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Final Master Project

Statistical models to analyse recurrent fragility fractures

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Abstract

Previous studies have shown that bone density loss increases with advancing age and fragility fractures are one of the consequences. As this type of fracture is caused by small mechanical forces rather than major trauma, the occurrence of recurrent fractures is common. However, future progression is not considered in most studies, which focus only on the initial event.

This study aims to evaluate different recurrent event models to identify risk factors of fragility fractures.

Data were obtained from the EPIC study. A cohort of subjects aged 50-85 years between 2007 and 2017, was extracted from the Catalan Information System of Development of Research in Primary Care (SIDIAP). Patients with less than one year of follow-up or less than 65 years of age on 1st January 2012 were excluded. Data from major fractures (clinical, vertebral, hip, humerus and wrist) were analysed, including data up to the third fracture. Prentice-Williams-Peterson stratified proportional hazards models were adjusted for the time between events. Age was used as the time scale; so that we had left truncation in addition to right censoring. Cause-specific PWP models were adjusted for the three gaps time, between data entry and first fracture, between first and second fracture and between second and third fracture. Proportional hazard assumption was verified graphically by means of the Schoenfeld residuals and the correspondent p-value; and the log(-log(S(t))) plots.

Differences in profile have been observed based on the history of previous fractures at study entry. The most common risk factors from previous studies have been considered, including sex, diabetes diagnosis, COPD diagnosis, history of stroke, history of falls, and corticosteroid use at study entry. The effect of these covariates has been examined, as well as how it changes depending on the number of events.

In conclusion, it has been observed that the Prentice, Williams, and Peterson models are suitable for the type of data and peculiarities of fragility fractures. On the other hand, the effect of covariates varies depending on the number of fractures experienced and on if a subject have previous fractures at the study. In subjects without a previous fracture, all covariates are significant for the first fracture, whereas the effect of sex changes for the second and third fractures. Among those with a previous fracture, neither stroke nor falls are statistically significant for the first fracture during the study.

Keywords: recurrent events, survival analysis, fracture risk, osteoporosis

Resumen

Estudios previos han demostrado que la pérdida de densidad ósea aumenta con la edad y que las fracturas por fragilidad son una de sus consecuencias. Este tipo de fracturas no se producen por grandes traumas, si no que ocurren debido a pequeñas fuerzas mecánicas, además, una vez que la primera fractura se ha producido, es común que encontrarse con fracturas recurrentes. Sin embargo, la mayoría de los estudios no consideran la progresión de futuras fracturas, centrándose sólo en el evento inicial.

El objetivo principal de este estudio es evaluar diferentes metodologías para el estudio de eventos recurrentes con tal de identificar factores de riesgo de las fracturas por fragilidad.

Los datos provienen del estudio EPOC. Una cohorte de sujetos con edades entre 50-85 ayos recogidos entre 2007 y 2017 y extraídos del Sistema d'Informació per al desenvolupament de la Investigació en Atenció Primàri (SIDIAP). Se excluyeron pacientes con menos de un año de seguimiento y que tuvieran menos de 65 años a fecha de 1 de Enero de 2012. Se estudia la información de las fracturas mayores (fracturas clínicas de vertebras, cadera, húmero y muñeca), incluyendo hasta la tercera fractura. Los modelos estratificados de riesgos proporcionales de Prentice, William y Peterson se ajustan para el tiempo entre eventos. Además, se toma la edad como escala temporal, de manera que nos encontramos con truncamiento por la izquierda a la vez que censura por la derecha. Modelos de PWP de causa específica se ajustan para cada uno intervalos de tiempo, entre la entrada al estudio y la primera fractura, entre la primera y la segunda fractura y entre la segunda y la tercera fractura. La suposición de riesgos proporcionales se verificará de manera gráfica mediante los residuos de Schoenfeld y el p-valor correspondiente; y los gráficos log(-log(S(t))).

Se han visto diferencias de perfil en función historial de fracturas previas a la entrada al estudio. Se ha considerado los factores de riesgo más habituales en estudios previos, es decir, sexo, diagnóstico de diabetes, diagnóstico de EPOC, antecedentes de ictus, antecedentes de caídas y consumo de corticoides en el momento de entrada al estudio. Se ha visto el efecto de estas covariables, así como este cambia en función del número de eventos.

Para concluir, se ha visto que los modelos de Prentice, William y Peterson son adecuados para el tipo de datos y las peculiaridades de las fracturas por fragilidad. Por otro lado, el efecto de las covariables cambia en función de cuántas fracturas se han experimentado y de si ya habían tenido fracturas previas antes de entrar al estudio. En los sujetos sin fractura previa, todas las covariables son significativas para la primera fractura, mientras que el efecto del sexo cambia para la segunda y tercera fracturas. Entre los sujetos con fractura previa, ni el ictus ni las caídas son estadísticamente significativos para la primera fractura durante el estudio.

Palabras clave: eventos recurrentes, análisis de supervivencia, riesgo de fractura, osteoporosis.

Acronyms

AIC: Akaike Information Criterion

AG: Andersen and Gil models.

CI95%: Confidence interval of 95%

COPD: Chronic Obstructive Pulmonary Disease

CSHR: Cause-specific Hazard Ratio

GT: Gap time.

HR: Hazard Ratio

HTA: Hypertension

PWP: Prentice, William and Peterson models.

RR: Relative Risk

TT: total time.

WLW: Wei, Lin and Weissfeld models.

Index

Chapter 1 Introduction

1.1 Fragility fractures

Fractures are a major cause of morbidity and mortality worldwide. Both the bone in which they occur, and the cause of the fracture vary according to the profile of the individual and they have different complications depending on these factors. We can distinguish between high and low trauma, depending on how the fractures have occurred. The former is caused by a major impact, such as a road traffic accident, while the latter are caused by a minor impact and are also known as fragility fractures (Warriner et al., 2011).

In this study we are only interested in the fragility fractures, that are fractures caused by a trauma that would not cause a fracture in a healthy adult (*Overview | Osteoporosis*, 2012); for example, those caused by a fall from a standing or sitting position or in the absence of an obvious trauma. These types of fractures are also known as osteoporosis fractures, as the fragility of the skeleton is due to this disease. Classically a major osteoporosis fracture is defined as a fracture of the hip, spine (clinical), wrist or humerus. They are considered to be major because of the importance of the consequences they entail.

These types of fractures are the main consequence of osteoporosis and are usually the first symptom seen. Osteoporosis is a systematic metabolic disease characterized by reduced bone mineral mass and changes in the architecture of the bone tissue, making the bones weak and fragile. Two features, quantity and quality, are used to diagnose the disease (Peck, 1993).

Bone Mass quantity refers to how much bone a person has, measured by bone mineral density (BMD). The most commonly used BMD test is a densitometric technique called DXA (dual-energy X-ray absorptiometry), which can be measured in vivo and has been validated by many studies for fracture risk (Johnell et al., 2005). For someone to be considered to have low bone mass, it needs to be less than or equal to 2.5 standard deviations below the average bone mass of a healthy young adult of the same sex.

When we talk about quality, we mean the microarchitecture of the bone (Seeman & Delmas, 2006). Good architecture makes the bone elastic enough to absorb the forces of a fall without fracturing. Testing bone quality is more difficult than testing bone quantity because it requires a bone biopsy, which is more invasive than DXA and therefore more risky. For this reason, osteoporosis is usually diagnosed one the basis of bone quantity, measured by BMD.

There are two defined types of osteoporosis, primary and secondary, depending on the cause of the disease. Primary osteoporosis is osteoporosis that is not the result of another. This category includes juvenile idiopathic osteoporosis, which occurs primarily in teenagers and pregnant women; postmenopausal osteoporosis, which occurs in women who have gone through the menopause with ages over 60, and senile osteoporosis which occurs in people over 70. Secondary osteoporosis is caused by certain medical conditions (Compston et al., 2017) or medications (Panday et al., 2014) that can cause bone loss.

From a pathophysiological point of view, osteoporosis is due to an imbalance between bone resorption and bone formation (Appelman-Dijkstra & Papapoulos, 2015). Bone resorption is the biological mechanism by which the old bone is broken down and resorbed, while the bone formation produces new bone tissue (Rowe et al., 2023). If the resorption process is higher than the formation process, we lose more bone than we make, resulting in osteoporosis.

As the main clinical outcome of osteoporosis is bone fracture, there has been an increase in studies trying to identify the common profile of patients at risk. The main fracture risk factors can be divided into two groups: fixed risk factors, which cannot be changed such as age, being female, family history of osteoporosis, having previous fractures, or having menopause or hysterectomy; and modifiable risks, which can be avoided or ameliorated such as alcohol consumption, smoking, low body mass index, low dietary calcium intake, vitamin D deficiency,

sedentary lifestyle or having frequent falls (*Risk Factors | International Osteoporosis Foundation*, 2023).

Although the fragility fracture is the first symptom of osteoporosis that it is seen, the consequences of the disease far-reaching. The most important of these are chronic pain, reduction in mobility leading to increase dependency, early mortality, and more future fractures.

In Spain, it is estimated that 5.4% of the population suffers from osteoporosis and that 285.000 fractures occur each year (*International Osteoporosis Foundation | IOF*, 2023). From the age of 50 onwards, the lifetime risk of developing a major fracture is 46% in women and 22% in men (Gómez-Vaquero et al., 2020) and it is estimated that the prevalence will increase 30% in the next 15 years. It has become a health problem that consumes almost a 4% of the Spanish health expenditure (Etxebarria-Foronda et al., 2015).

1.2 Recurrent events

Classical studies look at the time to an event, without considering what might happen in the future. This approach is useful for absorbing events such as death, but other possible events of interest, such as fractures, injuries or relapses, can occur more than once during a follow-up period. This type of event is more common in biomedical, demographic, and quality control studies (Cai & Schaubel, 2003). In these situations, the individuals may be at risk for subsequent events after the first one.

If we have more than one event, the main aim of our study might change. We could study the individual's event occurrence processes, or we could study the subject-to-subject variability. Or as in classical studies, we can also find the relationship of fixed covariates and more interestingly, time-dependent factors. Finally, we may be interested in studying the duration of event-free periods (Cook & Lawless, 2002).

The main characteristic of recurrent events in the analysis is that we do not have independent measures; on the contrary, we will be dealing with within-subject correlation. This correlation can have two sources, the first one is due to event dependence, that is, having an event influences the occurrence of the next event. The second source is due to heterogeneity, some people are more likely to have the time event for reasons that are neither considered nor included in the study. On the other hand, there are also time-varying covariates, that will have a different effect on different events as they change over time (González Ruiz, 2005).

Different approaches to dealing with the difficulties of recurrent events can be found in the literature. On the one hand, there are studies that propose the use of counting processes, such as Poisson processes or renewal processes, where events are considered to be uncorrelated and their rates constant over time(Lawless & Nadeau, 1995). We also find trend analysis, where the main objective is to see how event rates vary over time (Cox & Lewis, 1966).

In other studies, methods have been proposed for the analysis of recurrent events, taking into account the presence of a competing event that hinders the observation of the event of interest. In these studies, similar to the previous ones, the focus is not on analysing the time to events, but rather the expected number of events over time (Andersen et al., 2019).

As mentioned before, one of the consequences of a fragility fracture is that you may have more fractures in the future. But most studies that look at fracture risk focus on the first fracture. This is done by well-known fracture risk calculators such as FRAX (Kanis et al., 2008) or QFRACTURE (Hippisley-Cox & Coupland, 2009). To consider fragility fractures as a recurrent event, different approaches need to be considered to avoid a biased analysis. Therefore, the main objective of this study is to model recurrent fragility fractures using and extending the Cox model. Further details of the methodology and data used in this work are provided in the following chapters.

Throughout the document, in Chapter 2, we will explore the different methodologies that are used in survival analysis and focus on the methodology for recurrent events. We begin by explaining the classical approaches of the Cox model, which is the basis for most of the models that can be used with recurrent events, such as the extension of the Cox model or frailty models. The competing risk methodology is also explained, as well as the method to be used when age is considered as time scale.

Chapter 3 describes the cohort using descriptive analysis and applies the regression modelling strategies already defined in the previous chapter. The statistical results are reported together with the most relevant graphical approaches to interpret and communicate the quality of data result.

Chapter 4 discusses the results of the models and the differences between the risk factors for each fracture and the differences in time and hazard between fractures. Finally, the conclusion summarises the main points that have been explored and considers possible continuations for future projects.

Chapter 2 Methodology

2.1 Survival analysis

Survival analysis is a branch of statistics that focuses on the study of the time between an important event and the occurrence of another event. The special feature of this approach is that subjects can be censored. This means that the study ends before the event of interest occurs, so that it cannot be seen.

Let's call T a random variable representing the time until an event ε occurs; C the random variable representing the time of censorship; Y the random variable observation time that is defined as $Y: = min(T, C)$; δ the event indicator and $\boldsymbol{Z}(t)$ the set of covariates that we have for each subject at each time t.

A random variable T is usually characterized by its cumulative distribution function ($F(t)$). However, in the case of survival analysis, T can be characterised by other functions such as the survival function, the hazard function and the cumulative hazard function and the relationship between them (Cox & Oakes, 1984)

We are going to define these functions:

- Cumulative distribution function, which is defined as the probability that the event occurs before or at time t.

$$F(t) = P(T \leq t)$$

- Density function, which is defined as the relative likelihood that the event occurs at an exact time t.

$$f(t) = \frac{d}{dt}F(t)$$

- Survival function, which in contrast to the cumulative density function, is the probability that the event occurs after time t.

$$S(t) = P(T > t) = 1 - F(t) = 1 - \int_{-\infty}^{t} f(s)ds = \int_{t}^{\infty} f(s)ds, \qquad t \geq 0 \qquad (1)$$

- Hazard function is defined as the instantaneous rate of events at time t, conditional on the individual not having experienced the event up to that point.

$$\lambda(t) = \lim_{\Delta t \to 0} P(t \leq T < t + \Delta t | T \geq t)\frac{1}{\Delta t}$$

It can be related to S(t) and F(t) as

$$\lambda(t) = \frac{f(t)}{S(t)} = -\frac{\delta}{\delta t}\ln\left(S(t)\right)$$

In the same way that the hazard function is defined as a function of the survival function (1), we can define the survival function as:

$$S(t) = \exp\left(-\int_{0}^{t} \lambda(s)ds\right)$$

- Cumulative hazard function, has not an intuitive interpretation and is defined as the accumulative sum of instantaneous hazards from initial time to time t.

$$\Lambda(t) = \int_0^t \lambda(u)du = -\ln\left(S(t)\right)$$

Cox proportional hazards models.

The most used model for modelling survival data is the Cox proportional hazard model. This approach models the hazard function according to a baseline hazard function $\lambda_0(t)$ and a set of covariates **Z**(t) of interest (Therneau & Grambsch, 2000). Hence the probability of an event occurring at a given time, is a function of the covariates through a proportional relationship.

$$\boldsymbol{\lambda}_i(t|\boldsymbol{Z}(t)) = \lambda_0(t)\exp\left(\sum_{j=1}^{p} \boldsymbol{\beta}_j \boldsymbol{Z}(t)_j\right) \quad (2)$$

The Cox model is a semi-parametric model since the distribution of the baseline hazard over the time $\lambda_0(t)$ has an associated distribution. The likelihood function depends on that baseline hazard function and on the coefficients of the covariates (β).

Given a sample of size n and $Y_i = \max_i(T_i, C_i)$, the likelihood function is expressed in function of the baseline hazard function $\lambda_0(y_i)$ and the baseline survival function $S_0(y_i)$ as:

$$L(\lambda_0(\cdot), \boldsymbol{\beta}) = \prod_{i=1}^{n} (\lambda_0(y_i)\exp\left(\boldsymbol{\beta}'\boldsymbol{Z}\right))^{\delta_i} S_0(y_i)^{\exp\left(\boldsymbol{\beta}'\boldsymbol{Z}_i\right)}$$

However, the likelihood function in Cox models depends on the unknown baseline risk function $\lambda_0(t)$. As a result, the partial likelihood function is employed for estimating the coefficients β. The partial likelihood function considers the covariates $\boldsymbol{Z}_i$, the ordered times of the observed r events denoted as *t(j)*, and the number of individuals at risk at each respective time denoted as *R(t(j))*. By utilizing the partial likelihood function, we can estimate the **β** coefficients without requiring knowledge of the baseline risk function $\lambda_0(t)$.

$$L(\boldsymbol{\beta}) = \prod_{j=1}^{r} \frac{\exp\left(\boldsymbol{\beta}'\boldsymbol{Z}_{(j)}\right)}{\sum_{l \in \boldsymbol{R}(t_{(j)})} \exp\left(\boldsymbol{\beta}'\boldsymbol{Z}_{\boldsymbol{l}}\right)}$$

The regression coefficients can be used to estimate the effect of each covariate on the hazard function. The exponential function of the regression coefficient for the covariate of interest in the Cox model is the hazard ratio (HR), which compares the risk of an event occurring for a particular profile compared to the baseline profile.

$$HR = \frac{\lambda(t|\boldsymbol{Z}(t))}{\lambda(t|\boldsymbol{Z}(t) = 0)}$$

The validation of the Cox model depends on strong assumptions, one of which is that the hazard ratios between two subjects must be constant over the time. This assumption could be checked using Schoenfeld residuals (Schoenfeld, 1982). These residuals compare the value of the observed value of the covariate with its conditional expectation given the individuals at risk. Therefore, we need to check the assumption for each of the k covariates by calculating them as follows:

$$\boldsymbol{r}_{SC_{ik}} = \boldsymbol{\delta}_i \boldsymbol{J}_i(t)\{\boldsymbol{Z}_{ik} - \overline{\boldsymbol{Z}_k}(\boldsymbol{T}_i)\}$$

Where $\mathbf{J}_i$(t) indicates if the individual i is at risk before the time t and $\overline{\boldsymbol{Z}_k}(\boldsymbol{T}_i)$ is the expected value of the covariate at time $\mathbf{T}_i$.

If the assumption is verified, it is expected that the plot of the residuals versus the time should not show patterns or trends in the residuals. In addition to the graph, a hypothesis test could be performed to complement the graph.

Another way to verify this assumption for categorical variables is to use the graph of the log(-log(S(t))) (Hess, 1995). The value of log(-log(S(t))) is calculated for each of the different categories of a covariate as:

$$\log\big(S(t)\big) = -\lambda(t);\ \log\big(-log\big(S(t)\big)\big) = \log(\lambda) + \log(t)$$

In this case, for categorical covariates, the graph plots the log(-log(S(t)) versus the time for each category, e.g., for binary variables, we are representing two curves. Under the proportional hazards assumption, the curves are expected to be a straight line with constant slope, so they should be parallel without crossing (Kleinbaum & Klein, 2012).

2.2 Age as time scale

The starting point for survival analysis is usually an important and meaningful event, such as the start of a treatment, a surgery, or a diagnostic. However, in many cases, the event up to which we begin to measure, the time to our event of interest, is the date of entry into the study. On the other hand, in older populations, the interest of the study can be seen as a study of the ageing process, as is the case of studies where the main outcome is mortality.

In this situation when we do not have an initial meaningful starting point, if the study population consist of older individuals and the outcome of interest is related to the aging process, we can use the age of the individual as the time scale. To do this, we fix the starting point to the moment of reaching 65 years of age (Lamarca et al., 1998).

With this approach, we are dealing with right censoring, as in usual survival analysis, because there are events that they will not see, and left truncation, because those individuals who have the event before the start of the study are not observed.

It is necessary to define some notation, Y remains as in the classical approach, as the time from the date of entry into the study until the event, the end of follow-up or censoring. W is the time from the subject's 65^{th} birthday to entry into the study. Those who enter at the age of 65 will have $W = 0$, while those who enter older than 65 will have a different and specific value. Finally, we have T as the total duration of the study, which is calculated as $T = Y + W$.

In contrast to studies with only right censoring, the number of subjects at risk does not decrease monotonically with time. Subjects at risk at time t are only those who have entered at the study at an age younger than t + 65 and that did not experience the event.

The advantage of this approach is that it provides a straightforward interpretation of the event of interest, as it cannot be misunderstood by the effect of the age.

2.3 Recurrent event approaches

The Cox model is an appropriate method when there are no recurrent events, but it cannot take into account the within-subject correlation that we have when more than one event occurs, nor the dependence between events.

Different approaches have been developed to deal with this situation. The extension of the original Cox model such as Andersen and Gill (AG), Wei, Lin and Weissfeld (WLW) or Prentice, William and Peterson (PWP) models; the frailty models, marginal mean or rate models and the multistate model (Amorim & Cai, 2015).

Unlike in Section 2.1.1, the event can now occur more than once for each subject. Thus, we will have j number of events and therefore, T_1, T_2, ..., T_j times to the event. Again, we will have the random variable C that measures the time to censoring, and finally, the set of covariates **Z**(t), which in this case, and depending on the methodology, may be different for each event and may vary over time.

2.3.1 Andersen and Gill models

The AG model is a counting process that is formulated in terms of increments in the number of events over the time (Andersen & Gill, 1982). It assumes that the correlation between event times for a subject can be explained by past events, so that the time increments between events are conditionally uncorrelated, given the covariates.

$$\boldsymbol{\lambda}_i(t|\boldsymbol{Z}(t)) = \boldsymbol{J}_i(t)\lambda_0(t)\exp\{\sum_{j=1}^{p}\boldsymbol{\beta}_j\boldsymbol{Z}_{ij}(t)\},$$

where $\mathbf{J}_i(t)$ is the at-risk indicator of subject i at time t. In this approach, $\mathbf{J}_i(t)$ will always be 1, until something happens to the subject that makes it impossible to follow it, such as death or loss of follow-up. For example, we have two subjects, the first one who has two events during the study and the second one who has no events. Both subjects are counted as at risk for each of the two events throughout the entire study.

The main limitation of this approach is, first that we are considering that the baseline hazard function does not change from one event to another. Also, they give an overall effect of the covariates on the intensity of the occurrence of the events.

2.3.2 Wei, Lin and Weissfeld

The WLW models model the marginal distribution of each failure time with a Cox proportional hazards model (2) considering the ordered events as if they were unordered, as in competing risk models. An individual is assumed to be at risk of event 2 during their follow-up, whether or not the event 1 has occurred.

The hazard function is stratified by the maximum number of events a subject has, with only one observation in each stratum (Wei et al., 1989).

$$\boldsymbol{\lambda}_{ki}\big(t;\boldsymbol{Z}_{ki}(t)\big) = \boldsymbol{J}_{ki}(t)\boldsymbol{\lambda}_{0j}(t)\exp\{\sum_{j=1}^{p}\boldsymbol{\beta}_{jk}\boldsymbol{Z}_{jki}(t)\}$$

Where $\mathbf{J}_{ki}(t) = 1$ until the k^{th} event unless it is censored. This means, that we have different strata and that each subject is at risk for each stratum while the follow-up is possible. With the same example of the AG models, both subjects would be at risk for each of the three stratums (for the first, second and possibly third event).

By stratifying, the correlation between event times is not considered in the models and although the estimators of the parameters are robust, their standard errors need to be corrected for this association. In addition, different covariates can be fitted to each one of the events, making the model more flexible than the first one. On the other hand, the subject's history is not used and is only appropriate for studying total times (Gómez Melis et al., 2004).

2.3.3 Prentice, Williams, and Peterson models

As in the WLW models, PWP proposed stratification by events, so that there is no dependence between events. In this case, the subjects are at risk of a second event only if they have had the first event. The same method is used for subsequent events (Prentice et al., 1981). For example, the same two subjects

Continuing with the same example as in the two previous approaches, in this case, both subjects are at risk for the first stratum (the first event), but only the one who had a first event is at risk for the second stratum, and since he has a second event, he is also at risk for the third one.

More information on this approach is given later in this chapter.

2.3.4 Marginal means/rates models

Marginal means/ rates models can be interpreted in terms of the mean number of events in the absence of time-dependent covariates, so that all recurrent events of the same subject are considered as a single counting process. It does not specify a dependence structure between the recurrent events but score residuals and sandwich estimators are used to correct for the dependence structure. A disadvantage of this model compared to others is that we do not use temporal information (Amorim & Cai, 2015).

2.3.5 Fragility models

Frailty models introduce a random covariate into the model to explain the dependencies between events including the subject heterogeneity. In this way, recurrent event times are assumed to be independent of the covariate and the random effect (Liu et al., 2004).

$$\boldsymbol{\lambda}_{ij}\left(t_i|\boldsymbol{\alpha}_i, \boldsymbol{Z}_{ij}\right) = \boldsymbol{\alpha}_i \lambda_0(t) \exp\{\sum_{j=1}^{p} \boldsymbol{\beta}_j \boldsymbol{Z}_{ij}(t)\}$$

When we add the random effect of α_i we assume a parametric distribution under it. Usually, the gamma distribution with unit mean and variance θ is assumed. However, this assumption is not easy to verify (Cai & Schaubel, 2003).

