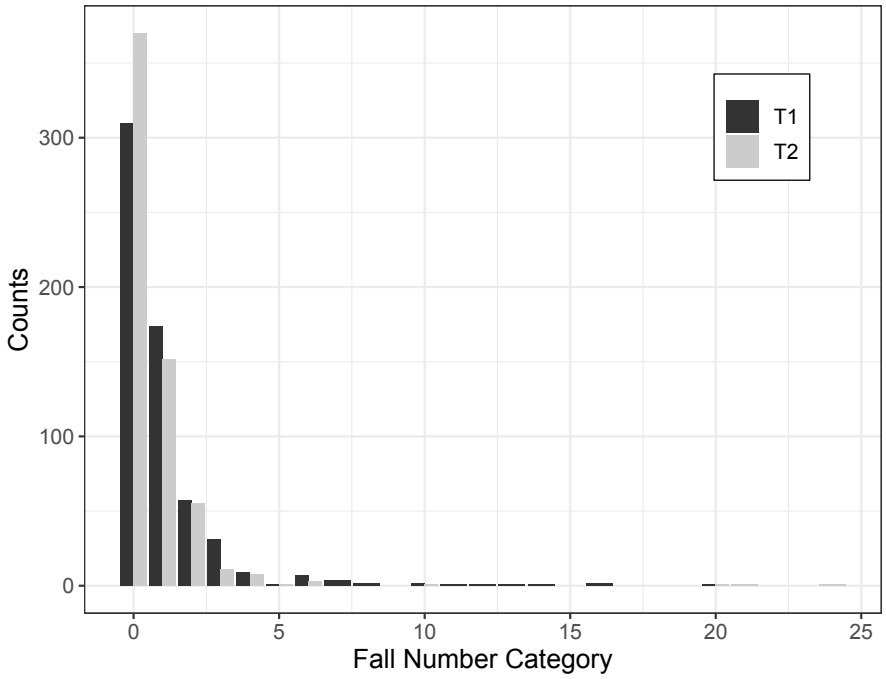

Figure 3.2: Distribution of the reported fall numbers at T1 and T2.

and 19.9% fell multiple times. This number decreased to 38.7% experiencing at least one fall and 13.6% falling multiple times at T2. Figure 3.2 presents the number of individuals per fall number category at T1 and T2. The reported numbers ranged from 0 to 20 for T1 and from 0 to 24 for T2. 220 participants reported no falls at T1 and T2, and 144 reported falls at T1 and T2. 150 persons fell before T1 but not before T2, and 90 participants experienced no falls prior to T1 but reported falls at T2. The total reported fall number was 630 at T1 and 425 at T2. At T1 and T2, in 9% of the cases, the falls resulted in injuries that required medical attention. 34% at T1 and 36% at T2 caused injuries requiring no medical attention and 54% at T1 and 50% at T2 had no consequences. 2% of the falls caused a fracture at T1. This number increased to 4% at T2. 53% of the falls reported at T1 and 50% at T2 occurred during locomotion or transfer, while 36% at T1 and 44% at T2 happened during running or sports activities. Falls from heights or ladders accounted for 1% at T1 and 4% at T2 of the falls. The rest of the cases was unclear or not reported.

RR estimates and 95% CI of the predictors for the univariable models, the global and the subset model are presented in Table 3.2. Reference levels of factor variables are reported with a RR = 1.00. For the univariable models, the fall number at T2

was associated with female sex (RR 0.67, 95% CI: 0.48 to 0.94, male sex as reference category); with the prior fall number reported at T1 (e.g., ≥ 5 falls: RR 10.19, 95% CI: 6.25 to 16.60, 0 falls as reference category); with the HGS (RR 1.16, 95% CI: 1.01 to 1.33); with the OLST when reaching 21 – 40s (RR 0.59, 95% CI: 0.40 to 0.86, 41 – 45s as reference category); with the physical activity level (RR 1.29, 95% CI: 1.13 to 1.47); with the CCI when scoring 2 – 8 (RR 2.08, 95% CI: 1.18 to 3.67, a score of 0 – 1 as reference category); and with the number of medication (RR 0.82, 95% CI: 0.71 to 0.95). In the global model, associations were found for the prior fall number at T1 (e.g., 3 falls: RR 2.67, 95% CI: 1.61 to 4.45, 0 falls as reference category); and the number of medication (RR 0.82, 95% CI: 0.68 to 0.98). For the subset model, the number of falls at T2 was associated with the prior fall number at T1 (e.g., 4 falls: RR 2.69, 95% CI: 1.08 to 6.65, 0 falls as reference category). All other predictors were not associated with the fall number reported at T2.

Figure 3.3 depicts the rate ratios and their 95% CI presented in Table 3.2, visualizing the differences in the estimates between the models.

The baseline rates represent the expected fall number for an individual belonging to the reference category of factor variables (e.g., sex: male), or belonging to the mean value of a continuous variable. For the univariable models, the baseline rate ranged from 0.67 to 0.95 (supplementary material, Table 3.4). The baseline rate for the global model was 0.44 (95% CI 0.31 to 0.64), for the subset model 0.44 (95% CI 0.31 to 0.62), and for the univariable model including the number of falls at T1 0.42 (95% CI 0.35 to 0.52).

The coefficient estimates of the models excluding all observations with ≥ 5 falls at T1 or T2 were comparable to the here presented results (supplementary material, Table 3.5).

The following results are only presented for the univariable model including fall number at T1 as factor variable (referred to as falls model), the global model, and the subset model. The complete list of all univariable models can be found in the supplementary material (supplementary material, Table 3.4).

Table 3.2: Rate ratios and 95% confidence interval for the univariable, the global and the subset models.

Variables	**Univariable**	**Global**	**Subset**
Sex			
Male	1.00	1.00	1.00
Female	0.67 (0.48, 0.94)	0.94 (0.67, 1.32)	0.94 (0.67, 1.31)
Assessed at T1			
Age [years]	1.07 (0.92, 1.23)	1.08 (0.94, 1.23)	1.07 (0.94, 1.22)
Fall number			
0	1.00	1.00	1.00
1	1.67 (1.23, 2.27)	1.65 (1.22, 2.23)	1.64 (1.21, 2.22)
2	1.16 (0.71, 1.90)	1.20 (0.74, 1.95)	1.20 (0.74, 1.96)
3	2.60 (1.54, 4.37)	2.67 (1.61, 4.45)	2.56 (1.53, 4.31)
4	2.63 (1.06, 6.54)	3.31 (1.38, 7.98)	2.69 (1.08, 6.65)
≥ 5	10.19 (6.25, 16.60)	7.70 (4.74, 12.51)	8.92 (5.47, 14.57)
BMI [kg/m^2]	0.95 (0.82, 1.10)	0.96 (0.83, 1.10)	-
SPPB (score 0 - 12)			
[10 - 12]	1.00	1.00	1.00
[0 - 10]	0.82 (0.44, 1.53)	0.88 (0.49, 1.57)	0.94 (0.53, 1.65)
HGS [kg]	1.16 (1.01, 1.33)	1.08 (0.95, 1.22)	-
OLST [s]			
[41 - 45]	1.00	1.00	-
[1 - 20]	1.11 (0.81, 1.54)	1.17 (0.85, 1.62)	-
[21 - 40]	0.59 (0.40, 0.86)	0.71 (0.49, 1.01)	-
Assessed at T2			
Physical activity [kcal/day]	1.29 (1.13, 1.47)	1.11 (0.97, 1.26)	1.12 (0.98, 1.28)
CCl (score)			
[0 - 1]	1.00	1.00	1.00
[2 - 8]	2.08 (1.18, 3.67)	1.40 (0.81, 2.43)	1.38 (0.81, 2.36)
Comorbidity (number)	0.99 (0.86, 1.14)	1.18 (0.99, 1.41)	-
Medication (number)	0.82 (0.71, 0.95)	0.82 (0.68, 0.98)	-

Reference levels of factor variables are indicated with a rate ratio = 1.00. For continuous variables, rate ratios correspond to a standard deviation increase.
Abbreviations: BMI Body mass index; *SPPB* Short physical performance battery; *HGS* Hand grip strength; *OLST* One-legged stance test; *CCI* Charlson's comorbidity index

Table 3.3: Model comparison and prediction measures for the global, the subset, and the univariable falls model.

Model	**LL**	**BIC**	**LS**	**BS**	**MAE**	**CV MAE**	**CV median absolute error (IQR)**
Global	-630.79	1376.85	1.04	-0.47	0.79	0.83	0.51 (0.38, 0.72)
Subset	-637.59	1352.03	1.06	-0.46	0.81	0.84	0.53 (0.39, 0.69)
Falls	-640.75	1326.33	1.07	-0.45	0.82	0.84	0.50 (0.42, 0.71)

Abbreviations: LL Log-likelihood; *BIC* Bayesian information criteria; *LS* Logarithmic score; *BS* Brier score; *MAE* Mean absolute error; *CV* Cross-validated; *IQR* Interquartile range

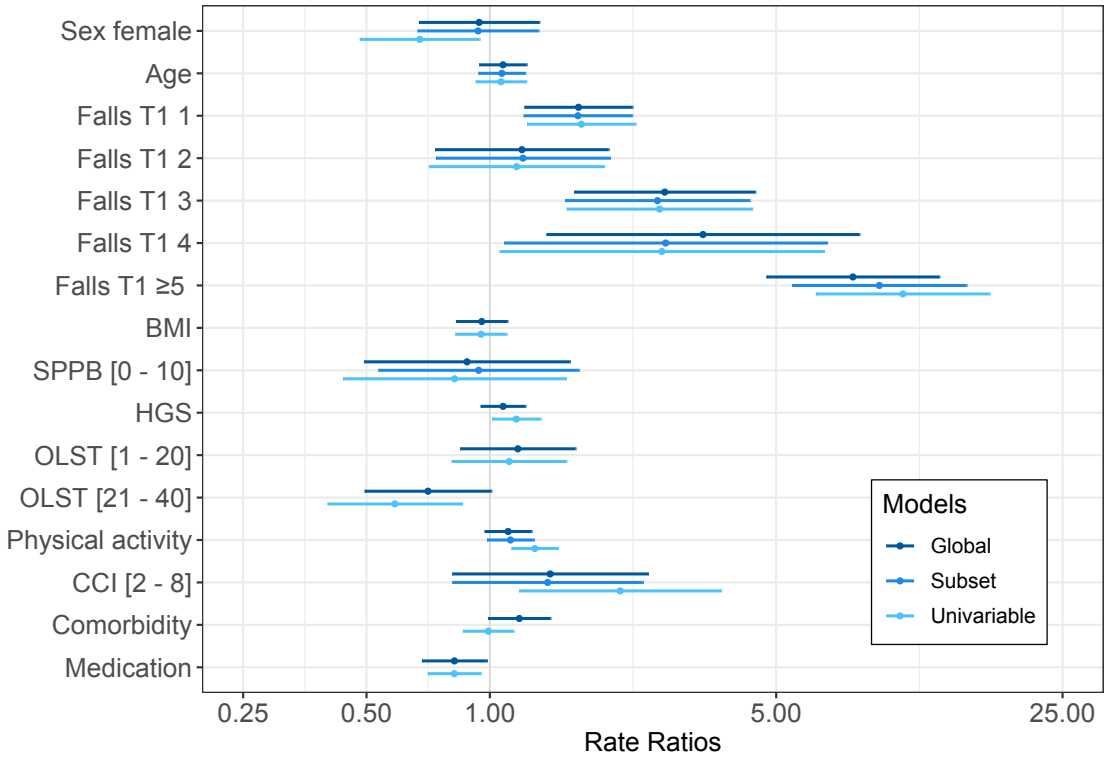

Figure 3.3: Rate ratios presented in a forest plot for the univariable, the global and the subset models. Confidence bands correspond to 95% confidence intervals. For continuous variables, rate ratios correspond to a standard deviation increase. Reference levels for factor variables: male sex; Falls T1 0; SPPB [11, 12]; OLST [41-45]; CCI [0 - 1]. *Abbreviations: BMI* Body mass index, *SPPB* Short physical performance battery, *HGS* Hand grip strength, *OLST* One-legged stance test, *CCI* Charlson's comorbidity index

Measures for model fit and model performance of the global, subset and the fall model are shown in Table 3.3. The log-likelihood was best for the global model followed by the subset model and lowest for the falls model (global: -630.79, subset: -637.59, falls: -640.75). Considering the BIC, the falls model performed best (global: 1376.85, subset: 1352.03, falls: 1326.33). The logarithmic score was best for the global model, and similar for the subset and falls model (global: 1.04; subset: 1.06; falls: 1.07), and the Brier score was also best for the global model (global: -0.47; subset: -0.46; falls: -0.45). The mean absolute error was lowest for the global model, followed by the subset and the falls model (global: 0.79; subset: 0.81; falls: 0.82). The cross-validated mean absolute error was for all models slightly higher compared to the apparent error (global: 0.83; subset: 0.84; falls: 0.84). The median absolute error was lower compared to the mean absolute error, showing that the

residuals are not normally distributed and skewed towards zero. It was again comparable for all three models (global: 0.51; subset: 0.53; falls: 0.50). All here presented measures for the other univariable models can be found in Table S1 in the supplementary material. In summary, none of the other models performed as good as the global, the subset or the falls model.

Figure 3.4 presents the models' marginal calibration plots, comparing the number of participants per reported fall number category at T2 (represented by the grey bars) to the predicted number of individuals per fall number category (red line) of (a) the global, (b) the subset and (c) the falls model based on the cross-validated leave-one-out prediction distribution as hanging rootograms. Deviations between actual and predicted numbers become visible when focusing on the position of the bar's lower ends: bars reaching the negative frequency range indicate underestimation of the predicted counts, while bars not reaching the x-axis represent overestimated frequencies. The predicted size of individuals per fall number category were similar for all three models. The models underestimated the number of individuals who experienced two and three fall events, while the number of individuals with zero falls and higher fall numbers were overestimated. Extreme events (e.g., an individual falling 20 times) could not be accurately predicted.

Pearson's Chi2 dispersion statistic was comparable for the three models (global: 1.05, subset: 1.05, falls: 1.08). GVI$F^{-\frac{1}{2}(n-p)}$ was smaller than 2.5 for all covariates in the global and subset model, indicating no multicollinearity. To understand how the models are used for predicting an individual's fall rate, this is demonstrated for the subset model. The rate ratios presented in Table 3.2 are reported on the response scale. To make predictions, it is easiest to transform the rate ratios to the

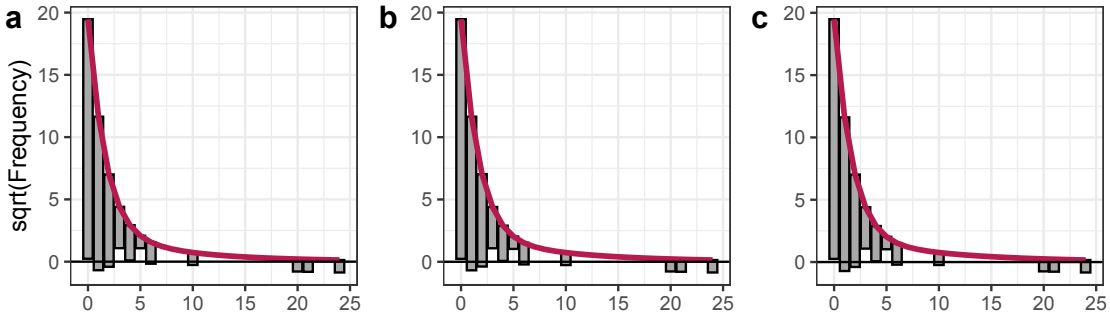

Figure 3.4: Hanging rootograms for (**a**) the global, (**b**) the subset and (**c**) the univariable fall model. Hanging rootograms as marginal calibration plots show the deviations between the actual (grey bars) and predicted (red line) number of individuals per fall number category.

link scale by taking the log. Following form that, the subset model writes as

$$\begin{aligned}\log(\text{fall rate}) = &\log(0.44) + \log(0.94) \cdot I_{Sex=female} \\ &+ \log(1.07) \cdot Age_{standardised} + \log(1.64) \cdot I_{Falls=1} \\ &+ \log(1.20) \cdot I_{Falls=2} + (2.56) \cdot I_{Falls=3} \\ &+ \log(2.69) \cdot I_{Falls=4} + \log(8.92) \cdot I_{Falls\geq 5} \\ &+ \log(0.94) \cdot I_{SPPB=[0-10]} + \log(1.12) \cdot Activity_{standardised} \\ &+ \log(1.38) \cdot I_{CCI=[2-8]}\end{aligned}$$

with

$$I_{condition} = \begin{cases} 1 & \text{condition is true} \\ 0 & \text{otherwise} \end{cases}$$

As an example, the fall rate of a female individual with a standardized age of 1.5, having experienced 3 falls within the last 12 months, reaching an SPPB score of 11, with a standardized physical activity level of -1.5 and a CCI of 3 calculates as

$$\begin{aligned}\log(\text{fall rate}) = &\log(0.44) + \log(0.94) \cdot 1 \\ &+ \log(1.07) \cdot 1.5 + \log(1.64) \cdot 0 \\ &+ \log(1.20) \cdot 0 + (2.56) \cdot 0 \\ &+ \log(2.69) \cdot 0 + \log(8.92) \cdot 0 \\ &+ \log(0.94) \cdot 0 + \log(1.12) \cdot (-1.5) \\ &+ \log(1.38) \cdot 1\end{aligned}$$

simplifying to

$$\text{fall rate} = 0.44 * 0.94 * 1.11 * 2.56 * 0.84 * 1.38 = 1.36$$

3.4 Discussion

This analysis examined the association of different fall risk factors and the number of falls reported within 12 months, and aimed to develop a model for personalized fall rate prediction. In contrast to most other cohort analyses, we derived rate ratios using negative binomial regression models.

The mean number of falls per person in the GERICO cohort was higher compared to other studies. For example, the federal office of Switzerland reported that 1 out of 4 adults aged 65 and older experienced a fall [115], while a questionnaire in the US resulted in 15.9% of people experiencing a fall [48]. However, the GERICO cohort is a comparably young and fit cohort, and many falls occurred during sports and recreative activities.

The main finding of our analysis is the strong association between the history of falls and future falls. Thereby, the more falls an individual experienced, the stronger the association was. This result is consistent with literature, reporting recurrent fallers to have a higher odds-ratio to fall again when compared to one-time fallers [61]. Interestingly, the rate ratio for falling when having experienced two previous falls is lower compared to one or three previous falls. While falling once might happen by chance, individuals who fell twice possibly become attentive to the risk of falling and initiate preventive measures. However, after having experienced three or multiple falls, the ability to prevent future fall events might be insufficient.

The association of other predictors in the univariable models with the number of falls was only partly congruent with other studies, reviews and meta-analyses assessing the risk of falling in community-dwelling older adults. We want to point out that the direct comparison with other cohort analyses must be handled with care, since differences in study design, participant's characteristics, assessment of tests and analysis methods need to be considered.

Compared to men, female participants were expected to fall less, while in literature the opposite is reported [61]. No association was found between age and the fall number in the GERICO cohort, although increasing age is a widely recognized risk factor for falls [44], [61]. Actually, the total number of reported falls in the previous 12 months as well as the percentage of fallers decreased from T1 to T2 in spite of 4 years advancing age. With its rather young median age and narrow age range, the GERICO cohort might not be suitable to detect such a relationship. A longer follow-up time and a wider age range might be required. In addition, we assume that the decrease in fall number and percentage from T1 to T2 reflects a decrease in recreational and sports activity of the study participants, resulting in fewer falls. Physical performance measures were also not associated to falls as reported in literature. The SPPB was not predictive for falls. However, this is not surprising when considering that more than 90% of the participants in the GERICO cohort scored 10—12 points. In another study examining the predictive value of the SPPB, it was reported that scores of less than 6 are associated with an increased fall risk in older adults [140]. Contrary to literature, HGS was positively associated with the number of falls [126], [141], [142]. Again, this might reflect the cohort's fitness level, resulting in recreational and sport-related falls. Additionally, a study comparing the performance of HGS with hip muscle strength to discriminate between fallers and nonfallers reported HGS to be less accurate compared to assessments including lower limb strength [143]. The results from the OLST were not conclusive and related the opposite way than reported in literature [144]. As reported in a meta-analysis assessing balance tests for fall risk prediction, the test might not be sensitive enough to discriminate between fallers and non-fallers [144]. The positive association between physical activity and falls might be best explained by the fact that many falls in this study were induced during recreational and sports activities. Considering comorbidities and medication, further inconclusive associations were found. In contrast to the results of other studies, no association was found between the number of comorbidities and falls [126]. However, CCI as a measure of comorbidity was associated with the fall number in the GERICO

cohort. Contrary to our expectations and other reported results, the number of medications was negatively associated with falls [126]. It is known that some medications are associated with an increase in fall risk [145], while others such as Vitamin D can have a preventive effect [146]. To better understand this finding, a detailed analysis of medication type would be required.

Considering the prediction accuracy of the models, particularly interesting is that the internally validated errors for the univariable model with the prior number of falls as the only predictor and the two multivariable models including additional predictors are comparable. Hence, the information included in the other predictors does not improve the model's predictive performance. The reported error for the falls model is lower than in a recently published study presenting a prediction model for falls in community-dwelling older adults using a comparable analysis method (bootstrapped mean absolute error 0.88) [126]. In order to evaluate the model's performance in detail, sensitivity analysis and external validation are required.

Although an error of less than one fall seems small, this variation could be critical to whether fall-prone individuals are correctly identified, especially in the lower range of fall numbers. With the ulterior motive to integrate a fall rate estimate in a fracture risk model, such a prediction error might have a considerable impact on subsequent fracture risk assessment.

The consequences of predicting a higher fall rate than effectively occurring seem less problematic compared to underestimating the number of expected falls. All three models presented here underestimated the number of individuals experiencing 1 and 2 falls while overestimating the number of 0 falls, bearing the risk of missing the identification of individuals who require fall prevention measures. Further predictive risk factors need to be identified that are sensitive enough to minimize such errors and improve prediction accuracy. Ideally, these predictors should also be suitable to identify first-time fallers without a history of falls.

In most fall risk assessments, not the number of previously experienced falls is recorded, but whether any falls have occurred at all [61], [121]. Based on our results, we believe that additional information on the number of prior falls has

great potential to improve the identification of individuals at risk for falling at a manageable cost. Therefore, we encourage other researchers to additionally record the number of previously experienced falls over a clearly defined time-period.

3.4.1 Limitations

This study and analysis has several limitations. First, the study design is not optimal for the development of a fall prediction model. A time interval of 4 years between the follow-up examinations at T1 and T2 is very long when physical performance parameters such as balance or muscle strength are examined. This makes it difficult to detect associations between fall risk predictors and the number of falls. Ideally, risk factors would be assessed at a baseline examination followed by an observation period in which the number of falls is recorded. Nevertheless, we chose to use the obtained data of the physical performance tests from T1 instead of T2 because we wanted to exclude the possibility of retrodiction (e.g., a participant performing medium in SPPB at T2 because of a recently experienced fall shortly before the examination). However, since comorbidity and medication were only assessed at T2, a certain risk of retrodiction for those variables could not be circumvented. Similarly, physical activity was assessed over the same time-period as the outcome variable, possibly resulting in a decreased activity level for individuals with severe falls at the beginning of this observation period. This again increases the likelihood of reverse causation.

Second, the participants were asked whether they had experienced any prior falls at the follow-up visits at T1 and T2 without knowing that this question will be asked. It was shown that self-reported retrospective recording of fall numbers might be inaccurate [147], [148]. Thirdly, not all domains of fall risk factors are covered with the available predictors. For example, no questions and tests considering fear of falling, vision or cognition have been included in the study protocol. Last, the GERICO cohort is a comparable young and fit cohort and is possibly not the best representation of older adults at risk of falling. Therefore, the study findings bear a potential lack of generalisability.

3.4.2 Conclusion

In the GERICO cohort, the prior fall number as single predictor information for a personalized fall rate is as good as a model including all available fall risk factors. Specifically, individuals who have experienced three and more falls are expected to experience multiple falls again. Because falling is a complex phenomenon and a broad range of conditions influence whether or not a fall occurs, it seems reasonable that the complex circumstances under which a fall occurs are best reflected by the history of falls itself.

