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***The savings factor between treatment of osteoporosis and treatment of subsequent osteoporotic fracture in the Netherlands.***

A calculation model based on the Dutch demography to project future costs and effects.

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## Abstract

Osteoporosis is characterized by reduced bone mineral density. Suffering from it implies that the risk of fracture increases. These so called fragility or osteoporotic fractures are regarded to be the most important clinical outcome of the disease for their inevitable ability to increase the financial and health burden in societies. Once experienced osteoporotic fracture, odds for subsequent fracture increase dramatically. Because of osteoporosis' asymptomatic nature, people can suffer from it without noticing until the occurrence of fracture. In order to diagnose the disease, fracture patients can be scanned by use of the DEXA technique. Research has estimated, however, that only about 10% of fracture patients are actually diagnosed and treated properly while a widespread arsenal of anti-osteoporosis medication is available to counter bone loss and hence decrease relative risk of fracture. This thesis describes a model which has been designed to take the most important determinants of Dutch health care costs to osteoporosis into account and calculates the magnitude of the economic costs and benefits from treating osteoporosis in order to prevent its consequences. This research is primarily based on the medication benefits with respect to the prevention of subsequent fractures due to prior fracture, rather than the prevention of first fracture. The model design is intended to calculate the magnitude of the cost relation between:

1. the prevention of subsequent fractures through DEXA scanning and prescribing anti-osteoporosis medication after first fracture; and
2. the health care costs of treating the consequences of osteoporotic fracture.

Where outcome estimates of the model tell that the financial burden of fragility fracture has been about € 700 million in 2010, it foresees a doubling of these costs by 2050. Moreover, this estimated extreme increase due to the ageing population too counts for the societal health burden. For 2010, the model estimates osteoporotic fracture to account for a total QALY loss of 40,800. This number is estimated to rise to 62,770 QALYs that will yearly be lost around 2050. These estimates are even likely to be underestimated. Since these predictions have solely been based on the ageing Dutch population, considering that the demographic evolution is an inevitable phenomenon, this raises the profile of an issue: How to minimize the increasing osteoporosis burden to society? This thesis describes the cost saving character of the prevention of subsequent osteoporotic fracture and the magnitude of the savings factor between the costs of preventing subsequent fracture and the costs of merely subsequent fracture repair, amounting 1.36 in 2020 in favor of fragility fracture prevention. This factor is likely to grow to a maximum of 12.82 by the year 2050 in the optimal scenario where all first and subsequent fractures can be prevented by i.e. risk assessment tools combined with adequate medication prescribing to people at high risk of fracture and where all anti-osteoporosis drugs are as cost-effective as the current most cost-effective available drugs. Fragility fracture prevention is predicted to enable an absolute cost saving per every 10% increase of combined screening and treating osteoporosis between the range of € 6 million (2020) to € 10 million (2050) per year in case of subsequent fragility fracture prevention and the range of € 18 million (2020) to € 28.5 million (2050) per year in the case of preventing both first and subsequent fragility fractures. Together with a predicted prevention of losing QALYs (i.e. 276 QALYs per year for subsequent fracture prevention and 827 QALYs per year for first and subsequent fracture prevention in 2020 for every 10% additional osteoporosis screening and treating) the study provides reason for discussion on the shift of focus from osteoporosis care to diagnosis and cure and justifies that the *osteoporosis diagnosis gap* should be closed instead of only focusing on the *osteoporosis care gap*.

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## 1. Introduction

This thesis is the last part in the completion of the one year Master of Health Economics at the Erasmus University Rotterdam. Although the main subject of the thesis is osteoporosis, its focus lies more on the primary consequence of the disease; fractures, as these are clinically the most relevant outcome events.<sup>1</sup> By use of a calculation model, diagnosing and treating of osteoporosis after first fracture to prevent subsequent fracture will be compared to mere treatment of fragility (osteoporotic) fracture. The term subsequent fracture has been used for the fractures osteopenia and osteoporosis patients suffer from because their fracture risk has been increased by already having suffered from earlier fragility fracture. The model provides estimates on absolute costs and savings associated with increasing the availability of screening and treating osteoporosis by a certain percentage. The model's calculations are programmed to use the effects of anti-osteoporosis medication on the relative risk of (subsequent) fracture. This investigation of the cost-effectiveness of prevention could serve as a basis for the discussion about screening and treating percentage estimates concerning osteoporosis in the Netherlands since the existence of room for improvement concerning diagnosis and treatment of osteoporosis has been shown in earlier research. The origin of the thesis lies in the middle of the osteoporosis care gap discussion and in the ongoing debate about getting value for money spent in the health care sector. As national health care expenditures have increased and are highly likely to ever increase in the future, so too will scrutiny over the economic value of new interventions and adaption of present clinical practice guidelines.<sup>2</sup> The outcome has as much as possible been based on published internationally acknowledged scientific literature on osteoporosis and (fragility) fractures. Where data about the Netherlands was unavailable, international figures have been used.

## 2. Osteoporosis

As people get older, their bone structure changes. Bones will get more porous. Regarding this to be a disease, the first disease stage is called *osteopenia*. It is considered to be a precursor to *osteoporosis*, the next disease stage. Compared to healthy, relatively young people, bone density of osteopenia patients is low, while that of osteoporosis patients is very low. Not every osteopenia diagnosed patient will develop osteoporosis however.

While the clinical expression of osteoporosis is a fragility (or: osteoporotic) fracture and sometimes merely considered to be a risk factor instead of a disease, osteoporosis does not allow easy defining.<sup>3,4,5</sup> Officially, internationally agreed, it has been defined as *a systemic skeletal disorder that is characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.*<sup>6,7</sup> The information provided by the diagnosis will, however, describe the clinical characteristics, fracture risk and epidemiology of osteoporosis differently.<sup>7</sup> Osteoporosis is the direct consequence of increased deterioration of bone by *osteoclasts* and the decreased bone marrow depositing by *osteoblasts*, called *osteoclastogenesis* and *osteoblastogenesis* respectively.<sup>8,9</sup> A distinction is made between primary and secondary osteoporosis. Primary osteoporosis can be divided into type 1 and type 2. Type 1 is the form that occurs in women after menopause, hence called postmenopausal osteoporosis. Type 2 is the form that is associated with age, hence affecting both women and men after the age of 75. In secondary osteoporosis, the rate of bone structure alteration increases, leading to a loss of bone mass.

Secondary osteoporosis can also occur from different disorders and diseases (comorbidity), causing bones to lose their strength.