2.3.6 Multi-state models

Multi-state models are defined as a stochastic process X(t) that occupies one of a set of states at any time t. They consider the trajectory of subjects as a series of states and the possible transitions between them (Castañeda & Gerritse, 2010). The possible paths are defined by the transition probabilities, which explain the instantaneous hazard of moving to the next state, given the state one is in and the historical path one has taken (Hougaard, 1999).

The transition probabilities, assuming the Markov property, may be defined as

$$P_{hj}(s,t) = Prob(X(t) = j|X(s) = h)$$

And the transition intensities

$$\boldsymbol{\alpha}_{hj}(t) = \lim_{\Delta t \to 0} \frac{P_{hj}(t, t+\Delta)}{\Delta t}$$

With this approach, Cox proportional hazards models can be used to model the instantaneous hazards. This means that different models are fitted to each one of the transitions and it is possible to include different sets of covariates for each transition.

2.4 PWP models with competing risks

In our data, the recurrent events are fragility fractures. It is known from previous studies that the hazard of having a fracture is different if whether or not the subject has had a previous fracture which can be seen as having a time dependent status per transition (Furberg et al., 2022). This means that the baseline hazard of the first fracture would be different from the baseline hazard of the second and third fractures. It has also been shown that the risk factor can change after a first fracture. With this in mind, the best approach are the PWP models.

2.4.1 PWP methodology

For recurrent events, PWP models propose that the dependence between events is resolved by stratification. These models work by ordering the events and using the previous number of events as a stratification variable (Prentice et al., 1981). They are proportional hazard model with time-dependent strata and different baseline hazard function for each one of the strata.

As in other models, we make several assumptions in this approach. First, censorship is assumed to be uninformative, i.e. the time of censorship is unrelated to the event. Also, as in Cox models, the hazard rate is assumed to be proportional over time.

Subsequent times depend on their previous times, so that T_k can be only observed if $T_1 + \ldots + T_{k-1}$ is less than or equal than the time of censure C (Gómez Melis et al., 2004).

Assuming that we have only two possible events, our main outcome will be a vector such as $(Y_{1i}, Y_{2i}, \delta_{1i}, \delta_{2i})$ that will be defined as:

$$(Y_{1i}, Y_{2i}, \delta_{1i}, \delta_{2i}) = \begin{cases} (C_i, undefined, 0, 0) & \text{if} \quad T_{1i} > C_i \\ (T_{1i}, C_i - T_{1i}, 1, 0) & \text{if} \quad T_{1i} < C_i < T_{1i} + T_{2i} \\ (T_{1i}, T_{2i}, 1, 1) & \text{if} \quad T_{1i} + T_{2i} \leq C_i \end{cases}$$

There are two different ways of looking at the time to the fragility fractures. The first one is called Total Times (TT), because for each one of the events, we are going to study the time from the starting point. Therefore, the hazard function for the event j is modelled in a similar way that the Cox model but considering for each one of the possible events, only the subjects that have had the previous event. This is defined by the at-risk indicator $\boldsymbol{J}_{ij}(t)$.

$$\boldsymbol{\lambda}_{ij}\big(t|\boldsymbol{Z}_{ij}(t)\big) = \boldsymbol{J}_{ij}(t)\boldsymbol{\lambda}_{0j}(t)\exp\{\boldsymbol{\beta}_j\boldsymbol{Z}_{ij}(t)\}$$

Meanwhile, if we are interested in studying the time that each event occurs after the first one, this called, Gap Time (GT). When studying the gap time, this index is reset to zero after each occurrence of the event. So, in this case, we are evaluating the effect of a covariate for the kth event since the time of the previous one. The hazard function is as follows:

$$\boldsymbol{\lambda}_{ij}\big(t|\boldsymbol{Z}_{ij}(t)\big) = \boldsymbol{J}_{ij}(t)\boldsymbol{\lambda}_{0j}(t - \boldsymbol{t}_{i,j-1})\exp\{\boldsymbol{\beta}_j\boldsymbol{Z}_{ij}(t)\}$$

In both methods we assume that recurrent events within the subject are related, so as we have said before, the subjects are at risk of the m^{th} event only if they have had the previous one $(m-1)^{th}$ event (Yadav et al., 2020). Thus, $\boldsymbol{J}_{ij}(t)$ is 0 if the previous event has not occurred and 1 if it has.

To estimate the coefficients $\boldsymbol{\beta}$ we will use the marginal partial likelihood. Let j denote the number of strata, $\widetilde{\boldsymbol{R}}(u, j)$ the set of subjects at risk in stratum j, u denotes the interval from immediately preceding failure in the same subject and $\tilde{t}_l$ the last failure time on subject l prior to entry into stratum j (Prentice et al., 1981), we can define the partial likelihood as follows:

$$L(\boldsymbol{\beta}) = \prod_{j\geq 1}\prod_{i=1}^{k_j}\left\{\frac{\exp\left(\beta_j\boldsymbol{Z}_{ji}\big(t_{ji}\big)\right)}{\sum_{l\,\in\widetilde{\boldsymbol{R}}(u_{s,i}s),}\exp\left(\boldsymbol{\beta}_j\boldsymbol{z}_l(\tilde{t}_l + u_{si})\right)}\right\}$$

Unlike the Cox model, with recurrent events we have a correlation structure between events and subjects. Estimating the variance of the coefficients β does not take this correlation into account, so the variance needs to be corrected. This can be done using the sandwich estimator, a general method for obtaining robust and unbiased estimates using the covariance matrix in situations where model assumptions are not met, such as in this case, that the measures are independent. (Carroll et al., 1998).

2.4.2 Competing risks

In addition to studying the time to fragility fracture, it is important to consider the death as a competing event. This is because death can be a cause of loss to follow-up and can affect at the estimation of the fracture's probabilities. If death is not included as a competing event in the study design, the probability of fracture may be underestimated in people who are more likely to die.

Before going into the methodology, let's define T as the random variable measuring the time to the event, and C as the cause of the event. While T is a continuous variable, C can only take a set of fixed values.

There are two different strategies for dealing with competing risks, modelling the cumulative incidence function, or modelling the cause specific hazard.

2.4.2.1 Cumulative incidence function

The cumulative incidence function ($F_k(t)$) is defined as the probability of that the event k occurs before the others at time t. It is used to determine which factors are associated with the incidence of a specific event k (Porta et al., 2007). This strategy takes into account that individuals with previous causes are still at risk for the other event. The estimate of the function can be obtained as

$$\hat{F}_k(t|\boldsymbol{Z}) = \int_0^t \hat{\lambda}_k(u|\boldsymbol{Z})\hat{S}(u|\boldsymbol{Z})du,$$

where $\hat{\lambda}_k(u|\boldsymbol{Z})$ are the estimated hazards resulting from Cox's or Aalen's analysis, and $\hat{S}(u|\boldsymbol{Z})$ the estimated survival function.

The way to test the effect of the covariates based on the $F_k(t)$ is with the Fine and Gray's model (Fine & Gray, 1999), where the sub-distribution hazard function for the kth type of event is defined as:

$$h_k(t|\boldsymbol{Z}) = \lim_{\Delta t \to 0} \frac{P(T < t + \Delta t, C = k|Z, \{T \geq t \text{ or } (T < t \text{ and } C \neq k)\})}{\Delta t} = \frac{f_k(t|\boldsymbol{Z})}{1 - F_k(t|\boldsymbol{Z})}$$

We can model the sub-distribution hazard function with a Cox proportional model, as follow:

$$h_k(t|\boldsymbol{Z}_k) = h_{0k}(t)\exp\{\beta_k^{SD}\boldsymbol{Z}_k\}$$

Under this model, the covariates are linear on a complementary log-log transformed cumulative incidence function. The subdistribution hazard ratio explains the association between the effect of a covariate on the risk of the event from cause k.

2.4.2.2 Cause-specific models

On the other hand, we have the cause-specific models, where each hazard is analysed separately considering the failures for other causes as censored observations. This approach is appropriate when your objective is to identify factors associated with the risk of a specific event.

In this approach, we define the cause-specific hazard of event k as

$$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{P(t < T < t + \Delta t, C = k|T > t)}{\Delta t}$$

And as we saw earlier, there is a relationship between the hazard function and the survival function, so that, given a cause-specific hazard function, $\lambda_k(t)$, we can define $S_k(t)$ a:

$$S_k(t) = e^{-\int_0^t \lambda_k(u)du}$$

Meanwhile, $S_k(t)$ does not correspond to the complementary of the incidence function. Therefore, two new functions can be defined. The first one, $S_k^*(t)$ as the complement of the cumulative incidence function:

$$S_k^*(t) = 1 - F_k(t)$$

$S_k^*(t)$ could be interpreted as the probability of not failing from cause j before t.

The second one, $\tilde{S}_k(t)$, is obtained by using the proper definition of $F_k(t)$:

$$\tilde{S}_k(t) = P(T > t, C = k)$$

On the other hand, $\tilde{S}_k(t)$ can be interpreted as the probability of failing from cause j after t.

It can also use a standard Cox model for each cause k. In this case, the cause-specific hazard ratio explains the association on the effect of a covariate on the rate of the event from cause k. To allow the interpretation of the cause-specific, it is necessary to make the assumption of independence between the events (Lau et al., 2009).

In this case the overall likelihood function is the product of the k likelihoods of each different event. And the likelihood function for a particular cause is the one that you get if you consider the subjects who have the event for other reasons as censored.

As our main interest is to see how the factors influence at the incidence of each one of the recurrent fractures, we will adjust the cause-specific models so that for each of the three strata defined by the number of fractures we consider those who died as censored.

Chapter 3 Analysis of recurrent fragility fractures in the EPIC cohort

For this analysis we will use data from the EPIC cohort study (Tebé et al., 2022). Data was extracted from the Information System for the Development of Research in Primary Case (SIDIAP), a database of clinical information collected by primary care centres in Catalonia. SIDIAP includes more than 6 million patients, almost the 80% of the Catalan population, with socio-demographic data, diagnostics and medications dispensed in health care pharmacies (García-Gil et al., 2011).

All subjects enrolled in the SIDIAP with an entry date before 31st December 2006, an exit date after 1st January 2012, with more than one year of follow-up, and aged 65 years or older were included in the study database. Participants were followed from 1st of January 2012 until the earliest of death, transfer out/migration, or the end of 2017. Eligible patients treated with any anti-osteoporotic drug (bisphosphonates, strontium, calcitonin, selective estrogen receptor modulators, and hormone replacement therapy) before the inclusion date were excluded. Subjects with multiple concurrent fractures were also excluded, as these are considered trauma fractures rather than fragility fractures, leaving a cohort of 805,539 subjects (Figure 1).

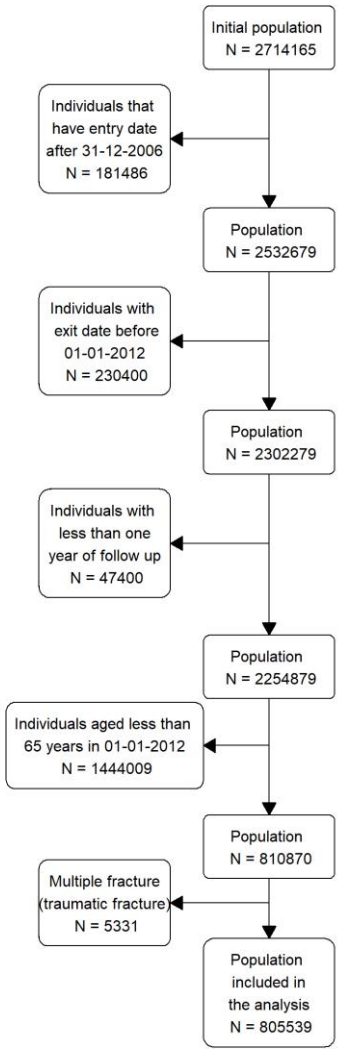

Figure 1: Study flow chart

3.1 Descriptive analysis

As described in Chapter 1, having a previous fragility fracture dramatically increases the risk of having another one. Therefore, we divided our cohort into those who had a prior fragility fracture (58901, 7.3%) and those who had not (746638, 92.7%).

We carried out a descriptive analysis of the data according to the two groups mentioned above in order to understand the differences that might exist between the two groups. In terms of demographic information, we have the sex and age of the cohort, which we show in the next table:

Table 1: Demographic data in the whole cohort and by previous fracture.

	[ALL]	**No**	**Yes**	**N**
	N=805539	*N=746638*	*N=58901*	
Sex, N (%):				805539
Woman	420238 (52.17%)	377615 (50.58%)	42623 (72.36%)	
Man	385301 (47.83%)	369023 (49.42%)	16278 (27.64%)	
Age, Mean (s.d.)	75.2 (6.8)	75.0 (6.7)	78.0 (7.0)	805539
Age, Median [Q1;Q3]	74.8 [69.2;80.5]	74.6 [69.0;80.2]	78.6 [72.0;83.9]	805539

If we look at the sex of the whole cohort, we can see that the proportions of women and men are similar (52.2% vs 47.8%), whereas, if we focus only on those with previous fractures, there is a higher proportion of women than men (72.4% vs 27.6%). In terms of age, we can see that those with a previous fracture are older than those without previous fracture (78 years vs 75 year on average). Thus, the pre-fracture group is an older group with a higher proportion of women.

Information is collected on subjects' comorbidities, including risk factors known to be associated with previous fractures.

Table 2: Baseline comorbidities in the whole cohort and by previous fracture.

	[ALL]	**No**	**Yes**	**N**
	N=805539	*N=746638*	*N=58901*	
Diabetes, N (%): Yes	185274 (23.00%)	170757 (22.87%)	14517 (24.65%)	805539
HTA, N (%): Yes	483969 (60.08%)	445526 (59.67%)	38443 (65.27%)	805539
Myocardial infarction, N (%): Yes	75612 (9.39%)	69954 (9.37%)	5658 (9.61%)	805539
Chronic Kidney disease, N (%): Yes	43307 (5.38%)	39092 (5.24%)	4215 (7.16%)	805539
Arthrosis, N (%): Yes	255209 (31.68%)	230954 (30.93%)	24255 (41.18%)	805539
Stroke, N (%): Yes	61905 (7.68%)	55340 (7.41%)	6565 (11.15%)	805539
COPD, N (%): Yes	49212 (6.11%)	45552 (6.10%)	3660 (6.21%)	805539
Cataracts, N (%): Yes	126020 (15.64%)	112901 (15.12%)	13119 (22.27%)	805539
Malabsorption syndrome, N (%): Yes	2906 (0.36%)	2666 (0.36%)	240 (0.41%)	805539
Early menopause, N (%): Yes	2320 (0.55%)	2104 (0.53%)	216 (0.51%)	420238
Diabetic neuropathy, N (%): Yes	6413 (0.80%)	5710 (0.76%)	703 (1.19%)	805539
Endocrine disease, N (%): Yes	10962 (1.36%)	9751 (1.31%)	1211 (2.06%)	805539

In general, subjects with previous fracture had a higher prevalence of comorbidities, mainly hypertension, arthrosis and cataracts. The former could be explained in part by differences of the subjects ages. Arthrosis is linked to the bones, as it is the loss of the cartilage that cushions and protects the bones, while the latter can lead to greater falls and blows that end in fractures. Other comorbidities in which somewhat smaller differences are seen are diabetic neuropathy, related to lower bone density, as it is produced by diabetes, and endocrine disease, whose hormonal imbalance again affects a subject's bone density.

On the other hand, it is important to consider the medication that people are taking. Some adverse effects of drug therapy are a major cause of secondary osteoporosis, as well as endocrine disorders, eating disorders, kidney disease and cancer, among others. The following table shows the use of different medications, some of which are directly related to the loss of bone density and others to the risk of falls.

Table 3: Baseline treatment in the whole cohort and by previous fracture.

	[ALL]	No	Yes	N
Proton pump inhibitor, N (%): Yes	546010 (67.78%)	499976 (66.96%)	46034 (78.15%)	805539
Anxiolytics, N (%): Yes	373133 (46.32%)	339029 (45.41%)	34104 (57.90%)	805539
Statin, N (%): Yes	366703 (45.52%)	340165 (45.56%)	26538 (45.06%)	805539
Diuretic, N (%): Yes	295957 (36.74%)	272559 (36.50%)	23398 (39.72%)	805539
Antidepressants, N (%): Yes	170414 (21.16%)	151553 (20.30%)	18861 (32.02%)	805539
Metformin, N (%): Yes	147824 (18.35%)	136684 (18.31%)	11140 (18.91%)	805539
Corticoids, N (%): Yes	129514 (16.08%)	117887 (15.79%)	11627 (19.74%)	805539
Anticonvulsants, N (%): Yes	110919 (13.77%)	99719 (13.36%)	11200 (19.01%)	805539
Vitamin D, N (%): Yes	106722 (13.25%)	90329 (12.10%)	16393 (27.83%)	805539
Sulfanilureas, N (%): Yes	79882 (9.92%)	73534 (9.85%)	6348 (10.78%)	805539
Antipsychotics, N (%): Yes	79040 (9.81%)	69714 (9.34%)	9326 (15.83%)	805539
Bisphosphonates, N (%): Yes	50337 (6.25%)	40974 (5.49%)	9363 (15.90%)	805539
Insulin, N (%): Yes	44596 (5.54%)	39999 (5.36%)	4597 (7.80%)	805539
Dipeptidyl peptidase-4 inhibitors, N (%): Yes	23176 (2.88%)	21660 (2.90%)	1516 (2.57%)	805539

	[ALL]	No	Yes	N
Anti-hormonal treatment (GNRH), N (%): Yes	11027 (1.37%)	10238 (1.37%)	789 (1.34%)	805539
Tiaziolindionas, N (%): Yes	9732 (1.21%)	8864 (1.19%)	868 (1.47%)	805539
Aromatase inhibitors, N (%): Yes	8903 (1.11%)	8029 (1.08%)	874 (1.48%)	805539
Strontium, N (%): Yes	8388 (1.04%)	6613 (0.89%)	1775 (3.01%)	805539
Estrogens, N (%): Yes	3218 (0.40%)	2961 (0.40%)	257 (0.44%)	805539
Teriparatide, N (%): Yes	2421 (0.30%)	1434 (0.19%)	987 (1.68%)	805539

As in the case of the comorbidities, in general, subjects with previous fracture had higher percentages of treatment.

Vitamin D, bisphosphonates, strontium and teriparatide are treatments prescribed to subjects with osteoporosis to increase bone density or reduce its decline. Anxiolytics and antidepressants can affect balance, leading to an increased risk of falls and therefore an increased risk of fracture. Finally, the use of corticoids or aromatase inhibitors use is a well-known cause of secondary bone loss and is recommended to be taking into account when assessing fracture risk.

3.2 Outcomes

The incidence of fragility fractures and death are the two outcomes of interest in this study. Only the first three fractures after cohort entry are included in the analysis. Death will be considered as a competing risk that will make it impossible to see potential future fractures.

3.2.1 Fractures

Having described the cohort in terms of the previous fracture, we will now describe the cumulative incidence and the incidence rate taking into account the number of fractures. As we differentiate according to whether or not they have had a previous fracture, it is important to bear in mind that in the group who have already had fractures, when we talk about the first one, we are really talking about the second or even the third fracture.

Table 4: Cumulative incidence and incidence rate of fracture by number of fractures and previous fractures

Group	At risk	Fracture	% (95%CI)	Person-years	Rate per 100 person-years (95%CI)
Global					
First fracture	805539	71496	8.88 (8.81, 8.94)	1132767.025	6.31 (6.27, 6.36)
Second fracture	71496	6787	9.49 (9.28, 9.71)	120439.480	5.64 (5.5, 5.77)
Third fracture	6787	1056	15.56 (14.7, 16.44)	20162.587	5.24 (4.93, 5.56)
Without previous fracture					
First fracture	746638	60333	8.08 (8.02, 8.14)	943944.975	6.39 (6.34, 6.44)
Second fracture	60333	5327	8.83 (8.6, 9.06)	93724.389	5.68 (5.53, 5.84)
Third fracture	5327	822	15.43 (14.47, 16.43)	15679.179	5.24 (4.89, 5.61)
With previous fracture					
First fracture*	58901	11163	18.95 (18.64, 19.27)	188822.051	5.91 (5.8, 6.02)
Second fracture*	11163	1460	13.08 (12.46, 13.72)	26715.091	5.47 (5.19, 5.75)
Third fracture*	1460	234	16.03 (14.18, 18.01)	4483.409	5.22 (4.57, 5.92)

* Seen along the study time

In the table 5 the fracture cumulative incidences are reported together with their respective 95% confidence intervals. Incidences are higher among those subjects with previous fracture. If we compare the cumulative incidence of the first fracture, we can see that in the group of subjects without a previous fracture, it is 8.08%, whereas in those with previous fractures, it is 18.95%, with a relative risk (RR) 2.35 and 95% confidence interval of 2.3 - 2.39. Therefore, the group with previous fractures has more than twice the risk of having a fracture than those without a previous fracture.

For the second fracture, the cumulative incidence in the group without previous fracture increased slightly to almost 9%, whereas in the group with previous fracture, the cumulative incidence decreased from 18.95% to 13.08%. In this case, the RR is 1.48 with 95% confidence interval of 1.40 - 1.56. The differences are smaller than for the first fracture, but they are still higher in the group with a previous fracture.

Finally, for the third fracture the cumulative incidence increased again in both groups. However, the differences between the two groups were not as great as for the other two fractures. In the group without previous fracture the incidence was of 15.43% compared to 16.03% in the group with previous fractures. The RR is 1.04 with a 95% confidence interval of 0.91 - 1.19, with no statistically significant differences for the third fracture.

Looking at the incidence rate, we can see that globally the incidence rate is higher for the first fracture, and it gets lowest as the number of fractures increases. For the first fracture we have an incidence rate of 6.31 people over 100 that have per year, while it goes to 5.64 for the second fracture and 5.24 for the third one.

If we look at the different groups, we can see that the behaviour is the same as globally. In those without a previous fracture, the incidence rate is 6.39 over 100 people per year for the first fracture, falling to 5.68 at second fracture and to 5.24 for the third fracture. In the group with previous fractures, the incidence rates for each one of the events are 5.91, 5.47 and 5.22 people over 100 per year, respectively.

3.2.2 Death

Although the main event in our study is the fragility fractures, because the cohort is an ageing one, deaths may occur, making it impossible to see future fractures. For this reason, we describe the proportion of people that died during follow-up as well as we have done for the fractures, comparing the results depending on whether they had a previous fracture and whether they had a fracture during follow-up.

Table 5: Cumulative incidence of death and mortality rate by group and by having a fracture during follow-up

Group	At risk	Dead	% (95%CI)	Person-years	Rate per 100 person-years
Global					
No fracture	734043	130952	17.84 (17.75, 17.93)	2386361.5	5.49 (5.46, 5.52)
Fracture	71496	17746	24.82 (24.5, 25.14)	358089.4	4.96 (4.88, 5.03)
Without previous fracture					
No fracture	686305	117721	17.15 (17.06, 17.24)	2119291.0	5.55 (5.52, 5.59)
Fracture	60333	14360	23.8 (23.46, 24.14)	287047.0	5.00 (4.92, 5.08)
With previous fracture					
No fracture*	47738	13231	27.72 (27.31, 28.12)	267070.5	4.95 (4.87, 5.04)
Fracture*	11163	3386	30.33 (29.48, 31.19)	71042.4	4.77 (4.61, 4.93)

*Seen along the study time

Looking at the global cohort, the cumulative incidence of death is lower in subjects who did not have a fracture than in those who had a fracture during follow-up (17.84% vs. 24.82%). Which a RR of 1.39 and 95% confidence interval of 1.37 -1.41. This difference is also seen when we differentiate by previous fracture, but the difference is smaller in the group with previous fracture.

On the other hand, the cumulative incidence is higher in the group with a previous fracture than in the group without a previous fracture, regardless of whether they had a fracture during the study.

Regarding the incidence rate of death in the entire cohort, we can see that the incidence rate is higher in those who do not have a fracture during the follow-up. Overall, regardless of whether they had fractures prior to the study or had fractures during the study, the occurrence of death is around 5 deaths per 100 people in one year.

However, in Table 5 we do not take into account the moment in which death occurs. The profile of an individual who died before the first fracture differs from that of someone who died before the second fracture. The latter group tends to be older and has a more likely to have complications than the former. Appendix A shows the differences in demographic information between these profiles.

3.3 Cumulative incidence function of fracture and death

Although our focus is on time to fracture, as we have already discussed, it is important to remember that the real situation we find ourselves in is one of competing risks between fragility fractures and death. In order to understand how both events occur over time, cumulative incidence graphs are constructed. Separate graphs are made to account for the different profiles and times seen between people without and with previous fractures. As women are known to have a higher risk of fracture than men, the curves are also stratified by sex.