Supplementary information

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Author's contributions

Authors' contributions Study design: EB, SF. Study conduct and data collection: EB. Analysis and data interpretation: CW, MZ, PZ. Drafting manuscript: CW. Revising of manuscript content: EB, SF, PZ, MZ. Approving of final version of manuscript: CW, EB, SF, PZ, MZ. All persons significantly contributing to this manuscript have been listed.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The experimental protocol was established according to the ethical guidelines of the Helsinki Declaration. The study was approved by the Geneva University Hospital Research Ethics Commission (approval 08–036 (Psy 08–007), 11–256 (Psy 11–031) and CER 15–133). Written informed consent was obtained from all participants in the GERICO study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Supplementary material

Table 3.4: Baseline rate ratio, dispersion statistics, model comparison and predictive performance measures for the univariable models.

Univariable Models	**Baseline RR (CI)**	**PChi2D**	**LL**	**BIC**	**LS**	**BS**	**MAE**	**CV MAE**	**CV median absolute error (IQR)**
Sex	0.95 (0.71, 1.28)	1.81	-686.77	1392.75	1.14	-0.44	0.86	0.87	0.64 (0.36, 0.96)
Age	0.70 (0.61, 0.81)	2.06	-689.09	1397.38	1.14	-0.44	0.86	0.86	0.69 (0.38, 0.75)
BMI	0.70 (0.61, 0.81)	2.03	-689.24	1397.69	1.14	-0.44	0.86	0.86	0.70 (0.41, 0.74)
SPPB	0.71 (0.61, 0.82)	2.04	-689.23	1397.67	1.14	-0.44	0.86	0.86	0.71 (0.43, 0.71)
HGS	0.70 (0.60, 0.80)	1.87	-687.66	1394.54	1.14	-0.44	0.86	0.87	0.67 (0.48, 0.78)
OLST	0.76 (0.62, 0.93)	1.87	-684.15	1393.91	1.13	-0.45	0.85	0.85	0.76 (0.45, 0.85)
Activity	0.68 (0.59, 0.79)	1.86	-683.46	1386.13	1.13	-0.44	0.87	0.88	0.61 (0.49, 0.80)
CCI	0.67 (0.58, 0.77)	1.81	-686.02	1391.25	1.14	-0.44	0.87	0.87	0.67 (0.40, 0.67)
Comorbidity	0.70 (0.61, 0.81)	2.04	-689.42	1398.04	1.14	-0.44	0.86	0.87	0.70 (0.32, 0.71)
Medication	0.68 (0.60, 0.80)	1.76	-685.93	1391.07	1.14	-0.44	0.86	0.86	0.70 (0.46, 0.81)

Abbreviations: RR rate ratio, *CI = 95 %* confidence interval, *PChi2D* Pearson's Chi2 dispersion statistic, *LL* log-likelihood, *BIC* Bayesian information criteria, *LS* logarithmic score, *BS* Brier score, *MAE* mean absolute error, *CV* cross-validated, *IQR* interquartile range

Table 3.5: Rate ratios and the corresponding 95% confidence interval for the data set excluding extreme fall events ($\geq$ 5 falls).

Variables	**Univariable**	**Global**	**Subset**
Sex			
Male	1.00	1.00	1.00
Female	0.84 (0.62, 1.14)	0.94 (0.68, 1.31)	0.91 (0.66, 1.26)
Assessed at T1			
Age [years]	1.02 (0.90, 1.16)	1.02 (0.89, 1.15)	1.02 (0.90, 1.15)
Fall number			
0	1.00	1.00	1.00
1	1.53 (1.15, 2.02)	1.52 (1.15, 2.01)	1.50 (1.13, 1.99)
2	1.20 (0.77, 1.88)	1.20 (0.77, 1.87)	1.22 (0.78, 1.90)
3	2.86 (1.12, 3.09)	1.86 (1.12, 3.07)	1.86 (1.12, 3.09)
4	2.72 (1.28, 5.80)	3.03 (1.43, 6.38)	2.75 (1.29, 5.84)
BMI [kg/m^2]	0.98 (0.86, 1.11)	0.96 (0.83, 1.10)	-
SPPB (score 0 - 12)			
[10 - 12]	1.00	1.00	1.00
[0 - 10]	0.83 (0.47, 1.47)	0.77 (0.43, 1.36)	0.83 (0.47, 1.46)
HGS [kg]	1.01 (0.98, 1.15)	1.01 (0.89, 1.14)	-
OLST [s]			
[41 - 45]	1.00	1.00	-
[1 - 20]	1.05 (0.78, 1.40)	1.05 (0.76, 1.45)	-
[21 - 40]	0.79 (0.57, 1.09)	0.78 (0.56, 1.09)	-
Assessed at T2			
Physical activity [kcal/day]	1.08 (0.95, 1.11)	1.06 (0.92, 1.21)	1.05 (0.92, 1.21)
CCl (score)			
[0 - 1]	1.00	1.00	1.00
[2 - 8]	1.31 (0.77, 2.21)	1.27 (0.74, 2.18)	1.24 (0.73, 2.10)
Comorbidity (number)	1.09 (0.96, 1.24)	1.23 (1.03, 1.46)	-
Medication (number)	0.98 (0.86, 1.11)	0.84 (0.70, 1.00)	-

Reference levels of factor variables are indicated with a rate ratio = 1.00. For continuous variables, rate ratios correspond to a standard deviation increase
Abbreviations: BMI Body mass index, *SPPB* Short physical performance battery, *HGS* Hand grip strength, *OLST* One-legged stance test, *CCI* Charlson's comorbidity index

4

History of falls and fear of falling are predictive of future falls: Outcome of a fall rate model applied to the Swiss CHEF Trial cohort

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Contributions The author of this thesis contributed to the preparation of the data, the statistical analysis, the interpretation of the result, and the writing of the manuscript.

Abstract

Background A third of adults aged 65 years and older fall every year, and falls are a common cause of unintentional injuries. Accurate identification of people at risk of falling is an important step in the implementation of preventive strategies.

Objective

Our aim was to investigate the association of fall risk factors with number of reported falls in terms of incidence rate ratios and to develop a fall rate prediction model. **Methods**

In the randomized controlled trial Swiss CHEF, multiple fall risk variables were assessed in community-dwelling older adults at baseline examination, including age, sex, body mass index, fear of falling, number of falls during the prior 12 months, scores on several physical performance tests, comorbidities, and quality of life. Over the following 6 months, interventions were administered in the form of three home-based exercise programs. Participants were subsequently followed up for another 6 months. Falls were reported prospectively using monthly calendars. Incidence rate ratios were derived via negative binomial regression models. Variable selection for the prediction model was conducted using backward elimination and the least absolute shrinkage and selection operator method; the model with the smallest prediction error was then identified.

Results Associations with the number of reported falls were found for number of prior falls, fear of falling, balance and gait deficits, and quality of life. The final model was derived via backward elimination, and the predictors included were prior number of falls and a measure of fear of falling.

Outcome Number of prior falls and fear of falling can be used as predictors in a personalized fall rate estimate for community-dwelling older adults. Recurrent fallers having experienced four or more falls are especially at risk of falling again.

Keywords older adults, falls, prediction, risk factors, count regression

4.1 Introduction

Approximately one-third of adults aged 65 years and older fall every year [44]. At the same time, falls are among the leading causes of unintentional injuries in this age group, resulting in increased morbidity and mortality [51], [53], [116]. Accordingly, it seems clear that the prevention of falls is an important topic and one of broad interest [44]. However, the identification of those at risk of falling and therefore in need of intervention is an ongoing challenge.

Various risk factors associated with falls have been identified, including older age, female sex, a history of falls, fear of falling, balance and gait deficits, and cognitive impairment [61]. To identify individuals at risk of falling, numerous fall risk assessment tools have been developed. Such tools normally consist of physical performance tests, questionnaires, or self-reported measures. While some evaluate individual risk factors, others integrate multiple factors within the same assessment [60], [121]. Up to this point, only a small number of tools have shown sufficient predictive power to successfully discriminate between fallers and non-fallers [64], [121].

Most tools produce a classification as to whether an individual is at risk of falling or not (either yes/no, or a probability between 0 and 1), and associations between fall risk factors and number of falls are usually reported in the form of odds ratios. However, since the risk of injury increases proportionally with each additional fall, a model able to predict an expected number of falls would potentially improve the identification of at-risk individuals. A statistical method capable of providing such an estimate is a count regression model [135], [150]. Ullah *et al.* showed that count regression is a suitable method for analysis of fall data [71]. Under this approach, the incidence of falls is the dependent variable, and fall risk factors are independent variables. The output takes the form of a baseline incidence of falls, reported along with rate ratios that describe how this baseline incidence changes depending on the value of each risk factor. So far, only a small number of studies have investigated risk of falling in terms of rate ratios [124], [126].

Against this background, the aim of this analysis was to investigate the association of prospectively recorded fall numbers with various fall risk factors, as assessed in the Swiss CHEF cohort, in terms of rate ratios, and to develop a prediction model to estimate an expected fall rate.

4.2 Methods

4.2.1 Reporting guidelines

This manuscript follows the guidelines for Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) [127]. The completed checklist is provided in the Supplementary Material.

4.2.2 Study design

The Swiss CHEF Trial is a multi-center randomized controlled trial that was conducted between 2016 and 2022 to compare the effects of three home-based exercise programs on fall prevention. The study was registered with the clinical trials registry ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02926105), and the study protocol has been published previously [151]. Briefly, after enrollment in the study, participants underwent a baseline examination in which their demographic characteristics, history of falls, fear of falling, physical performance on several tests, health state, and quality of life were assessed. Subsequently, the participants were divided into three intervention groups with block randomization and stratification for age, sex, and risk of falling (assessed as part of the inclusion criteria). The three intervention groups were: 1) a group who followed the experimental intervention program of interest, namely the Test&Exercise program; 2) a control group who followed the Otago exercise program; and 3) a second control group who were administered the "Helsana" intervention. Test&Exercise is a training program developed at the Haut école spécialisée de Suisse occidentale (HES-SO) located in Leukerbad, Switzerland. The program consists of 50 physical tasks that are combined to create a personalized training module depending on their perceived difficulty as rated by the participant during test exercises. Otago is a well-known

fall prevention program; it consists of 22 exercises whose levels are defined by physiotherapists [152]. Finally, the Helsana control intervention represented usual care; this consists of a booklet containing twelve exercise cards and safety advice produced by the Swiss healthcare insurance provider Helsana [153].

Participants in the Test&Exercise and Otago intervention groups received eight sessions of physiotherapist instruction and four phone calls over the course of 6 months. Those in the Helsana control group received one session of instruction and four phone calls over the same period. Follow-up lasted for 6 months. During the intervention and follow-up periods, incidents of falls were recorded prospectively using monthly fall calendars. After 6 and 12 months, participants were assessed by blinded assessors on the same variables as measured at the baseline examination. To avoid bias, the instructors who administered the intervention programs were not involved in conducting the examinations at baseline, 6, or 12 months. The study was approved by the relevant Swiss Ethics Committees on research involving humans (registration number 2016-00931).

4.2.3 Study participants

Participants included were community-dwelling adults at least 65 years old and classified as at risk of falling (having a history of falls in the previous 12months or a perceived fear of falling, as measured by a score of at least 20 points on the Falls Efficacy Scale - International, or FES-I). Exclusion criteria were severe visual impairment, receipt of physiotherapeutic treatment with balance training, cognitive impairment (<24 points on the Mini Mental State Examination), or contraindication by the referring physician. Participants with a follow-up time of less than 30 days were excluded from this analysis. All participants provided written informed consent.

4.2.4 Sample size

A sample size calculation was conducted to ensure that differences between the intervention groups would be detectable; this calculation is described in the openly accessible study protocol [151].

4.2.5 Outcome

The dependent variable was defined as the number of fall incidents as prospectively recorded over the course of 12 months during the intervention and follow-up periods using monthly fall calendars. A fall was defined as "an unexpected event in which the participant comes to rest on the ground, floor, or lower level, with or without injury" [154].

4.2.6 Predictors

Number of prior falls: Participants were asked how many times they had fallen within the 12 months prior to the baseline examination. The number of falls was recorded.

General characteristics: Age, sex, weight, and height were assessed. Body mass index (BMI) was calculated accordingly. Living environment (rural vs. urban) was also included as predictor. Finally, base of support width was assessed by measuring the distance in cm between the two legs when the participant was standing in a normal position.

Fear of falling: Participants were asked the question "Are you afraid of falling?" and provided with three response options: "never", "sometimes", or "always". In addition, the FES-I was administered, with possible scores ranging from 16 to 64 points [155].

Physical performance tests: The Timed Up and Go (TUG), the Four Stage Balance Test (FSBT), the Functional Reach Test (FRT), the Five Times Sit-to-Stand test (FTSTS), and a measure of gait speed were administered as tests of participants' physical performance. TUG measures the time taken to stand up from a chair, walk 3 m, turn around, walk back, and sit down again [156]. The FSBT is a balance test with four difficulty levels (1: feet sideby-side, 2: semi-tandem stance, 3: full tandem stance, 4: standing on one foot) [157]. A level is completed if the participant can hold the position for 10 s without moving the feet or requiring support. The FRT measure the distance a participant can lean forward in a standing position without bending the knees, raising the heels, or taking a step forward [158]. The FTSTS

measures the time required to stand up five times in a row form a sitting position with crossed arms. Finally, gait speed was measured via a 6-m-walk test. All test instruments are described in detail in the published study protocol [151].

Health state: Participants were asked whether they suffered from urinary incontinence, vision impairment, hearing impairment, central neurological disease, or musculoskeletal discomfort. Those who suffered from musculoskeletal discomfort and perceived pain were asked to classify the intensity of their pain with a number between 1 and 100.

Quality of life: Quality of life was measured using the Older People's Quality of Life Questionnaire (OPQOL-35), which consists of 35 questions covering eight domains [159]. Possible scores range from 35 to 175.

Offset and confounding factors: Study center and intervention group were treated as confounding factors and adjusted for in all univariable models. An offset measured in years to account for differences in follow-up time was included in all the models.

4.2.7 Statistical analysis

Processing of predictors

Age was centered around 70 years and BMI around a value of 25. FES-I and OPQOL-35 scores were shifted to a range with a minimum possible score of 0 by subtraction of 16 and 35 points, respectively. Number of prior falls was entered into the analyses in three forms: as a dichotomized variable representing the presence or absence of prior falls; as a continuous variable; and as a categorical variable with levels 0, 1, 2, 3, 4, and ≥ 5. For the FSBT, scores of 0 and one were aggregated into a single category due to a low number of observations of a score of 0. Scores on the FTSTS test were transformed into the form used in the Short Physical Performance Battery [160].

Missing data

We conducted a complete case analysis but report the number of missing observations.

Model fit and variable selection

Incidence rate ratios (IRRs) were derived via negative binomial regression models. Univariable models were fitfor all candidate predictors and adjusted for observation time, study center, and intervention group. In development of the predictive model, variables were selected using two different methods: backward elimination and the least absolute shrinkage and selection operator (LASSO) method [161], [162]. The stopping rule for backward elimination was the Bayesian information criterion. For variable selection under the LASSO method, each level of each categorical variable was treated as dummy variable, and the tuning parameter lambda was chosen by selecting the value associated with the smallest mean absolute error in a leave-one-out cross-validation analysis. No variables were forced to remain in the model. The two resulting models derived via these two variable selection methods were compared, and the model with the smaller root mean squared prediction error (RMSE) and mean absolute prediction error (MAE) was selected as the final model. Model stability for the backward elimination model was analyzed following the suggestions by Heinze *et al.* [162]. Briefly, variable selection was repeated 1,000 times using bootstrapped sample data sets. The frequency of inclusion of each candidate predictor was then derived by counting how many times it was included in the selected model across the bootstrapped sample data sets.

Software

Statistical analysis was conducted using R version 4.1.2 with the packages MASS, stats, base, and mpath [163], [164], [165], [166].

4.3 Results

In total, 405 participants were enrolled in the Swiss CHEF Trial between 2016 and 2021. Of these, 35 participants dropped out within less than 30 days of the start of the follow-up period. Of the remaining 370 participants, 17 (4.9%) had missing data and were excluded from the analysis. The flow of participants through the study is shown in Figure 4.1.

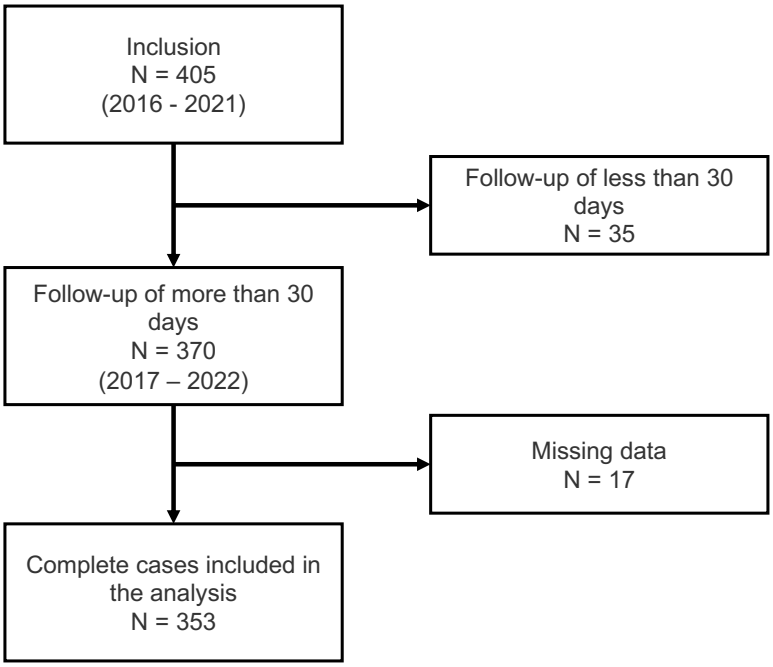

Figure 4.1: Flow of participants.

The majority of participants (235, 66.6%) were followed up over the course of 12 months; however, 59 (16.7%) dropped out during the intervention (i.e., during the first 6 months) and another 59 (16.7%) dropped out during follow-up (i.e., during the second 6 months). The median age of participants at the start of the study was 79 years, and the majority were female (72.8%). Most were living in a rural environment (80.7%). The median BMI was 25.10 kg/m2. In terms of fear of falling, 75 (21.3%) reported not being afraid of falling, 244 (69.1%) reported sometimes being afraid, and 34 (9.6%) reported always being afraid. The median FES-I score was 26 points. The median time for the TUG was 11.6 s, and the median distance measured on the FRT was 25.50 cm. The most common score on the FSBT was two points (138, 39.1%) and the most common score on the FTSTS was one point (126, 35.7%). The median gait speed was 1.07 m/s and median base of support width 29.00 cm. The majority of participants had no hearing problems (204, 57.8%) and did not suffer from urinary incontinence (241, 68.3%) or any neurological disorder (296, 88.5%). However, the majority were affected by vision impairment (291, 82.4%) and reported perceiving musculoskeletal discomfort (305, 85.4%). Around half required a walking aid (168, 47.6%). The median pain score was 45 and the

median OPQOL-35 score was 139. A detailed summary of all baseline characteristics and prospectively reported falls during follow-up is presented in Table 4.1.

Table 4.1: Baseline characteristics of the Swiss CHEF Trial cohort.

Variable	Level and measure	Value	NA's
General characteristics			
Age (years)	Median [IQR]	79 [73, 84]	-
Sex	Female, n (%)	257 (72.8)	-
	Male, n (%)	96 (27.2)	
Body mass index (kg/m^2)	Median [IQR]	25.10 [22.28, 28.89]	4
Living area	Urban, n (%)	68 (19.3)	-
	Rural, n (%)	285.80.7	
Participation in months	Control Helsana, n (%)	68 (19.3)	-
	Otago, n (%)	138 (39.1)	
	Test&Exercise, n(%)	147 (41.6)	
Falls and fear of falling			
Prior fall number	Mean	1.05	-
	Median [IQR]	0 [0, 1]	
	Range	0 - 20	
	0 falls, n (%)	113 (32.0)	
	1 falls, n (%)	124 (35.1)	
	2 falls, n (%)	62 (17.6)	
	3 falls, n (%)	25 (7.1)	
	4 falls, n (%)	11 (3.1)	
	$\geq$ 5 falls, n (%)	18 (5.1)	
Incident falls	Mean	1.47	-
	Median [IQR]	1 [0, 2]	
	Range	0 - 30	
	0 falls, n (%)	204 (57.8)	
	1 falls, n (%)	69 (19.6)	
	2 falls, n (%)	38 (10.8)	
	3 falls, n (%)	20 (5.7)	
	4 falls, n (%)	8 (2.3)	
	$\geq$ 5 falls, n (%)	14 (4.0)	
FES-I score	Median [IQR]	26 [21, 32]	-
Fear of falling	Never, n (%)	75 (21.3)	-
	Sometimes, n (%)	244 (69.1)	
	Always, n (%)	34 (9.6)	
Physical performance tests			
Timed Up and Go	Median [IQR]	11.61 [9.27, 14.38]	3
Functional Reach Test	Median [IQR]	25.50 [18.93, 31.23]	-
Four Stage Balance Test	Median [IQR]	3 [2, 3]	-
	Score 0, n (%)	5 (1.4)	-
	Score 1, n (%)	23 (6.5)	
	Score 2, n (%)	138 (39.1)	
	Score 3, n (%)	107 (30.3)	
	Score 4, n (%)	80 (22.7)	
Gait speed (m/s)	Median [IQR]	1.07 [0.82, 1.32]	-
Five Times Sit-To-Stand	Median time [IQR]	15.29 [12.34, 19.31]	41*
	Median score [IQR]	2 [1, 3]	-

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Table 4.1 – *continued from previous page*

Variable	Level and measure	Value	NA's
	Score 0, n (%)	37 (10.5)	
	Score 1, n (%)	126 (35.7)	
	Score 2, n (%)	74 (21.0)	
	Score 3, n (%)	69 (19.6)	
	Score 4, n (%)	47 (13.3)	
Base of support width (cm)	Median [IQR]	29.00 [26.45, 32.10]	
Health state and comorbidities			
Hearing problems	No, n (%)	204 (57.8)	3
	Yes, n (%)	149 (42.2)	
Vision Impairment	No, n (%)	62 (16.7)	4
	Yes, n (%)	291 (82.4)	
Walking aid	No, n (%)	185 (52.4)	1
	Yes, n (%)	168 (47.6)	
Urinary incontinence	No, n (%)	241 (68.3)	4
	Yes, n (%)	112 (31.7)	
Musculoskeletal disorder	No, n (%)	48 (13.6)	3
	Yes, n (%)	305 (86.4)	
Neurological disorder	No, n (%)	296 (83.9)	3
	Yes, n (%)	58 (16.2)	
Pain (range 0 - 100)	Median [IQR]	45 [12, 60]	-
Quality of life			
OPQOL-35	Median [IQR]	139 [129, 152]	1

* 41 participants were not able to perform the test, resulting in a score of 0 points.
Abbreviations: NAs Missing data; *n* Number; *%* Percentage; *IQR* Interquartile range; *OPQOL-35* Older People's Quality of Life Questionnaire

In total, 369 falls were registered during intervention and follow-up; 149 (42.2%) participants reported at least one fall, and 80 (22.7%) fell multiple times (Table 4.1). For the 12 months prior to the baseline assessment, participants reported 517 falls in total: 240 (68.0%) reported having fallen at least once during this period, whereas 116 (32.9%) had fallen multiple times.

IRRs for all candidate predictors are presented in Table 4.2. Associations with number of prospectively reported falls were found for the following variables: enrollment in the Otago intervention program compared to the control intervention (IRR: 2.25, 95% CI 1.28-3.95); number of prior falls operationalized as a dichotomized variable (IRR: 1.71, 95% CI 1.11-2.62) and as a continuous variable (IRR: 1.26, 95% CI 1.18-1.34); having experienced four falls (IRR: 3.15, 95% CI 1.28-7.70) or $\geq$5 falls (IRR: 7.20, 95% CI 3.62-14.31) on the measure of number of prior falls as a categorical variable; FES-I score (IRR: 1.05, 95% CI 1.03-1.07); reporting "always"

experiencing fear of falling as compared to "never" (IRR: 3.77, 95% CI 1.83-7.80); TUG time (IRR: 1.05, 95% CI 1.01-1.08); a score of 0 or 1 on the FSBT compared to a score of 4 (IRR: 3.05, 95% CI 1.53-6.08); base of support width (IRR: 1.05, 95% CI 1.01-1.09); and OPQOL-35 score (IRR: 0.98, 95% CI 0.97-0.99). All other predictors were not found to be associated with prospectively recorded number of falls.