Osteoporosis more often appears among white people compared to other races and the chance of having to deal with osteoporosis increases by age.<sup>8,10</sup> The disease has more often been associated with women than with men. Finally, osteoporosis in women is rare before menopause.<sup>11</sup> These findings justify why most research on this subject has been conducted on white women over 50 years old. Hence, less osteoporotic knowledge is available about non-white populations and about males.<sup>12</sup> Research about osteoporosis in men exists as well, but to a smaller extent.<sup>13</sup> Still research among males generates an increased understanding of osteoporosis in aged men because they also are regarded to be an increasing problem for the future concerning health care expenditures.<sup>13</sup> It is estimated that about 40 to 50% of women and 13 to 22% of men will experience at least one fragility fracture during life time.<sup>14,15,16</sup> Netelenbos et al. (2010) claim that even after the age of 50, one in two women and one in five men will get to deal with fracture related to osteoporosis.<sup>17</sup> Hip fracture, vertebral (spine) fracture and wrist fracture appear the most.<sup>18,19</sup> Other fractures are less prevailing. In the Netherlands about 800,000 people are estimated to be suffering from osteoporosis and its consequences, and about 83,000 fragility fractures occur yearly.<sup>12,20,21</sup> Apart from the costs due to fragility fractures, direct costs from osteoporosis treatment and care have been estimated to amount up to 120 million Euros per year (2005 estimate).<sup>22</sup>

## 2.1. Diagnostics and fracture risk

Osteoporosis has commonly been described a 'silent thief'.<sup>23</sup> This is because bone loss is asymptomatic, meaning that patients will not have symptoms of illness while bone deterioration proceeds. People often discover that they suffer from the disease when it is already too late because unnoticed decrease of bone strength might have major consequences. The most important clinical consequence of osteoporosis is that it leads to fracture, hence called *fragility fracture* or *osteoporotic fracture*. In severe cases of osteoporosis, fractures can even take place as a result of the slightest movement. Osteoporotic fractures are associated with extra (excess) morbidity, mortality and health care costs.<sup>24,25</sup> Approximately half of the fracture population does not regain their mobility degree such as it was prior to the fracture.<sup>26,27</sup> A great part of them will even become dependent on health devices or will have to be institutionalized (i.e. into rehabilitation clinics or nursing home facilities) after discharge from the hospital, while sometimes the fracture is regarded to be the trigger for this rather than the cause however.<sup>24</sup>

The asymptomatic nature of bone loss suggests that osteoporosis cannot be detected before a fragility fracture occurs. However, in 1994 The WHO<sup>i</sup> published diagnostic criteria for osteoporosis in postmenopausal women, which included measuring BMD<sup>ii</sup>.<sup>7,28</sup> These criteria were primarily intended for defining the disease.<sup>7,28,29</sup> They have ever since been widely accepted and are commonly used to provide intervention thresholds, while they were not designed for this. Meanwhile, the criteria have also been accepted as treatment and inclusion criteria for new medication trials, as research purposes standards and as the basis for health technology assessment in the osteoporosis scene.<sup>7,30</sup> According to the WHO, osteoporosis can be defined by means of statistics, in particular by using the T-score.<sup>28</sup> They consider osteoporosis as having a BMD value of at least  $-2.5 SD$ <sup>iii</sup> below the young

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<sup>i</sup> World Health Organization.

<sup>ii</sup> Bone Mineral Density; the amount of bone mass per unit volume or per unit area.

<sup>iii</sup> Standard Deviation.

adult mean, where between -1 and -2.5 SD is defined osteopenia. BMD can be calculated by dividing bone mass by the surface area of the irradiated bone tissue.<sup>36</sup> Each SD decrease in BMD is associated with a 1.5 to 3 fold increase in fracture risk.<sup>15</sup> In some countries thresholds for BMD, derived from the T-statistic, are even used to determine the reimbursement for the costs of treatment.<sup>31</sup> Such thresholds for decision making are discussed in various literature.<sup>32,33,34,35</sup>

The assessment of BMD is currently the only aspect of fracture risk that can clinically be measured because there are no other satisfactory clinical tools available yet for the assessment of people's bone quality.<sup>28</sup> This measurement, also referred to as densitometrics, has been made available by medical devices which use the Dual Energy X-ray Absorptiometry (DEXA or DXA) technique. DEXA is based on the absorption of X-rays by the calcium in bone tissue.<sup>36</sup> Since bone quality happens to correlate with BMD, DEXA scanning now forms the essential foundation for comparing performance characteristics of new methodologies and for the general management of osteoporosis.<sup>7,37</sup> Apart from DEXA scanning, assessment tools are available which are designed to estimate fracture risk, i.e. the FRAX<sup>iv</sup> developed by the WHO.<sup>38</sup>

Low BMD is a major risk factor for the occurrence of fracture. However, more risk factors are present.<sup>4</sup> In their paper, Dennison et al. (2006) sum up the most important risk factors for (osteoporotic) fracture, knowing that these factors are positively correlated with a high(er) chance of fracture.<sup>15</sup>

#### Constitutional factors

- Female gender
- Age
- White race
- Sex hormone deficiency
- Previous fragility fracture
- Family history of fragility fracture
- Bad early environment
- Co-morbidity
- Neuromuscular disorders

#### Lifestyle related factors

- Low body weight
- Cigarette smoking
- Excessive alcohol consumption
- Prolonged immobilization
- Low dietary calcium intake
- Vitamin D deficiency

Because of being associated with additional fracture risk, one of these factors takes in a major place in this thesis, namely the previous fragility fracture. Apparently, people who have undergone a fracture already, are likely to undergo this again or are 50 to 100% more likely to have another one of a different type.<sup>11</sup> The risk of a subsequent fracture can be increased up to fourfold due to prior fracture.<sup>11,39,40,41</sup>

## **2.2. The burden of fragility fracture**

Osteoporotic fractures increase the burden to society with respect to mortality, quality of life (i.e. loss of mobility) and health care costs (i.e. immediate hospitalization followed by expensive surgery).<sup>35,42</sup> Fragility fractures are clinically regarded osteoporosis' most important outcome events because they are costly to treat, often lead to rehabilitation and sometimes to long-term care and they are very likely to be debilitating to patients.<sup>36,43,44</sup> Regarding fractures as a main consequence of osteoporosis, societies indirectly have great health expenditures on osteoporosis through fractures.

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<sup>iv</sup> FRAX: Fracture Risk Assessment Tool.



From an economic point of view it can be stated that within the subgroups of osteoporotic fractures, most attention must be given to hip fractures because they account for the majority of direct medical costs to society.<sup>45</sup> Note that medical costs include more than one would initially think of and these are not always easily tracked or determined. For example, ambulance personnel, the hospital's properties and specialist fees will have to be paid for as well. Osteoporotic fractures already represent a significant public health burden by as much as 13.9 billion Euros on a European scale and are very likely to have health care costs increased in the future since life expectancy is increasing worldwide.<sup>15</sup> On Dutch level, health expenditures following from osteoporosis and its consequences have been estimated to approximate 500 million Euros in 1999.<sup>20</sup> More recent estimates provided insight in the costs of falling, leading to fractures, amounting up to € 674 million per year.<sup>46</sup> A large part of these have been estimated to be related to osteopenia and osteoporosis, hence called fragility fractures. Merely looking at the prospects for the Dutch demography, it is already very likely that the osteoporosis burden will grow in the near future. Thanks to the recognition of the severity of the consequences of osteoporosis and to the improving understanding of basic bone biology, a lot of research has been done with respect to the relative fracture risk reduction of different interventions, i.e. administering anti-osteoporosis medication. The intervention's efficiency depends on numerous determinants, i.e. risk of falling, the implementation of case finding, adequate patient selection on risk for developing osteoporosis, results of research, fracture assessment, laboratory research, tolerance, safety, follow-up and adherence.<sup>19</sup> Investigating the prevention of osteoporotic fracture is expected to bring up interesting results. Especially when it has been taken into account that the white women lifetime risk of sustaining an osteoporotic hip fracture is greater than the risk of developing breast cancer and the number of fall related incidents among 55+ people leading to hospitalization is ever increasing (by 39% between 2007 and 2011 in the Netherlands, corrected for the age effect).<sup>47,48,49</sup> As Fries (1990) once stated: *"If we can put helmets on motorcyclists, we ought to be able to find some effective way to reduce the incidence of osteoporotic fractures by prevention"*.<sup>50</sup>

### 2.3. The osteoporosis care gap

The difference in the number of diagnosed and treated osteoporosis patients compared to the estimated osteoporosis prevalence is called the osteoporosis care gap. In an international perspective, this care gap has been discussed more often. International literature does as well report a diagnostic and a therapeutic *gap* between theoretically possible achievement (best case scenario) and actual practice (real scenario) in the osteoporotic fracture framework.<sup>27,39,51,52,53,54</sup> A review of literature from different countries showed that only 30% of fracture patients with fragile bones were clinically diagnosed with osteoporosis and only 15% of them had BMD scans.<sup>27</sup> In the Netherlands, too, it has been indicated that adults who experience fragility fracture are not receiving adequate osteoporosis management while it has been described that an ever increasing number of the Dutch elderly suffers from (the consequences of) osteoporosis or osteopenia.<sup>20,55</sup> While in the Netherlands about 80,000 osteoporotic fractures occur per year among 50+ people, only 10% of them would actually be scanned for their BMD and be treated with anti-osteoporosis medication if diagnosed with osteoporosis.<sup>19</sup> This share of osteoporosis patients is even claimed to be only 5% in other literature.<sup>55</sup> Such low estimates may justify stating that, besides an *osteoporosis care gap*, in the Netherlands an *osteoporosis diagnosis gap* exists.