Our data have the date of entry into the trial as the starting point for studying survival. This event has no meaning in terms of time to fracture or death. In addition, by the definition of the disease and the cohort, we are dealing with an older cohort, where age itself has a relationship with the timing and risk of our events. Therefore, we decided to use age as the time scale, considering that the point of entry into old age will be the point at which individuals reach the age of 65.

3.3.1 First fracture

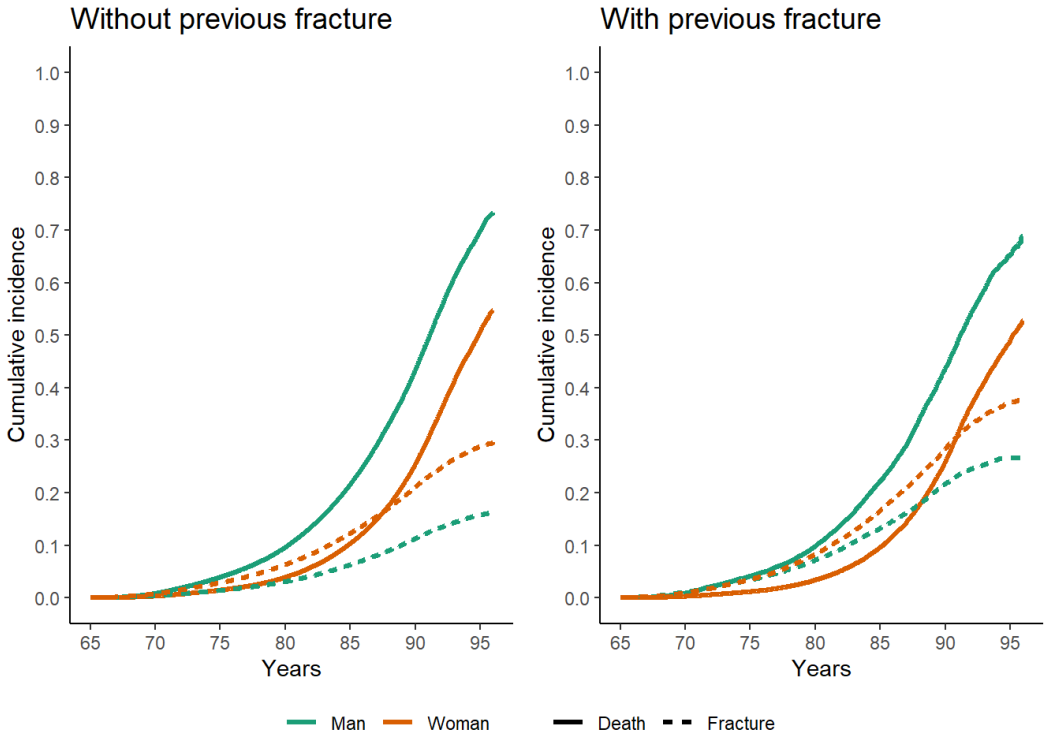

Figure 2: Cumulative incidence of first fracture and death by previous fracture and sex

Figure 2 shows the cumulative incidence function of the first fracture and death by sex and previous fracture. Each point on the graph represents the cumulative incidence of each event by sex at the age at which it occurs without the other event having occurred. Information for men is shown in green and the information for women is shown in orange. The type of line represents the event, the solid line is death, and the dashed line is fracture. For example, in the group without a previous fracture, at the age of 80, the probability of men of having a first fracture is close to 0, while the probability of men of dying before having of the first fracture is close to 0.1.

On the left we have subjects without previous fracture, we can see that the men have higher values earlier in relation to death than the women. The two curves remain parallel over time and grow in a similar way. In the case of fractures, however, it is the group of women who have the event at a younger age and who have a higher probability of fracture over time. From the age of 85, however, the differences between the sexes become greater.

On the right we have subjects with previous fracture, death acts in a similar way to the first graph, men are more likely to die earlier than women. In terms of fractures, the curves for men and women remain close until the age of 80, at which point they begin to diverge, with women again more likely to suffer a fracture.

3.3.2 Second fracture

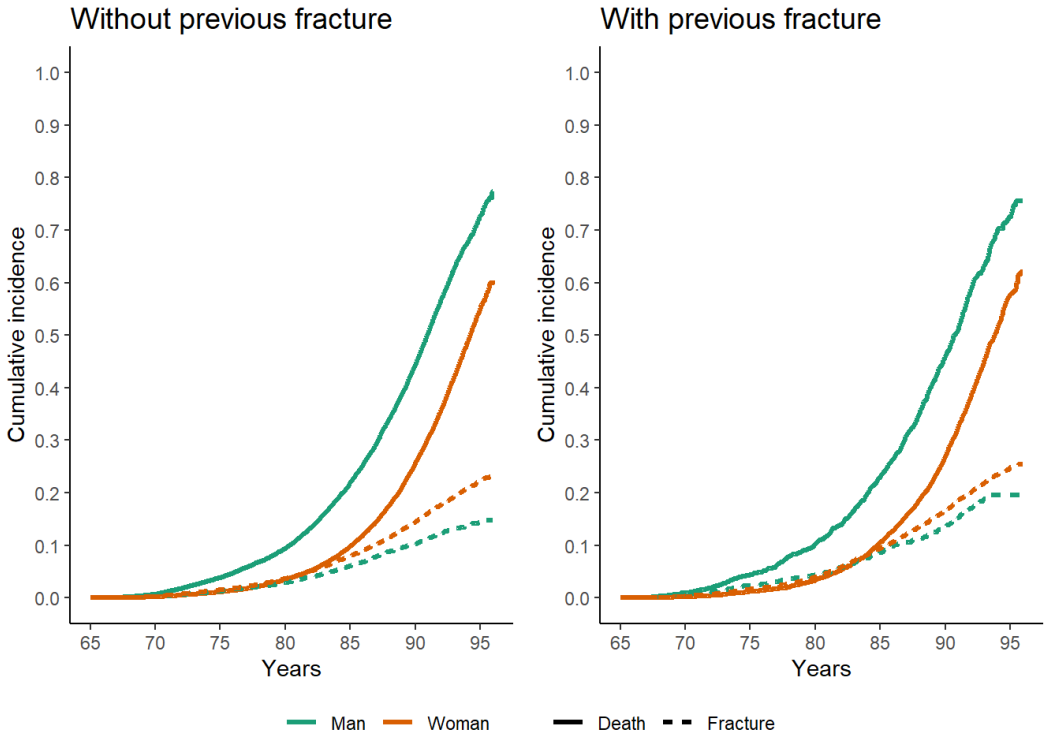

Figure 3 Cumulative incidence of second fracture and death by previous fracture and sex

As in Figure 2, we plot the cumulative incidence function of the two competing events, so that at each point in time we can see the probability of each event occurring before the other for each sex.

Similar to the first fracture, mortality is similar in both groups, i.e. the cumulative incidence of mortality after a first fracture is higher in men than in women. With regard to fractures, we can see that the curves by sex are the same up to the age of 80 in the group with no previous fracture and up to the age of 85 in the group with a previous fracture. After these ages, the curves separate, with the curve for women being higher. After a first fracture, the probabilities of having a second fracture before death are the same for men and women up to these ages, after which women are more likely to have a second fracture.

On the other hand, at older ages, the probability of death is quite high compared to fractures, regardless of whether there has been a previous fracture or not, and regardless of gender.

3.3.3 Third fracture

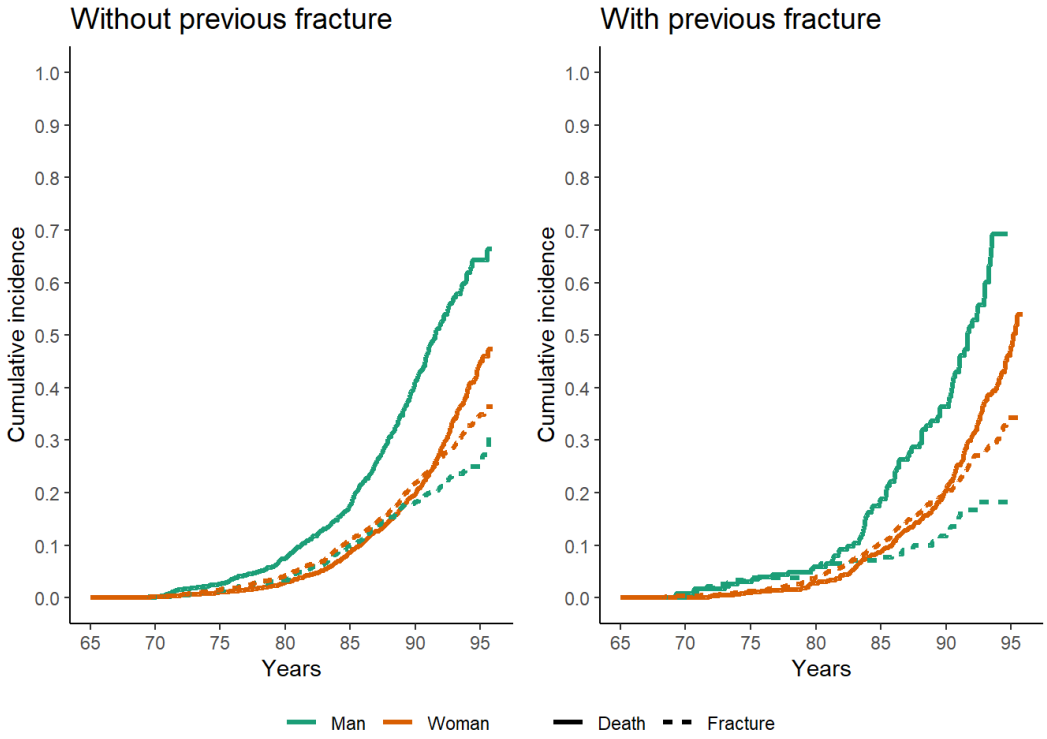

Figure 4: Cumulative incidence of third fracture and death by previous fracture and sex

For the third fracture, the pattern of death is similar to that for the previous two fractures. Men have higher cumulative incidence values than women, regardless of whether they have had a previous fracture or not. In the case of fractures, in the group with no previous fracture, although the curve for women remains higher than for men, it is not until around the age of 90 that the differences become apparent. This is similar in the group with previous fractures, but the differences appear at a slightly younger age (85 instead of 90).

3.4 Prentice-William-Peterson models

In the descriptive analysis, we have seen that there are important differences between the profiles of subjects without and with previous fracture and at the outcome's incidence. Therefore, we will estimate different cause-specific models for gap time to fracture among those subjects with no previous fracture and for those with a previous fracture.

The covariates chosen to explore their role as a risk factors are those more clinically relevant included in the EPIC fracture prediction tool (Tebé et al., 2022). These are sex, diagnosis of diabetes, diagnosis of Chronic Obstructive Pulmonary Disease (COPD), stroke, previous falls and use of corticoids.

3.4.1 Subjects without previous fracture

For the group of subjects without previous fracture, we have 746638 individuals, 60333 of them (8.08%) have had at least one fracture. Of these 60333, 5327 (8.83%) of them had a second fracture and of these, 822 (15.43%) had a third.

Before showing the models, we will look at how the cumulative incidence occur over time. For the first fracture we use age as the time scale, whereas for the second and third fractures we use years since the previous fracture.

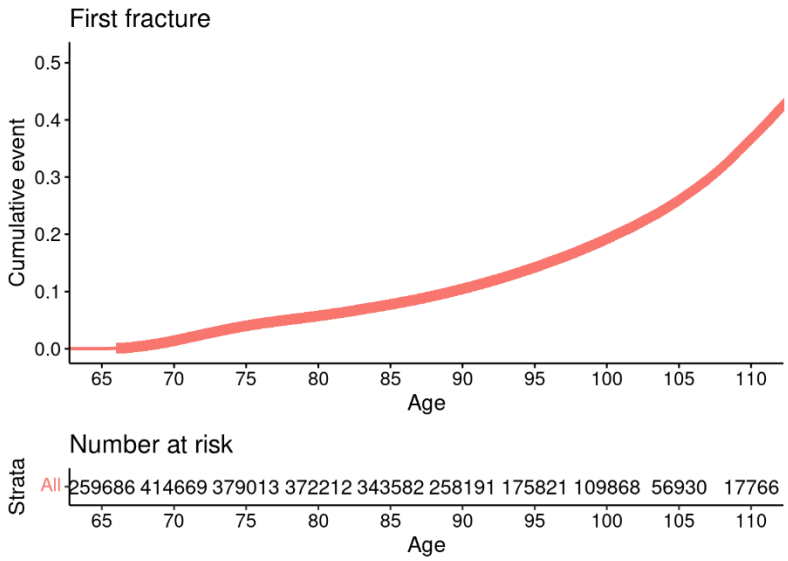

Figure 5: Cumulative event for the first fracture in subjects without previous fracture

As we can see, the probability of having a first fracture seems to increase exponentially with increasing age. Moreover, at the age of 100 years, the probability of experiencing this event is about 0.192 with 95% confidence interval of 0.19 – 0.194, which increases to 0.26 with 95% confidence interval of 0.253 – 0.263, in the following 5 years. It has been observed that the slope of the curve is even more pronounced from the age of 95. However, this effect could be due to the fact that the competitive effect of deaths is not taken into account when fitting cause-specific models.

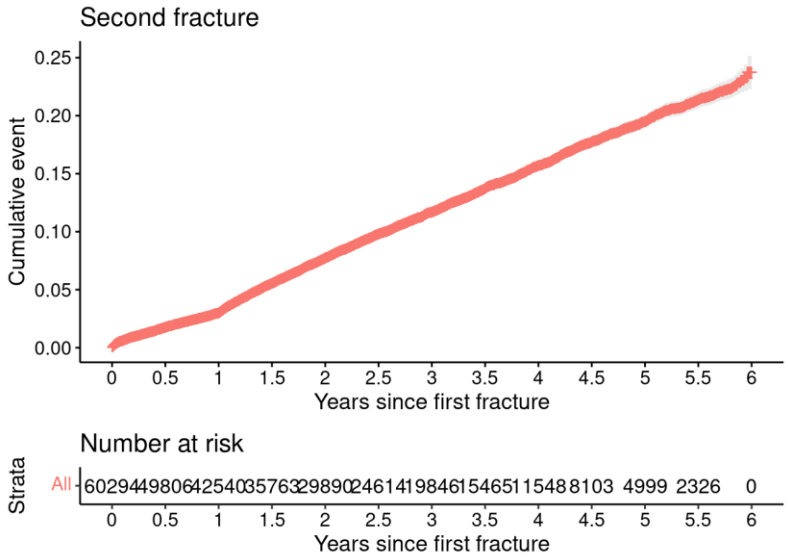

Figure 6: Cumulative event for the second fracture in subjects without previous fracture

In the case of the second fracture, we take as the time scale the years that have passed since the first fracture occurred, rather than the age at which the fracture occurs. We can see that all second fractures occur in the first six years and that the increase of the probability of event is linear, and at this point we have a probability of second fracture equal to 0.23 with 95% confidence interval of 0.22 – 0.24.

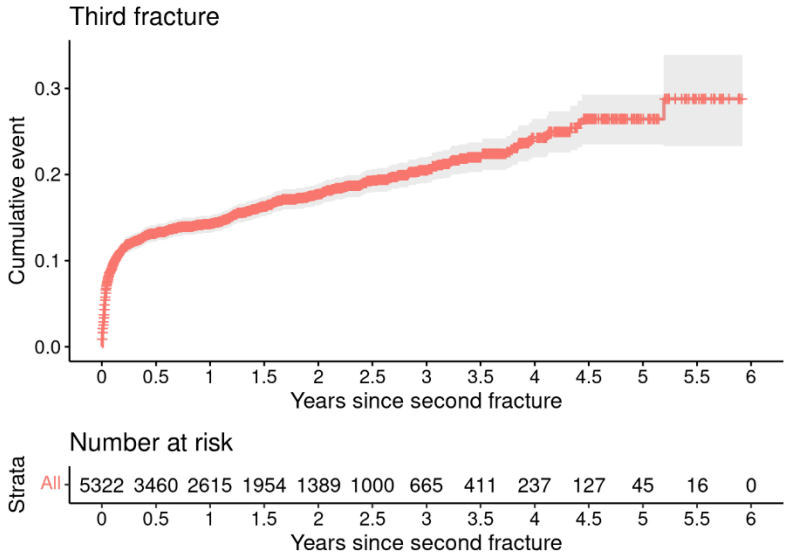

Figure 7: Cumulative event for the third fracture in subjects without previous fracture

Finally, for the third fracture, as for the second, the abscissa is the time since the previous one and again the fractures occur along the first six years. In this case, we can see that the probability of a third fracture increases very rapidly during the first six months, then the slope becomes more linear, as in the case of the second fracture.

Now that we have seen how the events are produced as a function of time for each of the fractures, we can see the results obtained by the PWP models.

Table 6: PWP models for subjects without previous fracture adjusted by covariates (left) and by covariates with the interaction of number of fracture (right). We show the β coefficient, the CSHR, the standard error of the estimate, the 95% confidence interval of the CSHR and the p-value.

	M1: Without interaction					**M2: With interaction**				
Predictors	**Coeff**	**CSHR**	**std.Error**	**CI**	**p**	**Coeff**	**CSHR**	**std.Error**	**CI**	**p**
Sex (Men vs Women)	-0.6	0.55	0.00	0.54 – 0.56	**<0.001**	-0.63	0.53	0.00	0.53 – 0.55	**<0.001**
Diabetes (Yes vs No)	0.09	1.1	0.01	1.08 – 1.12	**<0.001**	0.10	1.11	0.01	1.08 – 1.12	**<0.001**
COPD (Yes vs No)	0.15	1.17	0.02	1.13 – 1.20	**<0.001**	0.15	1.17	0.02	1.11 – 1.19	**<0.001**
Stroke (Yes vs No)	0.02	1.02	0.01	1.00 – 1.05	0.067	0.01	1.01	0.01	0.97 – 1.02	0.297
Fall (Yes vs No)	0.14	1.15	0.03	1.10 – 1.20	**<0.001**	0.11	1.11	0.03	1.03 – 1.14	**<0.001**
Corticoids (Yes vs No)	0.16	1.19	0.01	1.15 – 1.20	**<0.001**	0.17	1.18	0.01	1.15 – 1.20	**<0.001**
Sex (Men vs Women): Fracture 2						0.49	1.63	0.05	1.49 – 1.71	**<0.001**
Sex (Men vs Women):						0.59	1.81	0.15	1.50 – 2.10	**<0.001**

	M1: Without interaction					M2: With interaction				
Predictors	**Coeff**	**CSHR**	**std.Error**	**CI**	**p**	**Coeff**	**CSHR**	**std.Error**	**CI**	**p**
Fracture 3										
Diabetes (Yes vs No): Fracture 2						-0.05	0.95	0.03	0.90 – 1.02	0.116
Diabetes (Yes vs No): Fracture 3						-0.17	0.85	0.07	0.72 – 1.01	**0.047**
COPD (Yes vs No): Fracture 2						0.01	1.01	0.06	0.91 – 1.16	0.836
COPD (Yes vs No): Fracture 3						-0.41	0.66	0.12	0.48 – 0.94	**0.016**
Stroke (Yes vs No): Fracture 2						0.09	1.09	0.05	1.02 – 1.23	0.063
Stroke (Yes vs No): Fracture 3						0.12	1.12	0.13	0.92 – 1.43	0.312
Falls (Yes vs No): Fracture 2						0.29	1.34	0.10	1.18 – 1.59	**<0.001**
Falls (Yes vs No): Fracture 3						0.18	1.20	0.19	0.89 – 1.67	0.258
Corticoids (Yes vs No): Fracture 2						-0.01	0.99	0.04	0.93 – 1.06	0.753
Corticoids (Yes vs No): Fracture 3						-0.16	0.85	0.07	0.72 – 1.01	0.059
AIC	1589984.215					1589731.949				

Table 6 shows the results of two PWP models for time to fracture. On the left we have the model without considering the interaction between the covariates and the number of fractures, so that, we have the global effect of the covariates.

In the first model, we can see that all the covariates are statistically significant at 0.05 significant level, except for the stroke. Of those that are statistically significant, only being a male is a protective factor, while the other covariates are risk factors. This is consistent with the results of studies in the literature (*Risk Factors | International Osteoporosis Foundation*, 2023), but not for stroke.

On the right side of the table, we have a second model where we can see how the effect of the covariate changes over the number of fractures. In this model, we can see that the covariates without interaction maintain the same direction and significance as in the previous model. However, not all covariates for the second and the third fractures show statistically significant differences from the first fracture.

In the case of the second fracture, only those covariates that are statistically significant are commented on. For gender, the final β for men in this fracture is -0.63+0.49 = -0.14, this means that the risk gap between men and women is smaller when a second fracture occurs in relation to the first fracture. The sex CSHR we get is 0.87, so being male remains a protective factor, but at a lower level. The risk reduction by sex can be observed in figure 2 and 3 where the cumulative of incidence of first and second fracture are plotted by sex. Estimating the interaction effects between the remaining factors and the second and third factors could be done

in the same way. However, the interpretation and clinical implications are complex and it's reading goes far beyond this paper.

For the third fracture, the covariates that are significant are sex, diabetes and COPD. For this fracture the difference between men and women is also decreasing, the β we get for men for the third fracture is -0.63 + 0.59 = -0.04 with a CSHR of 0.96. For the covariate diabetes we get a coefficient of 0.1 - 0.17 = -0.07 and a CSHR of 0.93, so that the effect is lower than in the first one. Finally, for the covariate COPD, the estimated coefficient is 0.15 - 0.41 = -0.26 and a CSHR of 0.77.

We also calculated the Akaike Information Criterion (AIC), to determinate which model provides a better fit to the data based on the information that the model gives and its complexity, in this case the lower the better. Looking at the model's AIC we see that the model with interaction has a lower value, so we will focus on the second model between the two.

The proportional hazards assumption is tested using the log(-log(S(t))) plot and the Schoenfeld residuals. The log(-log(S(t))) plots are accompanied by the Kaplan-Meier estimators. Figures showing the plots of both methods for these, and subsequent models can be found in Appendix B.

From the log(-log(S(t))) plots we can see that not all covariates satisfy the proportionality of risks for all fractures. While for the first fracture we see that most curves are roughly parallel, for the second and third fractures we see that this assumption is no longer met.

For the second fracture, in the models for subjects without a previous fracture, we see that the curves for the covariates diabetes and COPD cross. Finally, for the third fracture, we observe that the covariate stroke does not meet the risk ratio.

3.4.2 Subjects with previous fracture

For the group with previous fractures, we have 58901 subjects at risk of a first fracture. 11163 (18.95%) of them had at least one fracture. Of those with a first fracture, 1460 of them (13.08%) had a second fracture and 1057 of them (16.03%) had a third one.

Again, for each of the three fractures, we will examine how the events occur over time.

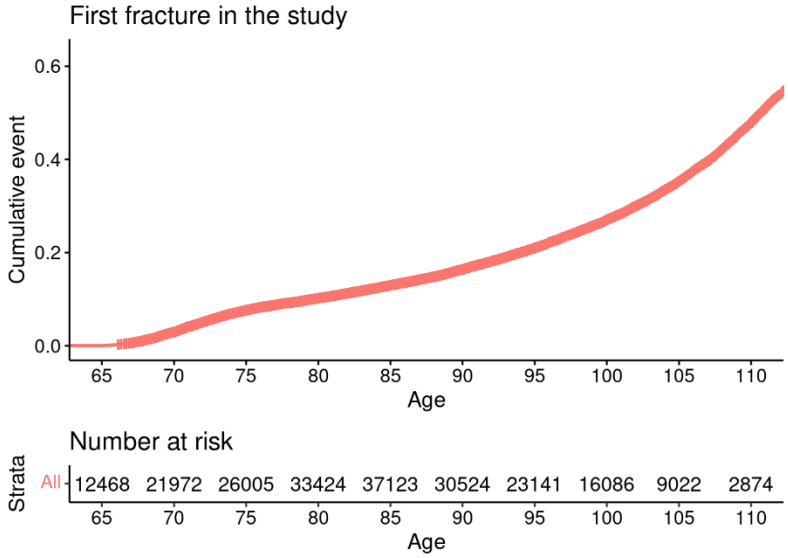

Figure 8: Cumulative event for the first fracture in subjects with previous fracture

The behaviour of the curve is similar to that already seen in Figure 5, with the difference that higher probabilities are obtained for the same ages. For example, in this case the probability at 100 years is 0.27 with 95% confidence interval of 0.264 – 0.277 instead of the 0.192 we saw for the group without previous fractures. Again, the high probability of experiencing an event

increases with age, even reaching values of 0.61 with 95% confidence interval of 0.588 – 0.627, which may be due to mortality.