Table 4.2: Incidence rate ratios derived via negative binomial regression models.

Variable and level for categorical variables		**IRR (95% CI)**
General characteristics		
Age (years)		0.99 (0.96, 1.02)
Sex	Male	*ref*
	Female	0.70 (0.46, 1.07)
Body mass index (kg/m^2)		1.01 (0.97, 1.05)
Living area	Rural	*ref*
	Urban	3.34 (0.27, 41.10)
Participation in months	Control Helsana	*ref*
	Otago	2.25 (1.28, 3.95)
	Test&Exercise	1.63 (0.92, 2.87)
Falls and fear of falling		
Prior falls (binary)	no	*ref*
	yes	1.71 (1.11, 2.62)
Prior fall number (continuous)		1.26 (1.18, 1.34)
Prior fall number (categorical)	0 falls	*ref*
	1 falls	1.04 (0.66, 1.62)
	2 falls	1.10 (0.64, 1.89)
	3 falls	1.89 (0.95, 3.73)
	4 falls	3.15 (1.28, 7.70)
	$\geq$ 5 falls	7.20 (3.62, 14.31)
FES-I score		1.05 (1.03, 1.07)
Fear of falling	Never	*ref*
	Sometimes	1.54 (0.92, 2.56)
	Always	3.77 (1.83, 7.80)
Physical performance tests		
Timed Up and Go		1.05 (1.01, 1.08)
Functional Reach Test		0.99 (0.97, 1.01)
Four Stage Balance Test	Score 4	*ref*
	Score 3	0.88 (0.53, 1.46)
	Score 2	0.82 (0.51, 1.34)
	Score 0 or 1	3.05 (1.53, 6.08)
Gait speed (m/s)		0.60 (0.32, 1.10)
Five Times Sit-To-Stand	Score 4	*ref*
	Score 3	1.39 (0.60, 2.82)
	Score 2	1.88 (0.94, 3.73)
	Score 1	1.25 (0.65, 2.39)
	Score 0	1.28 (0.56, 1.09)
Base of support width (cm)		1.05 (1.01, 1.09)
Health state and comorbidities		

Continued on next page

Table 4.2 – *continued from previous page*

Variable and level for categorical variables		**IRR (95% CI)**
Hearing problems	No	*ref*
	Yes	0.76 (0.51, 1.12)
Vision Impairment	No	*ref*
	Yes	1.05 (0.62, 1.77)
Walking aid	No	*ref*
	Yes	1.43 (0.97, 2.11)
Urinary incontinence	No	*ref*
	Yes	1.08 (0.71, 1.63)
Musculoskeletal disorder	No	*ref*
	Yes	0.77 (0.44, 1.33)
Neurological disorder	No	*ref*
	Yes	1.13 (0.67, 1.89
Pain (range 0 - 100)	0-25 points	*ref*
	26 - 50 points	0.98 (0.62, 1.55)
	51 - 75 points	0.62 (0.37, 1.04)
	76 - 100 points	1.84 (0.91, 3.72)
Quality of life		
OPQOL-35		0.98 (0.97, 0.99)

All univariable models were adjusted for study center and intervention group. *Abbreviations: IRR* Incidence rate ratio; *ref* Reference group; *OPQOL-35* Older People's Quality of Life Questionnaire

Variable selection with backward elimination resulted in a model including prior number of falls and FES-I score as the only predictor variables. The coefficient estimates together with prediction errors are presented in Table 4.3, and the corresponding rate ratios, in numerical form and as a forest plot, are presented in Figure 4.2.The RMSE and MAE were 2.02 and 1.15, respectively; internal cross-validation increased these values to 2.17 and 1.21, respectively. LASSO variable selection resulted in a model including having experienced five or more prior falls and a score of 0 or one points on the FSBT as predictors. Model coefficients and detailed prediction errors for the LASSO model are presented in Supplementary Table 4.4.Both apparent error and cross-validated error were higher for the LASSO model compared to the backward elimination model. Model stability investigation for the backward elimination model resulted in a bootstrap inclusion frequency of 80.8% for prior number of falls and 74.2% for FES-I score (Table 4.3). All other candidate predictors had an inclusion frequency of less than 50%; the complete list can be found in Supplementary Table 4.5. An example of how to use the model to calculate an individual's expected fall rate can also be found in the Supplementary Material S1.

Table 4.3: Coefficients, bootstrap inclusion frequency, and predictive performance for the backward elimination model.

Variable	**Coefficient (95% CI) on log scale**	**BIF (%)**
Intercept	-0.67 (-1.08, -0.27)	100
Prior number of falls 1	0.12 (-0.32, 0.57)	80.8
Prior number of falls 2	0.03 (-0.50, 0.56)	80.8
Prior number of falls 3	0.58 (-0.10, 1.27)	80.8
Prior number of falls 4	0.96 (0.07, 1.85)	80.8
Prior number of falls ≥ 5	1.83 (1.15, 2.52)	80.8
FES-I score	0.04 (0.02, 0.06)	74.2
Dispersion parameter θ	0.71 (0.46, 0.95)	
Predictive performance		
RMSE (IQR)	2.02 (0.43, 0.72, 1.24)	
MAE	1.15	
CV RMSE (IQR)	2.17 (0.51, 0.72, 1.17)	
CV MAE	1.21	

Abbreviations: CI Confidence interval; *BIF* Bootstrap inclusion frequency; *FES-I* Falls efficacy scale international; *RMSE* Root mean squared error; *MAE* Mean absolute error; *CV* Cross-validated

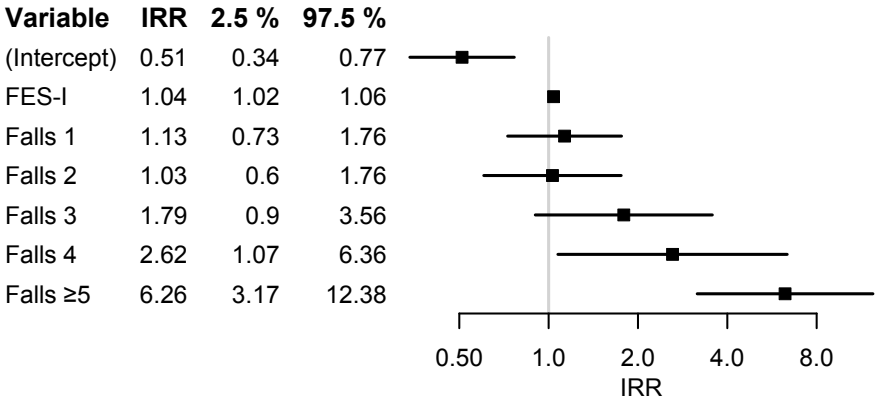

Figure 4.2: Incidence rate ratios (IRR) and corresponding 95% confidence intervals in the model generated with variable selection via backward elimination, in numerical form (left) and as forest plot (right).

4.4 Discussion

The aim of this study was to investigate the associations between various fall risk factors and number of prospectively reported falls, and to develop a personalized fall rate prediction model. This analysis made use of data from the randomized controlled trial Swiss CHEF, which investigated the effects of two different interventions for fall prevention compared to a control intervention in community-dwelling older adults. Candidate predictors included in the analysis were assessed prior to the start of the intervention. Rate ratios were derived via negative binomial regression models, and variable selection for the prediction model were conducted using backward elimination and LASSO. The final prediction model was selected on the basis of smallest prediction error. We followed the TRIPOD reporting guidelines for the development of a multivariable prediction model.

The associations observed between risk factors analyzed and prospectively reported number of falls are comparable to other results reported in the literature [59], [61], [121]. A history of falls, gait and balance deficits, fear of falling, and a decrease in quality of life are well-known risk factors for falls in community-dwelling older adults. The strongest associated factor in this analysis was found to be having experienced four or ≥ 5 prior falls, indicating that individuals with a history of multiple falls are at risk of falling multiple times again. While a single fall might occur at random, recurrent fallers are likely to suffer from persistent deficits that result in an inability to avoid falls.

A large decrease in the total number of falls could be observed in a comparison of the falls reported during the 12 months prior to baseline assessment and during the 12 months of intervention and follow-up. It is plausible that the intervention programs, as well as sensitization to the risk of falling as a result of participation in the study, were the cause of this decrease. Accordingly, this may potentially have resulted in underestimation of the derived incidence rate ratios in comparison to a randomly selected population. An observational study with no intervention program would be required to overcome this issue.

Number of prior falls and FES-I score (as a measure for fear of falling) were the only two predictors included in the final model generated by the variable selection algorithm. There are many reasons why it may not be possible to prevent a particular fall, and a broad combination of factors can plausibly function as causes of a fall. Hence, prior occurrences of falls might be the best reflection of whether factors causing falls are present in a given individual or not. Although other predictors investigated in this analysis were associated with prospectively reported number of falls, each of these variables measured only a single aspect of the risk of falling. Given this fact, the inclusion of prior number of falls in the model immediately produced superior predictive power for the number of future falls compared to the inclusion of other variables. The second predictor included in the model, fear of falling, is known to increase with experience of falls [60]. Therefore, an explanation for its predictive power might be the fact that it functions as an alternative measure of the presence of prior falls. Surprisingly, inclusion of the variable representing intervention group did not appear to improve predictive power, although the incidence of falls differed among the intervention groups, as we saw in the univariable analysis.

PREFALL, a fall rate model that was developed using the LASSO method in a recently published study, includes two variables similar to those included in our model, namely the presence of a history of falls (yes/no) and self-perceived risk of falling [126]. In a comparison of prediction error, PREFALL is superior to our model. Although the apparent prediction error of the model presented here was comparable to that of PREFALL, the cross-validated error was higher, indicating some bias. An error of more than one fall can have substantial influence when screening for people at risk of falling, introducing the potential to miss individuals who are in need of preventive measures. Thus, the identification of further risk predictors resulting in a more accurate prediction is required.

A strength of this study is that the outcome variable, namely the number of falls reported during intervention and follow-up, was recorded prospectively. Prospective recording is known to be more precise compared to retrospective assessment of number of falls [148]. In addition, this analysis provided insight into the form in

which history of falls is best included as a predictor variable. While use of the information in dichotomized form (yes versus no) can only produce changes in the prediction for fallers versus non-fallers, use of a continuous variable enables the prediction to be adjusted according to the number of prior falls experienced. However, by introducing the number of prior falls in the form of a categorical variable, we were further able to show that prospective fall rate does not merely increase in a log-linear relationship with increasing number of prior falls, as assumed for a continuous variable; rather, the relationship is a stronger one.

Most fall risk assessment tools evaluate the risk of falling via binary logistic regression to identify who is predicted to fall. We believe that analyzing fall count data with rate ratios, as suggested by Ullah *et al.* [71], is a better approach. The insight gained as to the probability that someone will fall at all is different from a prediction of how many times someone is expected to fall.

The analysis presented here also has several limitations. First, the Swiss CHEF cohort study was designed as an intervention study. An observational study would have been a superior design for the development of a prediction model. Second, the fall prevalence in this cohort was higher than the prevalence reported in the literature: e.g., in Switzerland the prevalence is reported to be around 25% [115]. This is a consequence of the inclusion criteria, which required participants to be at risk of falling, resulting in a sample population with a higher prevalence of falls compared to a random sample population. Third, the imbalanced nature of the cohort in terms of sex, with a large proportion of women compared to men, is not optimal for such an analysis, since risk factors for falls can differ between sexes. Finally, although count regression models can adjust for differences in observation time via an offset variable, shorter observation times can result in both under- and overestimation of an individual's true number off all compared to follow-up observation as planned. Further studies are required to overcome those issues, validate the model, and improve its prediction accuracy.

In summary, this analysis showed that history of falls, in terms of prior number of falls, and FES-I score are relevant variables in the prediction of future fall

rates. Methodologically, the inclusion of the number of prior falls as a categorical variable has the potential to improve the predictive accuracy of fall risk and fall rate estimation models.

Supplementary information

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethic statement

The studies involving human participants were reviewed and approved by the Swiss Ethics Committees. The patients/participants provided their written informed consent to participate in this study.

Author contribution

Study design, implementation, and data collection: A-GM and RG. Analysis and interpretation of data: CW and PZ. Drafting of manuscript: CW. Revision of manuscript content: A-GM, RG, and PZ. Approval of final version of manuscript: CW, A-GM, RG, and PZ.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

Supplementary tables

Table 4.4: Coefficients and predictive performance measures for the LASSO selected model.

LASSO model	
Variable	**Coefficient estimates (log-scale)**
Intercept	-2.44
Prior fall number = [$\geq$ 5)	0.60
Four stage balance test = [0, 1]	0.08
Predictive performance	
Measure	**Value**
RMSE	2.43
MAE	1.06
CV RMSE	2.76
CV MAE	2.19

Abbreviations: LASSO Least absolute shrinkage and selection operator; *RMSE* Rooted mean squared error; *MAE* Mean absolute error; *CV* Cross-validated

Table 4.5: Completed list of bootstrap inclusion frequency for model selection with backward elimination.

Variable	BIF (%)
Intercept	100
Prior fall number	80.8
FES-I	74.2
Four stage balance test	42.3
OPQOL-35	31.4
Pain	30.4
Five times sit to stand	23.4
Musculoskeletal problems	21.4
Age	18.5
Timed Up and Go	15.7
Functional reach test	12.0
Sex	11.8
Gait speed 6 meter	11.4
Randomisation	10.6
Fear of falling	9.0
Urinary incontinence	8.8
Hearing problems	8.8
Urban/rural	8.1
Neurological disease	7.9
Body mass index	7.1
Walking aid	7.0
Study center	6.6
Base of support width	6.4
Vision impairment	6.2

Abbreviations: BIF Boostrap inclusion frequency; *FES-I* Falls Efficacy Scale International; *OPQOL-35* Older People's Quality of Life Questionnaire

Example of how to use the prediction model

The model writes as

$$\begin{aligned}\log(\textit{fall rate}) = -0.67 &+ 0.12 \cdot I_{Falls=1} \\ &+ 0.03 \cdot I_{Falls=2} \\ &+ 0.58 \cdot I_{Falls=3} \\ &+ 0.96 \cdot I_{Falls=4} \\ &+ 1.83 \cdot I_{Falls=\geq 5} \\ &+ 0.04 \cdot (FESI - 16)\end{aligned}$$

where I is th indicator function given as

$$I_{condition} = \begin{cases} 1 & \text{condition is true} \\ 0 & \text{otherwise} \end{cases}$$

The expected fall rate of a person having reached a FES-I score of 24 with 4 falls experienced in the prior 12 months to examination results in

$$\log(\textit{fall rate}) = -0.67 + 0.96 \cdot 1 + 0.04 \cdot (24 - 16) = 0.61$$

$$\textit{fall rate} = exp(0.61) = 1.84$$

5

Validation of a fall rate prediction model for community-dwelling older adults: a combined analysis of three cohorts with 1850 participants

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Contributions The author of this thesis contributed to the preparation of the data, the statistical analysis, the interpretation of the result, and the writing of the manuscript.

Abstract

Background Fragility fractures in older adults are often caused by fall events. The estimation of an expected fall rate might improve the identification of individuals at risk of fragility fractures and improve fracture prediction.

Methods A combined analysis of three previously developed fall rate models using individual participant data (n = 1850) was conducted using the methodology of a two-stage meta-analysis to derive an overall model. These previously developed models included the fall history as a predictor recorded as the number of experienced falls within 12 months, treated as a factor variable with the levels 0, 1, 2, 3, 4 and $\geq$ 5 falls. In the first stage, negative binomial regression models for every cohort were fit. In the second stage, the coefficients were compared and used to derive overall coefficients with a random effect meta-analysis. Additionally, external validation was performed by applying the three data sets to the models derived in the first stage.

Results The coefficient estimates for the prior number of falls were consistent among the three studies. Higgin's I^2 as heterogeneity measure ranged from 0 to 55.39%. The overall coefficient estimates indicated that the expected fall rate increases with an increasing number of previous falls. External model validation revealed that the prediction errors for the data sets were independent of the model to which they were applied.

Conclusion This analysis suggests that the fall history treated as a factor variable is a robust predictor of estimating future falls among different cohorts.

Key Words Falls, fragility fractures, older adults, model validation, count regression

5.1 Introduction

Falls and fragility fractures are closely associated in older adults. While around one out of three individuals aged 65 years and older fall yearly, a substantial number of those events result in injuries [51]. The incidence of fall-related fractures increases with age, especially for women after 50 [168]. The fact that falls play an important

role in fracture prediction is increasingly recognised lately. A meta- analysis using the MrOS study showed that the number of prior falls predicted fractures independently of FRAX [58]. Furthermore, in the latest update of FRAX, the so-called FRAXplus, the history of falls is now included as a risk factor for fractures [36]. In a review paper, Komisar and Robinovitch summarised the relationship between fall biomechanics and fracture risk for distinct fracture sites [57]. Especially hip fractures are almost exclusively caused by falls [169]. Along with reduced bone strength, the risk of a fall and the inability to counteract such a fall event can lead to a fracture. Accordingly, individuals with a higher fall frequency and severity are simultaneously exposed to an increased fracture risk. Subsequently, predicting how often a person is likely to fall could help identify individuals at risk for fragility fractures.

However, the focus of fall risk assessments presented in the literature is on identifying people at risk of falling, not on predicting the number of expected falls. This becomes evident when reviewing the literature on this topic [60], [120], [121]. As an alternative to binary logistic regression that assesses the risk of falling as a probability between 0 and 1, count regression models allow the prediction of rate ratios and thus, the calculation of the expected number of falls within a time period [71]. However, only a few studies analysing the risk of falling in terms of fall rates have been published [124], [126]. For example, a study conducted by Gade et al. developed the fall rate prediction model for community-dwelling older adults by fitting a Poisson regression and using the least absolute shrinkage and selection operator penalization for variable selection [126].

Similarly, we analysed three independent cohorts investigating aspects of the risk of falling in community-dwelling older adults and developed fall rate prediction models in previous work. The three cohorts are the Geneva Retirees Cohort (GERICO) [129], the Swiss CHEF Trial (SCT) [151], and the Kuopio Fall Prevention Study (KFPS) [170], [171]. Fall rate prediction models were developed using a count regression modelling approach, and two of the three analyses have been published previously [114], [149]. In short, the results showed that the history of falls measured as the number of prior falls within 12 months before the study examination was

the best predictor for future falls in all three cohorts[114], [149]. Furthermore, we showed the importance of how the information about the fall history is treated as a predictor. In most prediction models, this information is included as binary information (yes/no) for fallers in general or recurrent fallers [61]. However, valuable predictive information gets lost by condensing the prior number of falls into a binary variable. When comparing the rate ratio for an individual who experienced 5 falls, we found the model coefficient estimate to be 4 times higher when the information is treated as a factor variable compared to a binary variable [149].

Against this background, and with the further goal of improving fragility fracture prediction by including information on falls, this study aimed to compare models for predicting fall rates that included the history of falls as a categorical predictor. We used the methodology of a two-stage meta-analysis to compare the model coefficients and suggest an overall prediction model. Additionally, we performed an external validation between the three previously developed models.

5.2 Methods

5.2.1 Cohorts and data

The two main criteria for inclusion in this combined analysis were that the data was analysed using a count regression method and that the predictor history of falls was treated as a factor variable. Apart from the three models that we developed previously, we are unaware of any other studies meeting those criteria.

Individual participant data were available from the original data sets of all cohorts. The analysis and development of the GERICO and SCT prediction models have been published previously [114], [149], and the analysis of the KFPS is available in the supplementary material. A list of all predictors investigated in the prior analyses can be found in the supplementary material, Table 5.4. The flow of participants and the inclusion and exclusion criteria for the cohorts and this analysis are presented in Figure 5.1.

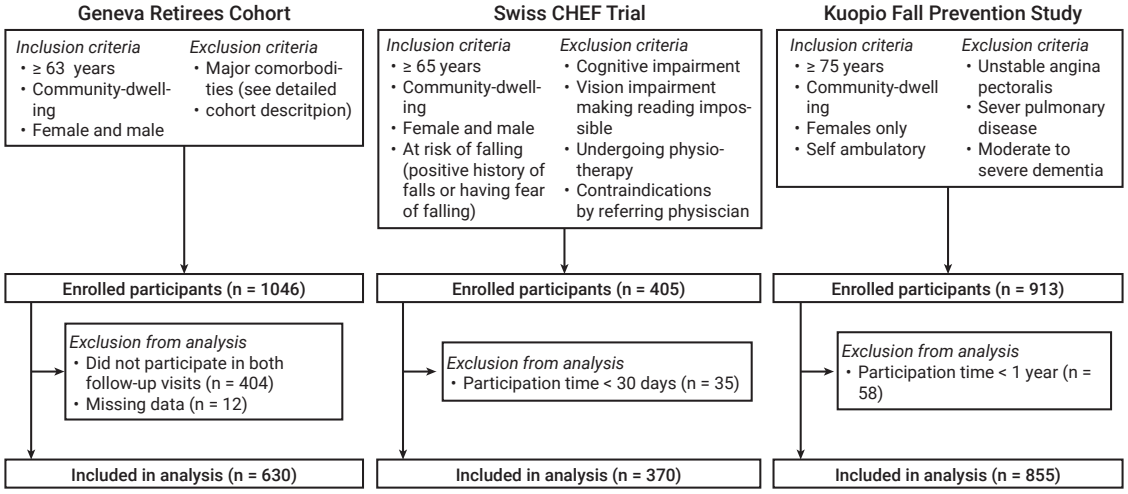

Figure 5.1: Flow of participants in the three cohorts.

Geneva Retirees Cohort

The Geneva Retirees Cohort (GERICO) is a prospective observational study conducted between 2008 and 2018 around Geneva, Switzerland. It aimed to investigate the risk factors for fracture and fall prediction in community-dwelling older adults. Participants were enrolled in the study between 2008 and 2011 and invited for a baseline examination. Two follow-up visits were conducted after 4 and 8 years each. The study was described previously [129], and the trial was registered under https://isrctn.com/ISRCTN11865958.

Participants Participants were community-dwelling older adults of both sexes, with a mean age of 67.9 years (1.6 standard deviation (SD), range 64.6 – 71.8) at follow-up visit 1 and living in rural or urban areas around Geneva.

Exclusion criteria Participants were excluded if they suffered from major comorbidities, particularly cancer treated within the last 5 years, chronic renal failure, liver or lung disease, corticosteroid therapy, primary hyperparathyroidism, Paget disease of bone, malabsorption or any neurological or a musculoskeletal condition affecting bone health.

Variables of interest Fall risk-related variables of importance for the fall rate model development were mainly recorded during the two follow-up visits. These included age, body mass index, short physical performance battery, hand grip strength, one-legged stance test, activity level, Charlson's comorbidity index, the number of comorbidities, and the number of medication.

Falls A fall was defined as an event resulting in unintentionally coming to rest on the ground, floor or any lower levels. Falls were assessed retrospectively at the two follow-up visits by asking whether any falls occurred during the last 12 months.

Swiss CHEF Trial

The Swiss CHEF Trial (SCT) is a randomised controlled trial investigating three home-based exercise programs for fall prevention in community-dwelling older adults. The study was conducted between 2016 and 2022 in Switzerland. The study was described previously [151], and the trial was registered under https://clinicaltrials.gov/study/NCT02926105.

Participants Participants enrolled in the study were community-dwelling older adults of both sexes with a mean age of 78.7 years (6.8 SD, range 65 – 100), who fell at least once in the previous 12 months or were afraid of falling (FES-I score of at least 20 points).

Exclusion criteria Exclusion criteria were severe visual impairment, cognitive impairment ($<$ 24 points on the Mini Mental State Examination), physiotherapeutic treatment with balance training, or contraindication by the referring physician.