Previous literature from Canada claims that the osteoporosis care gap has narrowed since the 1990's, while other literature (from the same country) has investigated that the situation is not

improving.<sup>52,53</sup> Anyway, the osteoporosis care gap seems to be still an up-to-date issue. Despite osteoporotic fracture to be (too) common in the Dutch population, despite the need to treat fragility fractures being well established, despite integration of diagnostic and treatment guidelines into health care provider's standards and despite the wide availability of different therapies, osteoporosis is very likely to be under-diagnosed and under-treated.<sup>19,51,52,56</sup> When it is considered that fracture risk is highest in the first year(s) after fracture, this problem is deemed to be of even greater magnitude than it already seems.<sup>11,40,41</sup> Research has suggested that osteoporosis management following fragility fracture is inadequate and hence Dutch physicians should recognize the importance of the osteoporosis burden and should act accordingly.<sup>27,56</sup>

### **3. Modeling of health care expenditures associated with osteoporosis**

Modeling is an important feature for making decisions about the efficient use of scarce health care resources.<sup>35,57,58</sup> Its purpose is to produce information on a prospective basis beyond that what is available from clinical studies.<sup>35</sup> Modeling will always play an important role in the assessment of the cost-effectiveness of prevention and treatment of osteoporosis.<sup>35</sup> In this case, it is used to provide future estimates on the Dutch burden of osteoporosis and osteopenia, expressed in morbidity and mortality, and especially in financial resources. The research should provide ground for a *return on investment factor* between treating osteoporosis and treating osteoporotic fracture. Where in the thesis 'osteoporotic fracture' will be discussed, also 'fragility fracture' can be read and vice versa. By this, both fracture associated with osteoporosis and with osteopenia is meant. In order to understand the logic behind modeling and decision making based on economic evaluation, section 3.1 will provide theoretical handhold while in the rest of section 3 the modeling method will be explained.

#### **3.1. Economic evaluation of health care interventions**

Economic evaluation of health care programs can be identified as a mechanism to value technologies that offer value for money in a sector where economic scarcity is a frequently stressed phenomenon.<sup>59,60,61</sup> In evaluating interventions to counteract the consequences of osteoporosis, differences have to be recognized between mere treatment of fragility fracture and the treatment of osteoporosis to prevent subsequent fragility fracture. Rather than a different set of criteria, it is the methodological choices which can lead to different outcomes for treatment and prevention, because of their different characteristics, set up and purpose.<sup>62,66,63,64</sup> Merely treating fragility fracture implies a direct solution to a fracture, whereas the benefits of prevention of subsequent fragility fracture by the treatment of osteoporosis lie in the future. However, the costs of both interventions start to count immediately after initiating the interventions. This is one of the methodological issues that makes the direct comparison of fragility fracture treatment and fragility fracture prevention by economic evaluation difficult. Without consideration of the issue of different *discounting* rates for health care costs and for effects, the cost-effectiveness of treatment will by definition be better than this of prevention because health effects *now* will be valued higher than health effects *in the future*. This can be explained by the fact that people show myopic behavior in making decisions related to time.<sup>65</sup>

Apart from the difference in short-term versus long-term health benefits in combination with discounting, the evaluation of treatment differs from prevention in (the setting of) other

methodological features as well. To mention some, think of identified versus statistical lives, intra versus intersectoral costs and consequences, comparator selection, uncertainty, time horizon, target population and the size of the target population.<sup>59,66</sup>

### **3.2. Model settings**

In the osteoporosis field, several models have already been developed to assess the cost-effectiveness of curative and preventive interventions.<sup>35</sup> While these models tend to show parallels, they do differ on various levels with respect to data sources used, chosen perspective and used validation. This makes it difficult to assess whether the cost-effectiveness results are a consequence of new insights, a new model, new technology or new data.<sup>35</sup> Therefore, advocating the importance of determining the study design upfront, the main model settings concerning this thesis' model will be discussed in this section.

#### **Target population**

This thesis regards an intervention where a specific group, the fragility fracture patients, will be targeted. Hence, only those with increased fracture probability incur the costs and potential health benefits from preventing additional fragility fracture by treatment of osteoporosis.

#### **Discounting**

Since in the model health effects have been measured in terms of relative fracture risk decrease, instead of in terms of QALY increase, discounting has not been incorporated in the model outcomes. Besides, there are ongoing discussions about which discounting rates to use for health effects and for costs and there are still discussions about the use of linear or hyperbolic discounting in modeling.<sup>67</sup> For the model input, however, linear discounting has been applied to calculate the incremental in-hospital costs per fracture at a 4% discounting rate because these have been determined following consolidation of three successive years.

#### **Perspective**

The model uses a health care perspective. This means that costs and benefits falling outside the health care sector have not been incorporated. Hence, the model does not include the societal implications of the interventional health program. Possible benefits or costs which would range wider than only the health care scene are therefore not regarded. Within the health care sector, not all costs have been included, however. Costs of added life years after prevention of subsequent fragility fracture have not been included. Motivation for this has been that costs are rather determined by time to death, cause of death and disability, instead of extra years of life.<sup>68</sup>

#### **Time horizon**

Considering fragility fracture probability, the model regards a time horizon of 10 years. These years are converted to 1 year estimates by averaging the 10 year estimate.

#### **Uncertainty**

Because the main model input, the Dutch demography, has been based on prognoses, the model calculates with statistical lives. Model uncertainty has been quantified through a sensitivity analysis.

### 3.3. Model method

The research conducted in this study is designed to model the feasibility of the preventing purpose of anti-osteoporosis medication as a solution to subsequent fragility fracture. Secondly, it is meant to explore the current and future problem of osteoporosis to society in terms of its financial and health burden. Empirical research on possible savings from preventing subsequent fracture has not been performed. Instead, the model has a prospective character based on the Dutch demography to enable estimation of future costs and possible savings with respect to in and out-hospital costs of fragility fractures. It employs a bottom-up approach based on prospective prevalence of osteoporosis and osteopenia linked to fragility fracture risk and associated costs. Where possible, the model determinants are based on empirical evidence from earlier research of several authors on osteoporotic consequences.