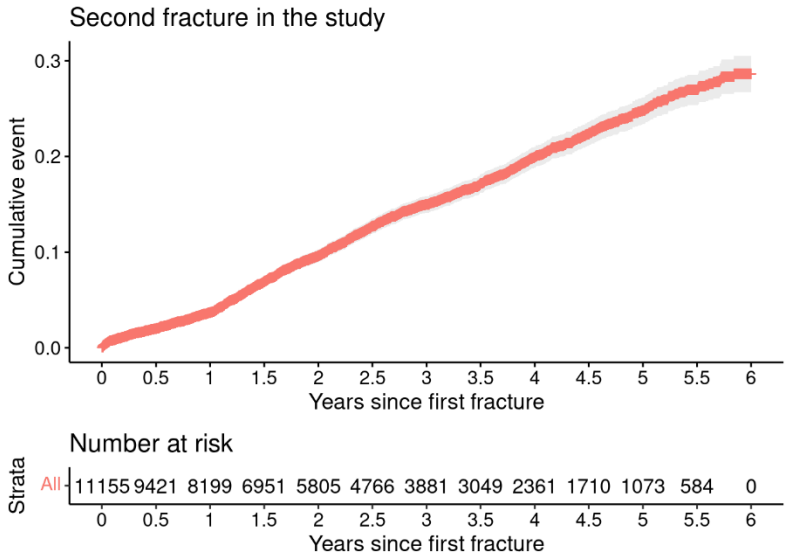

Figure 9: Cumulative event for the second fracture in subjects without previous fracture

Figure 9 again shows that the risk of a second fracture increases linearly with the number of years since the first fracture. As with the first fracture, the difference between this and the subjects without a previous fracture is that the probability is greater at a given time. In this case, at 6 years we have a probability of 0.284 with 95% confidence interval 0.265 – 0.302 of having a third fracture, whereas in Figure 6 it was 0.23.

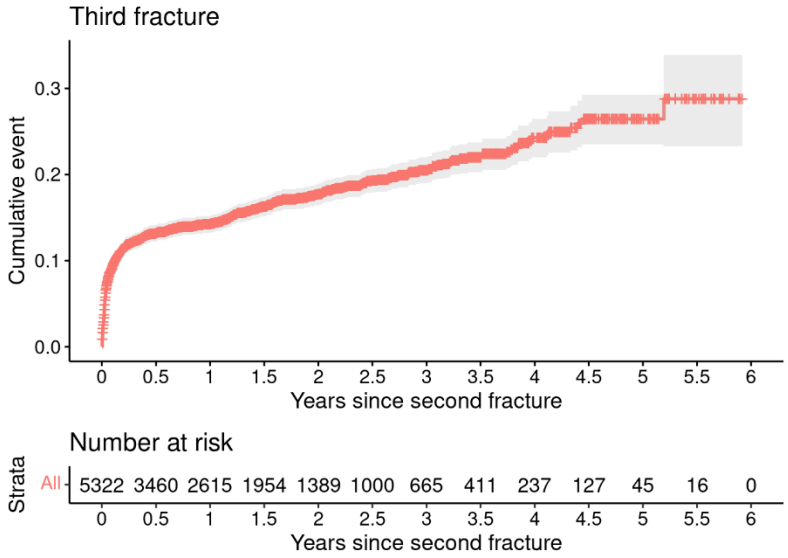

Figure 10: Cumulative event for the third fracture in subjects without previous fracture

Finally, for the third fracture, we again see a very rapid increase in the probability in the first six months, after which the increase slows down. This effect is due to deaths and loss to follow-up, as well as study termination, occurring within a few days after the second fracture. In some cases, these events even occur one or two days after the date of the fracture.

Having looked at the probability of the different events over time, we now turn to the effect estimates obtained using the PWP models.

Table 7: PWP models for subjects with previous fracture adjusted by covariates (left) and by covariates with the interaction of number of fracture (right). We show the β coefficient, the CSHR, the standard error of the estimate, the 95% confidence interval of the CSHR and the p-value

	M1: Without interaction					M2: With interaction				
Predictors	**Coeff**	**CSHR**	**std.Error**	**CI**	**p**	**Coeff**	**CSHR**	**std.Error**	**CI**	**p**
Sex (Men vs Women)	-0.22	0.81	0.02	0.77 – 0.84	**<0.001**	-0.23	0.80	0.02	0.76 – 0.84	**<0.001**
Diabetes (Yes vs No)	0.1	1.10	0.02	1.06 – 1.15	**<0.001**	0.11	1.11	0.02	1.07 – 1.16	**<0.001**
COPD (Yes vs No)	0.09	1.10	0.04	1.02 – 1.18	**0.013**	0.09	1.10	0.04	1.01 – 1.19	**0.020**
Stroke (Yes vs No)	-0.05	0.95	0.03	0.90 – 1.00	0.053	-0.09	0.91	0.03	0.86 – 0.97	**0.002**
Fall (Yes vs No)	0.02	1.02	0.04	0.95 – 1.10	0.543	0.02	1.02	0.04	0.94 – 1.11	0.586
Corticoids (Yes vs No)	0.13	1.14	0.02	1.09 – 1.19	**<0.001**	0.14	1.15	0.03	1.10 – 1.20	**<0.001**
Sex (Men vs Women): Fracture 2						0.14	1.05	0.09	0.99 – 1.33	0.069
Sex (Men vs Women): Fracture 3						-0.21	0.81	0.17	0.53 – 1.23	0.309
Diabetes (Yes vs No): Fracture 2						-0.04	0.96	0.06	0.85 – 1.08	0.496
Diabetes (Yes vs No): Fracture 3						-0.22	0.80	0.12	0.59 – 1.09	0.160
COPD (Yes vs No): Fracture 2						0.01	1.01	0.13	0.79 – 1.29	0.954
COPD (Yes vs No): Fracture 3						-0.04	0.96	0.31	0.50 – 1.82	0.893
Stroke (Yes vs No): Fracture 2						0.23	1.26	0.11	1.07 – 1.49	**0.006**
Stroke (Yes vs No): Fracture 3						0.55	1.73	0.31	1.22 – 2.45	**0.002**
Falls (Yes vs No): Fracture 2						0.06	1.06	0.12	0.85 – 1.34	0.601
Falls (Yes vs No): Fracture 3						-0.43	0.65	0.21	0.34 – 1.24	0.201
Corticoids (Yes vs No): Fracture 2						-0.06	0.94	0.06	0.83 – 1.08	0.389
Corticoids (Yes vs No): Fracture 3						-0.06	0.94	0.15	0.69 – 1.28	0.692
AIC	254342.261					254341.318				

In Table 7, as in the in Table 6, we have two models for the time to fracture, in this case, for the group of subjects with previous fracture.

In the first model, on the left, we can see that neither the history of falls nor the history of stroke are significant. The first may be related to the fact that we are working with people who have

already had fractures before entering the study, so the proportion of cases with falls is similar between those who have new fractures and those who do not. This can be seen in Appendix C. In this model we have a global estimate for all the fractures, and we see that sex is the only protective factor. It is show that being a man is a protective factor with CSHR 0.81 with 95% confidence interval of 0.77 – 0.84. On the other hand, diabetes, COPD and use of corticosteroids are risk factors. Again, the direction of these results is consistent with those seen in the literature.

On the right, we have the model with the interaction between the covariates and the number of fractures. In the same way that we have done with the subjects without a previous fracture, we will only comment on the covariates that were found to be significant.

When we tested the results of the covariates without the interaction with the number of fractures, we observed similar results to the first model, except for stroke, which is now significant and a protective factor. This may be due to the fact that stroke is also a risk factor for death, and therefore people who have had a stroke are more likely to die than to have a new fracture.

For the interaction with second and third fracture, the only variable which is statistically significant is the stroke. In both cases, the CSHR is higher than one, so that compared to the first one, it is a risk factor.

If we using the AIC, we can see that the value of the model M2, with the interaction between the covariates and the number of fractures, is slightly lower. Therefore, as with the subjects without previous fracture, we will consider the second model.

Finally, we check whether proportional risk taking is fulfilled. Again, for the first fracture, all covariates show parallel curves. However, for the second fracture, both the sex and COPD covariate curves cross, and for the third fracture, it is COPD and falls that do not satisfy proportional hazards.

3.4.3 Summary

Throughout this chapter we have seen the differences in profile between subjects with previous fractures and those without it. The first group is on average three years older and the proportion of women is larger (72.4% vs 52.2%) in this group. In addition, subjects with previous fractures have more comorbidities and take more medication.

Furthermore, if we look at the incidence of first, second and third fractures in both groups, we see that those with previous fractures have higher values for the three events than those without: 18.95 vs. 8.08 for the first, 13.08 vs. 8.83 for the second and 16.03 vs. 15.43 for the third.

Concerning mortality, the incidence within each group was compared according to whether or not they had a fracture during the trial. Irrespective of this, the group with previous fractures has a higher incidence of death. Within each group, those who had a fracture also had a higher incidence.

About the PWP models, several models have been adjusted according to the same groups already discussed. In subjects without prior fractures, when examining the covariates without interaction, all of them are significant except for stroke. Among the significant ones, the only protective factor is being male. For the second fracture the significant covariables are sex and falls. The effect of the variables sex changes, where the differences between men and women are reduced. In the case of falls, the effect as a risk variable increases. For the third fracture, the effect of the covariates that vary are sex and diabetes and COPD. In all three cases, the differences in survival are reduced. The results of both models (for those with and without previous fracture) are represented in the following forest plot.

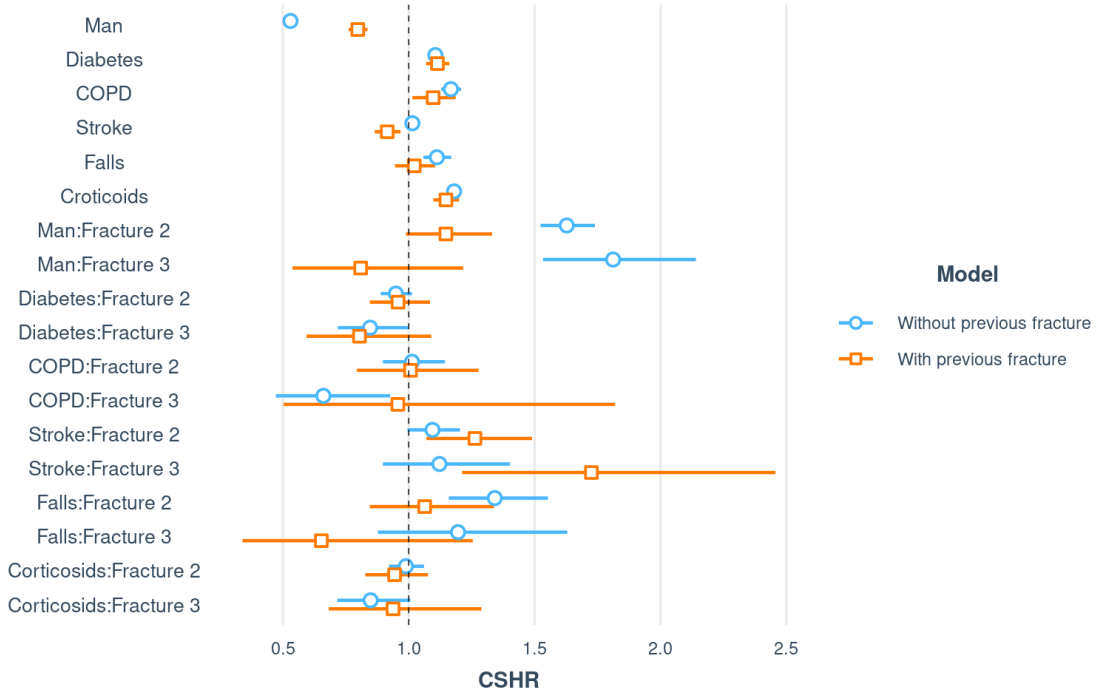

Figure 11: forest plot of the CSHRs of the models with interaction. Blue shows the results of the subjects without previous fracture and orange shows the results of the subjects with previous fracture.

Finally, among those with at least one previous fracture, we have seen that the effect of the covariates without interaction maintain the same direction as in the models without prior fracture, except for stroke, which has a protective effect. In the case of the interaction there is only one covariate that is significant for both the second and third fractures, and that is stroke.

However, the proportional hazards assumption could not be demonstrated for all covariates in either group, with or without previous fractures.

Chapter 4 Discussion

Recurrent events require different techniques to account for within-subject correlation and inter-event dependence. Among the various extensions of Cox models, as well as fragility and multistate models, the stratified models of Prentice, William and Peterson were considered the most appropriate for use in the EPIC fragility risk fracture cohort. These models allow each of the fractures to have different baseline risk functions, which is consistent with the fact that the risk fracture changes once a fracture has already occurred.

In the cumulative incidence graphs it has been seen that the curve behaves differently depending on whether it is the first, second or third fracture. In the case of the third fracture, we saw a very rapid growth during the first months. This could be explained by the fact that there is a significant number of subjects who lost the follow-up or died immediately after the second fracture.

In PWP models, we have seen that, in subjects without previous fractures, although all the covariates usually considered as risk factors maintain their effect for the first, some of them, such as sex, change according on the occurrence of the following fractures. Whereas in the case of subjects who had already suffered a fracture, not all the factors are significant from the very first moment, and the only one that varies over the number of fractures is stroke. However, the interpretation and clinical implications are complex, and it is reading goes far beyond this paper.

In addition to the complexity of the analysis posed by recurrent events, we found other peculiarities, such as the left truncation when using age as a time scale and the treatment of death as a competing event. Despite the complexity of the analysis, the interpretation of the result is simple because we can estimate the CSHR, and it is also easy to implement thanks to the statistical software R. In addition, by working with the SIDIAP data, we obtained a large and representative sample of the elderly population at risk of fragility fractures, providing robust estimates.

On the other hand, the presence of death as a competing event introduces a challenge in estimating the hazard function and impacts the interpretation of the results. The study of fracture times at advanced ages, using the cause-specific model that treats death as censoring, overestimates the probability of fractures, as the number of individuals at risk declines rapidly due to the same effect of death. Additionally, we have observed that the models we have adjusted do not satisfy the proportionality of risks for all covariates considered in the analysis, specifically when examining the log(-log(S(t))) curves for the second and third fractures.

Future research could explore strategies to address the issue of non-proportionality of hazards in PWP models. To address the overestimation of the probability of the first fracture in ages above 95 years, the analysis could be replicated considering as censoring everything that occurs beyond this age. By calculating the probability of the first fracture following this approach (shown in Figure 59 at Appendix D), it is observed how the event probabilities have decreased. Other lines that could be pursued include the study of the methodology required to analyse recurrent models with competing events using Fine & Gray models, and their possible implementation with R.

Another point of interest would be to compare the second and third fractures in subjects with no previous fractures with the first fractures seen during the study in those with previous fractures, as this first fracture will be at least a second, although it could be a third or even a fourth.

It is possible to consider other methods beyond the extension of Cox models, such as multi-state models. Where any of the fracture can lead to another fracture or to death. The design of the relationship between transitions and states is shown in Figure 60 in Appendix D. Finally, the exploration of new covariates beyond those known as risk factors, so that specific factors may emerge at the second or third fracture.

To conclude with, PWP models are an appropriate approach for studying recurring events, where the occurrence of the event itself changes the risk of a new event. In the specific case of fragility fractures, it has been shown that both incidence and survival time differ substantially depending on whether or not there have been previous fractures and the interaction between known risk factors and the occurrence of further fractures modified the association in way that needs to be studied in more detail.

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Appendix A: Comparison of deceased subjects by whether they had died before the first fracture or not.

Table 8: Demographics of subjects who die, whether or not they die before the first fracture

	[ALL]	**No**	**Yes**	**N**
	N=148698	*N=17746*	*N=130952*	
Sex, N (%):				148698
Woman	67509 (45.4%)	10535 (59.4%)	56974 (43.5%)	
Man	81189 (54.6%)	7211 (40.6%)	73978 (56.5%)	
Age, Media (desviación estándar)	79.9 (6.53)	81.2 (6.02)	79.7 (6.58)	148698
Age, Mediana [Q1;Q3]	80.8 [75.4;85.2]	82.2 [77.6;86.0]	80.7 [75.2;85.1]	148698

Appendix B: Proportional hazard assumptions

Subjects without previous fracture

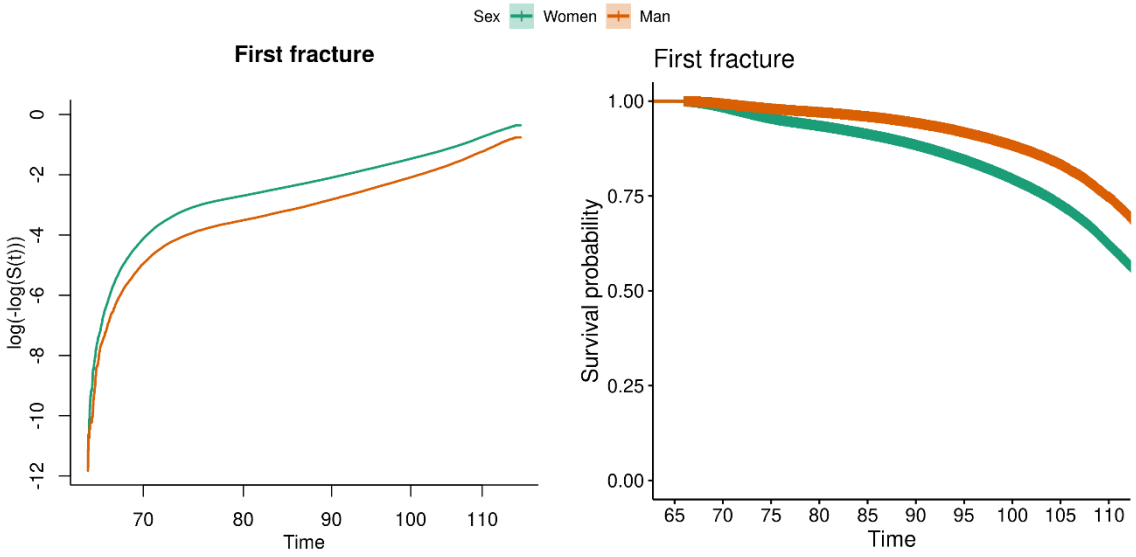

Figure 12: log(-log(S(t))) and KM curve by sex for first fracture of subjects without a previous fracture

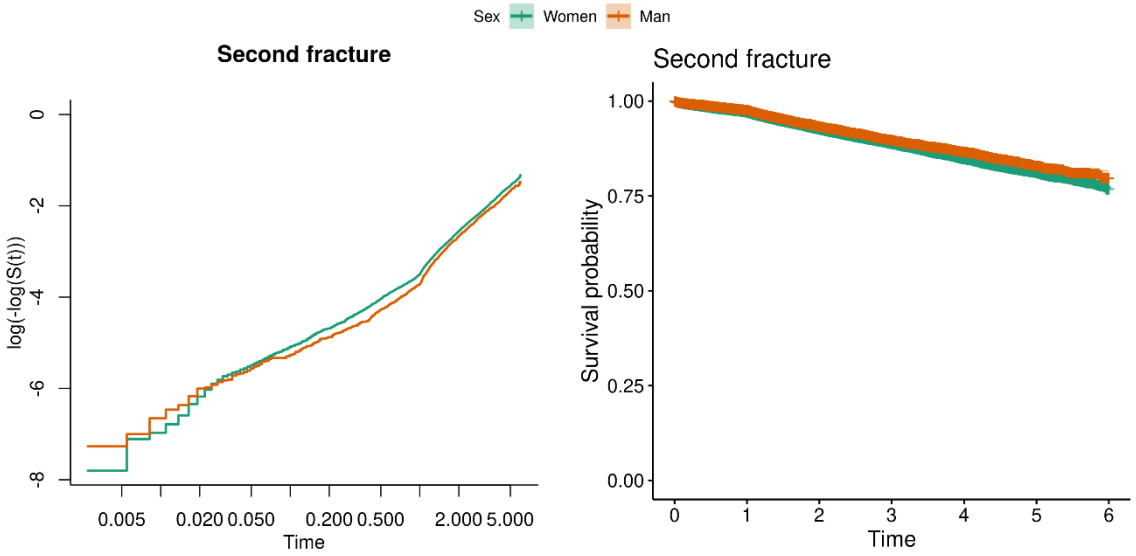

Figure 13: log(-log(S(t))) and KM curve by sex for second fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

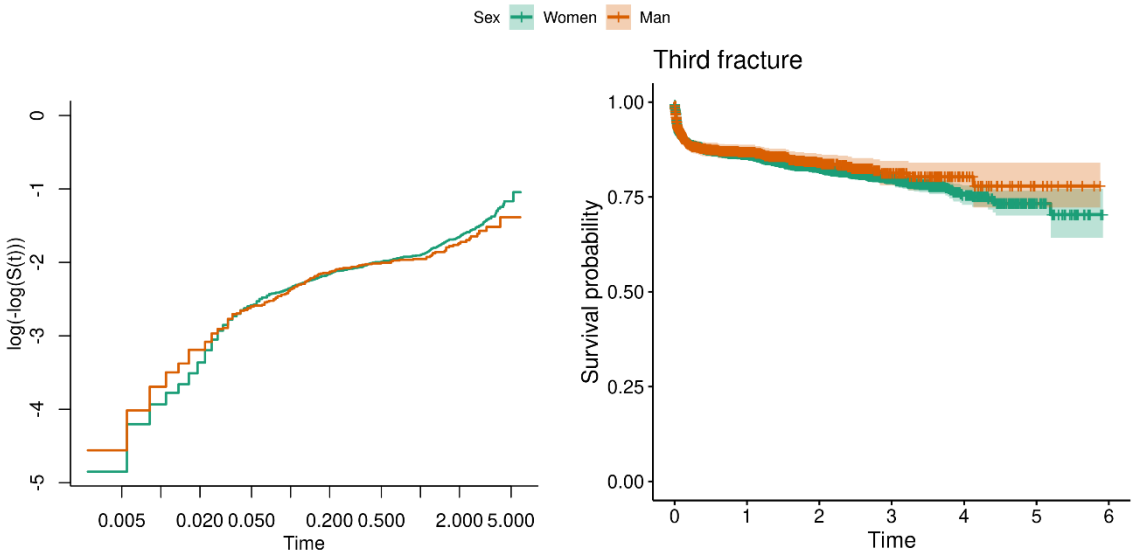

Figure 14: log(-log(S(t))) and KM curve by sex for third fracture of subjects without a previous fracture

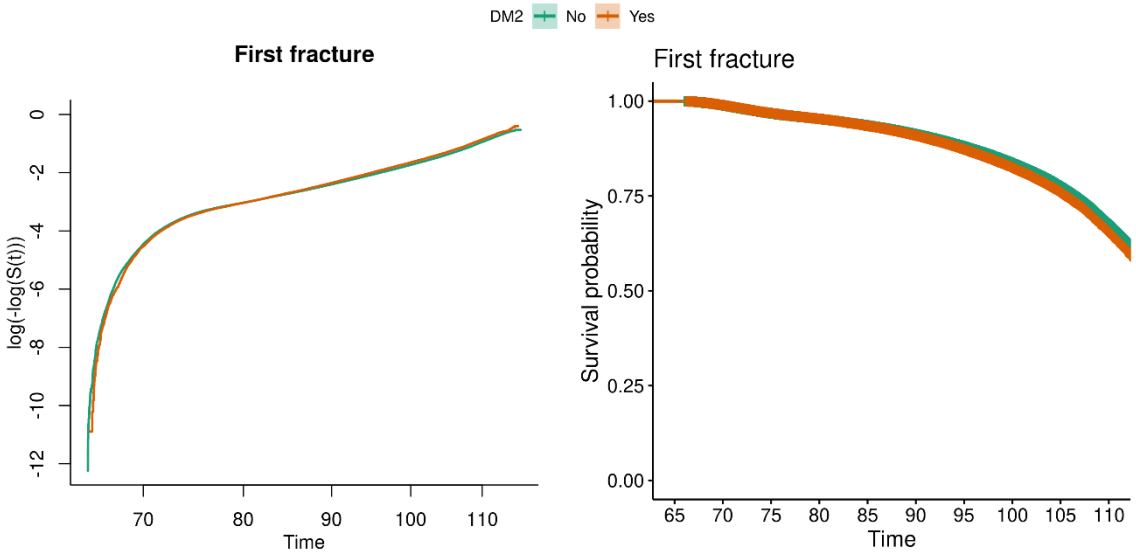

Figure 15: log(-log(S(t))) and KM curve by diabetes for first fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