Variables of interest Variables such as demographic characteristics, history of falls in the previous 12 months, fear of falling, physical performance tests, health state and quality of life were assessed at a baseline examination.

Intervention Participants were divided into three intervention groups using block randomisation. The intervention programs were (1) a newly developed intervention program called Test&Exercise, (2) the Otago exercise program as a reference group [152], and (3) an intervention representing usual care in Switzerland as control group. This consisted of a small booklet with 12 exercises for balance and strength training, as a control group. The intervention lasted 6 months, with another 6 months of follow-up afterwards. After 6 and 12 months, the baseline examinations were remeasured.

Falls A fall was defined as an unexpected event in which the participant comes to rest on the ground, floor, or lower level, with or without injury. Incident falls were prospectively self-reported with a monthly fall calendar during the 12 months of intervention and follow-up. History of falls was assessed at baseline by asking how many falls occurred during the previous 12 months.

Kuopio Fall Prevention Study

The Kuopio Fall Prevention Study (KFPS) is a 2-year randomised controlled trial to estimate the effect of a fall prevention exercise program in community-dwelling older women in Kuopio, Finland. The trial was launched in 2016. The study was registered under https://clinicaltrials.gov/study/NCT02665169, and the detailed trial protocol was published in BMJ Open [170].

Participants Participants enrolled were female only, had a mean age of 76.5 years (SD 3.2, range 71.2 – 84.8), were living around the City of Kuopio, were able to attend exercise sessions twice a week and were in an adequate health state (self-ambulatory, no unstable angina pectoris, no severe pulmonary disease, no moderate to sever dementia).

Exclusion criteria Individuals living in institutional long-term care homes were excluded from the study. Variables of interest These included functional tests, social well-being, cognitive performance, sarcopenia and frailty measurements.

Intervention After baseline examination, participants were divided into intervention and control groups using block randomisation. The intervention included initial 6 months of supervised exercise including the free acces to municipal exercise facilities, another 6 months of unsupervised use and free access to exercise facilities, and following 12 months of low-cost access to exercise facilities. The control group also had low-cost access to exercise facilities without supervision for 24 months. Variables of interest were assessed at the baseline, at 12 months and 24 months. *paragraph* A fall was defined according to the WHO International ICD diagnosis code. Falls from the same level, on stairs, and from height were included. Incident falls were recorded biweekly via SMS, and in case of positive reports assessed with telephone interviews. History of falls was assessed at baseline by asking how many falls occurred during the previous 12 months.

Participants included in the meta-analysis

Inclusion criteria for the meta-analysis were defined for every cohort separately. Participants of the GERICO cohort had to have participated in the two follow-up visits from the study. For the SCT analysis, the participants were required to remain enrolled for at least one month after the baseline examination. For the KFPS study, participants had to have participated for at least one year. The flow of participants with inclusion and exclusion criteria for every cohort and this analysis are presented in Figure 5.1. A completed case analysis was conducted.

5.2.2 Statistical analysis

Outcome

The outcome variable was the number of incident falls. For SCT and KFPS, this referred to the reported number of falls during intervention and follow-up. For GERICO, the outcome was the number of falls reported at the second follow-up visit.

Predictors

The final models of all three cohorts included the history of falls measured as the prior number of falls during 12 months as a predictor. In the GERICO and KFPS

study, it was the only predictor included in the suggested models. In the SCT model, fear of falling measured with FES-I was the only additional predictor. Since fear of falling was not assessed in the other two cohorts, it was not included in this analysis. In the analysis of the SCT study, we showed that the number of prior falls is best treated as a factor variable with levels 0, 1, 2, 3, 4 and ≥ 5, in contrast to using it as binary information (previous falls yes vs. no) or a continuous variable [149]. Therefore, the number of prior falls was introduced as a factor variable with those six levels. No falls was defined as the reference category in all three cohorts.

Combined analysis

The combined analysis was performed using the methodology of a two-stage meta-analysis as described by Burke *et al.* [172]. In the first stage, the prediction models were fit separately for every data set with negative binomial regression models, resulting in a coefficient estimate for every level of the factor variable. The SCT model included an offset because not all participants were followed up for 12 months.

In the second stage, the three resulting coefficient estimates and standard deviations were meta-analysed for each factor level and the dispersion parameter θ . A random effect model with inverse variance weighting was fitted. τ^2 was estimated with the restricted maximum likelihood estimator. Higgin's I^2 was computed to investigate the percentage of variance attributable to the study heterogeneity among the true effects.

Model validation and calibration

The apparent absolute mean prediction error for the three first-stage models was calculated. In addition, the three models were externally validated by calculating the prediction error for unseen data, e.g. using the GERICO model, the prediction error was derived for the SCT and the KFPS data set. The prediction error of the overall model derived with the combined analysis was calculated with all three cohorts. The method for calibration-in-the-large was adapted from Crowson et al. [173], suggesting a regression model-based framework for calibrating survival data. The following steps were performed on the link scale: (1) fit the new data to the

existing model, resulting in a linear predictor $p0$ (2) fit a new negative binomial regression model with the outcome variable from the new data set $outcome_{new}$ and using the linear predictor $p0$ as an offset, (3) use the intercept α_{new} derived from the model fitted in step 2 to update $p0$ such that the updated prediction $p1$ is derived as $p1 = anew + p0$. α_new is referred to as the calibration-in-the-large or the recalibration constant. A detailed example of the R code can be found in the supplementary material. Calibration was assessed by plotting the expected versus the observed number of falls in form of a rootogram [137], [139].

Statistical program

All statistical analysis was conducted with R Studio Version 4.2.2. For the meta-analysis, the package "metafor" was used [174].

5.3 Results

5.3.1 Study characteristics

All three studies were prospective trials including community-dwelling older adults. While the SCT and the KFPS were randomised controlled trials to investigate new fall prevention interventions, the GERICO study was an observational study. The number of participants enrolled in the GERICO, SCT, and KFPS were 1046, 405, and 913, respectively. Of these, 642, 370, and 855, respectively, fulfilled the inclusion criteria for the analysis. Twelve participants had missing fall data in the GERICO study, resulting in 630 participants included in the analysis. The GERICO and SCT cohorts included both sexes, with mostly females (GERICO: 80%, SCT: 73%). Only women participated in the KFPS. The mean age was 67.9 years for GERICO, 78.7 years for SCT, and 76.5 years for KFPS. In total, 1810 falls were reported before the baseline examination, and 1565 falls after the baseline examination. For the GERICO trial, the mean number of falls during the 12 months before the follow-up visit 1 was 1.03 and decreased to 0.69 falls during the 12 months before the follow-up visit 2. In the SCT, the mean number of reported falls during 12 months before the baseline examination was 1.45, and 1.30 falls per person-year were reported for the

Table 5.1: Comparison of the trial designs and cohort characteristics.

	GERICO	**SCT**	**KFPS**
Country	Geneva, Switzerland	Valais, Switzerland	Kuopio, Finland
Study design	Prospective observational trial	Prospective RCT	Prospective RCT
Setting	Community-dwelling older adults	Community-dwelling older adults	Community-dwelling older adults
No. of participants enrolled in study	1046	405	913
No of participants included in analysis	630	370	855
Sex (male/female)	126/504	100/207	0/855
Mean age (SD) [years]	67.9 (1.6)	78.7 (6.8)	76.5 (3.2)
Previous falls during 12 months			
Number	646	537	627
Mean	1.03	1.45	0.73
Reporting	Self-reported retrospective	Self-reported retrospective	Self-reported retrospective
Incidence falls			
Number[a]	439	371	755
Mean	0.69	1.30	0.83
Reporting	Self reported, retrospective	Self-reported with monthly falls calendar, prospective	Biweekly SMS and phone-calls, prospective

Abbreviations: GERICO Geneva Retirees Cohort; *KFPS* Kuopio Fall Prevention Study; *RCT* randomised controlled trial; *SCT* Swiss CHEF Trial; SD standard deviation; [a] per person year

year following the baseline examination. In the KFPS, 0.73 falls per person have been reported before baseline examination, and 0.83 in the subsequent 12 months. All results comparing the trial and cohort characteristics are presented in Table 5.1.

5.3.2 Combined analysis

The results of the three models fitted in the first stage and of the random effect models derived in the second stage are shown in a forest plot in Figure 5.2; Table 5.2. The heterogeneity measures for the coefficients are also presented Table 5.2.

The baseline rate or intercept varied among the three cohorts (GERICO: 0.43 [95% CI from 0.35 to 0.52]; SCT: 0.83 [95% CI from 0.61 to 1.14]; KFPS: 0.61 [95% CI from 0.54 to 0.79]). The overall estimate for the baseline rate derived with the random effect model was 0.59 (95% CI from 0.41 to 0.85) and showed a high heterogeneity (τ^2:0.088, I^2: 89.24%). The rate ratios for one prior fall (GERICO: 1.64 [95% CI from 1.22 to 2.21]; SCT: 1.00 [95% CI from 0.64 to 1.54]; KFPS: 1.46 [95% CI from 1.15 to 1.87]) were in a comparable magnitude as for two prior falls (GERICO: 1.13 [95% CI from 0.70 to 1.82]; SCT: 1.07 [95% CI from 0.63 to 1.82]; KFPS: 1.65 [95% CI from 1.21 to 2.25]). Accordingly, the overall estimates were 1.41 (95% CI from 1.13 to 1.76) for one prior fall and 1.33 (95% CI from 0.98 to 1.81) for two prior falls. Heterogeneity was also comparable and lower for the baseline rate (one prior fall: τ^2: 0.013, I^2: 33.50%; two prior falls τ^2: 0.026 I^2: 34.55%). The rate ratios for three prior falls increased similarly in all three studies (GERICO: 2.55 [95% CI from 1.52 to 4.29]; SCT: 2.18 [95% CI from 1.15 to 4.15]; KFPS: 2.98 [95% CI from 1.90 to 4.68]), resulting in an overall effect estimate of 2.64 (95% CI from 1.96 to 3.57). The two heterogeneity measures τ^2 and I^2 were equal to zero. The rate ratios for four prior falls were more heterogenous, with the highest estimate for the KFPS (GERICO: 2.33 [95%CI from 0.96 to 5.65]; SCT: 3.09 [95% CI from 1.26 to 7.58]; KFPS: 6.24 [95% CI from 3.71 to 10.48]). The overall estimate was 3.89 (95% CI from 2.06 to 7.34), with the heterogeneity reflected in the corresponding measures (τ^2: 0.169, I^2: 53.19%). The highest estimates were reached for five or more prior falls (GERICO: 10.02 [95% CI from 6.17 to 16.27]; SCT: 7.39 [95% CI from 3.77 to 14.46]; KFPS: 7.40 [95% CI from 4.15 to 13.20]) resulting in an overall effect estimate of 8.48 (95% CI from 6.13 to 11.74) with no heterogeneity present (τ^2: 0.000, I^2: 0.00%).

Table 5.2: Rate ratios with 95% confidence interval and heterogeneity measures for all models.

	Rate ratios (95% CI				**Heterogeneity**	
	GERICO n = 630	**SCT** n = 370	**KFPS** n = 855	**Overall** n = 1855	τ^2	I^2 (%)
Baseline rate per year	0.43 (0.35 to 0.52)	0.83 (0.61 to 1.14)	0.61 (0.54 to 0.70)	0.59 (0.41 to 0.85)	0.088	89.24
Prior falls 1	1.64 (1.22 to 2.21)	1.00 (0.64 to 1.54)	1.46 (1.15 to 1.87)	1.41 (1.13 to 1.76)	0.013	33.50
Prior falls 2	1.13 (0.70 to 1.82)	1.07 (0.63 to 1.82)	1.65 (1.21 to 2.25)	1.33 (0.98 to 1.81)	0.026	34.55
Prior falls 3	2.55 (1.52 to 4.29)	2.18 (1.15 to 4.15)	2.98 (1.90 to 4.68)	2.64 (1.96 to 3.57)	0.000	00.00
Prior falls 4	2.33 (0.96 to 5.65)	3.09 (1.26 to 7.58)	6.24 (3.71 to 10.48)	3.89 (2.06 to 7.34)	0.169	53.19
Prior falls ≥ 5	10.02 (6.17 to 16.27)	7.39 (3.77 to 14.46)	7.40 (4.15 to 13.20)	8.48 (6.13 to 11.74)	0.000	00.00
θ	1.06 (0.71 to 1.42)	0.66 (0.44 to 0.87)	1.18 (0.86 to 1.50)	0.94 (0.61 to 1.27)	0.25	73.85

Abbreviations: *n* number of participants; $^I2$ Higgin's $^I2$; *CI* confidence interval; θ dispersion parameter; *GERICO* Geneva Retirees Cohort; *SCT* Swiss CHEF Trial; *KFPS* Kuopio Fall Prevention Study

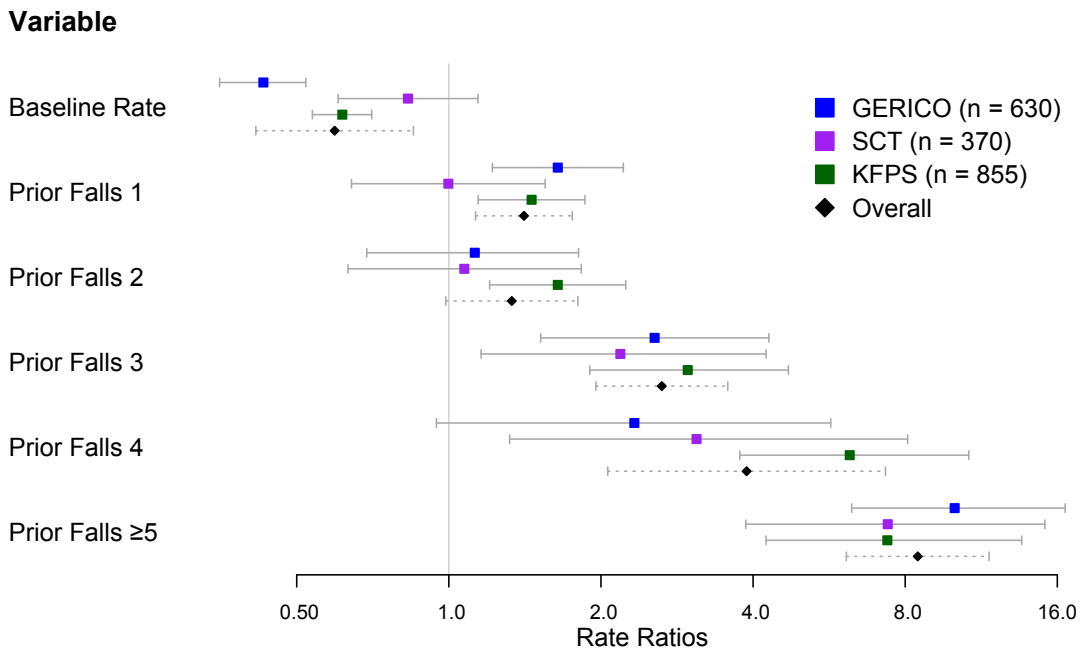

Figure 5.2: Baseline rate and rate ratios for the model coefficients with 95% confidence intervals.

5.3.3 Model validation and calibration

The apparent mean absolute prediction error was highest for the SCT followed by KFPS and GERICO (GERICO: 0.82; SCT; 1.16; KFPS: 0.92). For the external model validation, the mean absolute prediction error for the GERICO data set was comparable to the apparent error when applied to the other three models, (SCT model: 0.82; KFPS: 0.81 model; Overall model: 0.81). Similar results were found for the SCT data set (GERICO model: 1.19; KFPS model: 1.14; Overall model: 1.15), and the KFPS data set (SCT model: 0.94; KFPS model: 0.92; Overall model: 0.92). These results indicate that the models here are not prone to overfitting and hardly any bias. In addition, the method used for recalibration can catch the baseline rate of the cohorts. The result of the model validation and the recalibration constant between the models are summarised in the supplementary materials in Table 5.5. Marginal calibration plots for the three data sets applied to the overall model in the form of a hanging rootogram are presented in Fig. 3. The bars represent the observed frequency per fall number category, while the red

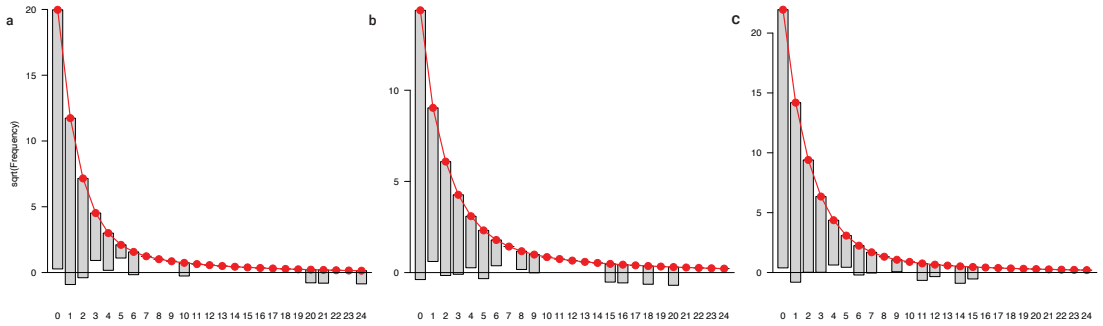

Figure 5.3: Hanging rootograms as marginal calibration diagrams for **(a)** the GERICO data, **(b)** the SCT data and **(c)** the KFPS data applied to the overall model showing the deviation between the actual (grey bars) and predicted (red line) number of individuals per fall number category.

curve shows the expected frequency. Deviations between expected and observed can be seen when focusing on the x-axis: whereas overshooting into the negative y values means underestimation, floating bars not reaching the x-axis indicate overestimation of the expected frequency estimated by the prediction model. The diagrams show that the overall model is well calibrated, especially in the range of low fall numbers. The biggest difference can be found for high-frequency fallers, such as 20 falls or more. The rootograms for the other combinations of models and data sets (e.g., SCT data applied to the GERICO model) can be found in the supplementary materials in eFigure 1.

5.4 Discussion

This analysis compared three fall rate prediction models that were previously developed in independent cohorts and derived overall model coefficients using the methodology of a two-stage meta-analysis. Additionally, external model validation including model recalibration was performed. We found that the coefficient estimates among the three models were reasonably consistent, which was also reflected in heterogeneity measures such as Higgin's I^2. The heterogeneity seen in the baseline rate can be explained by the different fall incidences in the cohorts. However, such differences can be adjusted for with proper calibration methods, as for example

suggested by Crowson et al. [173]. Our findings suggest that the number of prior falls as a factor variable is a robust predictor for future falls in community-dwelling older adults among different cohorts. Further studies and investigations are required to find out whether the model can be transferred to even more different settings, for example, to older adults living in institutions, or the oldest old.

Despite the differences in study design and cohort characteristics, the prediction error for the cohorts was shown to be independent of the model that was used to compute the prediction, indicating that no bias in the first-stage models was present. However, no external validation was done for the overall model. In order to check for bias in the overall model towards the data it was derived with, an unseen dataset is required. When comparing the prediction errors presented in this analysis with literature, only one study comes in quest. The prediction error of the PREFALL model that was derived using a similar development strategy is in the same range as our results [126]. They report a bootstrapped mean absolute error of 0.88 falls per year. Further comparisons with other studies are only possible to a limited extent, as most fall prediction models are based on predicting the fall risk and not the fall rate.

Although it is known that there exists a vast amount of risk factors that are associated with falling, the previously conducted analysis of the three cohorts showed that prior falls were superior in predicting future falls compared to other predictors. Variables such as physical performance tests, age, sex, comorbidities, medication, or quality of life were not improving the predictive accuracy of the models in combination with the history of falls [114], [149]. Fear of falling was the only additional predictor selected with variable selection in the SCT study. However, this information was not recorded in all three studies and could not be considered in this analysis. One reason for the lack of further predictors in the models could be the complexity and multifactorial nature of the fall, which can vary greatly from person to person. While one person may be falling due to the combination of vision impairment and balance problems, another may fall because of a lack of strength and a medication that has a side effect of dizziness. It may not be possible to capture or assess all relevant combinations of risk factors for

each person in a statistical model. Hence, the presence of prior falls themselves might be the best reflection of whether an individual is exposed to the relevant combination of risk factors for falling. Nevertheless, this bears the risk that the model cannot properly catch first-time fallers. All individuals without a history of falls have an identical predicted fall rate, which does not reflect reality. Therefore, further risk factors sensitive enough to catch first-time fallers must be identified, even if information about the fall history is available. Once identified, the model proposed here could be updated accordingly.

5.4.1 Strength and limitations

A strength of this study is the large number of data points available for this analysis: In total 1855 participants were included in this combined analysis. In addition, individual participant data were accessible, enabling the identical treatment of outcome and predictor variables among the three cohorts and thus the application of a two-stage meta-analysis methodology. Furthermore, the history of falls was recorded as the number of previously experienced falls, providing more detailed information than a dichotomised variable (yes versus no).

This analysis also has some limitations, which mainly concern the study design. First, the SCT and KFPS studies were designed as prospective randomised controlled trials with preventive interventions that potentially impact the observed fall incidence rates. Accordingly, the results could differ compared to purely observational data. However, when comparing with the results from GERICO analysis as an observational data set, such differences were not found. Yet, in the GERICO study, incident falls and history of falls were recorded retrospectively at two time-points four years apart. Four years between the two visits is a long time span in a fall prediction setting. In addition, it has been reported that retrospective reporting can result in deviations of the true fall number [148]. Furthermore, the inclusion criteria for participants of the three studies differed: In the SCT study, participants were the only ones who had to be classified as at risk of falling for enrolment, while participants with major comorbidities were excluded in the GERICO study. This

might have led to a different selection of study participants. Next to that, the sex distribution among the participants was no balanced, with a vast majority of female participants. And last, the individuals who participated in these three studies have been enrolled out of self-motivation. It has been reported that such individuals are health-wise better off compared to nonparticipants, resulting in a selection bias and may limit the generalisability of such findings [175].

Clinical implications and applicability

As the majority of non-vertebral fragility fractures are the result of a fall, the risk of injury increases directly together with the frequency of falls. Accordingly, the estimate of how many times an individual is going to fall can help improve fracture prediction. However, not only fractures but many other injury types in older adults are a consequence of falls [1]. Therefore, estimating a fall rate might also be beneficial in other fields of injury prevention. The simple question "How many times did you fall in the last 12 months?" would be sufficient to derive the fall rate estimate. This information can be further used or integrated into subsequent models to estimate the risk of an event of interest. We want to stress that asking for the number of falls, and not just whether falls have occurred, is helping to improve prediction accuracy. Furthermore, we suggest that falls should be reported as numbers and not as binary variables in research articles.

To make the model applicable in different geographical settings, calibration considering the differences of fall incidences between regions or countries is required. The method presented here to recalibrate between cohorts [173] showed good performance and is easily implemented.

5.4.2 Conclusion

We found that the number of previous falls treated as a factor variable is a robust predictor of estimating fall rates among different cohorts. In addition, a proper recalibration can account for variations in fall incidences between different cohorts. Further investigations are required to find predictors that can identify first-time fallers.

Supplementary Information

Author contributions

Study design: C.W., M.Z.; Data collection: A-G.M.H, R.H., E.B., T.R., H.K., S.F.; Statistical analysis: C.W.; Interpretation of results: C.W., T.R., M.Z., P.Z.; Drafting of the manuscript: C.W.; Proofreading of the manuscript: all authors. Approval of the final draft: all authors.

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Data availability

R Code files and data will be made available upon reasonable request. Please get in touch with the corresponding author through christina.wapp@unibe.ch.

Ethical approval

This article is a combined analysis of previously developed model coefficients and does not need any ethical approval. For the three included studies in this analysis, ethics approval was provided by the local ethical committee.

Consent of publication

Not applicable

Competing interests

The authors declare no competing interests.

Supplementary material

Development of the prediction model for the Kuopio Fall Prevention Study

Methods

Participants Participants were included in the analysis if they completed at least 1 year of follow-up.

Outcome variable The outcome variable was the prospectively reported number of falls during the first 12 months after the baseline examination.