The model was built using Microsoft Excel. It is not a so-called Markov (health state) model, but it does distinguish between different health states (no fracture versus fracture) including different transition probabilities over different populations (people with a normal BMD, osteopenia patients and osteoporosis patients) divided into different age categories. Instead, it makes use of simple mathematical programming techniques to eventually enable budget impact analysis. Outcome of the model resulted in 'point estimations' of ten year osteoporosis costs, every ten years between 2010 and 2060. Hence, by assuming that the costs will be approximately equally spread over the years, average yearly costs to osteoporosis and its consequences can be calculated by dividing these ten year costs by ten. To demonstrate the estimated effects of increasing preventive interventions in the osteoporosis health care scene, the model considers two scenarios. Scenario one is regarded the baseline scenario and the second scenario has been set up exactly the same as the first, except for the adaptable input. Both calculation sheets contain the same calculation processes, only some figures within the calculations can be changed. In this way it is possible to compare the associated costs of preventive and curative care, like in a so-called *difference-in-difference* framework. What never changes are the demographics estimates. Prognosis figures from the Dutch Central Bureau of Statistics are used as point estimates for the years 2020 to 2060.<sup>69</sup> Keeping these equal in both scenarios allows differences from the comparison to be only due to the factors we want to compare (*ceteris paribus*):  $\Delta$  screening and  $\Delta$  medication.

By incorporating benefits of anti-osteoporosis medication which affect the relative risk of osteoporotic fracture, the model sheds light on a *savings factor* between costs of preventing osteoporotic fracture by treating osteoporosis and the total costs of osteoporotic consequences. The model is based on calculating the costs and benefits of medication that aims at preventing subsequent fractures of osteoporosis patients who already have had a fracture earlier. Disproving the assumption that, next to merely repairing osteoporotic fracture, treating osteoporosis after first fracture will increase the financial burden on the national health expenses budget, will provide reason for further investigation of the subject and/or reason for discussion.

To dispute the methodological issues raised by Tosteson et al. (2001) and Zethraeus et al. (2002), the following sections are intended to transparently describe the modeling structure of the calculation spreadsheets to face the modeling challenges.<sup>2,37</sup>

### 3.3.1. Prevalence of osteoporosis

The model is based on current Dutch demography and forecasts regarding demography. These data were derived from the Dutch central bureau of statistics (CBS).<sup>69</sup> Demography has been taken as a basis because the ageing population is seen as a significant determinant on health care costs since osteoporosis is a disease which is, next to and due to with BMD, highly correlated with age. Every one standard deviation (SD) decrease in BMD (~12% decrease) means a doubling of fracture risk.<sup>15</sup> Even if BMD is fixed for, older patients seem to be much more susceptible to fracture at any given BMD than younger patients.<sup>10</sup> This association can increase to a seven-fold fracture risk among 80 year old people compared to 50 year olds with the same BMD.<sup>70</sup> Age categories included in the model are 50-60, 60-70, 70-80, 80-90 and 90+. Years included are 2010, 2020, 2030, 2040, 2050 and 2060. In order to be able to estimate the prevalence of osteopenia and osteoporosis per age group and gender, obtained demography has been split up into subgroups according to the distribution from Schuit et al. (2004) who show a distribution of osteopenia and osteoporosis over age categories for men and women, by gender specific T-scores.<sup>71</sup> Their distribution first had to be translated into broader age categories by taking the mean of two abutting categories because they use 5 year age categories and in my model 10 year age categories are used. The age category of 55-59 years old has been transferred into 50-60, and 85+ has been transferred into 90+. This might lead to an overestimation of osteoporosis cases in the 50-60 category and to an underestimation of osteoporosis cases in the 90+ category since the osteoporosis prevalence percentage among people aged 50 is lower compared to the age group of 55-60, and among 90+ people the prevalence will be higher compared to 85+ people. After transferring, the rough distribution of normal BMD, osteopenia and osteoporosis prevalence as shown in Figure 1 is used for the calculations in the model. Figure 2 shows a schematic diagram of the demographic determinants of the prevalence of osteoporosis included in the model.

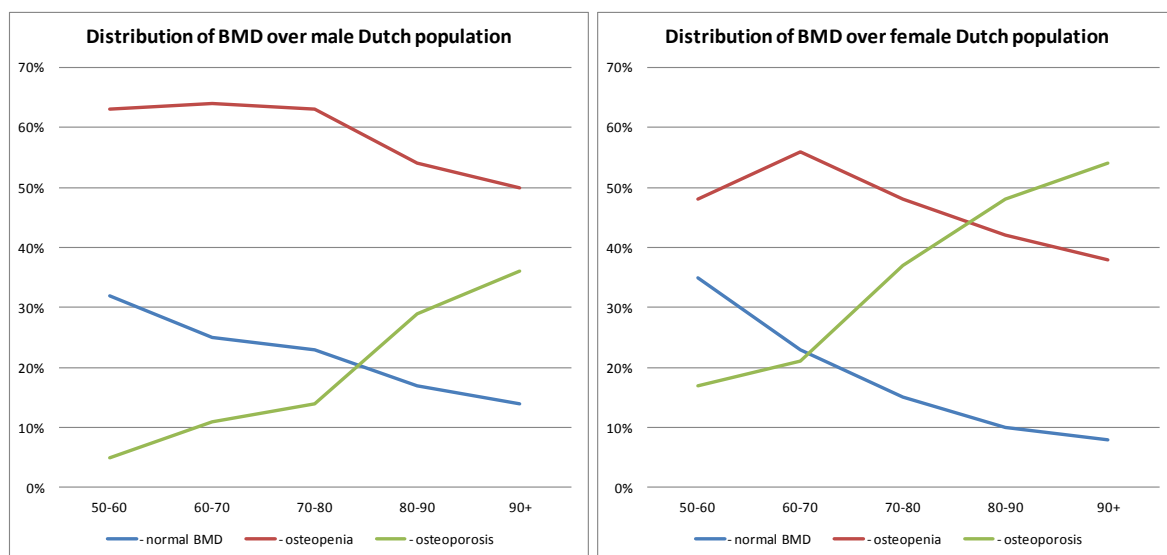


Figure 1, Distribution of BMD over male and female Dutch population by age category, used in the calculation model.

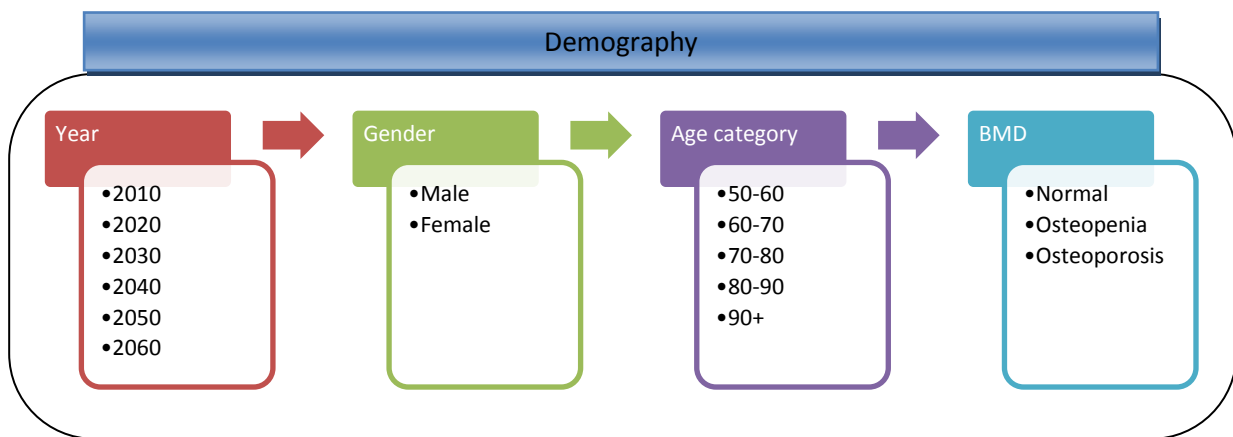


Figure 2, Included demographic determinants of the prevalence of osteoporosis.