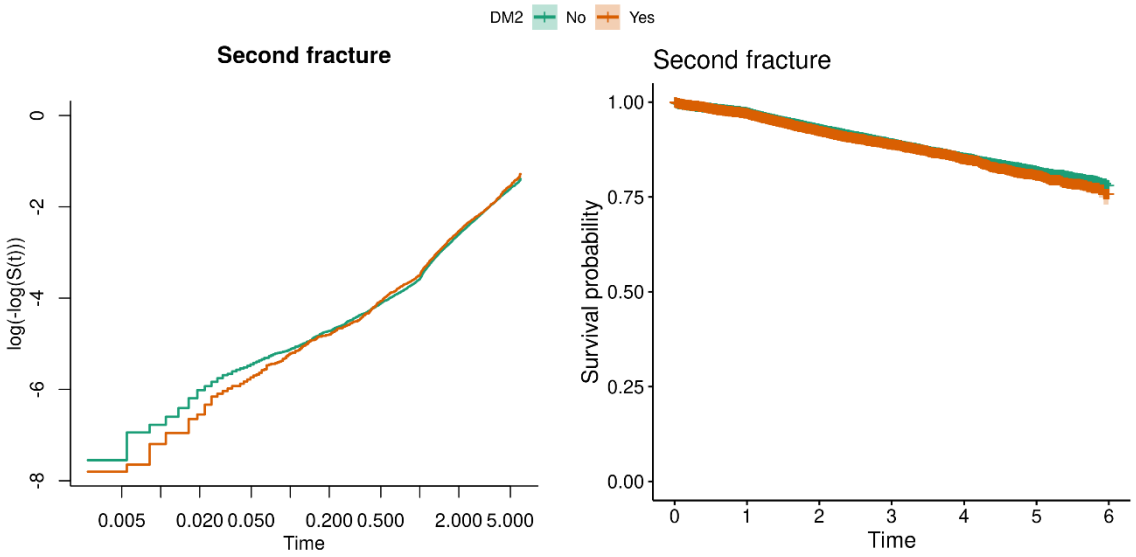

Figure 16: log(-log(S(t))) and KM curve by diabetes for second fracture of subjects without a previous fracture

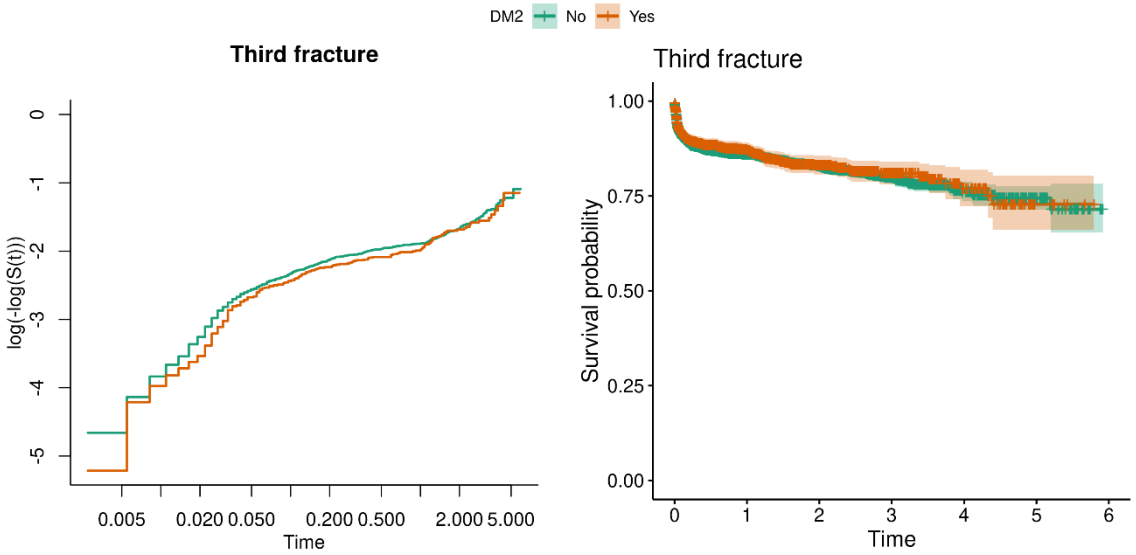

Figure 17: log(-log(S(t))) and KM curve by diabetes for third fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

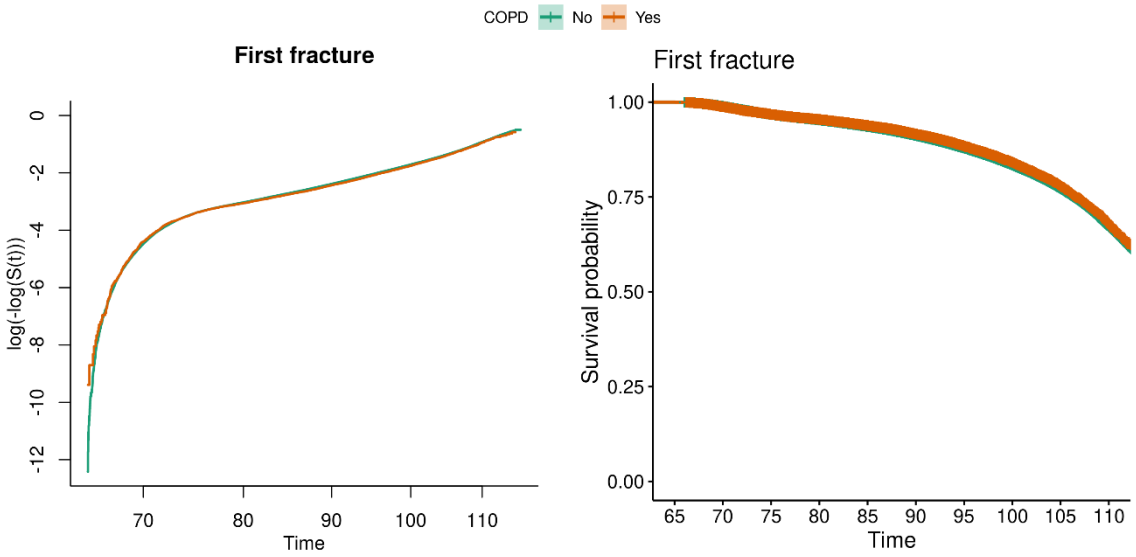

Figure 18: log(-log(S(t))) and KM curve by COPD for first fracture of subjects without a previous fracture

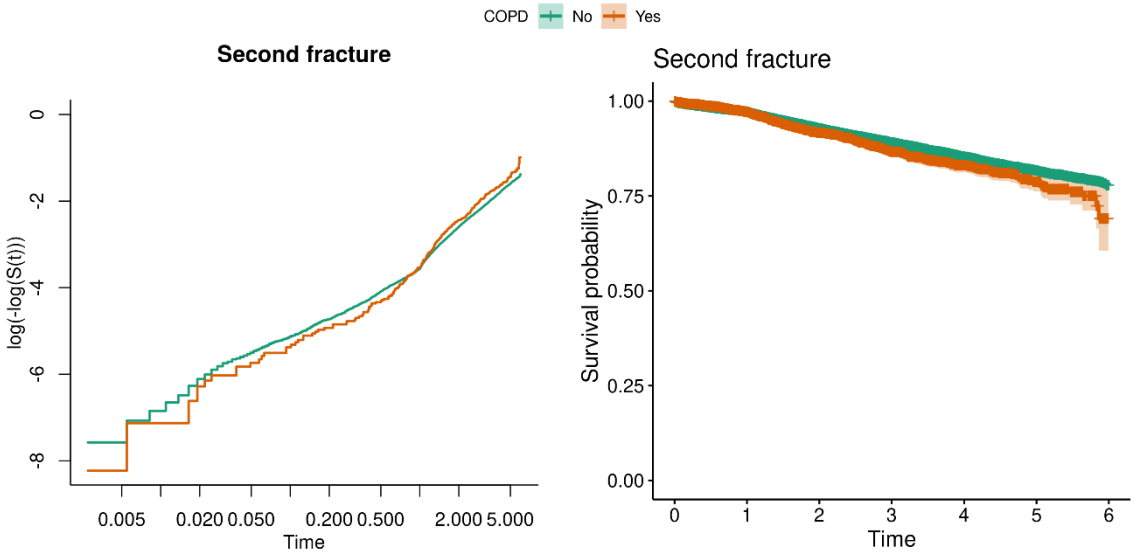

Figure 19: log(-log(S(t))) and KM curve by COPD for second fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

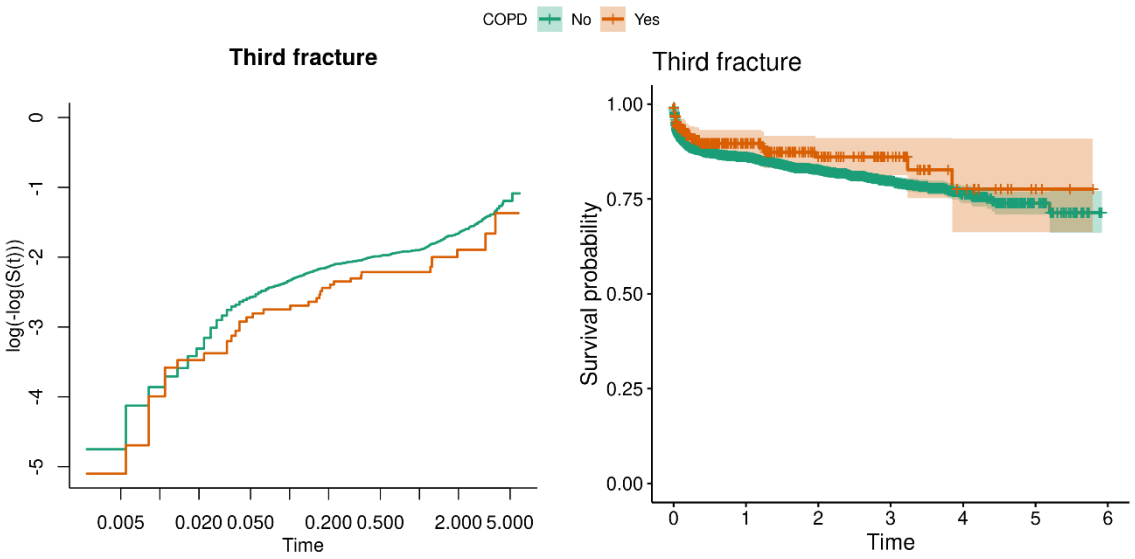

Figure 20: log(-log(S(t))) and KM curve by COPD for third fracture of subjects without a previous fracture

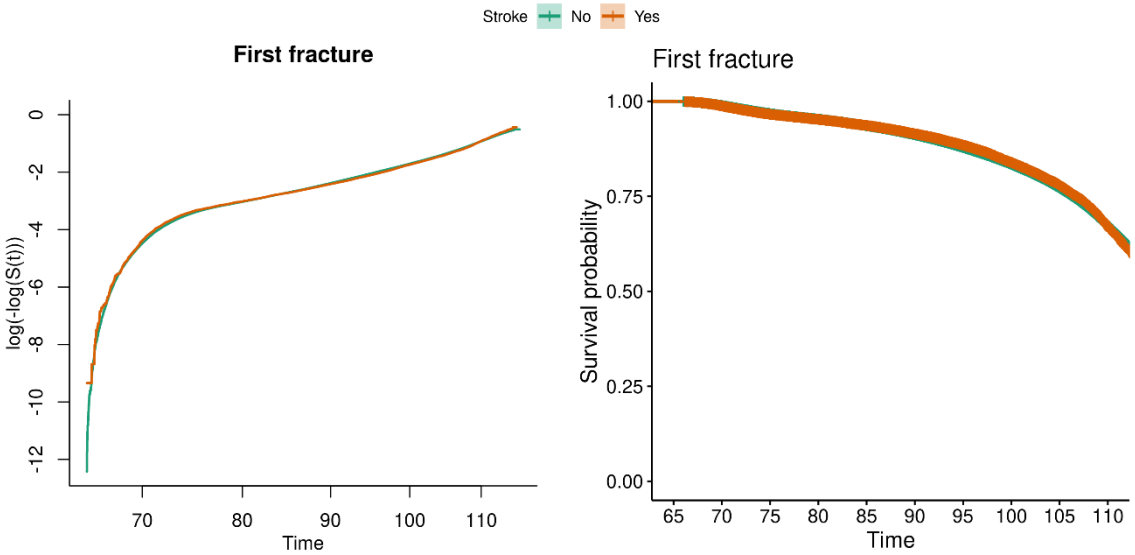

Figure 21: log(-log(S(t))) and KM curve by stroke for first fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

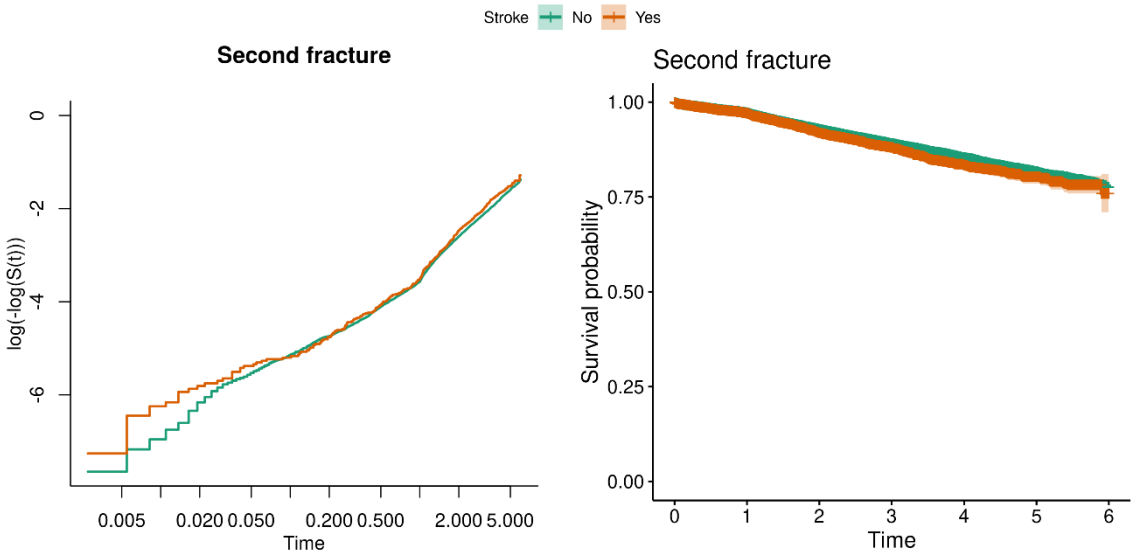

Figure 22: log(-log(S(t))) and KM curve by stroke for second fracture of subjects without a previous fracture

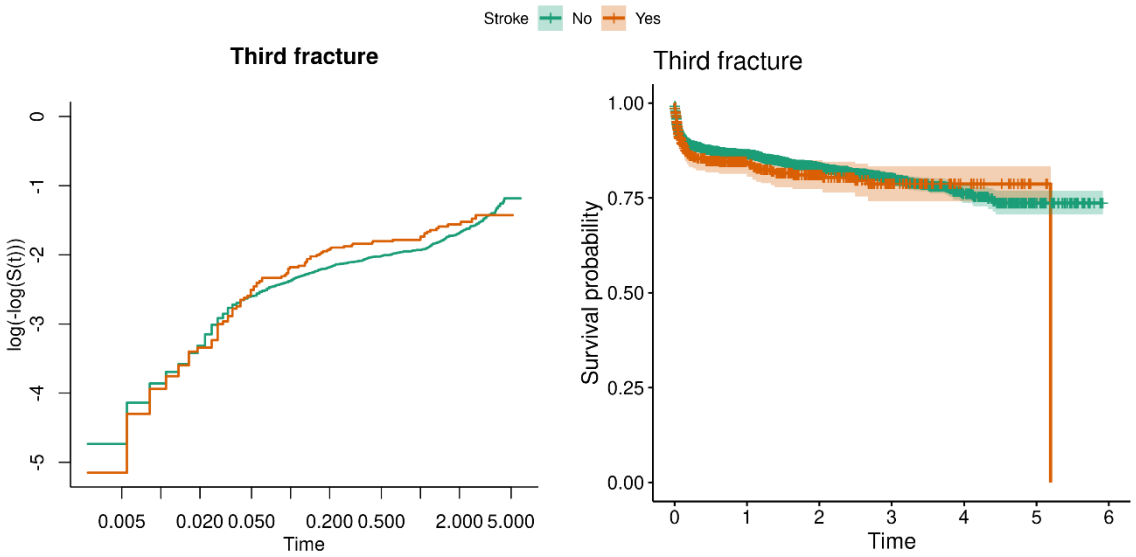

Figure 23: log(-log(S(t))) and KM curve by stroke for third fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

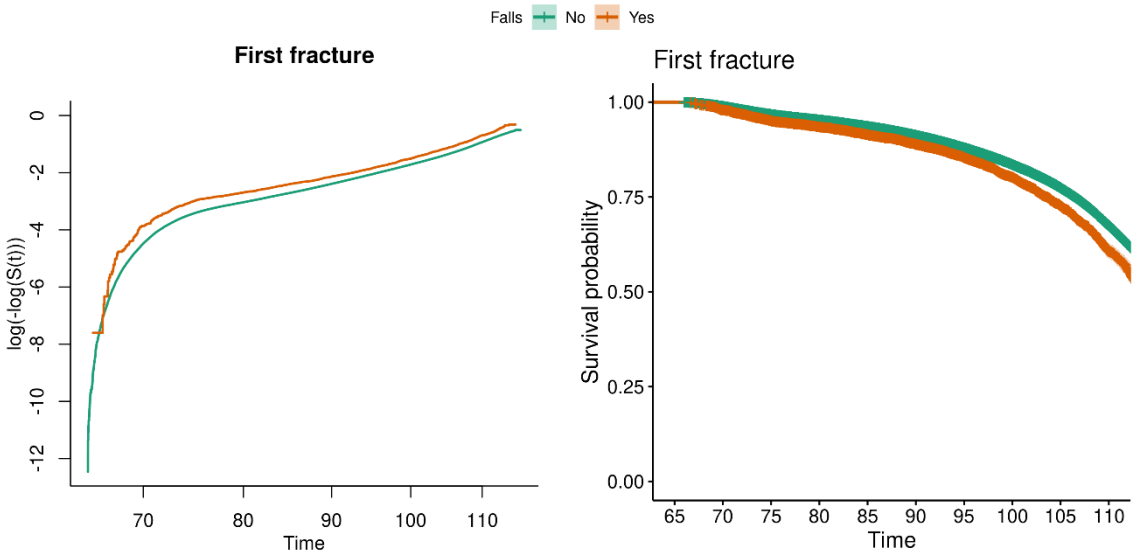

Figure 24: log(-log(S(t))) and KM curve by falls for first fracture of subjects without a previous fracture

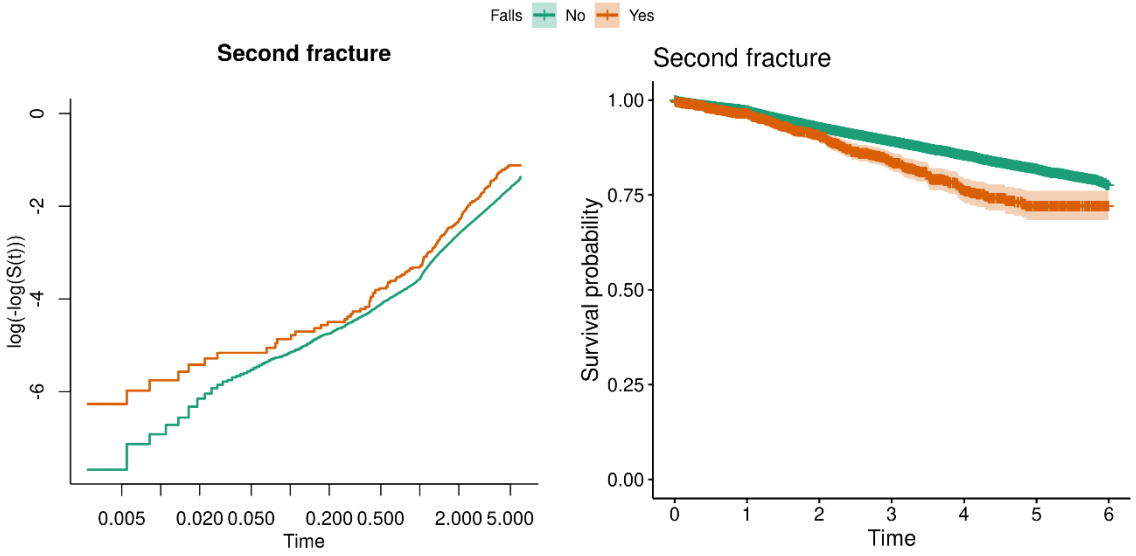

Figure 25: log(-log(S(t))) and KM curve by falls for second fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

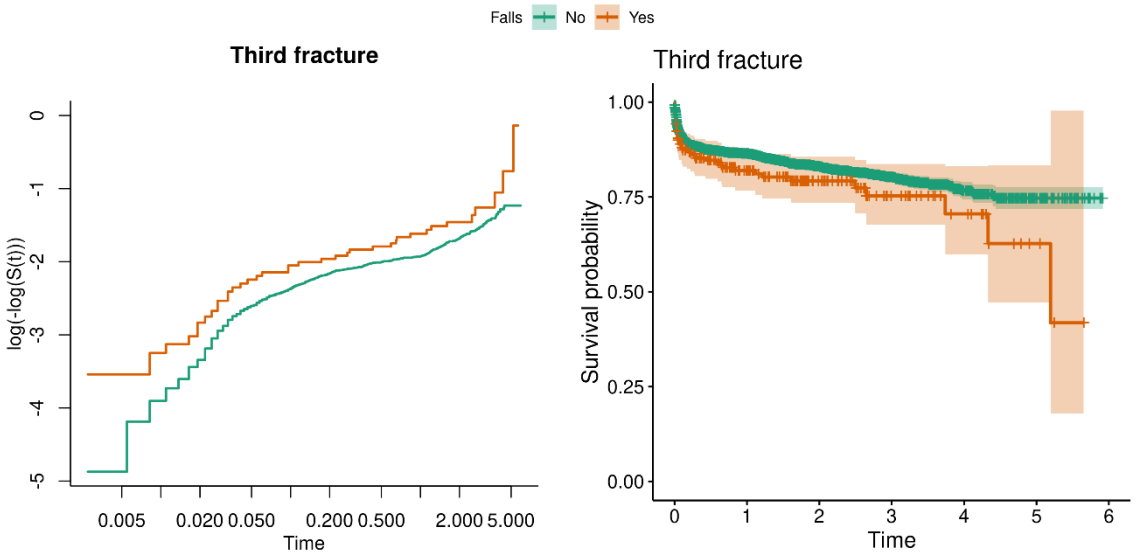

Figure 26: log(-log(S(t))) and KM curve by falls for third fracture of subjects without a previous fracture

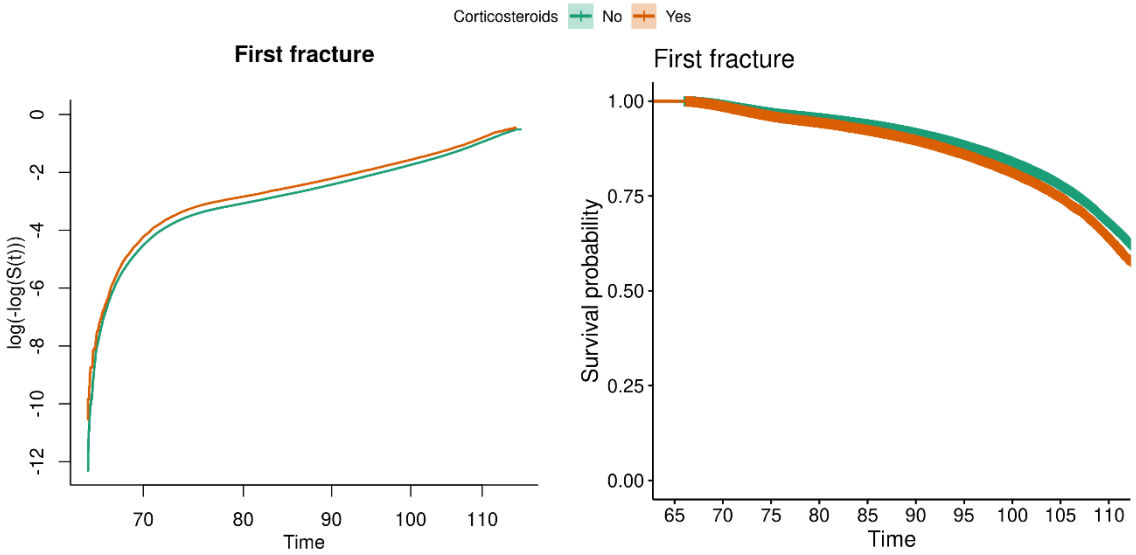

Figure 27: log(-log(S(t))) and KM curve by corticosteroids for first fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