Predictors *General characteristics:* Age; Body mass index; living alone (yes/no)
History of falls: Number of falls experienced during the 12 months before the baseline examination
Fear of falling: The following question was asked: "Are you afraid of falling today?" Answer options were: no / yes, rarely / yes, sometimes / yes, often / yes, constantly.
Physical performance tests: Able to squat to the floor (yes/no); One-legged stance test (at least 3 seconds, maximum 30 seconds); hand grip strength (maximum dominant hand, measured in kg), Timed Up and Go (seconds); body sway (open and closed eyes, normal stance and semi-tandem, measured in mm); isometric leg extension force (left and right leg, two attempts each, measured in Nm)
Activity and physical performance: Self-perceived physical condition (very bad / pretty bad / satisfactory / pretty good / very good); Exercise frequency (almost never / 1-3x a months / 1x a week / 2x a week / 3x a week /4x a week / 5x a week / (almost) daily); physical inactive hours per day
Health state: Self-perceived health state (very good / good / mediocre / bad); number of medication
Intervention group: Intervention vs control group

Processing of predictors Age was centred at 65 years. The number of prior falls was treated as a categorical variable with the levels 0, 1, 2, 3, 4 and ≥5 falls. Fear of falling was summarised to three levels (no / yes, rarely + yes, sometimes / yes, often + yes, constant). Body sway was included as the difference between open and closed eyes with normal stance. The self-perceived physical condition was summarised into three levels (very bad + pretty bad / satisfactory / pretty good + very good). Exercise frequency was summarised into four levels (almost never + 1-3x a month / 1-2x a week / 3-4x a week / 5x or more a week). The number of medication was also dichotomized (0-2 / 3-4 / 5-6 / ≥7).

Missing data A completed case analysis was conducted.

Model fit and variable selection A model including all candidate predictors was fit. Variable selection was then conducted with backward elimination using the Bayesian information criteria as a stopping rule.

Results

Participants In total, 913 participants were enrolled in the study. Thereof, 855 completed at least one year of follow-up. 38 (4.4%) had missing data and were excluded from the analysis, resulting in 817 participants used for the prediction model development.

Selected model The final model included the prior number of falls as the only predictor (Table 5.3).

Table 5.3: Model coefficients.

	Incidence rate ratios (95% CI)
Intercept	0.62 (0.54 to 0.71)
0 prior falls	*ref*
1 prior fall	1.47 (1.15 to 1.88)
2 prior falls	1.62 (1.19 to 2.23)
3 prior falls	2.97 (1.90 to 4.65)
4 prior falls	6.21 (3.71 to 10.40)
≥ 5 prior falls	7.37 (4.16 to 13.09)

Prediction error The apparent mean absolute prediction error of the selected model was 0.92.

R Code: Calibration in the large

```
# fit the original model for the SCT data
> model_sct <- glm.nb(falls ~ prior_falls +
offset(log(participation_time), data = data_sct)

# calculate the linear predictor for the KFPS data with the SCT model
> p0_kfps <- predict(model_sct, newdata = data_kfps, response = "link")

# fit a new negative binomial model with the falls from KFPS as outcome
variable and p0_kfps as offset
> recal_model <- glm.nb(falls ~ offset(p0_kfps), data = kfps)

# use the intercept alpha derived from the recal_model to update the
predictions p0_kfps
> p1_kfps <- alpha + p0_kfps

# if wanted, the updated linear predictor can now be transformed to the
response scale with exp(), resulting in expected frequencies
> p1_kfps_resp <- exp(p1_kfps)
```

Supplementary tables

Table 5.4: Variables assessed in the different cohorts related to the risk of falling.

Variables	GERICO	SCT	KFPS
General			
Age	x	x	x
Sex	x	x	x
BMI	x	x	x
Living area (urban/rural)		x	

Continued on next page

Table 5.4 – *continued from previous page*

Variables	**GERICO**	**SCT**	**KFPS**
Living alone (yes/no)			x
Fear of falling			
FES-I		x	
Fear of falling		x	x
Physical performance tests			
Gait speed	x	x	
Five Times Sit-to-Stand	x	x	
Balance test	x		
Hand grip strength	x		x
One Legged Stance Test	x	x	x
Functional reach test		x	
Timed Up and Go		x	x
Four Stage Balance Test		x	
Base of support width		x	
Body sway			x
Able to squat to floor (yes/no)			x
Isometric leg extension force			x
Physical activity (kcal/day)	x		
Exercise frequency			x
Physical condition (self-perceived)			x
Health state and comorbidities			
Charlson's Comorbidity Index	x		
Comorbidity number	x		
Medication number	x	x	x
Hearing problem (yes/no)		x	
Vision impairment (yes/no)		x	
Walking aid (yes/no)		x	
Urinary incontinence (yes/no)		x	
Musculoskeletal disorder (yes/no)		x	
Neurological disorder (yes/no)		x	
Perceived pain (range 0 - 100)		x	
Self-perceived health state			x
Quality of life			
OPQOL-35		x	

Abbreviations: *GERICO* Geneva Retirees Cohort; *SCT* Swiss CHEF Trial; *KFPS* Kuopio Fall Prevention Study; *OPQOL-35* Older People's Quality of Life Questionnaire

Table 5.5: Mean absolute prediction error for every data set applied to the different models

	Data used for prediction					
Model	GERICO		SCT		KFPS	
	MAE	RC	MAE	RC	MAE	RC
GERICO	0.82	-	1.19	0.47	0.94	0.41
SCT	0.82	-0.47	1.16	-	0.94	-0.12
KFPS	0.81	-0.35	1.14	0.06	0.92	-
Overall	0.81	-0.29	1.15	0.15	0.92	0.09

Abbreviations: GERICO Geneva Retirees Cohort; *SCT* Swiss CHEF Trial; *KFPS* Kuopio Fall Prevention Study; *MAE* Mean absolute error; *RC* Recalibration constant

6

A novel fragility hip fracture risk calculator based on a mechanistic and stochastic modelling approach

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Author contributions The author of this thesis contributed to the clinical data collection, the conceptualisation of the model, the development of the methodology, the qualitative analysis, and the writing of the manuscript.

Abstract

Fragility hip fractures in older adults are a major burden for the individual and society, as they result in increased morbidity, mortality and substantial health care expenditure. The vast majority of hip fractures are caused by falls resulting in an impact on the hip, inducing a force that exceeds the femoral bone strength. The risk of fracturing depends on the rate of falling, the fall-induced impact force, and the femoral bone strength. This article presents the framework of a novel fragility hip fracture risk calculator based on a mechanistic and stochastic modelling approach. The model integrates the stochastic aspects of a fall and its dynamics together with a 1D mechanical model predicting the impact force in the hip to calculate a one-year absolute fracture risk. The required input parameters can be estimated with anthropometric and densitometric data, and can be refined using QCT images. A sensitivity analysis was conducted with data from the AFFIRM-CT cohort, confirming that the fall rate, the trochanteric soft tissue thickness and the bone strength are the dominating parameters influencing the risk of fragility hip fractures. Furthermore, output variables such as the predicted impact velocity (mean (SD): 2.24 m/s (0.41)) and impact force (0 - 11802 N) aligned well with experimental data. Thus, the model is able to reflect observations from empirical data, indicating that it can capture the intrinsic aspects that affect the risk of fragility hip fractures.

Keywords fragility hip fracture, prediction, falls, impact force

6.1 Introduction

In 2019, around 82'000 fragility fractures were registered in Switzerland in individuals aged 50 and older, referring to an annual fracture rate of 23.5 fractures per 1000 individuals [1]. Due to the ageing of the population, this number is expected to increase by 37.5% by 2034. The consequences of fragility fractures include morbidity, mortality, and substantial health care expenditure [176], [177], [178]. Fractures of the hip are the most serious type, with a mortality risk of up to 20%

[13]. Against this background, it is of great interest to identify individuals at risk of fragility fractures, especially of the hip.

Fragility fractures are the clinical outcome of osteoporosis, a silent metabolic bone disease affecting primarily older adults. Osteoporosis is characterised by bone loss [179] and can be assessed by measuring areal bone mineral density (aBMD) with dual energy X-ray absorptiometry (DXA) [18]. FRAX® is a frequently used model for fracture risk assessment that combines clinical risk factors such as sex, current smoking status, alcohol consumption or prior fragility fractures with aBMD using a statistical regression model [4], [180], as aBMD alone has limited predictive power [23], [28], [176].

When looking at the mechanism leading to hip fractures, it is found that around 95% of the cases are caused by falls resulting in an impact on the hip [42], [168]. From a biomechanical point of view, the bone fractures when the impact force exceeds femoral strength. Since only 1-3% of all falls result in a fracture [43], this suggests that either the available energy is not sufficient to cause a fracture or that energy-dissipating mechanisms reduce the impact force below a critical level [57]. Thus, the risk of hip fracture is dependent on different factors that can be summarised by three main points, namely (1) the actual risk of falling, respectively the frequency of falls, (2) the impact force on the hip and (3) the femoral bone strength.

Bone strength can be estimated with finite element analysis (FEA) based on quantitative computed tomography (QCT) images, a method that has been thoroughly studied and validated [20]. The assessment of bone mineral density (BMD) and fracture risk with the use of clinical QCT scans that were performed for other diagnostic purposes is known as opportunistic screening [22]. However, also aBMD values from DXA can be used to derive bone strength, as these two measures are known to strongly correlate [15].

Factors that influence the impact force can be divided into two main areas: the impact velocity and the visco-elastic behaviour of the hip complex. First, the impact velocity determines the magnitude of the impact force when the hip is hitting the ground. It depends on different factors such as the initial height of

the fall, the effective mass, the initiation mechanism of the fall, the pre-impact movement strategies or the landing configuration [43], [57], [83]. These aspects can vary significantly from fall to fall and influence the impact velocity accordingly. The second point to consider is the visco-elastic behaviour of the hip complex. The hip consists of skin, muscle, fat, ligaments and cartilage, in which the femur and the pelvis bone are embedded. The force attenuation during the transmission through the hip determines the force magnitude reaching the proximal femur. Various *in vivo* and *ex vivo* experiments were conducted to characterise this behaviour upon impact [72], [92], [93], [95], and damped vibrational systems were used to model and predict the impact response [74]. Thereby, the trochanteric soft tissue, respectively its thickness, was shown to be a critical factor influencing the effective stiffness and damping properties [72], [97], [99], [100]. A further parameter that was reported to influence these properties is the condition of the muscles (relaxed/contracted) [72], [108]. And last, the floor type influences the impact force, too [109]. To sum up, various subject-specific parameters but also fall-dynamic related factors influence the impact force, making the accurate prediction a difficult task. Nasiri and Sarvi summarised these aspects in a thorough review [45].

Several mechanistic hip fracture prediction models have been developed. While some derived the impact force through a standardised formula accounting for height, weight and soft tissue thickness [46], others tried to integrate the subject-specific fall dynamics and joint forces of a standard sideways fall [110], [181], or showed the importance of subject-specific parameters when modelling the impact force for fracture prediction [112]. However, most models do not predict an absolute fracture risk but try to evaluate the ratio between impact force and bone strength and subsequently assess the correct classification of fracture cases [95], [112]. Others derive the relative risk, e.g. by using this ratio as a predictor in a Cox proportional hazard model [46]. Bhattacharya *et al.* integrated a mechanistic model into a probabilistic setting, allowing the prediction of an absolute fracture risk within a year [113]. The multi-scale model consists of three submodels: a model that derives the impact force given different fall dynamics, a model to estimate the

force attenuation during the impact of the hip complex, and an FEA model to estimate bone strength given different impact orientations. In a further step, probability distributions are assigned to the different parameters modelling the fall dynamics, and with the assumption of a constant fall rate, a probability of a fracture within a year is derived.

In summary, most mechanistic risk calculators assess the impact force, bone strength, and some aspects of the fall dynamics, but they do not integrate the probability of different fall scenarios. When looking at the clinical standard of care for fracture risk assessment, the recently updated version of FRAX®, FRAXplus®, has now integrated the risk of falling with information about the number of falls in the preceding year [182]. However, as it is a regression-based tool, the information is treated as a risk factor for hip fractures and not its cause.

In 2010, a hip fracture risk prediction model using an alternative modelling approach than previously known in literature was presented [8]. It is based on a mechanistic stochastic framework and derives the probability of at least one hip fracture in a given time interval (0,T] by combining the stochastic aspects of a fall and the fall dynamics with femoral bone strength. Briefly, the occurrence of a fall is modelled using a Poisson process characterised by the rate parameter λ. The chances of the fall-induced impact force exceeding the femoral strength are modelled with a random variable following a probability distribution. Hence, the probability distribution is an indirect representation of the countless possibilities of fall scenarios resulting in different load cases. By the introduction of a so-called thinned Poisson process, only the fall events resulting in a fracture are retained. Without the use of any empirical data but the simple assumptions that bone strength is defined through BMD and that the fall rate λ is increasing with age, the model is able to describe several key aspects of hip fractures observed in clinics. First, it shows that the fracture probability increases with decreasing bone strength in an age-dependent manner. Second, it demonstrates that the BMD has limited predictive power, as the distribution of individuals experiencing a fracture strongly overlaps with those who do not fracture. And last, by using a Bayesian approach,

it shows that the fracture risk increases significantly when having experienced a prior fracture, especially in the lower BMD range.

Nonetheless, several aspects could be further developed and refined. First, a model to estimate an individual's fall rate λ could be integrated, and second, further insights into the probability distribution describing the chances of the impact force exceeding the femoral bone strength is required.

The goal of our work was to personalise the model suggested by Schechner *et al.* by integrating a personalised fall rate estimate, and by extending the probability distribution representing the chances of the femoral bone to break upon impact with a mechanical impact force model. In previous work, we have developed a model to predict a personalised fall rate λ. [114], [149], [167]. Here, we present a model to predict a personalised impact force using subject-specific parameters, mostly derived from QCT images, that is then combined with a probability distribution that describes the stochastic nature of the fall dynamics. In case QCT images are not available, we provide substitution equations for the required parameters. In a further step, we conducted a sensitivity analysis of the calculator using clinical data from the AFFIRM-CT cohort with the aim of assessing the influence of the different parameters on the risk of hip fractures.

6.2 Methods

6.2.1 Impact force model

The probability of at least one hip fracture in the time interval $(0, T]$ is given by the thinned Poisson process such that

$$P(\textit{Fracture in } (0,T]) = 1 - e^{-\lambda p_s T} \tag{6.1}$$

with λ as the fall rate, and $p_S = P(Fracture|\textit{Fall in } (0,T])$ as the conditional probability of a hip fracture given a fall [8]. A detailed description of the derivation of this formulation can be found in the supplementary material or in the original publication by Schechner *et al.* [8]. The conditional probability of a fracture given a fall p_S is defined as the probability of the fall-induced load exceeding the femoral

strength, with the load modelled as a random variable accounting for the varying fall dynamics. In the following sections, we present a personalised impact force model characterising p_S. We introduce a mechanical 1D mass-spring-damper system consisting of rheological elements representing the hip complex and the ground. It models the non-linear visco-elastic response of the hip upon impact, allowing the calculation of the impact force in the hip. Thereby, the impact velocity is the critical factor that defines the magnitude of the impact force. Since the impact velocity varies with the fall dynamics, a second model that derives the range of possible impact velocities given different fall scenarios is introduced. And last, we present a probability distribution that describes the probability of different impact velocities given the fall dynamics, allowing for the calculation of an absolute fracture risk.

Mechanical model

The mechanical model is a 1D model that reflects a standardised lateral impact on the hip. It is composed of rheological elements representing the pelvis bone, the femur, the soft tissue and the ground. As the centre of mass at the impact is assumed to be in the centre of the torso, the model only depicts half of the hip. The hemi-pelvis (HP), the femur and the ground (G) are modelled with linear springs, and the visco-elastic behaviour of the soft tissue (ST) is represented by a standard non-linear solid (Figure 6.1).

The equations of motion of the mechanical model are given as a system of differential algebraic equations (DAE) such that

$$\begin{aligned} m * x_4'' + F_{BR} + F_{HP} + m * g &= 0 \\ F_{HP} - F_{Femur} &= 0 \\ F_{S0} + F_{S1} - F_{Femur} &= 0 \\ F_{S1} - F_{D1} &= 0 \\ F_{S0} + F_{S1} - F_G &= 0 \end{aligned} \tag{6.2}$$

Table 6.1: List of symbols and abbreviations for the hip fracture risk calculator in alphabetic order.

Symbol/abbreviation	Meaning
cmh	Height of the centre of mass at the start of the fall measured from $x = 0$
cmi	Height of the centre of mass at the start of the impact measured from $x = 0$
$F_{()}$	Forces in the rheological elements of the ground (G), soft tissue (ST), femur and hemi-pelvis (HP)
FSR	Ratio between the fall-induced peak force applied to the femur F_{Femur} and the femoral strength $F_{Strength}$
fas_{S0}, fas_{S1}	Spring force amplitude of the soft tissue
$h_{()}$	Initial height of the ground (G), soft tissue (ST), femur and hemi-pelvis (HP)
$height$	Full body height
$k_{()}$	Stiffness of the rheological elements of the ground (G), soft tissue (ST), femur and hemi-pelvis (HP)
$k_{BR_{crit}}$	Critical stiffness of the body resistance, resulting in a $FSR = 1$
m	Effective mass
p_S	Conditional probability of a fracture given a fall
rk_{BR}	Relative value of the stiffness of the body resistance so that $rk_{BR} \in [0, 1]$
T	Time interval of the Poisson process
t_{imp}	Time at impact with $t = 0$ at the start of the descent phase of a fall
v_{imp}	Velocity at impact, when the hip touches the ground
$weight$	Full body weight
α	Exponent of the probability distribution describing the fall dynamics
λ	Fall rate characterising the Poisson process
μ_{D1}	Soft tissue damping coefficient

with $F_{()}$ as the rheologic elements' corresponding forces that depend on the variables $x_1(t)$, $x_2(t)$, $x_{21}(t)$, $x_3(t)$, $x_4(t)$, and $m = 0.5 * 0.678 * weight$ as the effective mass of the upper body [73] and $g = 9.81 m/s^2$ as the gravitational acceleration. The

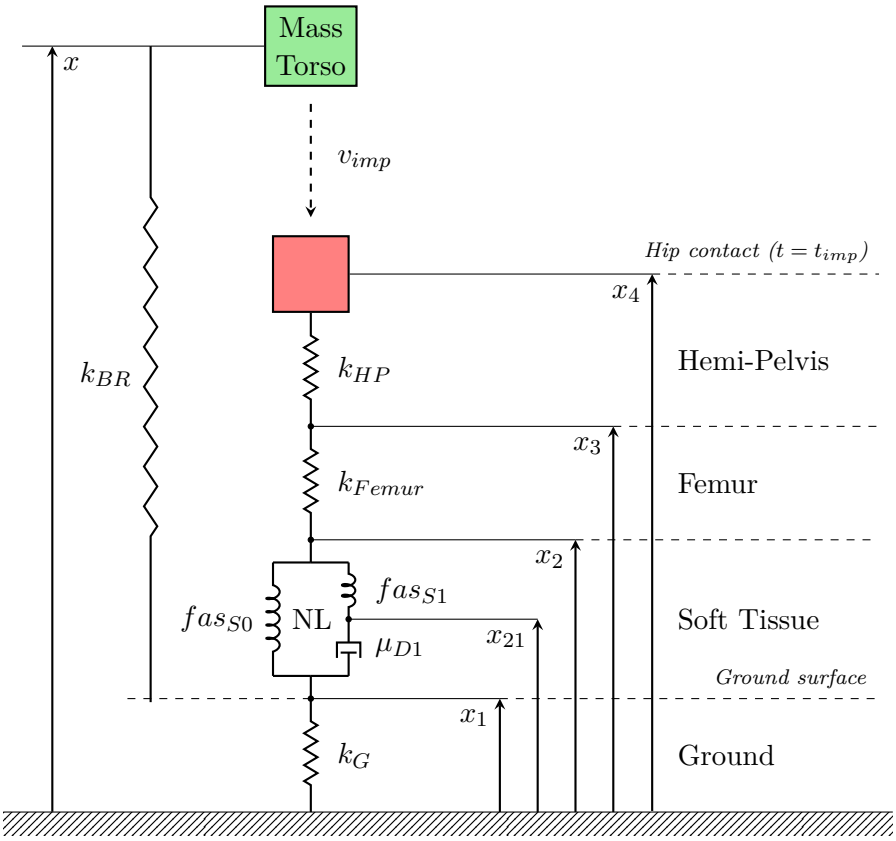

Figure 6.1: Drawing of the impact force model: The fall dynamic model consists of the spring k_{BR}, which is used to calculate the impact velocity. The mechanical 1D model consists of rheological elements representing the hip complex and the ground. It requires the impact velocity as defined by the fall dynamics model as an initial condition.

initial conditions of the DAE system are defined as follows:

$$\begin{aligned} x_4'(0) &= -v_{imp} \\ x_4(0) &= h_G + h_{ST} + h_{Femur} + h_{HP} \\ x_3(0) &= h_G + h_{ST} + h_{Femur} \\ x_{21}(0) &= h_G + h_{ST} \\ x_2(0) &= h_G + h_{ST} \\ x_1(0) &= h_G \end{aligned} \tag{6.3}$$

with v_{imp} as the impact velocity and $h_{()}$ as the initial height of the respective rheological elements. By solving the DAE for $x_1(t)$, $x_2(t)$, $x_{21}(t)$, $x_3(t)$ and $x_4(t)$,

the impact force can be calculated. Thereby, the impact velocity v_{imp} is the only initial condition that changes depending on the fall dynamics. Thus, it is the critical factor that determines the magnitude of the impact forces in the mechanical systems. The explicit formulations of the forces can be found in the supplementary materials (Section 6.5).

Fall dynamics model

We decided to model the fall dynamics resulting in different impact velocities with a linear spring representing the resistance of the body (BR) to the fall (Figure 6.1). Thereby, the spring, characterised by the constant k_{BR}, acts as an energy storage mechanism during the fall and the impact, with more energy stored, resulting in a lower impact velocity. The spring constant represents all parameters that can vary from fall to fall and that are difficult to quantify. This includes different fall scenarios and pre-impact movement strategies, e.g. the initial height of a fall, a rotational movement during the descent, the activation of muscles, or the use of an outstretched hand to dampen the fall, which may, in particular, be represented by the parallel spring. But k_{BR} also accounts for other parameters of the 1D mechanical model that vary from fall to fall and thus are not realistically reflected by a standardised lateral fall, as, for example, the influence of impact site and orientation on the soft tissue thickness [107].

To cover all possible fall scenarios of an individual, k_{BR} can be any number within its physically defined range. Thereby, the upper limit of the range was derived by equating an individual's potential energy to the elastic potential energy of a spring, given by $m*g*(cmi-cmh) = 0.5*k_{BR}*(cmi-cmh)^2$, with $cmh = 0.53*height+h_G$ as the height of the centre of mass at the start of the fall when standing [73], and $cmi = h_{HP} + h_{Femur} + h_{ST} + h_G$ as the height of the centre of mass at the start of the impact. It follows that the upper limit of the spring constant is given by $k_{BR_{max}} = \frac{-2*m*g}{cmi-cmh}$. This represents a fall scenario in which all potential energy is stored in the spring, resulting in an impact velocity of $v_{imp} = 0$. The lower limit of the spring constant was set to $k_{BR_{min}} = 0$, representing a fall scenario in which

all potential energy is converted into kinetic energy. Accordingly, the maximum impact velocity is reached when the spring constant is set at its minimum.

Calculating the impact velocity v_{imp} requires the time at impact t_{imp}, defined as the time of the hip complex, respectively, the soft tissue, starting to touch the ground. It can be obtained by solving the differential equation $m*x''+k_{BR}*(x-cmh)+m*g = 0$ with the initial conditions $x(0) = cmh$ and $x'(0) = 0$, simulating a fall from standing height without initial velocity. By setting the solution of the differential equation to $x(t) = cmi$ and solving for t, the time at impact t_{imp} is given by

$$t_{imp} = \sqrt{\frac{m}{k_{BR}}} * \arccos\left(\frac{k_{BR} * (cmi - cmh) + g * m}{g * m}\right) \tag{6.4}$$

The impact velocity v_{imp} can be derived by differentiating the solution of the differential equation $x(t)$ and solving it for $t = t_{imp}$, resulting in

$$v_{imp} = -\sqrt{\frac{m}{k_{BR}}} * g * sin\left(\sqrt{\frac{k_{BR}}{m}} * t_{imp}\right) \tag{6.5}$$

In view of the preceding derivations, it is clear that the spring constant k_{BR} defines the impact velocity of the hip. The impact velocity, in turn, defines the magnitude of the impact force in the hip complex and, consequently, also in the femur. Thus, k_{BR} is the critical factor determining whether the peak impact force in the femur F_{Femur} exceeds the femoral strength S_{Femur}. Let's define the force to strength ratio (FSR) as $FSR = F_{Femur}/S_{Femur}$, and $k_{BR_{crit}}$ as the critical value of k_{BR} within its range resulting in $FSR = 1$. It follows that for all $k_{BR} \leq k_{BR_{crit}}$, $FSR \geq 1$ is reached, and thus a fracture will occur, while all $k_{BR} > k_{BR_{crit}}$ result in $FSR < 1$, and subsequently no fracture will occur.