### 3.3.2. Prevalence of osteoporotic fracture

After modeling the (future) prevalence of osteoporosis and osteopenia, the prevalence of osteoporotic fracture could have been modeled. Estimations on fragility fracture numbers are important in the determination of the osteoporosis burden to society. Societal costs of ageing are probably correlated with the loss of mobility, a phenomenon often caused by skeletal problems and (fragility) fracture. Hence, rather than osteoporosis and osteopenia *an sich*, it is their consequences which increase the financial and health burden to society since in and out-hospital costs to osteopenia and osteoporosis are not *directly* attributable to a low BMD. Instead, it is the fractures, being a common result from an increasing fracture risk due to decreasing BMD, that lead to direct incremental health care costs to society.<sup>24,35,44,72</sup> Note that most patients presenting with a fracture do not have BMD based osteoporosis, defined according to the WHO's definition as a T score of  $-2.5$  or below.<sup>3</sup> Being able to estimate the distribution of an absolute number of people within the three categories of BMD among the Dutch population over several years, it is possible to estimate an absolute number of fractures for 10 subsequent years over several years because fracture risk by gender and at various ages has been frequently estimated in the past.<sup>24,38,74</sup> By incorporating 10 year fracture risk, treatment decisions will not only be based on an 'arbitrary' BMD threshold.<sup>73</sup> For this model, estimates of Van Staa et al. (2001) have been used for including 10 year fracture risk.<sup>74</sup> Although these estimates originate from English and Welsh GP records, they suit the method of the model as to the separation of age categories and gender. Besides, the 10 year risk of fractures over the most important osteoporotic fracture sites has been estimated.<sup>19</sup> Integrating the latter allows the model to calculate the number of fractures per fracture site, necessary to distinguish costs over certain fractures. Van Staa et al. have estimated fracture risk per fracture site for different ages, not age categories. Therefore, to include their findings into the calculation model, the assumption has been made that the fracture risk in an age interval of 10 years shows a linear relation with age. Hence it was possible to create fracture risk estimates over age categories suitable for the model, by weighting two subsequent estimates. Two more problems had to be overcome concerning the adaptation of fracture risk estimates of Van Staa et al. into my model. First, fracture risk findings were not yet differentiated over BMD categories (i.e. normal BMD/osteopenia/osteoporosis). Not being able to differentiate fracture risk estimates across BMD categories would hamper the proper evaluation of the burden of an increasing number of osteoporosis patients. Second, the 10 year fracture risk of 'any fractures' had to be converted to 'other fractures' to suit the model. To deal with the BMD categories issue, the estimates on 10 year fracture risk for any male or female of Van Staa

et al. have been set as the 10 year fracture risk for osteopenia patients and have been linked to a (changeable) relative risk button in the model for converting these estimates to higher fracture risk estimates for osteoporosis patients and lower fracture risk estimates for normal BMD people (see figures from Table 1). As multiplying factor for normal BMD : osteopenia has been used 0.57 and for osteoporosis : osteopenia 2.7, according to the findings of Black et al. (2001).<sup>75</sup> To deal with the issue of having fracture risk estimates for 'any fractures' instead of 'other fractures', the column 'other fractures' in the model has been filled with estimates of 'any fractures' from Van Staa et al. minus their estimates for wrist, hip and spinal fractures, being the only other specific fractures they regard.

<b>Weighted estimated 10 year fracture risk at various age categories for men</b>					
	50-60	60-70	70-80	80-90	90+
Other	4,8%	3,8%	3,5%	3,5%	3,5%
Wrist	1,0%	0,9%	0,9%	0,9%	0,9%
Hip	0,3%	0,9%	2,2%	2,9%	2,9%
Spine	0,3%	0,4%	0,6%	0,7%	0,7%
<b>Weighted estimated 10 year fracture risk at various age categories for women</b>					
	50-60	60-70	70-80	80-90	90+
Other	6,4%	6,7%	6,3%	5,9%	5,9%
Wrist	4,1%	5,3%	5,6%	5,5%	5,5%
Hip	0,7%	2,3%	6,1%	8,7%	8,7%
Spine	0,5%	1,0%	1,5%	1,6%	1,6%

Table 1, Weighted estimated 10 year fracture risk at various age categories over gender and over specific fracture site. Extracted from Van Staa et al. (2001) after weighting their point estimates of fracture risk at various ages into age categories.<sup>74</sup> This was used as input for 10 year fracture risk for people with osteopenia. Fracture risk input for osteoporosis and normal BMD was derived from this.

Having calculated a ten year number of estimated fractures per fracture site from estimates on the Dutch demography combined with fracture risk, the number of fractures would have been underestimated. Literature on fracture risk shows that another step in estimating a ten year number of fractures has to be included. Studies have reported increased fracture risk among people with prior fractures.<sup>11,40,41</sup> To incorporate this into the model, results of Klotzbuecher et al. (2000) on associations of prior and subsequent fractures have been used.<sup>11</sup> These results provide relative risks on subsequent fractures per fracture site. In the calculation model, these results have been converted into incremental risks by subtracting the relative risk by 1, since these risks have been used as a multiplier for the 'normal' ten year fracture risk of the estimated osteoporotic fracture population. After estimating the incremental fractures due to prior fractures, it was possible to add up these subsequent fractures to the estimates already obtained from the ten year fracture risk.

An important note has to be made for the understanding of the model output. In estimating the total ten year number of fractures, only the osteoporotic fractures have been regarded. Thus, only the fractures which were estimated to occur in different periods of ten years (2010-2020, 2020-2030, 2030-2040, 2040-2050, 2050-2060 and 2060-2070) within the subgroups osteopenia and osteoporosis and are associated with originating from osteoporotic nature were counted. In evaluating the results, this should be taken in mind. Otherwise the results might be mistaken with an estimate of total number of fractures in ten years, including fractures without osteoporotic nature and the fractures in people with normal BMD.

Figure 3 schematically shows how the model calculates an estimate of number of osteoporotic (fragility) fractures in ten years, based on osteoporotic fracture risk.