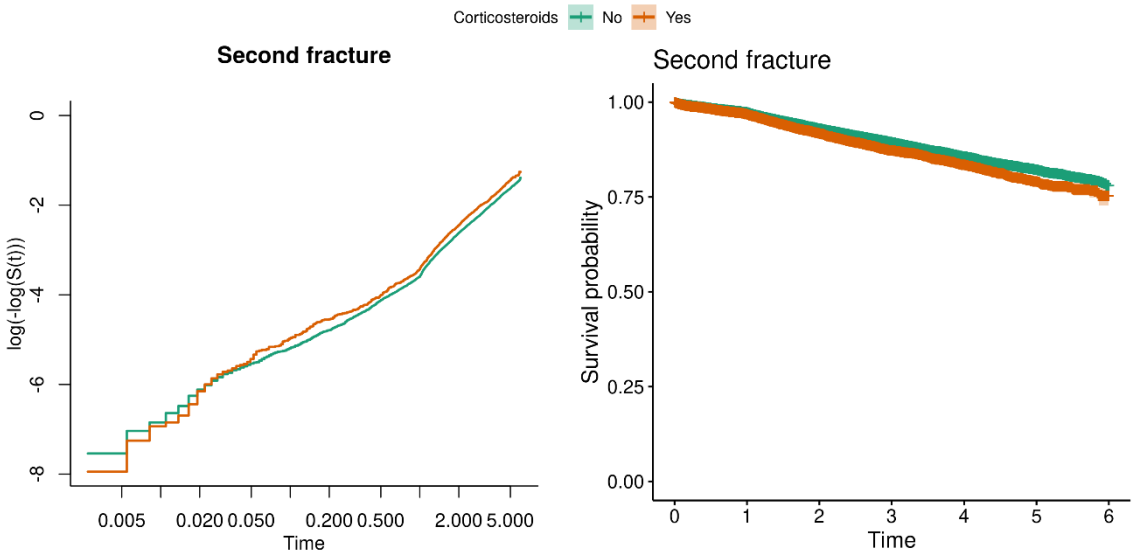

Figure 28: log(-log(S(t))) and KM curve by corticosteroids for second fracture of subjects without a previous fracture

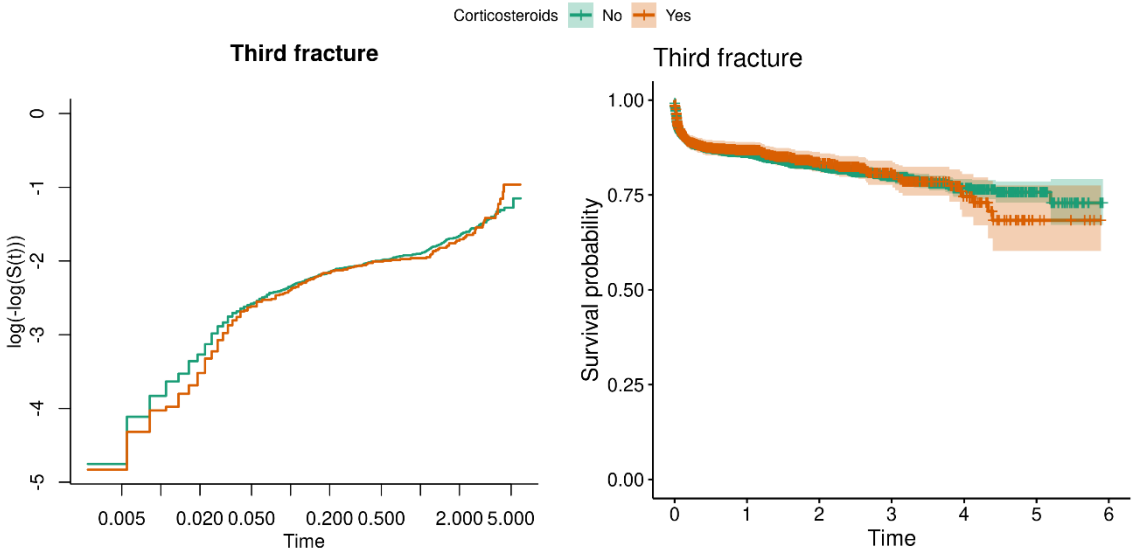

Figure 29: log(-log(S(t))) and KM curve by corticosteroids for third fracture of subjects without a previous fracture

Appendix B: Proportional hazard assumptions

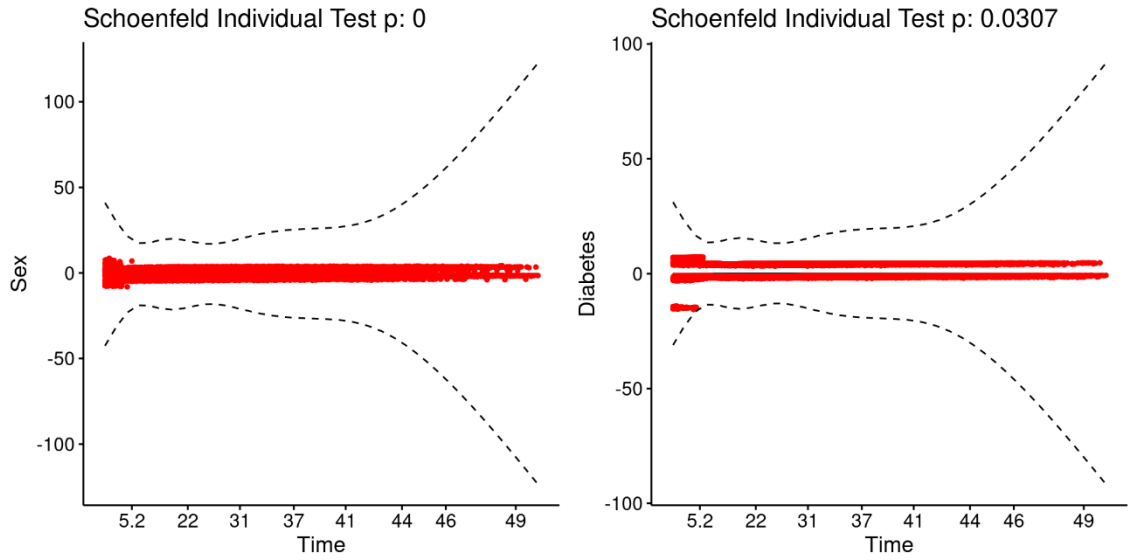

Figure 30: Schoenfeld residuals of sex and diabetes for subjects without previous fracture

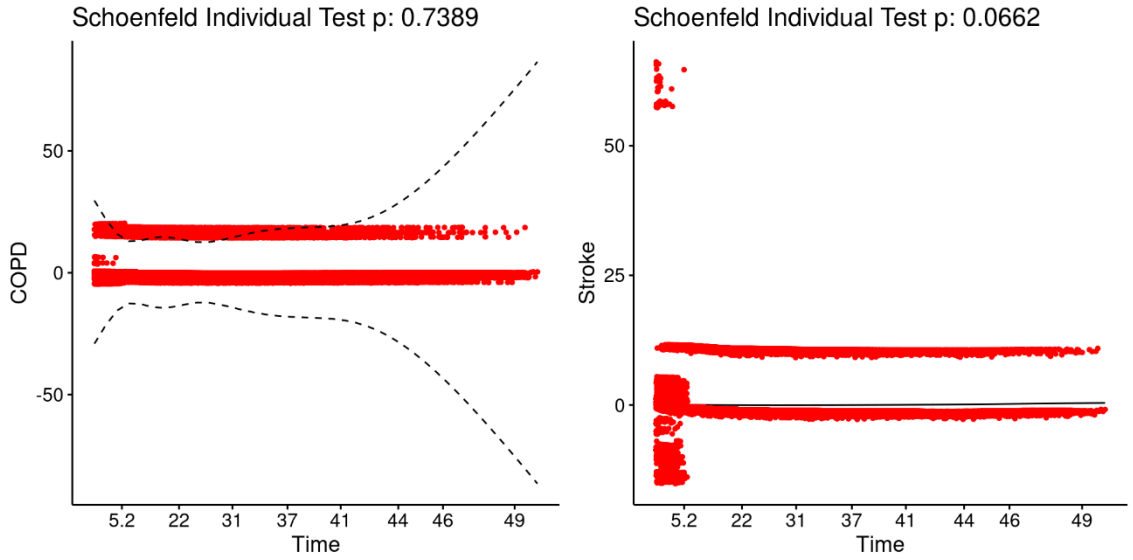

Figure 31: Schoenfeld residuals of COPD and stroke for subjects without previous fracture

Appendix B: Proportional hazard assumptions

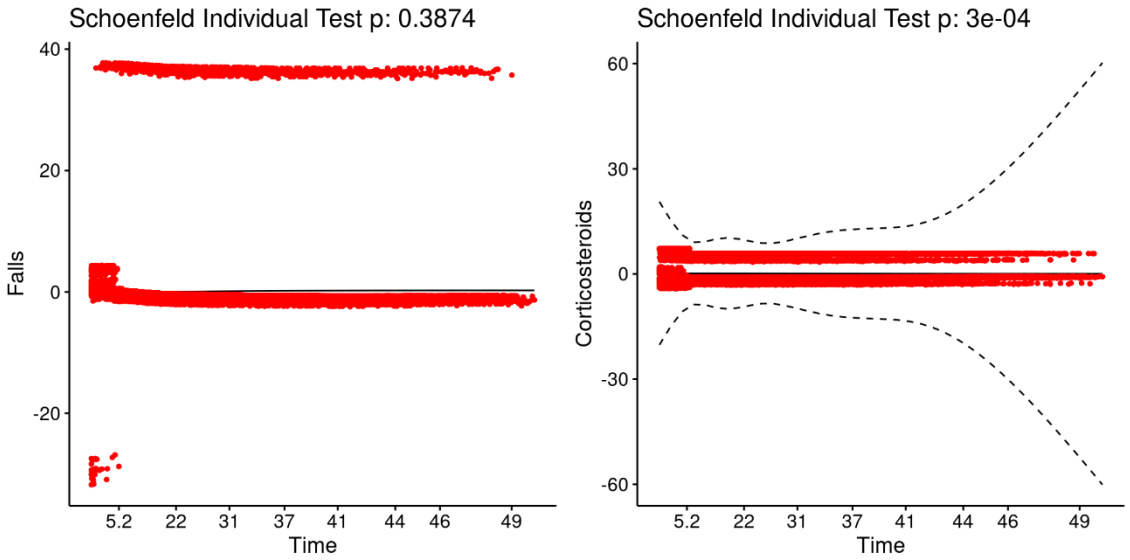

Figure 32: Schoenfeld residuals of Falls and corticosteroids for subjects without previous fracture

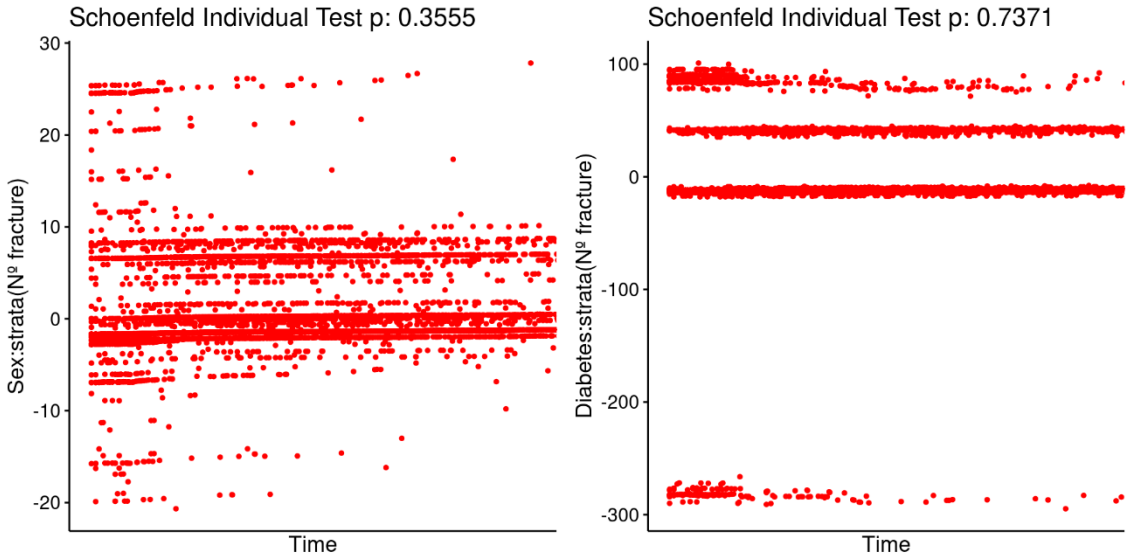

Figure 33 Schoenfeld residuals of sex and diabetes with the number of fracture for subjects without previous fracture

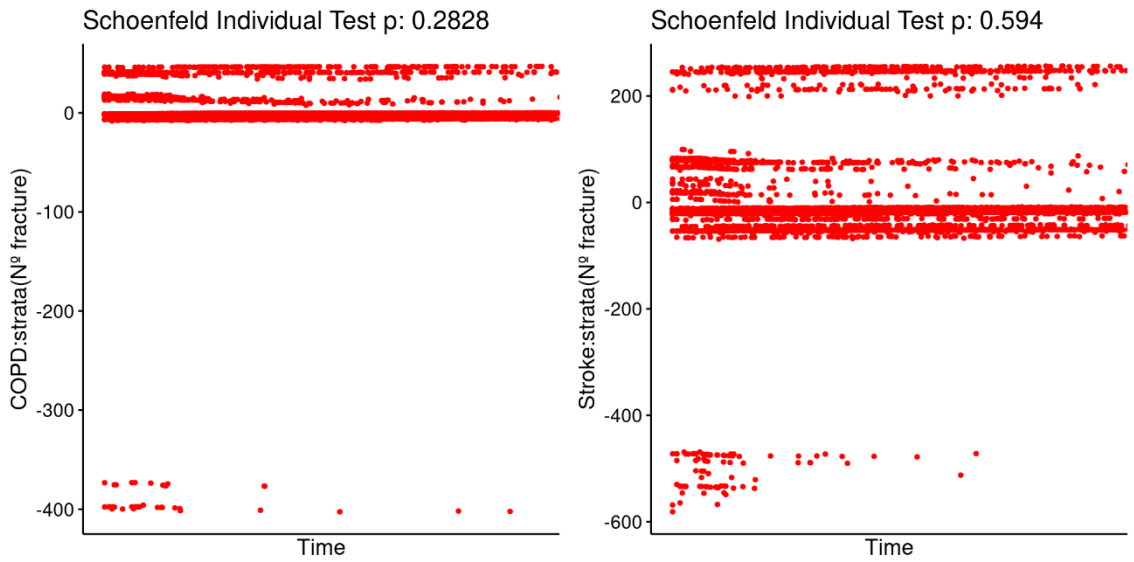

Figure 34: Schoenfeld residuals of COPD and stroke with the number of fracture for subjects without previous fracture

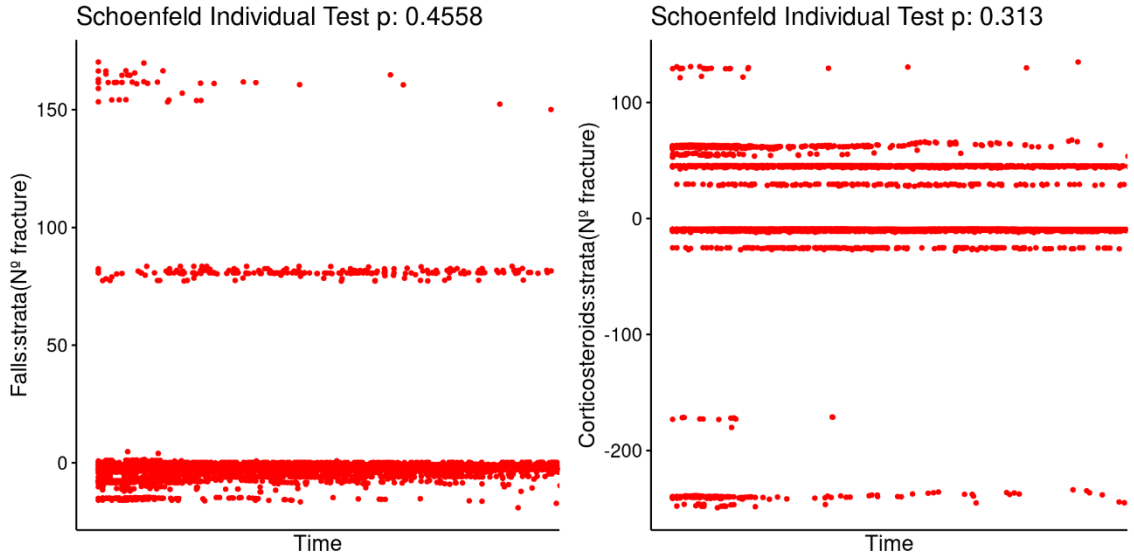

Figure 35: Schoenfeld residuals of falls and corticosteroids with the number of fracture for subjects without previous fracture

Subjects with previous fracture

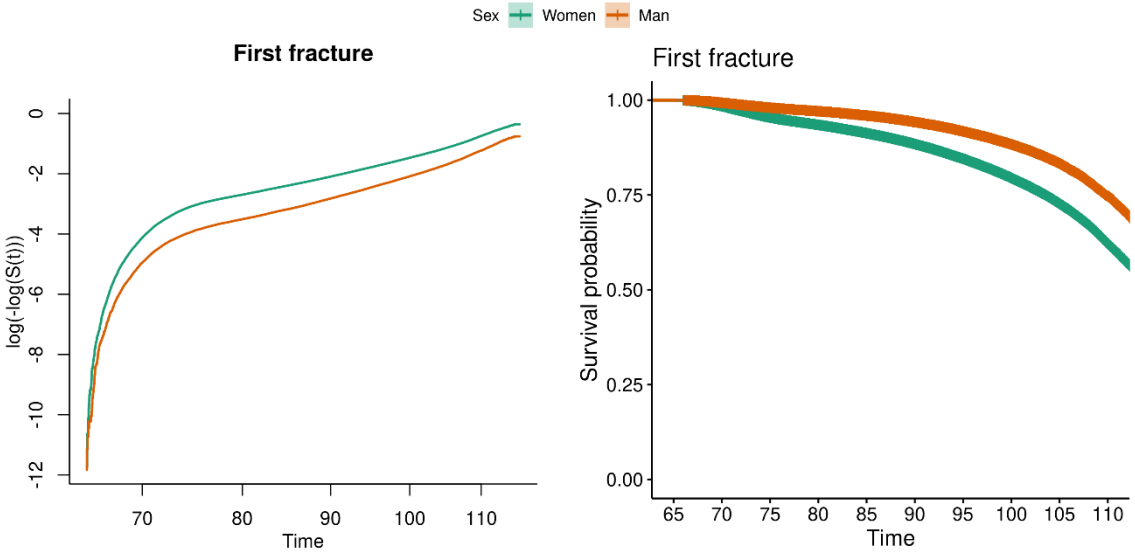

Figure 36: log(-log(S(t))) and KM curve by sex for first fracture of subjects with a previous fracture

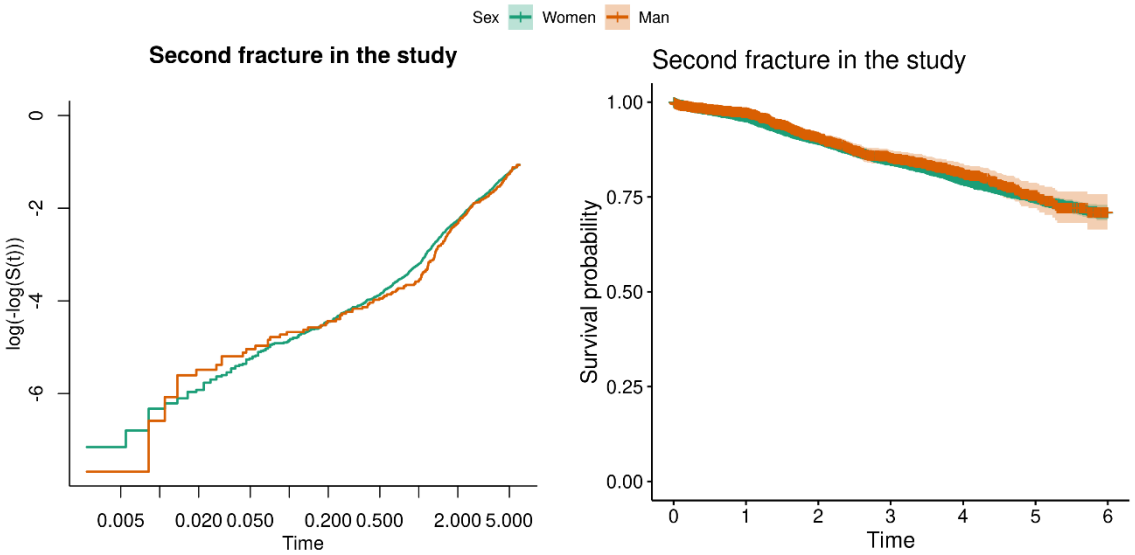

Figure 37: log(-log(S(t))) and KM curve by sex for second fracture of subjects with a previous fracture

Appendix B: Proportional hazard assumptions

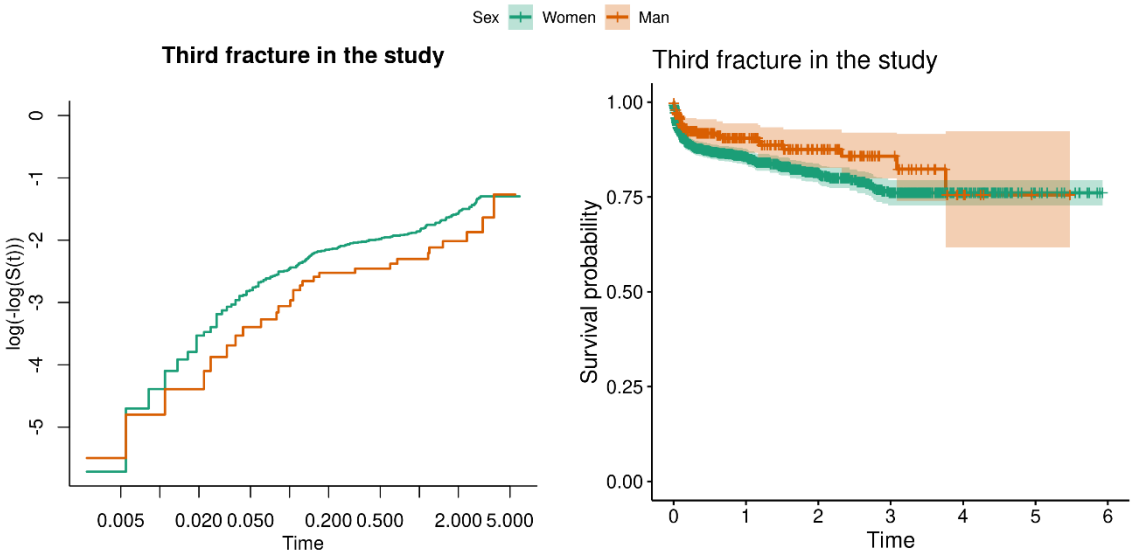

Figure 38: log(-log(S(t))) and KM curve by sex for third fracture of subjects with a previous fracture

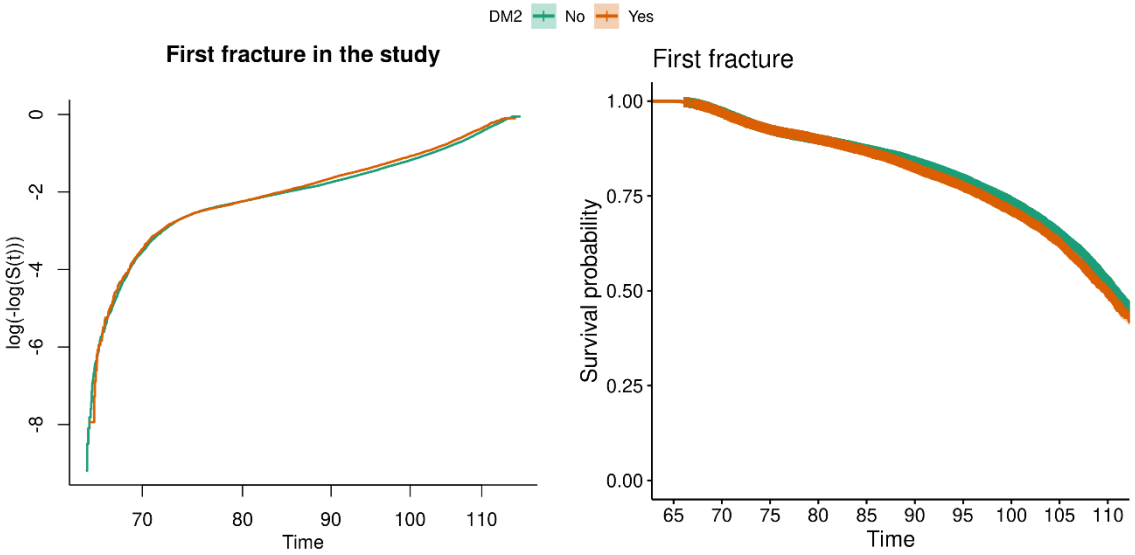

Figure 39: log(-log(S(t))) and KM curve by diabetes for first fracture of subjects with a previous fracture