Probability of the fall dynamics

The previous section showed how the critical body resistance spring constant $k_{BR_{crit}}$ that results in a $FSR = 1$, and thus in a fracture, is defined. However, deriving the absolute fracture risk requires the likelihood that a specific fall scenario reflected by k_{BR} occurs. To do so, k_{BR} is modelled as a random variable following an exponential probability distribution of the form $f(y) = (\alpha + 1) * y^{\alpha}$. We chose an exponential distribution because of its inherent non-linearity, monotony and simplicity, as it

requires only one parameter to be characterised. With a positive value of α, the function is monotonically increasing in a non-linear way, and the distribution's shape eventually reflects what can be observed in reality: Only around 3% of all falls result in a hip fracture [43], indicating that falls with an impact force high enough to cause a fracture are relatively rare. Falls with an impact force below the critical force level are more frequent and occur with a significantly higher probability.

To assign k_{BR} to the probability distribution, the relative k_{BR} given as $rk_{BR} = k_{BR}/k_{BR_{max}}$ was calculated, so that $rk_{BR} \in [0, 1]$. Accordingly, the probability mass function describing the occurrence of a fall resulting in specific impact velocity is given by

$$f(y = rk_{BR}) = P(y) = (\alpha + 1) * y^{\alpha} \tag{6.6}$$

and the cumulative distribution function is given by

$$F(y = rk_{BR}) = P(Y \leq y) = y^{(\alpha+1)} \tag{6.7}$$

Since all $k_{BR} \leq k_{BR_{crit}}$ result in a fracture, it follows that the probability of a fracture conditioned on a fall p_S can be derived by evaluating Equation (6.7) for the relative $rk_{BR_{crit}}$, given by

$$p_S = F(y = rk_{BR_{crit}}) \tag{6.8}$$

6.2.2 Model parameters

Personalised parameters

The majority of the personalised parameters required for the model can be extracted from QCT images. These include femoral height h_{Femur}, hemi-pelvis width h_{HP}, soft tissue thickness h_{ST}, femoral strength S_{Femur} and femoral stiffness k_{Femur}. Ultimate strength and stiffness of the femur can be estimated using FEA, which normally requires a BMD calibration. The various modelling options when performing FEA may require the use of correction factors or cross-calibrations between specific modelling approaches. In particular, a correction may be applied for the strain-rate-dependent behaviour of bone tissue, which is not accounted for in commonly

used quasi-static models. The processing of the computed tomography (CT) images and the FEA pipeline used in this work is presented in Section 6.2.3. Other personalised parameters needed include height, weight, and the number of falls during the past 12 months.

Substitution equations for QCT-based personalised parameters

In case no QCT images are available, substitution equations using sex, height, weight and aBMD from DXA can be used to estimate the QCT-based input parameters. Alternatively, if available, other sources could be imagined to substitute QCT-based parameters, e.g. whole-body DXA scans for body composition purposes.

In this work, relationships to substitute femoral height h_{Femur}, femoral strength S_{Femur} and femoral stiffness k_{Femur} were derived using the FEA results of the AFFIRM-CT cohort that was analysed in this work (see Section 6.2.3). Trochanteric soft tissue thickness h_{ST} can be calculated with BMI, using the relationship described by Cameron *et al.* [183]. Hemi-pelvis width h_{HP} can be derived using the relationship presented by Contini *et al.* [184], calculating hip width given the height and sex. As this relationship calculates total hip width, femoral height and soft tissue thickness need to be subtracted. The detailed derivation of these substitution regressions can be found in the supplementary materials (Section 6.5). Table 6.2 gives an overview of the personalised model parameters and their substitution equations.

Soft tissue material model

The parameters for the standard non-linear solid characterising the soft tissues were fitted using data from indentation experiments, which investigated the non-linear visco-elastic behaviour of excised human trochanteric soft tissue samples (unpublished work by Cameron *et al.* [186]). In that work, stress-relaxation experiments using three different step-strains during a constant loading time and a quasi-static force-controlled experiment were conducted. The experimental data showed that the stiffness and, to a lesser extent, the damping properties are dependent on the soft tissue thickness h_{ST}. In a first approximation, we hypothesised that the trochanteric soft tissues are a homogeneous material with

Table 6.2: Overview of the personalised parameters.

Parameter	Unit	Source	Substitution equations
Fall rate λ	Falls/Year	Derived with previously developed models; requires the number of falls in the previous year as input variable [167]	-
Height	[m]	needs to be measured	-
Weight	[kg]	needs to be measured	-
Soft tissue thickness h_{ST}	[m]	from an algorithm based on the femur coordinate system [183]	using BMI and sex: $h_{ST_{female}} = -13.1 + 2.6 * BMI$ $h_{ST_{male}} = -33.7 + 2.6 * BMI$
Femoral height h_{Femur}	[m]	from femur coordinate system [185]	using height: $h_{Femur} = -0.011260 + 0.044806 * height$
Hem-pelvis width h_{HP}	[m]	from femur coordinate system [185]	using height, h_{ST}, h_{Femur} and sex: $h_{HP_{female}} = (0.5 * 0.219 * height) - h_{ST} - h_{Femur}$ $h_{HP_{male}} = (0.5 * 0.200 * height) - h_{ST} - h_{Femur}$
Femoral strength S_{Femur}	[N]	from QCT based FEA [185]	using total hip aBMD: $\log(S_{Femur}) = 8.53757 + 1.56856 * \log(aBMD)$
Femoral stiffness k_{Femur}	[N/m]	from QCT based FEA [185]	using aBMD-derived femoral strength: $k_{Femur} = 146600 + 353.4 * S_{Femur}$

The substitution equations for S_{Femur} and k_{Femur} calculate the quasi-static values.

constant properties and that the varying mechanical properties among individuals can be modelled using a personalised soft tissue thickness alone. Consequently, the parameters that constitute the standard non-linear solid, fas_{S0}, fas_{S1} and μ_{D1} are not personalised but fixed (see Table 6.3). The detailed derivation of these parameters is described in the supplementary materials (Section 6.5).

Fixed parameters

Due to the lack of a method to compute a personalised hemi-pelvis stiffness, k_{HP} was defined as the median of the quasi-static stiffness values reported in an experiment testing 10 isolated pelvis bones in a sideways configuration [187]. As these values were obtained using quasi-static experiments, we applied a strain-rate correction. We are not aware of any relationship to calculate the pelvis stiffness using other body parameters, hence no substitution equation could be provided. Ground stiffness k_G was calculated as follows:

$$k_G = E_G \frac{R_{impact}^2 \pi}{h_G} \tag{6.9}$$

E_G and h_G are Young's modulus and height of the ground, and R_{impact} is the radius of the contact area upon impact, which is assumed to be circular. R_{impact} was set to 2.5cm, which is in line with different studies that investigated forces and contact areas upon impact on the hip [89], [188], [189]. Ultimately, a strain-rate correction factor was used to correct the quasi-static femoral strength and stiffness of the femur and hemi-pelvis. The quasi-static strain rate was derived from Guillemot *et al.* [187] and defined as $5.13 \times 10^{-4} s^{-1}$. The strain rate of a fall was calculated from analytically derived values and was set to $0.275 s^{-1}$. Using the relationship $E \sim \dot{\epsilon}^{\,0.05}$ presented by Peruzzi *et al.* [190] resulted in a correction factor of 1.369. This is in line with the results of a study that compared the prediction accuracy of quasi-static FEA for the ultimate strength and stiffness values assessed experimentally in drop tower tests with thirteen proximal femora [191]. An overview of the fixed parameters is given in Table 6.3.

Table 6.3: Overview of the fixed parameters.

Parameter	Unit	Value	Source
fas_{S0}	[N·m^2]	0.0133	from Cameron *et al.* [186]
fas_{S1}	[N·m^2]	0.2581	from Cameron *et al.* [186]
μ_{D1}	[N·m^2·s]	0.0063	from Cameron *et al.* [186]
k_{HP}	[N/m]	587'000	median value from isolated pelvis experiments [187]
h_G	[m]	0.05	
E_G	[Pa]	3×10^{10}	elastic modulus of concrete
R_{impact}	[m]	25×10^{-3}	estimated based on data from literature [89], [188], [189]
k_G	[N/m]	7.854×10^{10}	
Strain rate correction factor	[-]	1.369	derived with the relationship described by Peruzzi *et al.* [190]

k_{HP} refers to the quasi-static value.

6.2.3 Calibration and sensitivity analysis of the calculator

Data

For the calibration and sensitivity analysis of the calculator, data from the AFFIRM-CT dataset ("A Fragility Fracture Integrative Risk Model for CT Recycling") were used. The AFFIRM-CT study is a prospective observational study that was conducted between 2021 and 2024 with the aim of identifying factors for fall and fragility fracture risk prediction. Briefly, community-dwelling older adults aged 65 and older who underwent a CT scan that included the hip at the University Hospitals of Bern and Geneva were eligible for study participation. Exclusion criteria were a prior hip fracture, life expectancy of less than one year, being bedridden or in a wheelchair, living in a nursing home, suffering from a bone pathology, or cognitive impairment. Eligible individuals were contacted by phone call or letter for enrolment in the study. Enrolled participants were invited for a single visit to the respective medical centre. During the visit, participants underwent DXA scans of the lumbar spine and hip. At the same time, various variables in the field of medical history, cognitive status and physical performance were assessed. After the examination, individuals were followed up for 18 to 36 months, and phone calls were made to assess incident falls and fractures. The study was approved by

the local ethics commissions in Bern and Geneva (BASEC ID: 2019-01327). All participants provided written informed consent.

CT processing and FEA

CT processing and FEA were performed using existing methods from our group [185], [192]. Details can be found in the respective publications. CT images were calibrated with an asynchronous calibration procedure using monthly calibration scans containing a hydroxyapatite phantom (QRM-BDC6 from QRM GmbH, Mohrendorf, Germany) with six inserts covering volumetric bone mineral density (vBMD) values ranging from 0 to 800mg/cm^3. Femur and pelvis bones were segmented using a model based on the nnU-Net method [192]. Segmentation masks and calibrated vBMD images were used as input for a bilateral version of the vBMD pipeline described in Dudle, Gugler *et al.* [185]. The segmentation masks of both femurs are used to estimate an implicit coordinate system of the proximal femur consisting of two intersecting axes: a neck and a proximal shaft axis. The knowledge of the coordinate system is used to define a rigid body transformation of the segmentation mask in voxel space. Based on the transformed mask, a voxel mesh file is written for a load case mimicking a standardised fall to the side with the diaphysis axis inclined by 10° with respect to the ground. The voxel mesh is used in a nonlinear quasi-static finite element (FE) solver with an elastic-perfectly plastic constitutive model. A load is applied to the femoral head. Femoral strength is defined as the reaction force acting on the femoral head when it reaches a vertical displacement of 4% of the vertical distance between the femoral head centre and the most lateral point of the greater trochanter in the fall configuration. The same distance is used for the femoral height h_{FH} in the mechanical model. The knowledge of the two femoral head centres is used to estimate the personalised pelvic width, from which the hemi-pelvis width h_{HP} is derived. Trochanteric soft tissue thickness h_{ST} was measured with an algorithm based on the same femoral coordinate system, finding the shortest distance from the most lateral point of the greater trochanter in fall configuration to the air-soft-tissue boundary [183].

Since the femur is represented by a linear spring in the mechanical model, femoral stiffness k_{Femur} was calculated by dividing femoral strength S_{Femur} by the displacement when the respective point is reached in the force-displacement curve. Femoral strength, as well as femoral and pelvis stiffness, were corrected for strain-rate dependence using the correction factor given in Table 6.3

Calibration of the calculator

The first step to calibrate the model was calculating $k_{BR_{crit}}$ for every participant. If both sides of the femur could be computed, the side-dependent parameters (S_{Femur}, k_{Femur}, h_{Femur}, h_{ST}) were taken of the side with the smaller femoral strength. If only one side was computable, those values were used. If the soft tissue thickness h_{ST} was not detectable on the weaker strength side but was available on the other side of the body, that value was used. All missing variables were substituted with the regression equations presented in Table 6.2. Observations with a follow-up time of less than 6 months were excluded. The number of prior falls was derived by adding up the number of reported falls during the 6 months prior to the examination and the number of falls prospectively reported in the first 6 months of follow-up.

The critical value of the body resistance spring constant $k_{BR_{crit}}$ was derived by solving the DAE system (see Equation (6.3)) so that the $FSR = F_{Femur}/S_{Femur} = 1$, with a tolerance level of 1%. To calibrate the model, the parameter characterising the probability function that assigns the chances of different fall scenarios (see Equation (6.7)) was fitted so that the predicted fracture incidence of the AFFIRM-CT cohort corresponded to the annual age-adjusted hip fracture incidence in Switzerland (men: 160 per 100'000 per person years, women: 400 per 100'000 per person years) [10]. The incidence was weighted according to the share of male and female participants in the analysed data, resulting in an incidence of 234 per 100'000 person years.

Sensitivity analysis

The goal of the sensitivity analysis was to assess the influence of the model parameters on the fracture risk. The data of the AFFIRM-CT cohort was used to define

the mean and standard deviation (SD). Due to the lack of information about the pelvis stiffness, these numbers were calculated from the data presented by Guillemot *et al.* [187]. SD were calculated for all variables except the fall rate. A parameter's influence on the fracture risk was examined by computing the conditional fracture probability p_S and the one-year fracture probability $P(\textit{Fracture in } (0, T = 1])$ for SD between -2 and 2 while holding all other parameters at the mean value (SD = 0). For the calculation of the fracture probability, the fall rate was also held at its mean.

Risk gradients within 1 SD around the reference values were calculated to quantify the influence of a parameter. To assess the influence of decreased bone strength on the sensitivity of the other parameters, the procedure was repeated with all parameters being held at their mean values (SD = 0) except for bone strength, which was set to a constant value of -1 SD below the populations mean.

As defined in Equation (6.1), the probability of a fracture is dependent on the fall rate λ and the conditional fracture probability p_S (see Equation (6.1)). To get insight into the influence of those two parameters on the fracture risk, the risk was calculated for the range of possible fall rates and different p_S.

Furthermore, the influence of the soft tissue thickness h_{ST} on the peak impact force was assessed by evaluating the DAE system (see Equation (6.3)) when all parameters (inclusive rk_{BR}) were held constant at the cohorts' mean, and varying h_{ST} in its range. A linear regression was then fit to compare the influence of the soft tissue thickness on the peak impact force to the results derived by Robinovitch *et al.* [97]. Similarly, the influence of the stiffness parameter k_{BR} on the peak impact forces was evaluated by varying it from its minimum to maximum while holding all other parameters at the mean value.

6.2.4 Software

The software for the impact force model was implemented in python using the packages pandas and numpy. The DAE system was solved with a solver for dynamic simultaneous simulations (mode 4) provided by the gekko package [193], [194].

6.3 Results

In total, 374 participants were enrolled in the AFFIRM-CT study. Two were lost before the examination, and ten individuals were excluded due to a follow-up time of less than six months. Of these, 42 did not converge when solving the DAE system, resulting in a total of 320 evaluated data points. Since some QCT images were not successfully processed or did not include the full region of interest, several observations had missing variables. Of the 320 individuals included in the analysis, 97 (30.3%) were female, and 168 (52.5%) were recruited in Bern. The summary statistics of the minimal required parameters and the QCT derived parameters are presented in Table 6.4.

Table 6.4: Summary statistics of the model parameters and the output values. The numbers include substituted missing values.

Variable	Mean (SD)	Min	Max	NA's [a]
Minimal required parameters				
Weight [kg]	75.6 (14.7)	39.5	120.4	-
Height [cm]	169.5 (8.6)	139.7	189.8	-
Prior falls	0.62 [b]	0	15	-
aBMD [g/cm^2]	0.751 (0.132)	0.452	1.314	3
QCT derived parameters				
h_{ST} [mm]	40.38 (15.23)	8.01	77.55	13
h_{HP} [mm]	86.89 (8.20)	47.91	105.12	38
h_{Femur} [mm]	64.46 (5.93)	46.75	77.75	44
S_{Femur} [c] [N]	4207 (1366)	1704	10015	44
k_{Femur} [c] [N/m]	1.616×10^6 (4.985×10^5)	6.497×10^5	3.736×10^6	44
Model output				
Fall rate λ	0.794 [b]	0.594	5.035	-
$rk_{BR_{crit}}$ [-]	0.624 (0.143)	0.000	0.908	-
v_{imp} [d] [m/s]	2.24 (0.41)	1.12	3.72	-
p_S	3.495×10^{-3} [b]	0.000	1.481×10^{-1}	-
P(Fracture)	2.330×10^{-3} [b]	0.000	8.424×10^{-2}	-

[a] number of missing values before substitution; [b] no standard deviation provided due to non-normal distribution; [c] quasi-static values; [d] for $k_{BR} = k_{BR_{crit}}$
Abbreviations: SD = standard deviation; NA's = missing values

The mean value of the critical relative body resistance stiffness $rk_{BR_{crit}}$ was 0.624. The corresponding average impact velocity of the hip with k_{BR} at its critical value was 2.24 m/s. All these values are also presented in Table 6.4. The parameter α defining the shape of the exponential distribution describing the chances of

different fall scenarios was fit to $\alpha = 18.87$. The probability mass function for rk_{BR} describing the chances of varying fall dynamics is presented in Figure 6.2. The blue dotted line indicates the cohort's mean of $rk_{BR_{crit}}$. The area under the curve from 0 to 0.62 refers to the conditional fracture probability p_S.

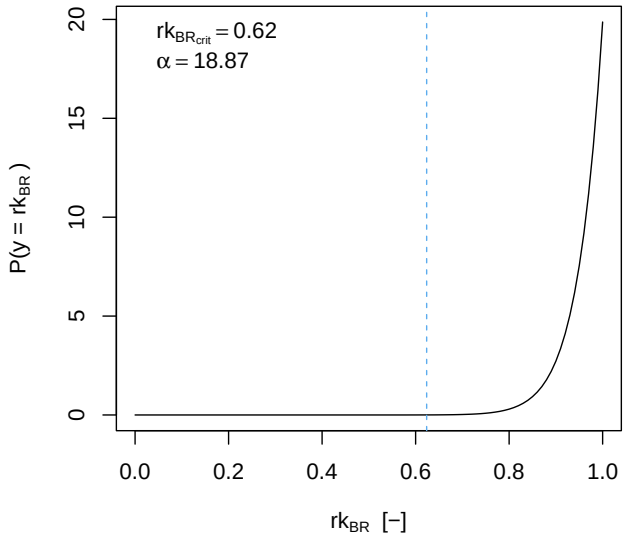

Figure 6.2: Probability mass function modelling the stochastic aspects of the fall dynamics represented by rk_{BR}. The blue line indicates the mean value of $rk_{BR_{crit}}$ in the AFFIRM-CT cohort. The exponent α was fitted so that the hip fracture incidence of the cohort corresponds to the age-adjusted annual incidence in Switzerland.

The mean of the conditional fracture probability was $p_S = 3.495 \times 10^{-}3$, and the mean of the probability of at least one hip fracture $P(\textit{Fracture in } (0, T = 1]) = 2.330 \times 10^{-3}$ (Table 6.4). This corresponds to the annual fracture incidence in Switzerland for which the model was calibrated [10].

In Figure 6.3a, an example of the relative displacement during the impact in every component of the mechanical model is presented. It is clearly visible that the soft tissues deflect the most upon impact. Figure 6.3b shows an example of the resulting impact force. The example is calculated with the AFFIRM-CT data's mean values for all parameters.

Figure 6.4 shows the influence of the different parameters on the conditional fracture probability p_S, and the fracture risk $P(\textit{Fracture in } (0, T])$. Figure 6.4a and

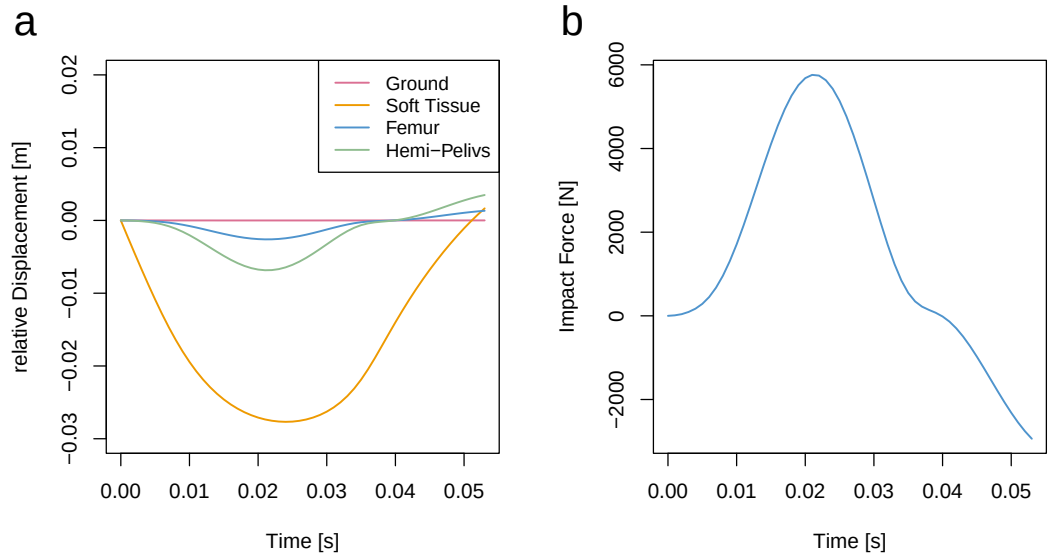

Figure 6.3: Example plots of (a) the relative displacement in every component of the mechanical model upon impact and (b) the resulting impact force. The time $t = 0$ is defined as the start of the impact on the ground.

b present the results of the influence of every parameter when all others are held at the population mean (SD = 0). Thereby, the femoral strength S_{Femur} and the soft tissue thickness h_{ST} are the two dominant factors, increasing the fracture risk with decreasing values. Increasing weight resulted in a slight increase in the fracture risk, too. In Figure 6.4c and d, all parameters were held at their mean values (SD = 0) except for bone strength, which was set to a constant value of 2801 N (-1SD below the population mean). It can be observed that the overall fracture risk is substantially higher when bone strength is decreased. Furthermore, the influence of the parameters on the fracture risk changed slightly and became stronger. The soft tissue not only resulted in an increased fracture risk with decreasing thickness but also appeared to be protective with increasing thickness. Similarly, an increase in weight led to a higher fracture risk, while a decrease in weight had the opposite effect. These findings were also reflected in the results of the fracture risk gradients (Table 6.5). For the analysis of the influence of the parameters when all others were held at the mean values, the gradients of femoral strength, soft tissue thickness and weight were around one order of magnitudes larger (Column 1). Furthermore, the

gradients were increased by approximately one order of magnitude for the analysis with a decreased bone strength (Column 2), indicating that the influence of the other parameters on the fracture risk is substantially higher with decreasing bone strength.