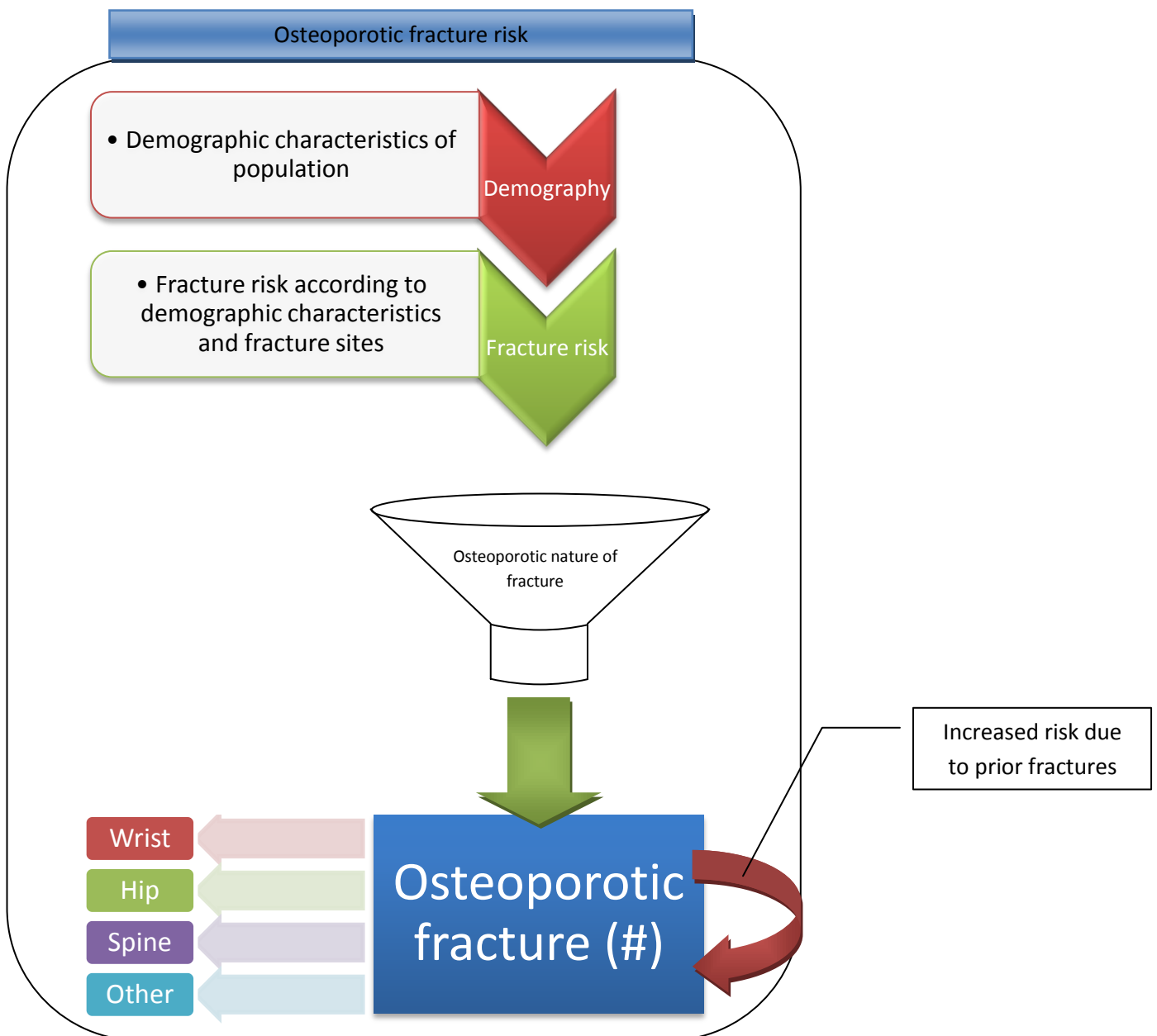


Figure 3, Fracture risk leading to osteoporotic fracture.

### 3.3.3. Inhospital costs

The next step in estimating osteoporotic health care costs (due to fragility fractures) is linking the number of estimated osteoporotic fractures to direct and indirect in-hospital costs. Now that the ten year number of fractures have been modeled, it was possible to simply multiply them by incremental medical costs estimates per fracture site from existing literature. Both direct and indirect costs have been considered by not only incorporating the incremental in-hospital costs due to fracture, but by also looking at the costs within the two years after the fracture. For hip and spinal fracture, findings on incremental costs by De Laet et al. (1999) have been used because of their nested case cohort design, while for wrist fracture Belgian cost findings of Bouee et al. (2006) have been weighted over their format of with and without surgery before incorporating into the model.<sup>24,76</sup> The estimate for



'other fractures' is based on the 2002 CBO guidelines. Because of uncertainty around the in-hospital costs of this large subgroup, it has been assumed that about half of CBO estimates concerning 'other fractures' can be attributed to in-hospital care. The model will calculate additional out-hospital costs. After discounting the two years after the year of fracture at a 4% discount rate, the costs were translated into 2010 Euros by use of yearly inflation rates derived from consumer price indexes.<sup>77</sup> An overview of the input for incremental in-hospital costs is shown in Table 2 below.

Fracture site	Estimated incremental in-hospital costs of treatment per fracture
Wrist	€ 1,948
Hip	€ 10,075
Spine	€ 1.594
Other	€ 800

Table 2, estimated incremental direct and indirect medical in-hospital costs of fracture treatment per fracture site in 2010 Euros. These were used as the in-hospital input for the calculation model.

In order to know whether someone who has had a fracture at a random site is also actually an osteoporosis patient, a DEXA scan has to be made to determine this person's BMD. In the model, this scan is regarded an in-hospital cost since a DEXA scan will usually be performed within a hospital.<sup>19</sup> Note that every person over 50 years old with a random fracture will have to be scanned to find out whether he or she suffers from osteopenia or osteoporosis. Not only those persons who are osteopenia or osteoporosis patients will have to be scanned, because the scan in fact leads to the diagnosis. A button has been integrated in the spreadsheets that allows the possibility of adapting the rate (in %) of 50+ men and women who can undergo a DEXA scan after osteoporotic fracture. By increasing the percentage of people who are to be scanned after having experienced a fracture, not only limited to those with an osteoporotic nature, the pool of people who are known to be osteoporosis patients will grow and they can hence be helped by i.e. anti-osteoporotic medication. Keep in mind that osteopenia and osteoporosis patients are not yet known as such before they are scanned by densitometric devices to determine one's BMD. This means that all estimated people with a fracture are included in calculating the number of DEXA scans performed in a period of ten years. Including the ones who turn out not to be estimated osteoporosis patients.

Scanning the bone densitometric of an increasing percentage of people aged over 50 years old will increase awareness of osteoporosis as being a slowly progressive disease that can be treated to prevent it from worsening. Moreover, having more people scanned for low bone mass density will increase the known prevalence of people suffering from osteoporosis who can be treated properly. Without scanning, people with osteoporosis would also suffer from the disease, but they would lack diagnosis for it and can hence not be treated for it. Saying this, the other side of the coin involves rising in-hospital costs due to the costs of DEXA scans. Those scans cost only a fraction of the in-hospital treatment due to a fracture, however. In the model the 2011 costs of a full bone densitometric research according to the NZA (free translated: the Dutch Care Authorities) are used. These costs are € 106.63, regardless the number of researched anatomic sites. A site specific DEXA scan only has to cost € 89.10 and densitometric costs for the whole body amount to € 144.64, but these figures are not included in the model since diagnostics of osteoporosis are mainly brought about by scanning particular bone sites.<sup>78,79</sup>