Appendix B: Proportional hazard assumptions

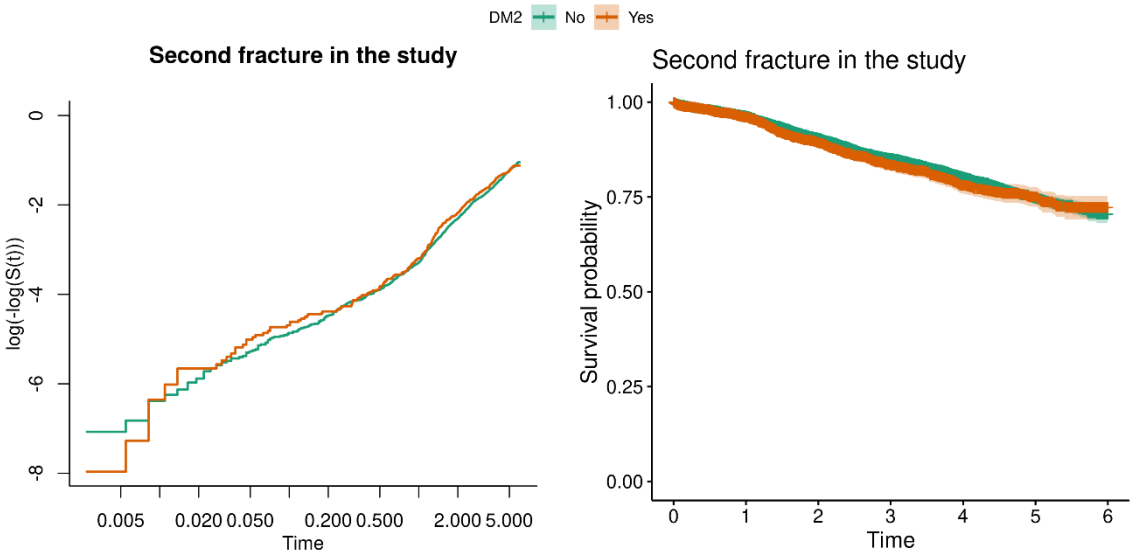

Figure 40: log(-log(S(t))) and KM curve by diabetes for second fracture of subjects with a previous fracture

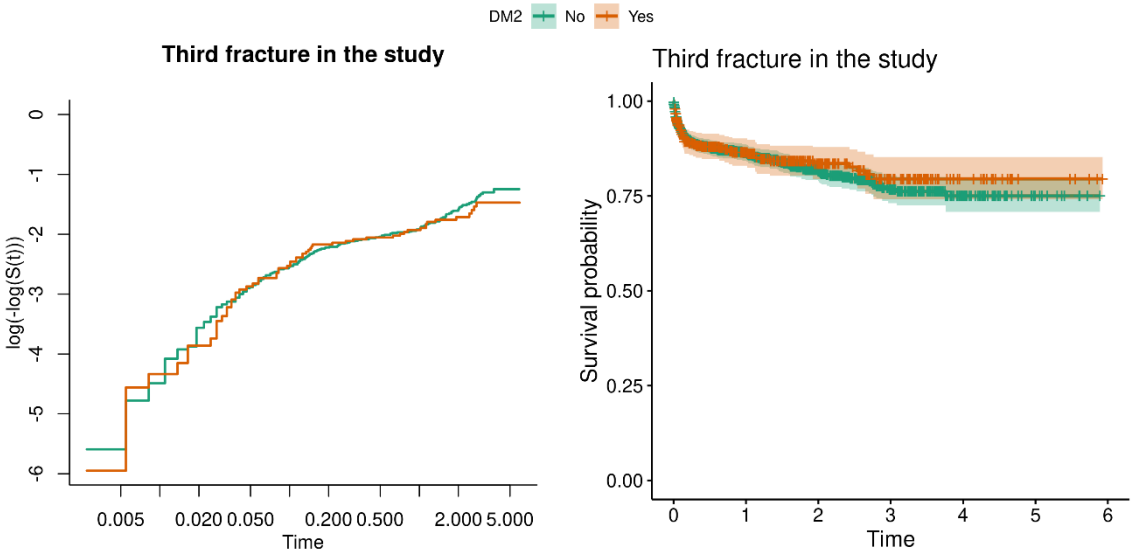

Figure 41: log(-log(S(t))) and KM curve by diabetes for third fracture of subjects with a previous fracture

Appendix B: Proportional hazard assumptions

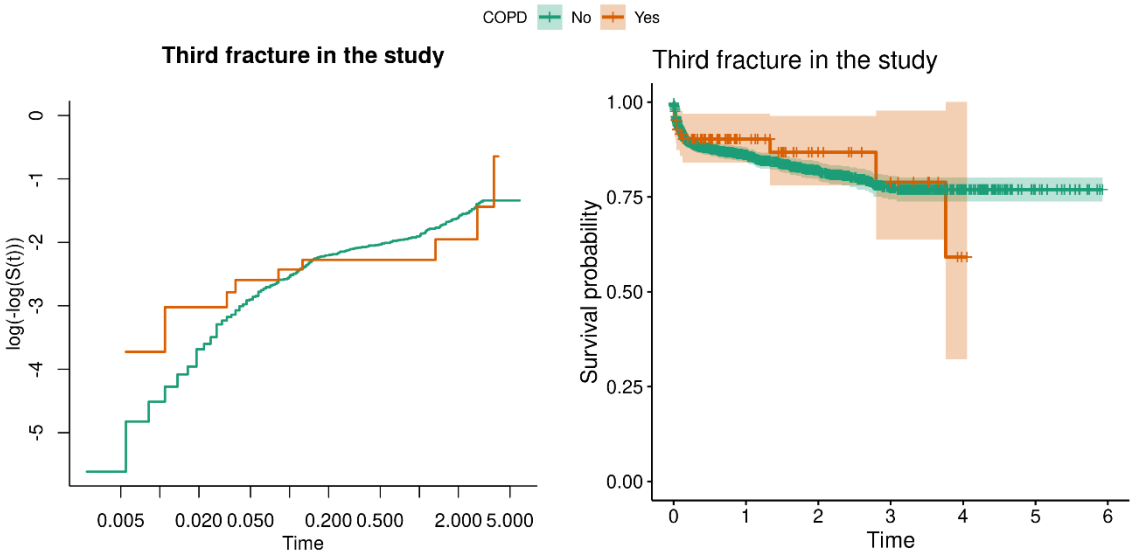

Figure 42: log(-log(S(t))) and KM curve by COPD for first fracture of subjects with a previous fracture

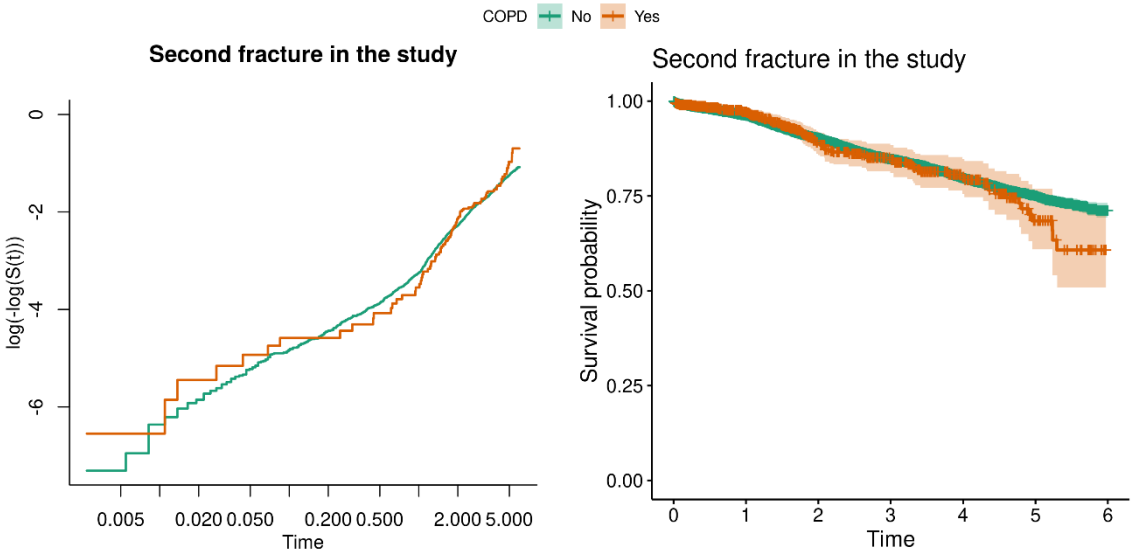

Figure 43: log(-log(S(t))) and KM curve by COPD for second fracture of subjects with a previous fracture

Appendix B: Proportional hazard assumptions

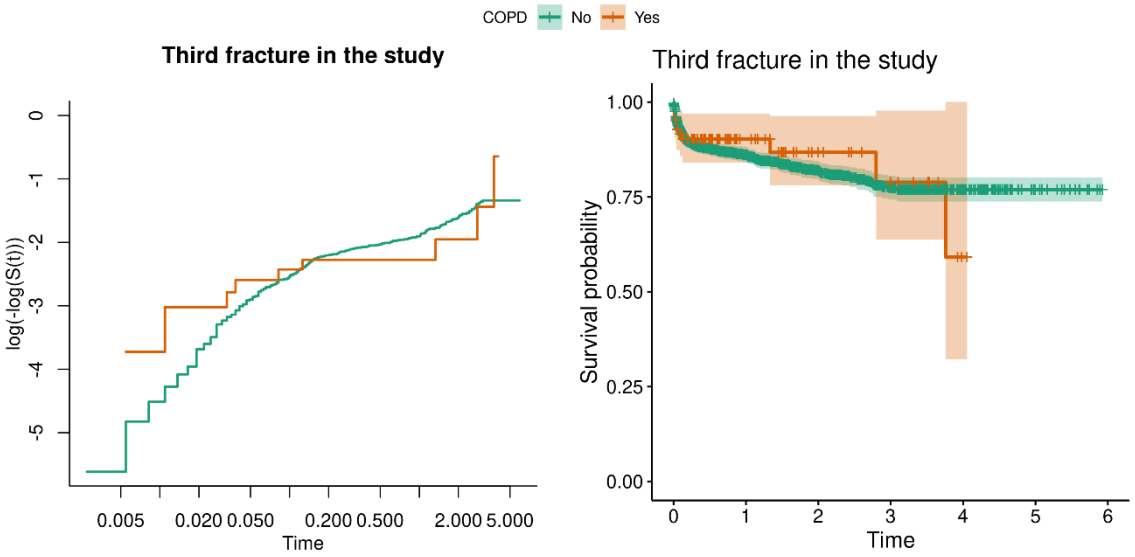

Figure 44: log(-log(S(t))) and KM curve by COPD for third fracture of subjects with a previous fracture

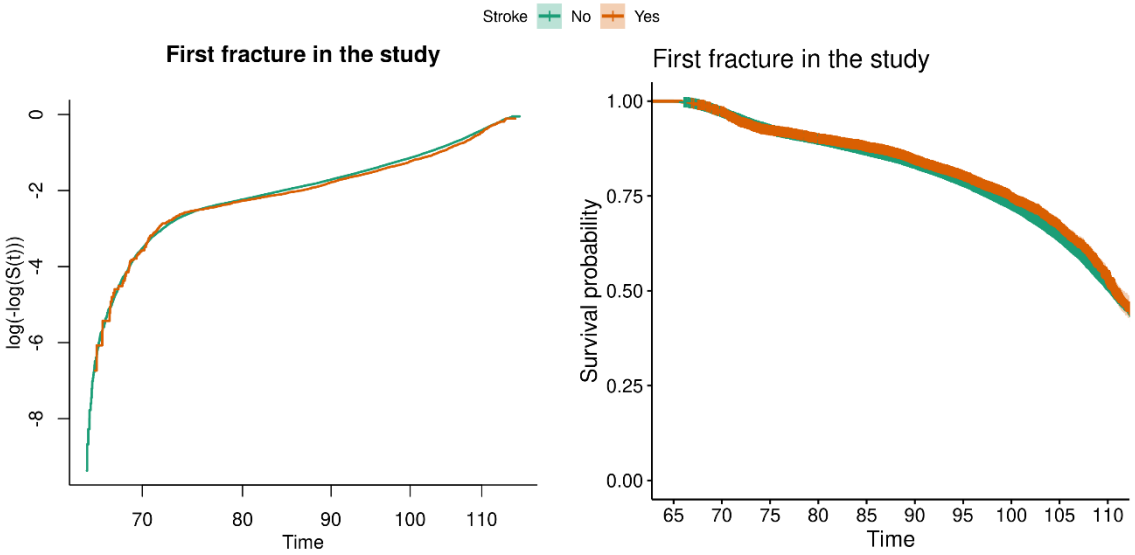

Figure 45: log(-log(S(t))) and KM curve by stroke for first fracture of subjects with a previous fracture

Appendix B: Proportional hazard assumptions

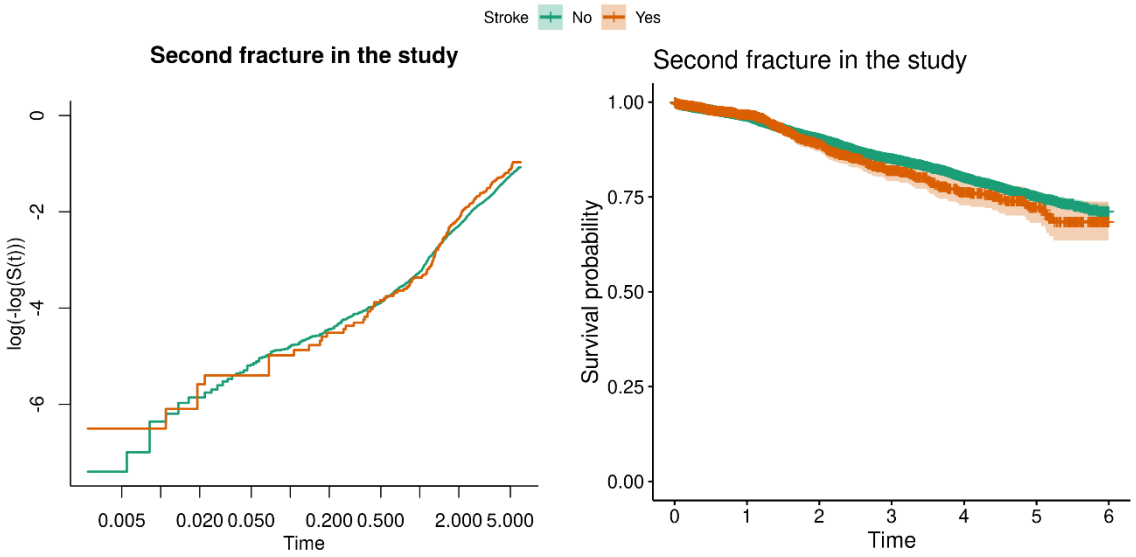

Figure 46: log(-log(S(t))) and KM curve by stroke for second fracture of subjects with a previous fracture

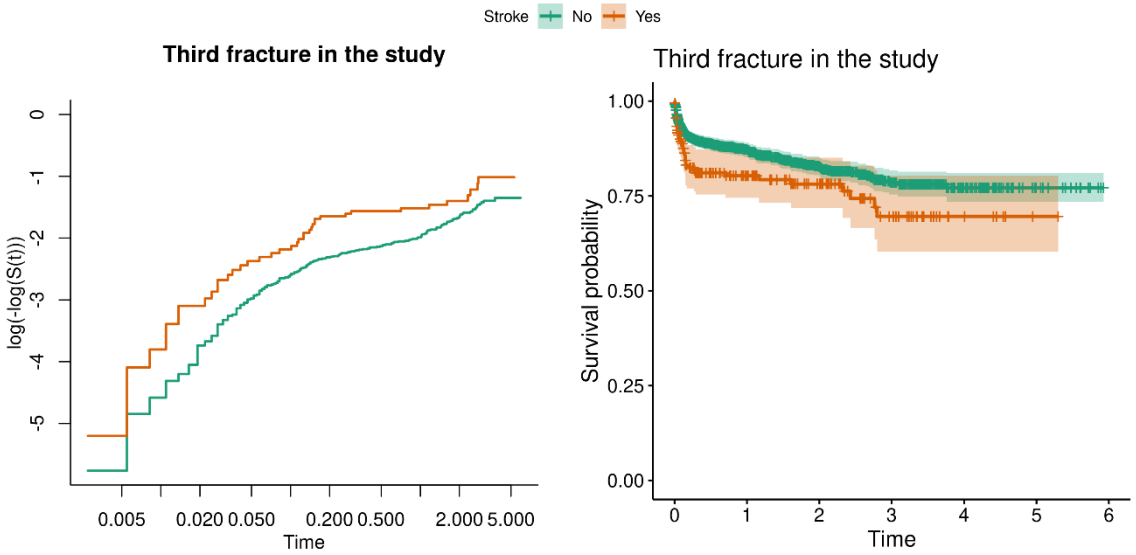

Figure 47: log(-log(S(t))) and KM curve by stroke for third fracture of subjects with a previous fracture

Appendix B: Proportional hazard assumptions

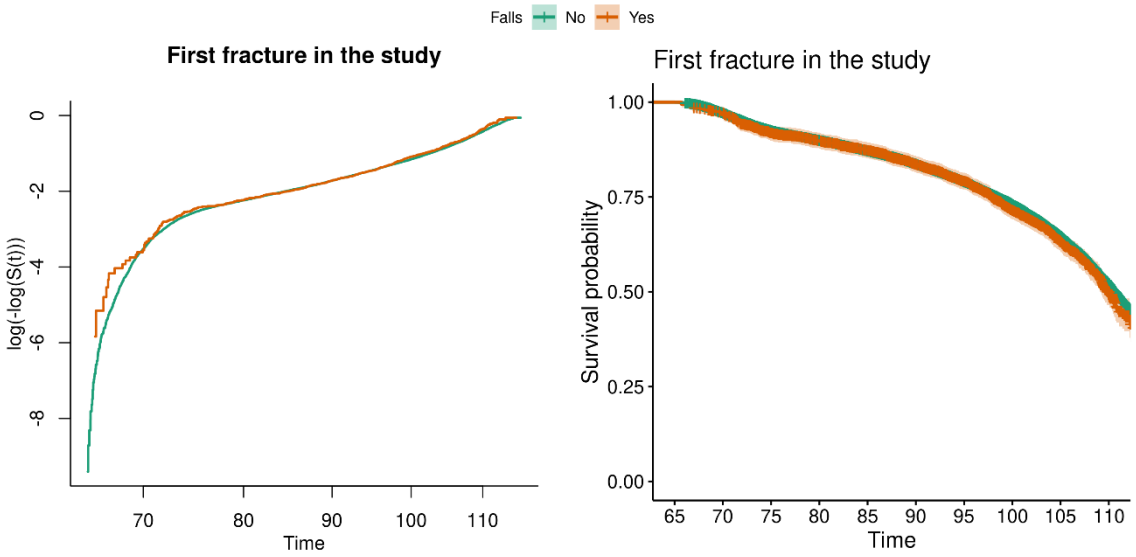

Figure 48: log(-log(S(t))) and KM curve by falls for first fracture of subjects with a previous fracture

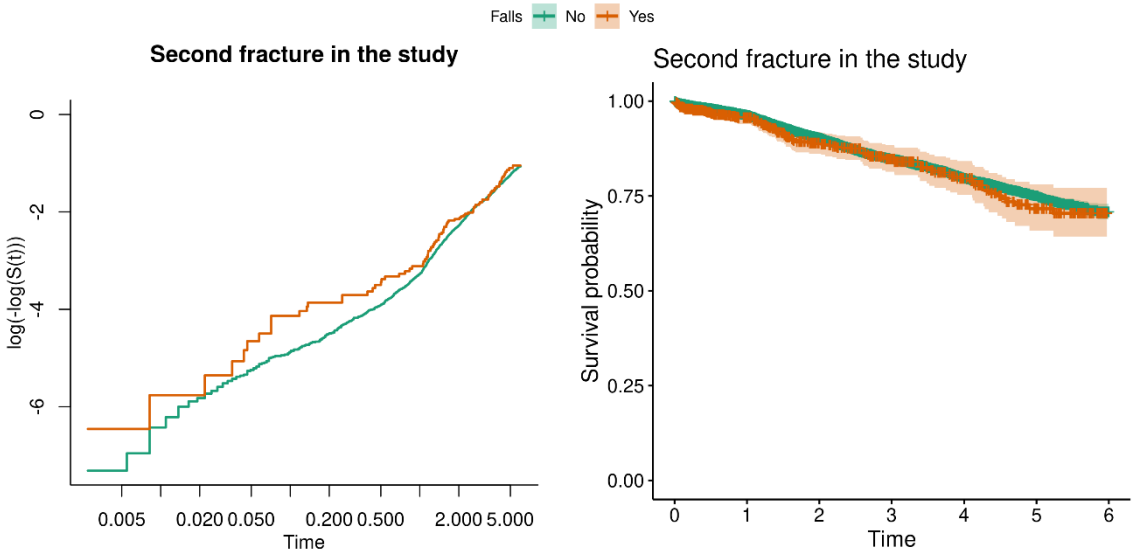

Figure 49: log(-log(S(t))) and KM curve by falls for second fracture of subjects with a previous fracture

Appendix B: Proportional hazard assumptions

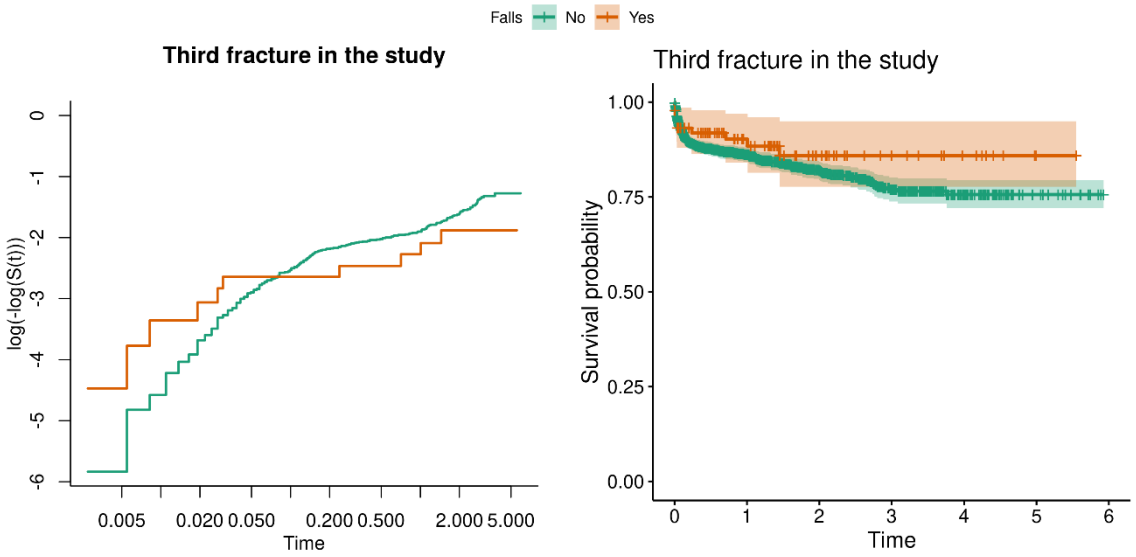

Figure 50: log(-log(S(t))) and KM curve by falls for third fracture of subjects with a previous fracture