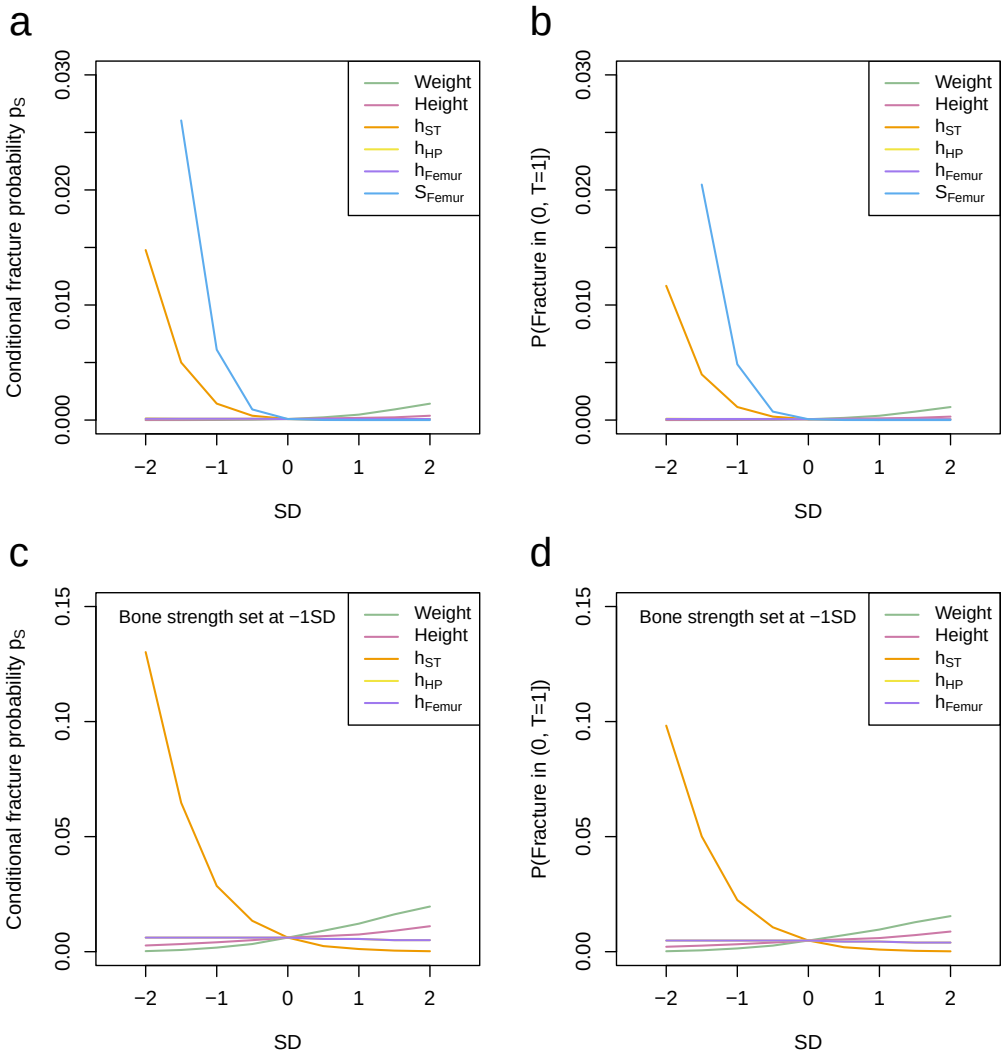

Figure 6.4: Results from the sensitivity analysis showing the influence of the model parameters on the (left column) probability of a fracture conditioned on a fall p_S, and (right column) on the probability of at least one fracture in the time period of one year $P(Fracture\ in\ (0, T = 1])$. Plots a and b show the influence of every parameter when all others are held at the population mean (SD = 0). Plots c and d show the influence with all parameters held at their mean values except for bone strength, which was set to a constant value of -1 SD below the population mean (2801 N).

The influence of the soft tissue thickness h_{ST} on the peak impact force is shown in Figure 6.5a. Thereby, the peak impact force increases with decreasing soft tissue thickness. The linear regression fitted to these data points reveals a

Table 6.5: Fracture risk gradients of the model parameters quantifying the influence of every parameter when all others are held at the mean (Column 1), or with all parameters held at their mean values (SD = 0) except for bone strength, which was set to a constant value of -1 SD below the population mean (2801 N; Column 2).

	1	**2**
Variable		
Weight	1.610×10^{-4}	4.555×10^{-3}
Height	6.060×10^{-5}	1.392×10^{-3}
h_{ST}	-2.722×10^{-4}	-8.673×10^{-3}
h_{HP}	-1.984×10^{-5}	-4.625×10^{-3}
h_{Femur}	-1.984×10^{-5}	-4.623×10^{-4}
S_{Femur}	-7.284×10^{-4}	-1.973×10^{-2}

decrease of -68.6 N per every additional mm of soft tissue thickness (p-value = 3.15e-07) in peak impact force.

In Figure 6.5b, it is shown how k_{BR} influences the peak impact force through its energy-storing mechanism. The minimum peak impact force of 0 N is reached when all energy is absorbed during the fall, reflected by $rk_{BR_{crit}} = 0$. On the contrary, when no energy is absorbed during the descent, represented by $rk_{BR_{crit}} = 0$, the peak impact force is at its maximum (here 11802 N). This example was calculated with all parameters set to the cohort's mean values.

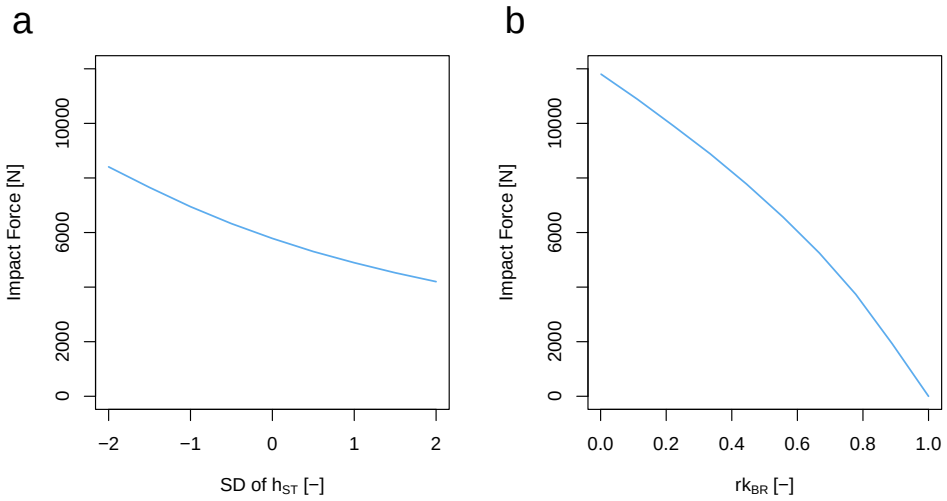

Figure 6.5: Influence of (a) h_{ST} and (b) rk_{BR} on the peak impact force in the hip. The displayed forces are strain-rate corrected.

When comparing Figure 6.4a and Figure 6.4b, it can be seen that the probability

of at least one fracture $P(\textit{Fracture in } (0,T])$ is a scaled version of the conditional fracture probability p_S. In Figure 6.6, the influence of the fall rate λ and the fracture probability conditioned on a fall p_S on the absolute fracture risk is illustrated. It is clearly visible that the risk of a fracture increases with an increasing fall rate λ and an increasing conditional fracture probability p_S in a non-linear manner.

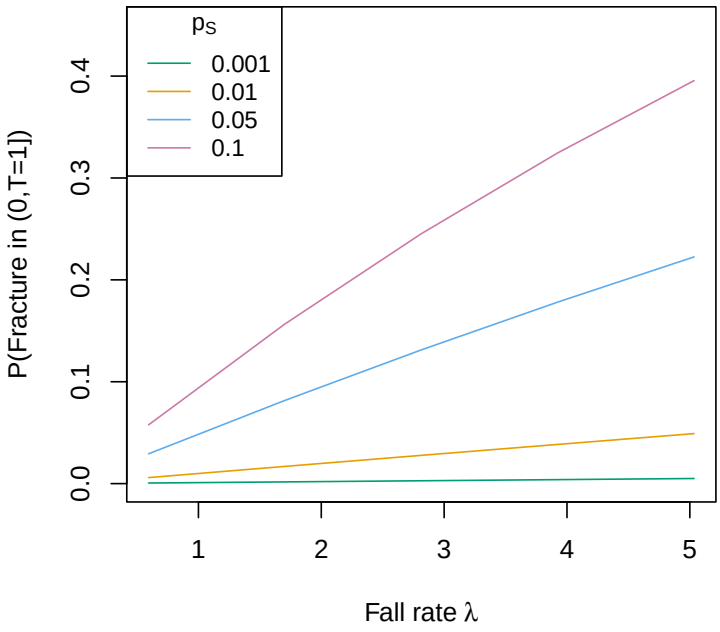

Figure 6.6: Influence of the fall rate λ and the conditional fracture probabilities p_S on the fracture risk.

6.4 Discussion

In this article, we present a new mechanistic stochastic hip fracture risk calculator that is based on mechanistic and stochastic modelling approaches. The calculator integrates the stochastic aspects of falls and the fall-induced impact force and uses bone strength estimate from QCT FEA to calculate a one-year absolute fracture risk. In contrast to other mechanistic prediction tools, the mechanical model presented here is composed of rheological elements representing the trochanteric soft tissue, the femur, the pelvis and the ground, allowing the evaluation of the influence of the

different elements on the fracture risk. Furthermore, no specific fall scenarios are modelled, but the range of possible impact forces given the anthropometric measures for an individual is calculated. An exponential probability distribution is then used to derive the probability of an impact force high enough to initiate a fracture to occur. By integrating this probability with the probability of at least one fall, an absolute fracture risk is derived. Next to height, weight, and the number of falls during the prior 12 months, all input variables can be extracted from QCT images. In case such images are not available, substitution equations to calculate the required input parameters based on anthropometric and densitometric data are provided.

Comparing the output variables of the mechanical model with the literature, these are quite consistent with experimentally derived values. The average impact velocity for $k_{BR_{crit}}$ is 2.24 m/s. This is comparable with experimental values measured during unintentional sideways falls of young, healthy volunteers, reporting a mean velocity of 2.75 m/s (SD 0.42m/s) [80] and 3 m/s (SD 0.83 m/s) [75]. The models' predicted impact forces, given the fall dynamics, range from 0 to 11802 N when all parameters are held at the cohort's mean value. Robinovitch *et al.* reported peak impact forces between 4050 - 6420 N measured with an impact pendulum [97], and Fleps *et al.* derived impact forces between 2947 - 7601 N using a sideways fall simulator [95]. Thus, the impact forces derived from the model presented here cover a wider range when compared to experimentally derived values. However, this was to be expected, as the full range of k_{BR}, representing all fall scenarios from no energy storage at all to complete energy absorption during the descent, was modelled. The regression equation that quantifies the influence of the soft tissue thickness on the peak impact force is close to what was reported by Robinovitch *et al.* [97] (model here: - 67.3 N/mm; Robinovitch *et al.*: - 71 N/mm). This indicates that the 1D soft tissue model developed by Cameron *et al.* [186] can model the non-linear visco-elastic behaviour of the trochanteric soft tissue during an impact on the hip.

The sensitivity analysis showed that bone strength, soft tissue thickness, and fall rate are the parameters that dominate the fracture risk. Decreased bone strength and low soft tissue thickness result in a high fracture probability; the influence of

these two parameters on the fracture risk is even more pronounced in individuals with both decreased bone strength and low soft tissue thickness. At the same time, increased soft tissue thickness or decreased weight in individuals with decreased bone strength can be protective of fragility fractures. The thinned Poisson process scales the conditional fracture probability p_S by combining it with the fall rate λ and, through that, calculates an absolute fracture risk. The fracture risk increases with an increasing fall rate, but its influence is also dependent on the conditional fracture probability p_S itself; the absolute risk is low if the conditional probability is low but rises in a non-linear way if this number is increasing. It shows clearly that both a high conditional fracture probability p_S (e.g., due to decreased bone strength, low soft tissue thickness, or the inability to dampen a fall), together with a high fall rate, are required for a fracture to occur. The exposure to either a high conditional fracture probability or a high fall frequency might be insufficient to initiate a fracture. Hence, the model eventually gives insight into why aBMD alone, known for its low sensitivity and high specificity [23], [28], [176], is not a robust predictor for hip fractures, and why many fractures happen in individuals with non-osteoporotic aBMD [25], [26], [27]: the overall fracture risk appears to be fall rate dependent. This seems logical when considering that falling is the underlying mechanism causing hip fractures. In line with these findings, several studies have demonstrated the predictive ability of falls for fragility fractures [58], [195]. Thus, the model seems to capture the relevant aspects of the risk of fragility hip fractures observed in empirical data and eventually is able to explain why individuals with identical bone strength can have different fracture outcomes.

The here presented model might be criticised for various assumptions and simplifications. First, we used a simple mass-spring model to calculate the impact velocity that neglects the biomechanics of a fall. However, although it is possible to model fall scenarios with dynamic models, the countless possibilities of how a fall could occur raises the question: Which fall scenarios should be modelled? Due to the limited information to answer these questions, we decided to model the fall dynamics and influence of pre-impact movement strategies on the impact

velocity indirectly by deriving the range of physically possible impact velocities given an individual's anthropometric parameters. Therefore, aspects that vary from fall to fall and that can not be predicted, such as the initial height, the presence of rotational movement, the activation of muscle, or the outstretching of the hand, are represented by the range of k_{BR}.

Next, we acknowledge that the use of a 1D mechanical model to simulate an impact on the hip following a sideways fall is a simplification of reality. In addition, the model presented here lacks elements representing the skin, cartilage, and ligaments of the hip complex. And last, the computation of bone strength in just one loading configuration could be criticised. Nonetheless, we believe that modelling different impact orientations of the hip is a complex problem that again relies on many assumptions and simplifications, e.g. the variation of the soft tissue thickness given impact orientation or the lack of knowledge about the anisotropic material behaviour of the tissues in the hip complex. Similarly, the computation of bone strength for different impact orientations with an FEA pipeline that was validated with experimental data of one loading case eventually introduces an undefined error in the strength estimation due to the anisotropy of the bone tissue. Based on these considerations, we have decided to model the impact on the hip with a simplified 1D mechanical model. The influence of factors that affect the visco-elastic behaviour of the hip and that can vary among different fall scenarios (e.g. the impact orientation or muscle activation) was again indirectly modelled with the fall dynamics, represented by the range of k_{BR}.

The use of a stochastic distribution to assign a probability to different fall-induced impact forces opens several opportunities but also has its limitations. On the one hand, it allows the calculation of an absolute fracture risk within a mechanistic setting. Although mechanistic models can precisely estimate the outcome of an event (here, the impact force following a fall), they do not directly inform about the chances of this happening. To derive a risk, the output needs either to be analysed with a statistical regression model (e.g. by relating the force-to-strength ratio to the fracture risk using a Cox proportional hazard model [46]) or a stochastic

distribution is needed to describe the occurrence of an input variable of the model. To our knowledge, there exists only one other mechanistic model following the latter approach [113]. In this model, the impact force is derived by modelling a sideways fall with an inverted pendulum. A stochastic distribution is used to assign the probability of possible angles of the inverted pendulum, characterising different scenarios of a sideways fall.

However, the assumption about the shape of such probability distribution is a major limitation. We chose an exponential distribution because its shape eventually reflects what is observed in clinical data: Only around 1 - 3% of all fall events are severe enough to result in a fracture [43]; falls resulting in an impact force below the critical level, here defined through $k_{BR} > k_{BR_{crit}}$, are more likely to occur. With $\alpha = 18.87$, low values of k_{BR} are highly unlikely, while the probability of $k_{BR} > 0.8$ that represents impact forces in the lower range increases exponentially. In addition, the exponential distribution has the advantage of being characterised by only one parameter and its inherent non-linearity.

The direct validation of whether the chosen distribution and its parameter α are appropriate is challenging, as the collection of the required empirical data is not feasible. Nevertheless, this can be done indirectly by evaluating the model's prediction accuracy with a receiver operating characteristic curve in a cohort with sufficient statistical power. Here, we have fitted α indirectly so that the fracture incidence in the AFFIRM-CT data set corresponds to the age-adjusted fracture incidence in Switzerland. This could also be done for other countries or geographical regions by using the respective incidence. Furthermore, since the fracture incidence differs between men and women, α could be fitted separately for each sex. Following an even more personalised approach, the distributions could be adjusted based on an individual's physical ability to dampen a fall. Thereby, α could be defined by a function that depends on age, sex, physical performance tests and other factors that reflect this ability.

The mechanistic nature of the model allows for the assessment of different aspects of fracture prediction and prevention strategies. First, it could give insights

into whether improved femoral bone strength estimates, e.g. from HR-pQCT, in comparison to aBMD or QCT-FEA based bone strength can improve fracture risk prediction. Thereby, it could be assessed whether the precision errors of the respective methods have a relevant influence on the change in fracture risk. Furthermore, the effect of changes in aBMD upon osteoporosis treatment on the fracture risk could be quantified. In addition, the model allows the assessment of the protective effect of an individual wearing hip protectors as suggested by Robinovitch *et al.* [92], [196] by adding it as an additional rheological element into the mechanical model. And last, the model could be used to quantify the effect of different flooring materials on the fracture risk, as already investigated by Laing *et al.* [109].

A further strength of the here presented model is the selection of the required input parameters. For individuals with an available QCT image, the only additional parameters needed are weight, height and the number of falls within the prior year. In the case of no QCT image, bone strength can be estimated with other densitometric measures, as for example, aBMD from DXA. With the exception of the substitution equation that uses sex to calculate the soft tissue thickness and the hemi-pelvis width, the model is solely based on physical parameters. Accordingly, it is not necessary to consider the epidemiological variation of risk factors by sex, age or ethnicity. In fact, these factors affect the mechanical parameters in a complex way. To ensure that the substitution equations also apply to data other than the AFFIRM-CT data, they must be validated with other data sets. Looking at the time required to derive the fracture risk, this lies in a range that is feasible in a clinical setting. Calculating femoral bone strength using the FEA pipeline developed by Dudle, Gugler *et al.* takes approximately 15 minutes [185], with an additional 2 minutes needed for solving the DAE system and calculating the fracture probability. With the use of the substitution equations, the calculation takes around 2 minutes.

Several aspects of the calculator could be improved and further developed. Due to the lack of a method to estimate a personalised pelvis stiffness, we assumed a constant value based on data from literature [187]. The mechanical model could be improved with a method to extract a personalised pelvis stiffness from QCT

images. At the same time, the results from the sensitivity analysis indicate that pelvis stiffness has a limited influence on the fracture risk. Furthermore, instead of modelling the femur with a linear spring, the nonlinear force-displacement curve of the FEA could be integrated to derive the peak impact force. Another aspect is the time horizon of prediction. For the analysis of the data presented here, a time span of T = 1 was chosen to predict a one-year fracture risk. However, by adjusting T to the time interval of interest, the model allows the risk prediction for any time horizon. To do so, variables that are known to change over time, such as the bone strength or fall rate, would need to be adjusted accordingly. This would allow a comparison with FRAX® that predicts a 10-year fracture probability.

6.5 Conclusion

This article presents the framework of a novel mechanistic and stochastic fragility hip fracture risk calculator, integrating the mechanical aspects of an impact on the hip together with the stochastic aspects of a fall. The model's output variables such as the impact velocity of the hip or peak impact force in the hip complex align well with experimental data from the literature. Furthermore, the sensitivity analysis showed that the fall rate, trochanteric soft tissue thickness and bone strength are the dominating parameters that influence the risk of fragility hip fractures. Thus, the model is able to reflect observations from empirical data, indicating that it can capture the intrinsic aspects that affect the risk of fragility hip fractures. The mechanistic nature of the model allows to concentrate the stochastic aspects of hip fractures in the fall dynamics. Furthermore, several aspects can be explored, such as the effect of improved bone strength estimates on the prediction accuracy, drug treatment effects on the fracture risk, or the preventive effect of hip pads or different flooring material. To make the model clinically applicable, extensive analysis of its prediction accuracy using cohorts with enough statistical power is required to demonstrate its validity.

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Author contributions

CW: Conceptualisation, Investigation, Formal analysis, Methodology, Software, Visualisation, Writing - original draft, Writing - review and editing

YG: Formal analysis, Data Curation, Writing - review and editing

PC: Data Curation, Writing - review and editing

AD: Formal analysis, Data Curation, Writing - review and editing

DF: Data Curation, Writing - review and editing

MP: Data Curation, Writing - review and editing

EB: Writing - review and editing

SF: Writing - review and editing

KL: Writing - review and editing

PZ: Conceptualisation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - review and editing

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Supplementary material

Derivation of formulas in the Schechner publication

The probability of k falls occurring in a specific time period $(0, T]$ is modelled with a Poisson process given by

$$P(k \text{ falls in } (0,T]) = \frac{e^{-\lambda T}(\lambda T)^k}{k!}$$

with k as the number of falls and λ as the rate parameter characterising the Poisson process. Since a fracture event is only possible once a fall occurs, the measure of interest is the probability of at least one fall, given by

$$P(k \geq 1 \text{ fall in } (0,T]) = 1 - e^{-\lambda T}$$

The probability that the assigned load is bigger than the femoral strength can be described as the conditional probability of a fracture given as a fall and is given by $p_S = P(Fracture|Fall) = P(Load > Strength)$. By combining the fall rate parameter λ with the conditional probability of a fracture p_S, a thinned Poisson process given by

$$P(Fracture \text{ in } (0,T]) = 1 - e^{-\lambda p_s T}$$

Definition of the forces in the mechanical model

The forces of the mechanical model are defined as follows:

$$F_{BR} = k_{BR} * (x_4 - cmh - h_G)$$

$$F_{HP} = k_{HP} * (x_4 - x_3 - h_{HP})$$

$$F_{Femur} = k_{Femur} * (x_3 - x_2 - h_{Femur})$$

$$F_{S0} = \frac{fas_{S0}}{h_{ST}^2} * \log\left(\frac{(x_2 - x_1)}{h_{ST}}\right) + 100 * \frac{fas_{S0}}{h_{ST}^2} * \log\left(\frac{(x_2 - x_1)}{h_{ST}}\right)^3$$

$$F_{S1} = \frac{fas_{S1}}{h_{ST}^2} * \left(\log\left(\frac{(x_2 - x_1)}{h_{ST}}\right) - \log\left(\frac{(x_{21} - x_1)}{h_{ST}}\right)\right) + 100 * \frac{fas_{S1}}{h_{ST}^2} * \left(\log\left(\frac{(x_2 - x_1)}{h_{ST}}\right) - \log\left(\frac{(x_{21} - x_1)}{h_{ST}}\right)\right)^3$$

$$F_{D1} = \frac{fas_{D1}}{h_{ST}^2} * \frac{(x'_{21} - x'_1)}{(x_{21} - x_1)} + 100 * \frac{fas_{D1}}{h_{ST}^2} * \frac{(x'_{21} - x'_1)}{(x_{21} - x_1)} * 3 * \log\left(\frac{(x_{21} - x_1)}{h_{ST}}\right)^2$$

$$F_G = k_G * (x_1 - h_G)$$

Soft tissue material model

We conducted two types of experiments with human excised soft tissue to characterise its visco-elastic behaviour. First, stress-relaxation experiments with different step strains and a constant loading time of 50ms were performed. And second, quasi-static force-controlled indentation experiments were conducted. The detailed experimental setup is described in [186].

The experimental data were fit with a non-linear standard solid. The forces in the non-linear springs and the damper are given by

$$F_S = slope * \log(1 + \varepsilon) + 100 * slope * \log(1 + \varepsilon)^3$$

$$F_D = slope * \frac{\varepsilon'}{(1 + \varepsilon)} + 100 * slope * \frac{\varepsilon'}{(1 + \varepsilon)} * 3 * \frac{log(1 + \varepsilon)^2}{(1 + \varepsilon)}$$

with ε describing the relative displacement as strain. The slopes were based on a spring force amplitude given by $fas = fml * \pi * r^2$ with $fml = 135$ N as the linear force module and $\pi * r^2$ with $r = 0.025m$ as the indenter area. Hence, the two spring force amplitudes are given by

$$fas_{S0} = g_{\text{inf}} * fas$$
$$fas_{S1} = g_1 * fas$$

with $g_{inf} = 0.05$ and $g_1 = 0.95$. The damping force coefficient is given by

$$\mu_{D1} = fas * g1 * \tau_1$$

with $\tau_1 = 0.025s$ being fixed. The three parameters g_{inf}, g_1, and fml were fitted using the stress-relaxation data, with $g_{\text{inf}} = 1 - g_1$. Since the quasi-static data showed a dependency of fml on the soft tissue thickness h_{ST}, a correction factor $(1/h_{ST}^2)$ was introduced.