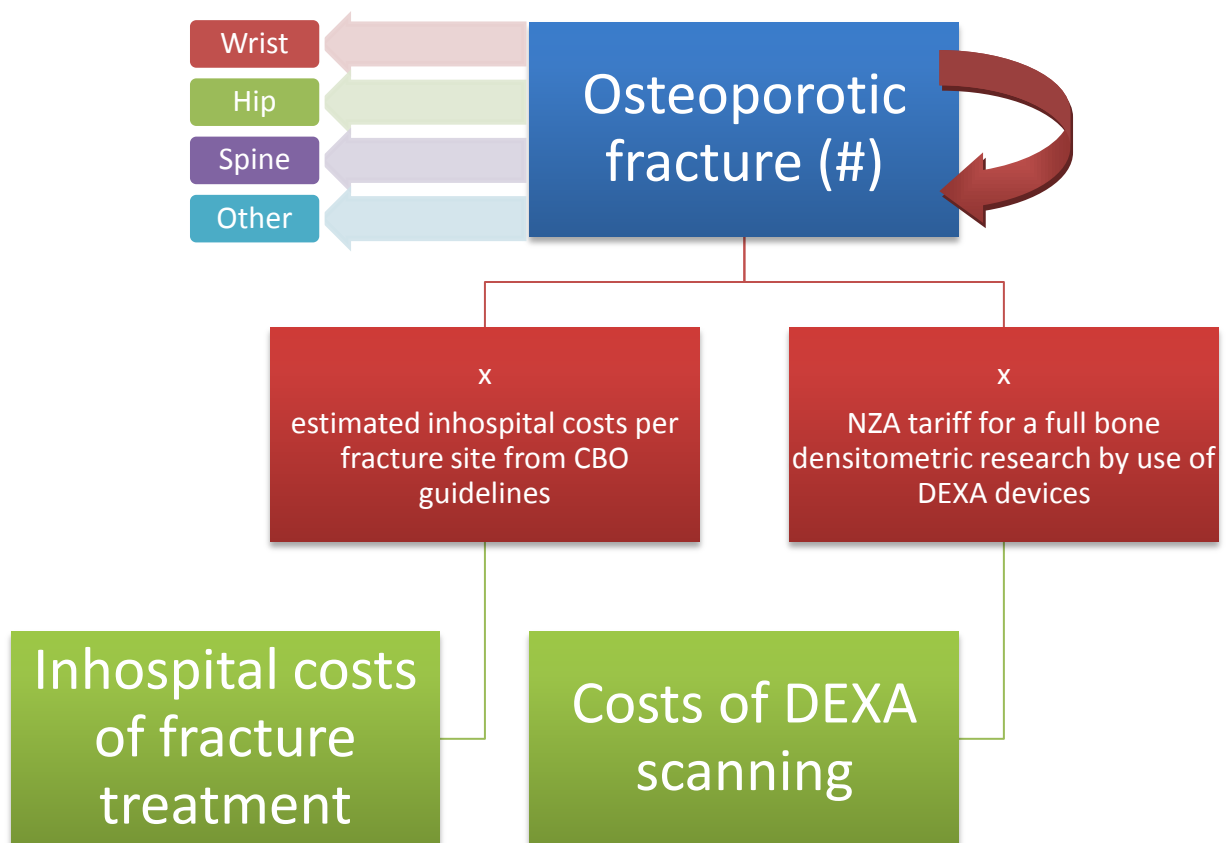


Figure 4, Inhospital costs derived from osteoporotic fracture regarded in the model.

### 3.3.4. Outhospital costs

After being treated for a fracture within a hospital or clinic, very often additional costs have to be made outside of the hospital. For instance, rehabilitation after a hip or spinal fracture, home help because of being limited by the aftermath of fracture, or even nursing home admission because of no longer being able to live independently after a fracture. Anti-osteoporosis medication is an important determinant in explaining additional health care costs of the prevention of osteoporosis, or actually the prevention of subsequent fractures after prior fractures. Figure 5 schematically shows the costly factors of outhospital health care following from osteoporotic fracture. In estimating the outhospital treatment costs after osteoporotic fracture, it has been taken into account that the economic consequences of long-term treatment are rarely observed in Randomized Controlled Trials (RCT's).<sup>2</sup>

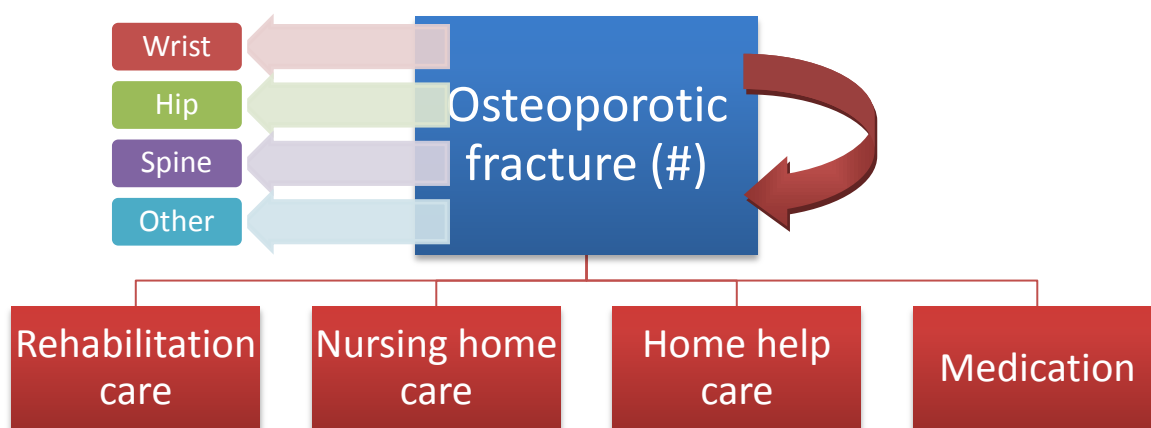


Figure 5, Outhospital costs derived from osteoporotic fracture regarded in the model.

### Rehabilitation

Depending on the severity of the fracture and on the specific fracture site, rehabilitation is often needed after fragility fracture. The average duration of rehabilitation after fracture has been estimated by several authors.<sup>24,76</sup> Because it is likely that the rehabilitation will take longer the older the osteoporosis patients get, the rehabilitation days estimates are increased by 2% per 10 year age category. No scientific articles have been found on this, however. Since it is a model, the percentage is adaptable. Rehabilitation estimates per fracture site which are associated with the results from the model can be found in the table below.

	Wrist	Hip			Spine	Other
		Months in institute				
		0	<3	>3		
Rehabilitation days needed after fracture	4.2	13	21	48	7	5.2

Table 3, mean number of rehabilitation days required after osteoporotic fracture derived from existing literature.<sup>24, 76</sup>

Taking account of the duration, average costs of rehabilitation after fracture have been found to merge into the calculation model. It is the costs of Meerding et al. (2006) which have been used in order to estimate the total yearly costs of rehabilitation due to fractures.<sup>80</sup> Table 4 contains these figures, translated to 2010 Euros by use of the yearly inflation rates of the years between 1999 and 2010.

Type of care	Costs (in 2010 Euros)
Rehabilitation	€ 334 per day
Nursing home care	€ 175 per day
Home help care	€ 42 per hour

Table 4, Outhospital care costs. Calculated by translating estimates from Meerding et al. (2006) to 2010 Euros, using inflation rates from the years in between.<sup>80</sup>

### Home help/care

Once treated for a fracture, patients might still not be able to live like they did before the fracture. Some may need to be helped in their daily activities (i.e. domestic help) and some may need home care in order not to be institutionalized (i.e. wound care). Table 5 shows the input used for the costs calculations with respect to home (help) care. Research on hours home care per week, used for

model input, could not have been verified in the literature. Data on this item could neither have been collected. It turned out to be very hard to obtain straightforward estimates on a mean number of home care hours per week used by fragility fracture patients divided into fracture site categories. The degree of home care usage is very dependent on fracture patient's individual situations. That is probably the reason why inquiry about data at different health care providers and at the Dutch central bureau for health care indications (Centrum Indicatiestelling Zorg) turned out to be futile. Propounded estimated mean hours per week as currently used in the model were nevertheless not believed to be incorrect according to spokespersons of these organizations, aside from considering the findings of Pasco et al. (2005) associated with the hours home care per week in the model.<sup>81,82</sup>

	Hip	Wrist	Spinal	Other
<b>% in need of home (help) care</b>	44.9%	15.8%	23.3%	24.2%
Duration of home care usage (weeks)	52	6	52	26
Hours home care per week	2.0	0.5	1.5	0.5

Table 5, Percentages of patients in need of specific amounts of home help care after a fracture, per fracture site. The hours per week are only estimates which are not empirically linked to the estimates of Pasco et al. (2005) and this input can be changed in the model. Source: Pasco et al. (2005).<sup>82</sup>

### Nursing home care

Osteoporotic fractures can even be the main cause of institutionalization into nursing homes. Where fractures in sites as the wrist or spine are mostly seen as the trigger rather than the cause for the admission in a nursing home, hip fractures are in fact regarded a serious cause.<sup>83</sup> Knowing this, the percentages of patients who are in need of nursing home care after a wrist, spinal or other fracture are set at 0%. In this way overestimating nursing home care costs after osteoporotic fracture is prevented. When fracture patients are institutionalized into a nursing home facility after being treated for their fracture in the hospital, it has empirically been found that 60% of them will be institutionalized for less than three months and 40% of them will have to stay for more than three months.<sup>24</sup> This separation has been made to associate an average length (LOS) of stay in the nursing home with each group. Within these groups, average LOS is different for men and women. Table 6 serves as a summary.