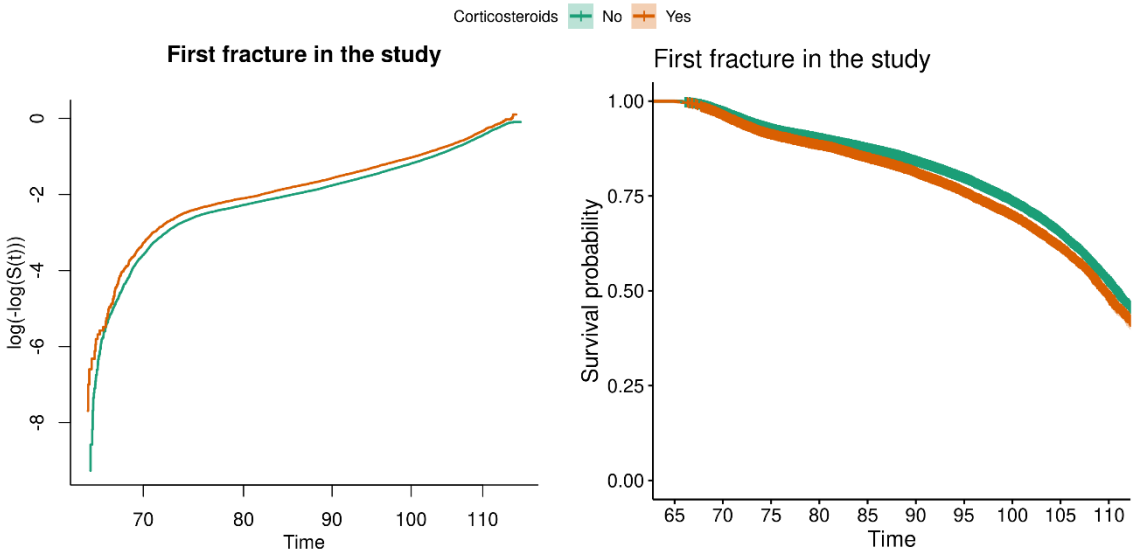

Figure 51: log(-log(S(t))) and KM curve by corticosteroids for first fracture of subjects with a previous fracture

Appendix B: Proportional hazard assumptions

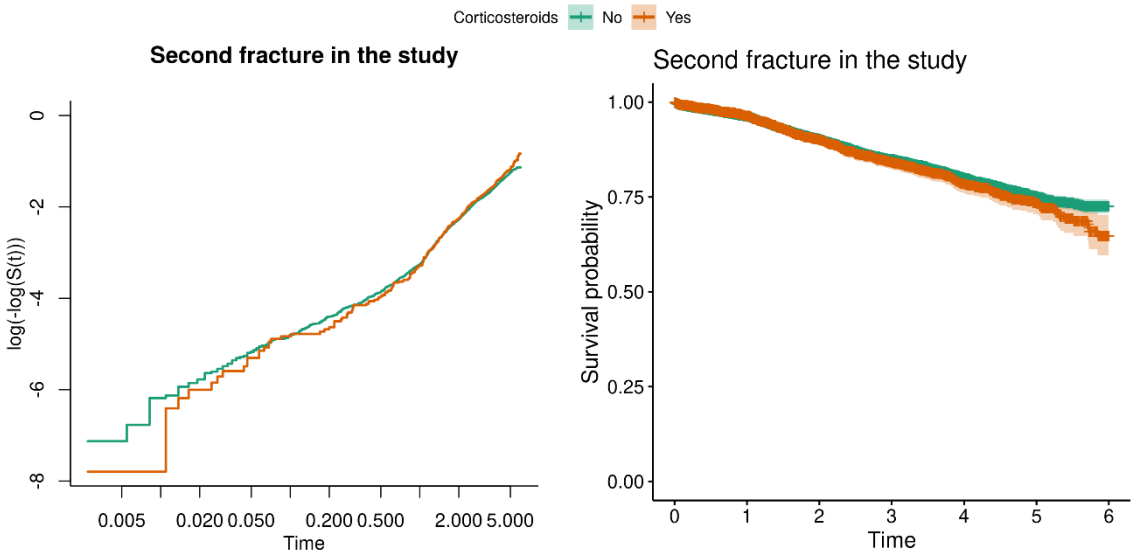

Figure 52: log(-log(S(t))) and KM curve by corticosteroids for second fracture of subjects with a previous fracture

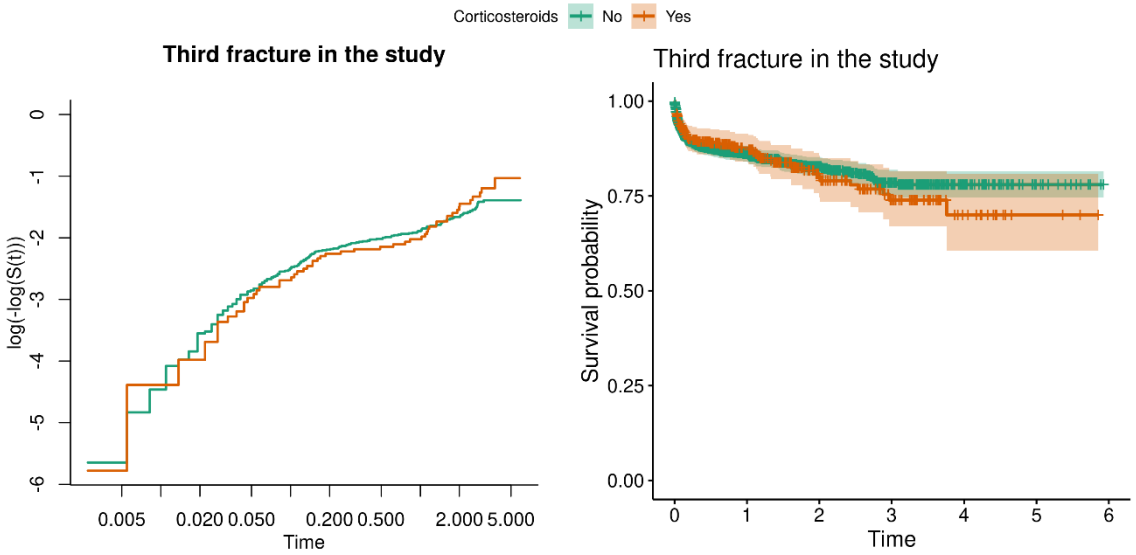

Figure 53: log(-log(S(t))) and KM curve by corticosteroids for third fracture of subjects with a previous fracture

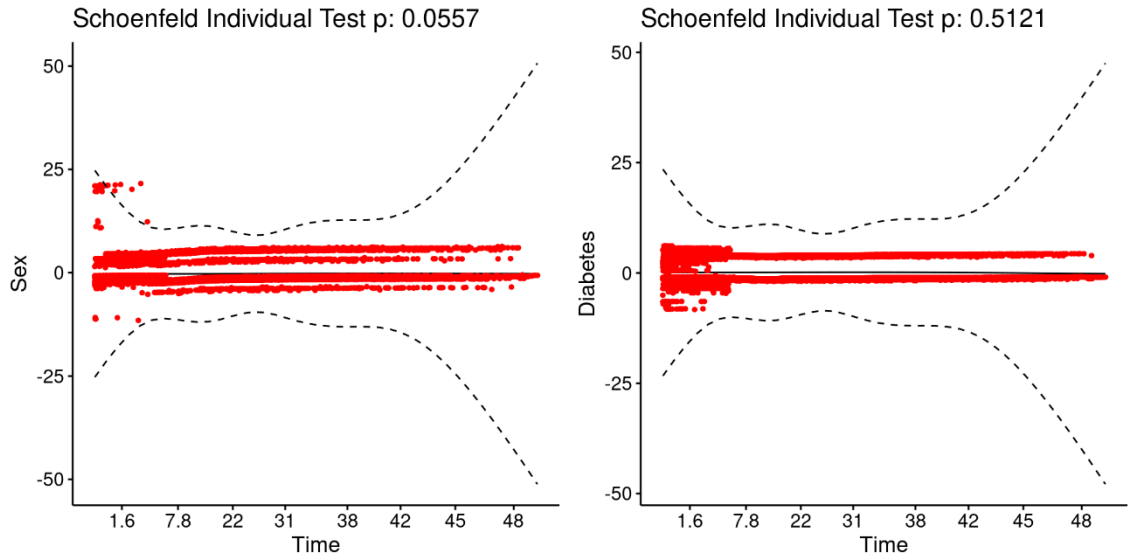

Figure 54: Schoenfeld residuals of sex and diabetes for subjects with previous fracture

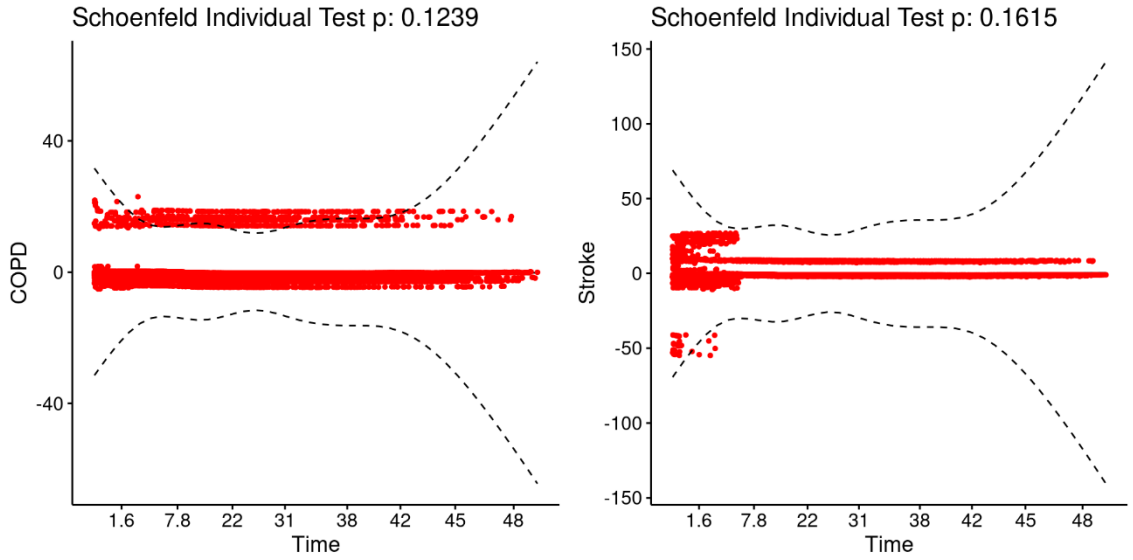

Figure 55: Schoenfeld residuals of COPD and stroke for subjects with previous fracture

Appendix B: Proportional hazard assumptions

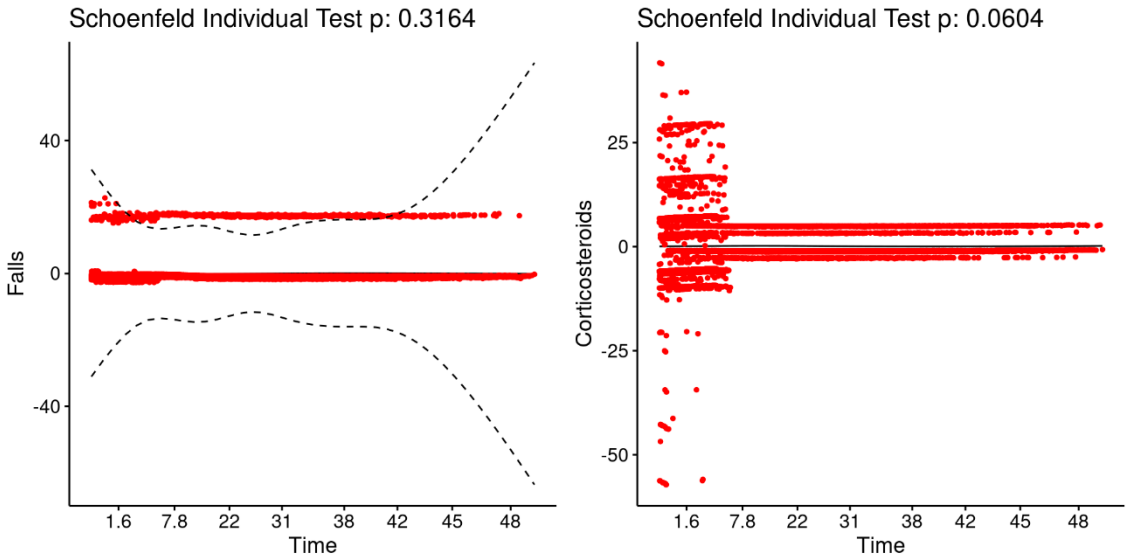

Figure 56: Schoenfeld residuals of falls and corticosteroids for subjects with previous fracture

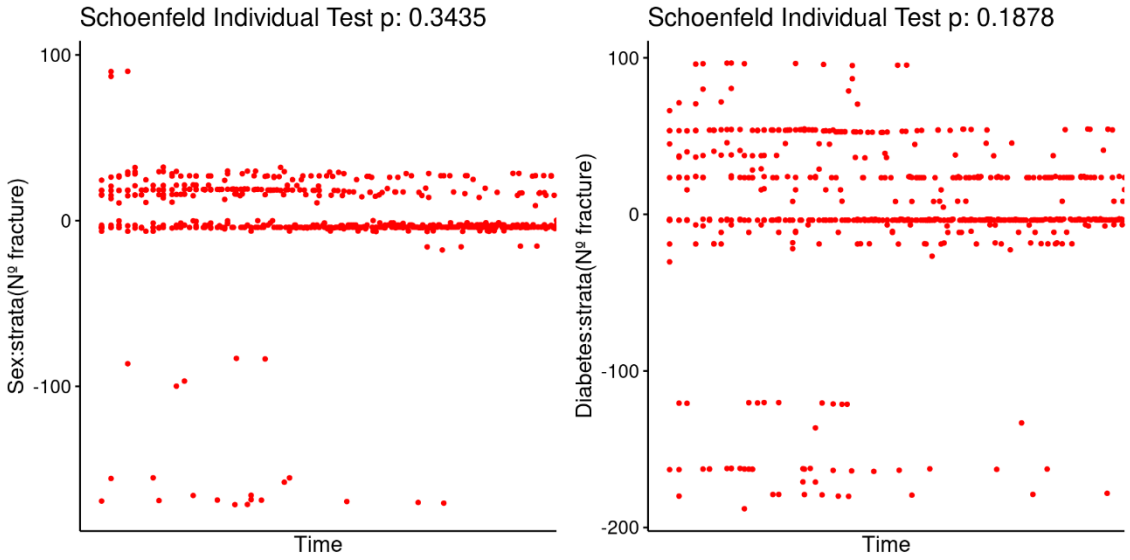

Figure 57: Schoenfeld residuals of sex and diabetes with the number of fracture for subjects with previous fracture

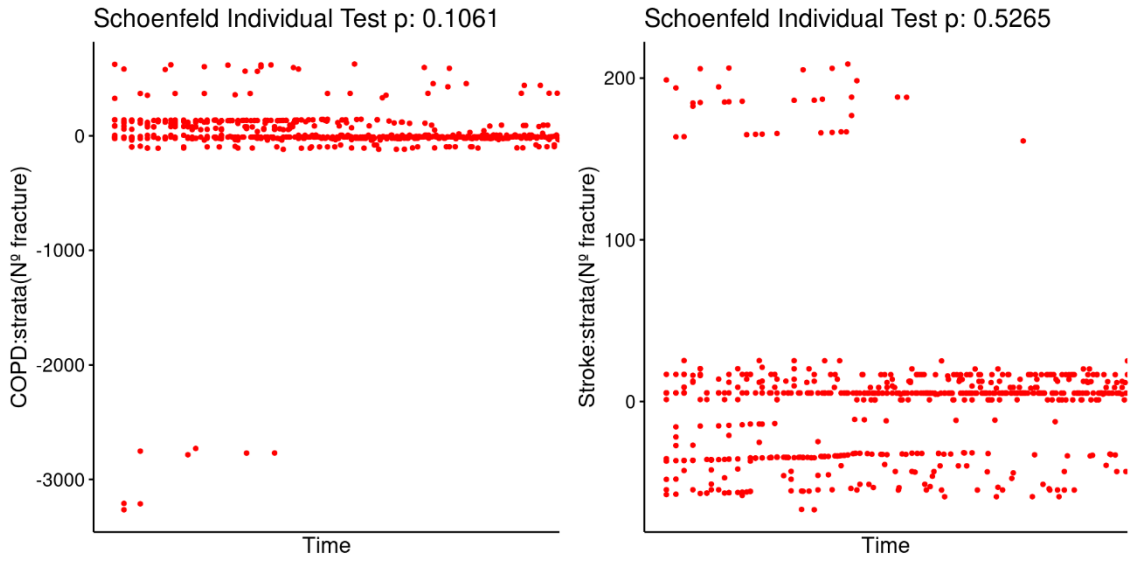

Figure 58: Schoenfeld residuals of COPD and stroke with the number of fracture for subjects with previous fracture

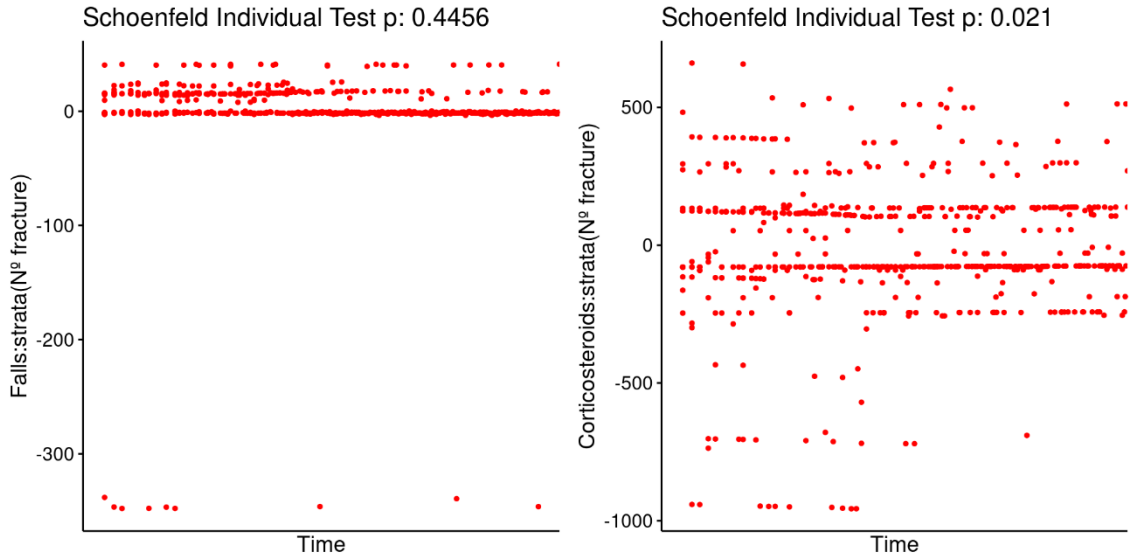

Figure 59: Schoenfeld residuals of falls and corticosteroids with the number of fracture for subjects with previous fracture

Appendix C: Covariates distribution by fracture

Subjects without previous fractures.

Table 9: Covariates described by fracture in subjects without previous fractures

	First fracture		Second fracture		Third fracture	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
Sex, N (%): Man	350341 (51.05%)	18682 (30.96%)	17337 (31.52%)	1345 (25.25%)	1160 (25.75%)	185 (22.51%)
Diabetes, N (%): Yes	156068 (22.74%)	14689 (24.35%)	13397 (24.36%)	1292 (24.25%)	1103 (24.48%)	189 (22.99%)
COPD, N (%): Yes	41801 (6.09%)	3751 (6.22%)	3421 (6.22%)	330 (6.19%)	293 (6.50%)	37 (4.50%)
Stroke, N (%): Yes	49656 (7.24%)	5684 (9.42%)	5165 (9.39%)	519 (9.74%)	431 (9.57%)	88 (10.71%)
Falls, N (%): Yes	9400 (1.37%)	1582 (2.62%)	1372 (2.49%)	210 (3.94%)	167 (3.71%)	43 (5.23%)
Corticosteroids, N (%): Yes	106572 (15.53%)	11315 (18.75%)	10183 (18.51%)	1132 (21.25%)	959 (21.29%)	173 (21.05%)

Appendix C: Covariates distribution by fracture

Subjects with previous fracture

Table 10: Covariates described by fracture in subjects with previous fractures

	First fracture		Second fracture		Third fracture	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
Sex, N (%): Man	14097 (29.53%)	2181 (19.54%)	1937 (19.96%)	244 (16.71%)	217 (17.70%)	27 (11.54%)
Diabetes, N (%): Yes	11633 (24.37%)	2884 (25.84%)	2500 (25.77%)	384 (26.30%)	326 (26.59%)	58 (24.79%)
COPD, N (%): Yes	2961 (6.20%)	699 (6.26%)	615 (6.34%)	84 (5.75%)	73 (5.95%)	11 (4.70%)
Stroke, N (%): Yes	5230 (10.96%)	1335 (11.96%)	1153 (11.88%)	182 (12.47%)	143 (11.66%)	39 (16.67%)
Falls, N (%): Yes	2179 (4.56%)	639 (5.72%)	550 (5.67%)	89 (6.10%)	79 (6.44%)	10 (4.27%)
Corticosteroids, N (%): Yes	9196 (19.26%)	2431 (21.78%)	2107 (21.71%)	324 (22.19%)	269 (21.94%)	55 (23.50%)

Appendix D: Future research

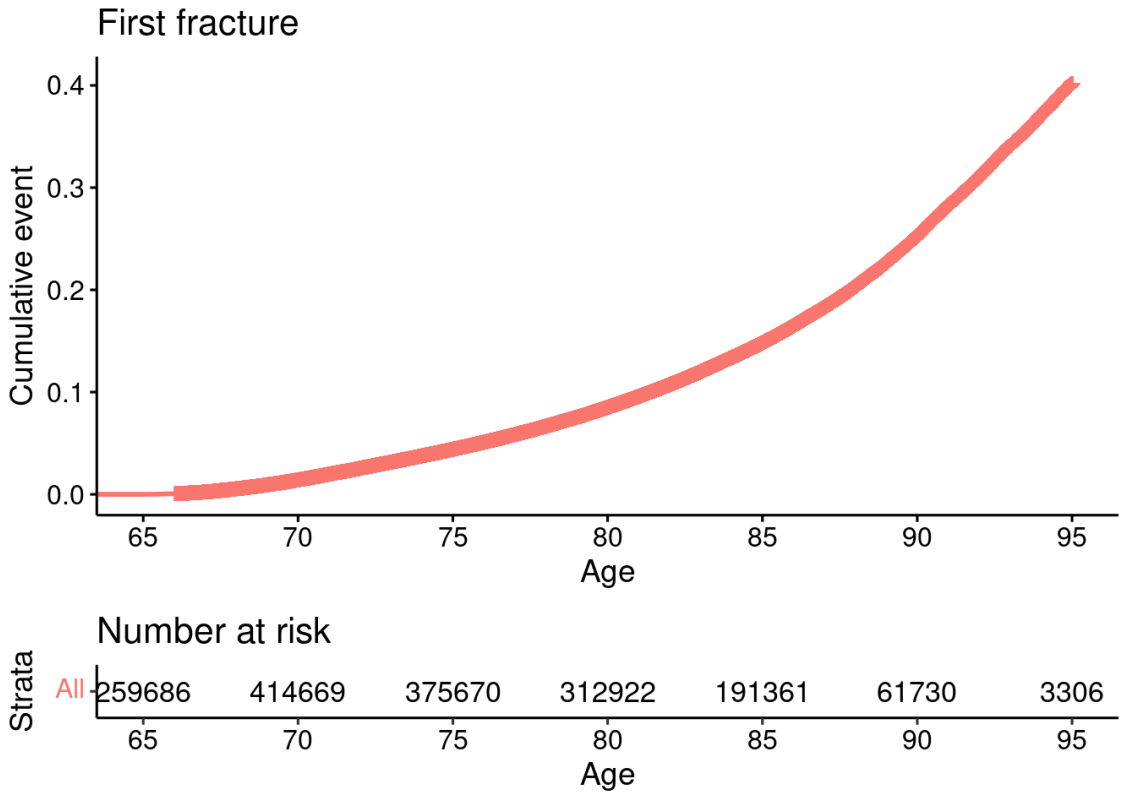

Figure 60: Cumulative event for the first fracture in subjects without previous fracture considering censure every event that occurs after 95 years old

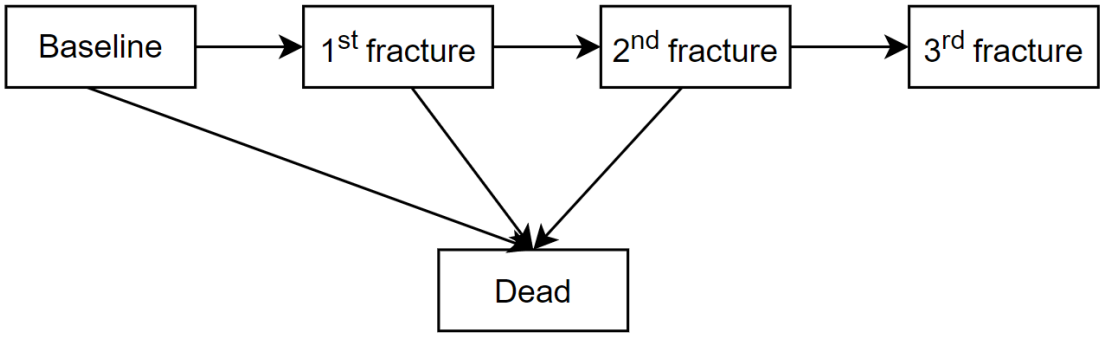

Figure 61: Multistate model states and transitions.