Detailed derivation of substitution equations

For the substitution equations of the QCT derived parameters, all available data points from the FEA analysis were used. For the femoral height h_{Femur}, both body sides were included in the analysis. Thereby, the average between the two femoral height values was calculated and regressed to the height. If only one side was available, this value was used. For the femoral strength S_{Femur}, the total hip aBMD was regressed to the femoral strength value of the corresponding site. For the femoral stiffness k_{Femur}, the equation was derived using the FEA results of both body sides.

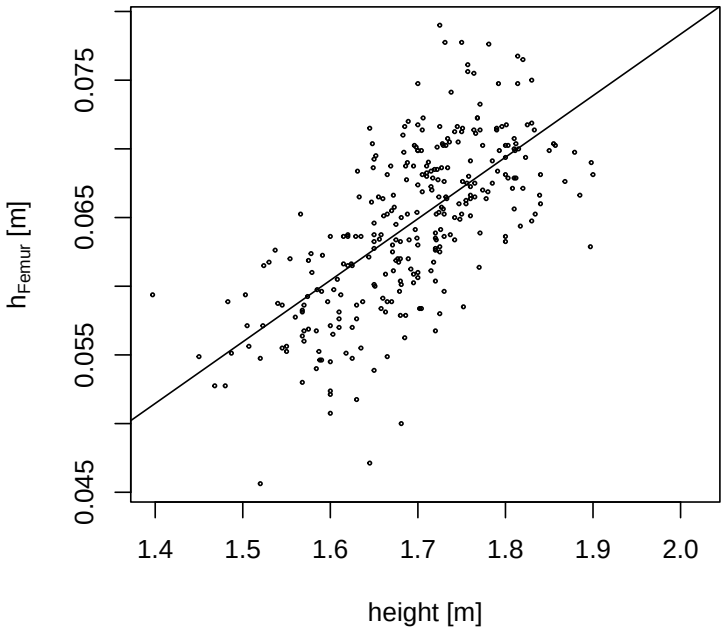

Figure 6.7: Relationship between femoral height h_{Femur} and body height.

Table 6.6: Results of linear regression model to substitute h_{Femur} from height.

Coefficients	**Estimate**	**Std Error**	**t value**	**Pr**$(>\|t\|)$
(Intercept)	-0.011260	0.004828	-2.332	0.0203
height	0.044806	0.002848	15.735	<2e-16

Adjusted R-squared: 0.4352. Residual standard error: 0.004516 on 319 degrees of freedom.

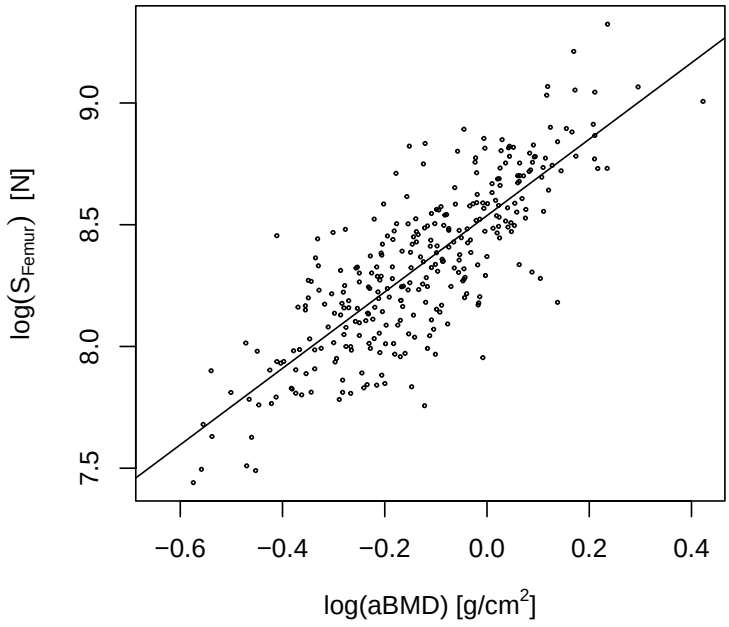

Figure 6.8: Relationship between total hip aBMD and femoral strength S_{Femur}.

Table 6.7: Results of linear regression model to substitute S_{Femur} from total hip aBMD.

Coefficients	**Estimate**	**Std Error**	**t value**	**Pr**$(>\|t\|)$
(Intercept)	8.53757	0.01387	615.76	<2e-16
log(aBMD)	1.56856	0.06471	24.24	<2e-16

Adjusted R-squared: 0.6557. Residual standard error: 0.1962 on 307 degrees of freedom.

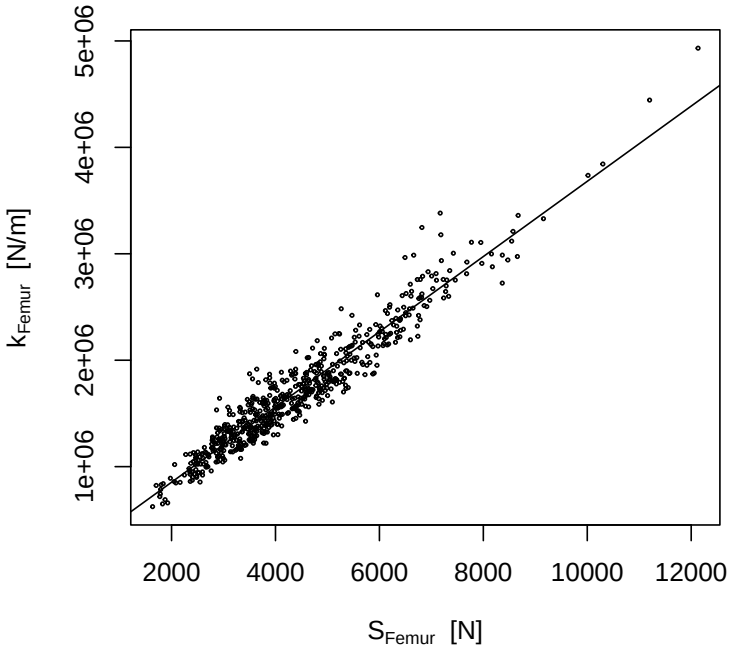

Figure 6.9: Relationship between femoral strength S_{Femur} and femoral stiffness k_{Femur}.

Table 6.8: Results of linear regression model to substitute k_{Femur} from S_{Femur}

Coefficients	**Estimate**	**Std Error**	**t value**	**Pr**$(>\|t\|)$
(Intercept)	1.466e+05	1.916e+04	7.651	7.68e-09
S_{Femur}	3.534e+02	4.106	86.069	<2e-16

Adjusted R-squared: 0.923. Residual standard error: 155000 on 617 degrees of freedom.

7 Discussion

7.1 Summary

In the previous chapters, the analyses undertaken to develop a novel fragility hip fracture risk calculator and the model itself have been presented.

Chapter 3 to Chapter 5 describe the work conducted to develop a personalised fall rate prediction model. Three cohorts that assessed various risk factors of falling have been analysed and used for model development. Subsequently, the coefficients of the three models were meta-analysed and compared. In contrast to most other fall risk assessment tools, the models were developed with count regression that allows the derivation of a fall rate. The presented work showed that the number of falls in the prior 12 months is a robust predictor for future falls among different cohorts. These findings were confirmed in the meta-analysis of the model coefficients. Although various variables were shown to be associated with the number of falls, fear of falling assessed with FES-I in the SCT cohort was the only additional predictor that improved the model's predictive performance. Nevertheless, the number of prior falls as the only predictor included results in the major limitation that the model cannot identify first-time fallers.

In Chapter 6, the framework of a novel fragility hip fracture risk calculator based on the model developed by Schechner *et al.* was presented. The model integrates a

personalised impact force model calculating the fall-induced impact force given the a simplified fall dynamics and introduces a stochastic distribution to describe the probability of different fall scenarios. The required parameters are estimated from anthropometric and densitometric measures, and can be refined with QCT images. Clinical data from the AFFIRM-CT study were used to assess the sensitivity of the parameters and to demonstrate how the calculator models the risk of hip fracture, confirming that the fall rate, the soft tissue thickness and the bone strength are the three dominant factors determining fracture risk. Furthermore, the calculator is able to model various observations from empirical data, such as the decrease in fracture risk with increasing soft tissue thickness, indicating that it can capture the intrinsic aspect affecting the risk of fragility hip fractures.

7.2 Essential points and noteworthy aspects

Developing a fragility hip fracture calculator based on mechanistic and stochastic modelling approaches to derive a fracture risk is relatively new. So far, only one model has been published that followed a comparable approach [113]. A prerequisite for that is the understanding of the underlying physical process and that the required methods to model these exist. Thus, the research conducted in the area of fall risk, impact biomechanics, QCT-based FEA methods and fragility fractures are indispensable for the development of a mechanistically and stochastically motivated model. In the next two sections, noteworthy aspects of stochastic and mechanistic aspects are discussed and related to literature.

7.2.1 Complexity of the model

Although almost exclusively all hip fractures are caused by a sideways fall that impacts the postero-lateral aspect of the hip, the exact mechanism of how such an event happens can vary significantly from case to case. Thereby, the fall dynamics influences the resulting impact force and impact orientation of the hip. Furthermore, the femoral bone strength is dependent on the loading direction, too. Accordingly, numerous variables that define the resulting fracture risk depend on the dynamics

of a fall. Nevertheless, even if the accurate modelling of the fall event is possible, the problem of which fall scenario to model is still not solved.

The presented model was built in a way that tries to separate the fall-related stochastic aspects from the mechanical aspects of the mechanism causing hip fractures. This allowed for the introduction of standardised mechanical models, while the stochastic aspects were concentrated in the probability distribution describing the fall dynamics. Accordingly, a simplified 1D mechanical model representing the hip impact of a standard sideways fall was introduced. In line with this, the FEA-derived bone strength was calculated for a single load case representing a standard sideways fall, and the soft tissue thickness algorithm measured a standardised distance between greater trochanter and tissue-air-boundary. In contrast to FEA modelling approaches that accurately represent the impact of the whole hip [91], [96], the simplified 1D mechanical model is computationally not expensive and allows for an easy subject-specific adaptation. Furthermore, by introducing separate rheological elements representing the soft tissues, the femur, the hemi-pelvis, and the ground, their influence on the impact force and fracture risk can be assessed.

The multiscale model presented by Bhattacharya *et al.* modelled specific fall scenarios by varying the joint angles of a sideways fall [113]. The varying probability of different falls was then introduced by assigning probability distributions to the angles. Here, due to the lack of knowledge about the fall dynamics, no specific fall scenarios were explicitly modelled, but a simplified model that derives the possible range of an individual's impact velocity using anthropometric data was introduced. As a result, the complex fall dynamics is only indirectly represented, and no additional assumptions, for example about the joint angles during a fall, are required.

7.2.2 Stochastic modelling aspects

The fall-related aspects determining the risk of hip fractures occur in a highly noisy environment. This considers both the occurrence of a fall and the fall dynamics itself. The fall rate parameter λ characterises the Poisson process that describes the occurrence of a fall. As shown in the analysis of the three cohorts for developing

a model that can estimate a personalised λ, no other predictors apart from the prior fall number improved the model's prediction accuracy. At first, it may seem surprising that factors such as poor sight, impaired balance or muscle weakness are not predictive of falling, as it is easy to imagine that these circumstances can result in a fall. However, considering that the list of risk factors for falling is long and countless combinations of factors can lead to a fall, it seems logical that the risk factors defining an individual's fall risk are highly subject-specific. Furthermore, certain skills may compensate for the presence of risk factors and can be protective of falls. Consequently, prior falls might be the best indicator of whether an individual is exposed to the relevant risk factors.

The second stochastic aspect that influences the hip fracture risk is the dynamics of a fall, which defines the resulting impact force. As mentioned in Section 1.4.2, it is difficult, if not impossible, to predict how a fall will happen and which pre-impact movement strategies will be triggered. Thus, both the occurrence of falls and the fall dynamics underly a highly stochastic nature.

The lack of consideration of the stochastic aspects of a fall may explain why bone strength alone is strongly associated with fragility hip fracture risk but has limited predictive power at identifying individuals at risk of hip fractures in the individual [28], [30], [31], [32], [33]. Furthermore, it can explain why the beneficial effect for fracture prediction using improved bone strength estimate derived with FEA in comparison to aBMD is smaller in the femur when compared to vertebral fractures. In contrast to vertebral fractures, femoral fractures are almost exclusively the result of a fall [20]. Thus, the effect of decreased bone strength on the hip fracture risk is fall-rate dependent, as shown in the sensitivity analysis of the presented model.

Although recognised as an important risk factor, falls have not been integrated into the original version of FRAX®, with the argumentation that they can not be prevented by drug treatment [4]. However, it could be hypothesized that some aspects of the risk of falling are indirectly covered by clinical risk factors such as age, sex, prior fractures and BMI, as they are all known to be related to the risk of falling.

The calculator presented by Schechner *et al.* integrated the stochastic aspects by using a Poisson process to model the occurrence of a fall, and the use of a random variable following a Weibull distribution to describe the probability of the fall-induced impact force exceeding the femoral strength. The presented model refined this approach by integrating a personalised impact force model and an FEA based bone strength estimate. Through that, the stochastic aspects of the fall-dependent fracture risk are concentrated in the parameter α that describes the probability of the fall dynamics. Furthermore, instead of using an age-dependent relationship for the estimate of the fall rate λ, a personalised model was developed. These adaptations allow the calculation of a personalised fracture risk for the individual.

7.2.3 Mechanistic modelling aspects

The model's mechanistic nature comes with several advantages. First, it allows the functional understanding of various observations in clinical data, such as the big overlap in bone strength between individuals suffering from a fracture and others who don't, the increase in fracture risk with age, or why a prior fracture is a risk factor for a future fracture [8].

Furthermore, it can capture the complex interaction between the parameters and allows the direct quantification of how these influence the fracture risk without the need for clinical data. To gain the same information from a regression-based model is more tedious and data-dependent. As an example, a review by De Laet *et al.* assessed the influence of BMI on fracture risk in a meta-analysis including 12 prospective cohorts [197]. They concluded that the influence of BMI is non-linear with a larger risk in the lower range and dependent on other factors such as BMD. In contrast, the model presented here allows for a direct understanding of these observations without requiring clinical data, e.g. by assessing the influence of height, weight, and soft tissue thickness on the fracture risk. This is a direct consequence because the model captures the underlying mechanism of hip fracture risk.

Other than that, the model can assess whether different methods used to measure the required model parameters improve the model's prediction accuracy. As an

example, bone strength estimates could be derived with aBMD from DXA, QCT-based FEA, or HR-pQCT, giving insight into whether improved bone strength estimates are beneficial for the predictive performance. Another example is the assessment of soft tissue thickness, which can be measured with ultrasound [198], with whole-body DXA [198], extracted from CT images [183], or calculated using substitution equations with BMI and sex. And last, it can give insight into which preventive measures, e.g. fall prevention, hip padding systems as suggested by Robinovitch *et al.* [97], or drug treatment affecting BMD are the most effective.

Nevertheless, to assess the model's performance, it needs to be calibrated and validated. Other than that, several aspects could be refined and extended. In the following section, these points are outlined and discussed.

7.3 Future directions

7.3.1 Model calibration and validation

To proof the model's validity, the assessment of the hip fracture risk in cohorts with sufficient statistical power is required. In a first step, the model needs to be calibrated by fitting the parameter α so that the mean fracture risk corresponds to the geographical corresponding fracture incidence. As the fracture incidence differs between sex, two different α's could be fitted. In a second step, the individual's fracture risk could be calculated, and a receiver operator characteristic (ROC) curve analysis assessing the sensitivity and specificity of different fracture probability thresholds could be assessed. The model's performance could be compared to other prediction models such as FRAX®. Time-sensitive parameters such as bone strength or the fall rate should be adjusted according to the chosen prediction time interval. Additionally, the influence of competing mortality on long-term fracture risk could be assessed [199].

Suitable data sets would be the AGES-Reykjavik cohort or data from the MrOS study. AGES-Reykjavik data set includes the required data for the here presented model, such as CT images and variables related to falls and fractures [200]. In the MrOS cohort, also aBMD from DXA and HR-pQCT images are available [201].

7.3.2 Model refinement

Fall rate model The risk of falling directly determines the risk of hip fractures. If an individual does not fall, chances are extremely low that the bone will fracture. The presented model captures this by making the risk of fracturing fall rate dependent. This results in a relatively small fracture probability for a low expected fall rate, even if the conditional fracture probability p_S varies significantly. Consequently, the accurate prediction of a fall rate is a prerequisite for an accurate fracture risk prediction. However, the fall rate model developed and presented in Chapter 3 - Chapter 5 solely includes the prior number of falls as a predictor. Thus, the fall rate of individuals without a history of falls is identical, and the model cannot catch first-time fallers. Accordingly, the identification of other variables that are predictive of falls is required.

It is conceivable that two individuals of the same age experience different types of falls, and their risk profiles are extremely diverse. Some might fall during recreational and sports activities, while others eventually trip during simple locomotion at home. For the former, the time spent with sports activities during the week could be relevant in predicting the number of falls, while for the latter, assessing balance deficits may be a more meaningful risk factor. Thus, it seems reasonable that prior falls are a good predictor for future falls among a heterogeneous population. Since most fall-related fractures occur in frail individuals, one could argue that all sport-related falls should be excluded when developing a fall-rate prediction model. On the other hand, all falls have the potential to result in a fracture, independent of its cause.

To overcome these limitations, several approaches could be pursued. First, separate models for different target groups could be developed. A possible distinction could be made between frail and fit older adults, and initial physical tests could be conducted to determine which model is appropriate. Another approach would be to develop models separately for first-time and recurrent fallers.

Again, taking a mechanistic perspective, a model that includes parameters that better reflect the underlying mechanism and causes of falls might be able to overcome these limitations. It is well-known that the sensorimotor system, proprioception

and neuro-muscular control play a central part in motor control and joint stability [77], [78]. Research has investigated how these systems change with age and how it affects locomotion [79], [202], [203], [204]. Accodringly, a possible approach would be the detailed assessment and characterisation of gait disorders that are a well-known risk factors for falling [59], [61]. Various research has already been conducted, and gait patterns measured with accelerometric methods have shown to be a promising method to assess fall risk [205], [206]. As an example, a study conducted by Gillain *et al.* developed a supervised machine-learning algorithm using accelerometer-based gait parameters to identify first-time fallers with a sensitivity of 0.84 and a specificity of 0.87 (internal validation) [207]. Thus, using such parameters as predictors might help improve fall prediction, as they more accurately reflect the underlying mechanism that causes falls.

Personalised fall dynamics As discussed in Section 1.4.2, an individual's ability to dampen a fall can be the critical factor in whether a fracture occurs or is prevented. However, these abilities are strongly subject-dependent, relying on an individual's functional performance. Accordingly, incorporating an individual's ability to use protective pre-impact movement strategies could improve the model's predictive accuracy.

This could be achieved by personalising the parameter α that characterises the exponential distribution describing the probability of the fall dynamics. Thereby, the larger α is, the lower the probabilities of fall scenarios with low values of k_{BR}, which lead to high impact forces. To do so, variables that can assess an individual's ability to dampen a fall would be required, such as measures for the proprioceptive and neuromuscular functions or an individual's ability to resist perturbation during walking or standing [57]. These parameters could then be related to α through a mathematical relationship.

To investigate whether the adaptation of this aspect improves the models' predictive accuracy, a clinical data set that assessed all required parameters with sufficient statistical power would be required. The comparison of ROC curves

would give insights on whether personalising this aspect would benefit hip fracture risk prediction.

7.3.3 Model extension

Approximately 90% of fractures in the radius and 75% of all humerus fractures are caused by falls [57]. Fragility fractures of the pelvis are also mainly caused by low-trauma events [208]. Thus, the presented model could be adapted to assess the fracture risk for other fall-related fracture sites. To do so, bone strength estimates of the respective bones could be derived with QCT-based FEA. For the radius, the strength value could also be derived with HR-pQCT or substituted with radius aBMD from DXA, as these two measures are known to correlate well [209]. Since the radius and the humerus are in the same loading axis, it could be assessed whether aBMD- or HR-pQCT-based bone strength of the radius correlates with the humeral strength, too. Furthermore, the fall dynamics model and the mechanical model would have to be adapted to model a fall that impacts the hand or the upper arm. Developing a mechanistic model to predict fragility fracture of the pelvis might be more challenging, as there exist various fracture sites within the pelvic ring [208]. Furthermore, only a few studies have assessed pelvis bone strength with FEA models [210], [211], and to the author's knowledge, no relationship between strength and aBMD values have been developed.

7.4 Final words

The presented work in this PhD thesis aimed at developing a prediction model to identify individuals at risk of fragility hip fractures using mechanistic and stochastic modelling approaches. According to the famous quote "All models are wrong, but some are useful." by Georg Box, the model does not precisely simulate specific sideways falls and impacts on the hip, but uses a pragmatic approach integrating simplified models that still can capture the underlying mechanism of hip fractures. The required parameters are estimated from anthropometric and densitometric data and can be refined using QCT images. Thus, because of their physical nature, no

calibration considering their epidemiological variation by age, sex or ethnicity is required. The model needs solely to be calibrated to the corresponding fracture incidence in the specific geographic area.

The successful identification of individuals at risk of a fragility hip fracture can contribute some good to society, as it prevents suffering, loss of independence and death. However, as Schechner *et al.* showed in his analysis, even with perfect knowledge of the relevant factors, the predictive accuracy of hip fractures is limited to an upper bound due to the stochastic nature in the underlying process [8]. Thus, the successful identification of individuals who will suffer from a fracture will always be limited. Accordingly, as is often the case in medicine, the most effective prevention strategy for a clinical outcome such as fragility fractures would be preventing the presence of risk factors in the first place. A healthy lifestyle that includes sufficient physical activity and a balanced diet would already address a large part of this [212], [213], [214], [215].

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Scientific Contributions

Publications

- **C. Wapp**, Y. Gugler, P. Cameron, A. Dudle, D. Frauchiger, M. Papageorgiou, E. Biver, S. Ferrari, K. Lippuner, P. Zysset. "A novel fragility hip fracture risk calculator based on a mechanistic and stochastic modelling approach". Manuscript in preparation.

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- S. Wangler, A. Kamali, **C. Wapp**, K. Wuertz-Kozak, S. Häckel, C. Fortes, LM. Benneker, L. Haglund, RG. Richards, M. Alini, M. Peroglio, S. Grad. "Uncovering the secretome of mesenchymal stromal cells exposed to healthy, traumatic, and degenerative intervertebral discs: a proteomic analysis". Stem Cell Res Ther. 2021 Jan 7;12(1):11. doi: 10.1186/s13287-020-02062-2.

Conference presentations, posters, and abstracts

- **C. Wapp**, A.-G. Mittaz Hager, T. Rikkonen, R. Hilfiker, E. Biver, S. Ferrari, H. Kröger, M. Zwahlen, P. Zysset. "Validation of a Fall Rate Prediction Model for Community-Dwelling Older Adults: A Meta-Analysis with three Cohorts". ASBMR 2023, Vancouver B.C., Canada.

- **C. Wapp**, T. Rikkonen, AG. Mittaz Hager, S. Ferrari, M. Zwahlen, P. Zysset. "Number of prior falls is predictive for future falls in three independent cohorts". ECTS 2023, Liverpool, UK.

- **C. Wapp**, A.-G. Mittaz Hager, R. Hilfiker, P. Zysset. "History of Falls is a Good Predictor for a Personalized Fall Rate Estimate in Community-Dwelling Older Adults: A Negative Binomial Regression Modelling Approach" ASBMR 2022, Austin TX, USA.

- **C. Wapp**, E. Biver, S. Ferrari, P. Zysset. "Development of a personalized fall rate prediction model: the GERICO cohort analysis". SVGO/SBMS 2022, Bern, Switzerland.

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Other contributions

- Organisation and conduction of the AFFIRM-CT study, including the recruitment and examination of all study participants at the study site Bern

Declaration of Originality

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I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations. All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such. I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Place, date

Bern, March 25, 2025

Signature