	Hip
<b>% in need of NH care &lt; 3 months</b>	60%
LOS institutionalized for <3 months, men	41.6
LOS institutionalized for <3 months, women	44.0
<b>% in need of NH care &gt; 3 months</b>	40%
LOS institutionalized for >3 months, men	238
LOS institutionalized for >3 months, women	241

Table 6, Average length of stay (LOS) in nursing home facilities of hip fracture patients over gender and institutionalization duration. Wrist, spinal and other fractures are not included since these are regarded to be merely the trigger rather than the cause of nursing home admission. Source: De Laet, 1999.<sup>24</sup>

Literature claims that age is a major determinant in the likelihood of nursing home admission after in-hospital treatment of hip fracture.<sup>24</sup> This finding has also been incorporated into the model, to make sure a fifty year old patient does not have the same chance of being admitted to a nursing home as a 90 year old after being treated in the hospital. The used discharge percentages can be found in Table 7.

Discharge percentage to nursing home after in-hospital treatment for men					
	50-60	60-70	70-80	80-90	90+
Hip fracture	12%	17%	23%	30%	55%
Discharge percentage to nursing home after in-hospital treatment for women					
	50-60	60-70	70-80	80-90	90+
Hip fracture	11%	19%	26%	32%	55%

Table 7, Discharge percentage to nursing home over gender and age category. Source: De Laet, 1999.<sup>24</sup>

### Medication

Medication costs for osteoporosis patients calculated in the model depend on the three most important determinants of the model:

1. the percentage of patients which gets scanned for osteoporosis after a fracture;
2. the percentage of osteoporosis patients that actually gets medication;
3. the percentage of medication users that fully adheres to the medication prescriptions.

Since these factors are regarded very important to the societal costs of osteoporosis in the Netherlands, the calculation model contains buttons which make it possible to change these factors to see what impact they have on the total (medication) costs on osteoporosis.

Not every estimated osteoporosis patient will be administered anti-osteoporosis medication however. Only the osteoporosis patients who are scanned for their bone density after a fracture, by for example dual X-ray absorptiometry devices, are known to be osteoporosis patients and can be treated as such. Figure 6 schematically shows who is eligible for being administered anti-osteoporosis medication, according to the model.

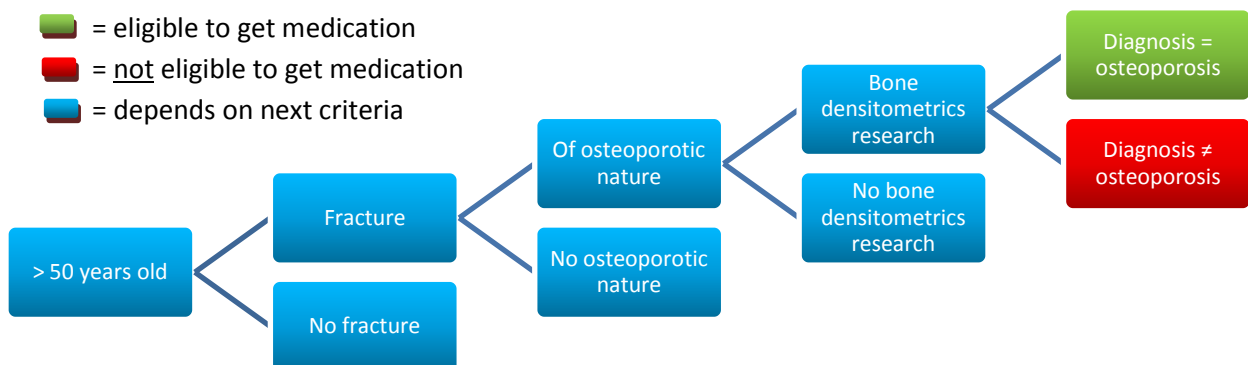


Figure 6, Schematic binary tree on eligibility to get medication after osteoporotic fracture where medication cost estimates from the calculation model are based on.

Once scanned, once found to be an osteoporosis patient and once actually getting anti-osteoporosis medication (regardless of adhering to it, since non-adherence is at least as costly as adhering), the medication costs start counting. The model contains different kinds of medication, associated with different costs per user per year. In the model, only one kind of medication can be used at the time. Total yearly medication costs to society are computed by the total number of *eligible* osteoporosis patients times the yearly costs per user of a certain kind of anti-osteoporosis drug. Table 8 contains the yearly costs per user per drug in The Netherlands, derived from the GIP database of the Dutch

College for Health insurance (CvZ). Only the drugs of which the relative effectivity could have been found are incorporated in the model. These are included in blue.

Osteoporosis medication (Dutch register name, including CvZ* code and brand name)	2009			2010			2011		
	# Users	Costs (€)	Costs per user	# Users	Costs (€)	Costs per user	# Users	Costs (€)	Costs per user
M05BA01 Etidroninezuur									
M05BA02 Clodroninezuur (Ostac *)	2.712	€ 3.669.900	€ 1.353	2.406	€ 3.316.400	€ 1.378	2.406	€ 2.922.700	€ 1.215
M05BA04 Alendroninezuur (Fosamax *)	141.610	€ 7.725.200	€ 55	144.060	€ 7.582.200	€ 53	144.580	€ 7.276.700	€ 50
M05BA05 Tiludroninezuur (Skelid *)	16	€ 13.727	€ 858	13	€ 10.134	€ 780	-	-	-
M05BA06 Ibandroninezuur (Bonviva *)	11.434	€ 3.885.200	€ 340	11.804	€ 3.897.800	€ 330	11.868	€ 3.848.700	€ 324
M05BA07 Risedroninezuur (Actonel *)	69.883	€ 21.098.100	€ 302	70.786	€ 20.670.000	€ 292	68.149	€ 10.176.500	€ 149
M05BA08 Zoledroninezuur (Zometa *)	1.367	€ 1.845.300	€ 1.350	2.447	€ 2.770.200	€ 1.132	3.216	€ 3.573.500	€ 1.111
Total M05BA (Bisphosphonates)	227.022	€ 38.237.427	€ 168	231.516	€ 38.246.734	€ 165	230.219	€ 27.798.100	€ 121
M05BB01 Etidroninezuur met calcium sequentiepreparaten (Didrokit *)	5.445	€ 1.584.200	€ 291	4.346	€ 1.243.500	€ 286	3.285	€ 964.120	€ 293
M05BB02 Risedroninezuur met calcium sequentiepreparaten (Actokit *)	12.073	€ 5.242.100	€ 434	11.919	€ 5.118.900	€ 429	10.616	€ 4.682.900	€ 441
M05BB03 Alendroninezuur met colecalciferol (Fosavance *)	23.866	€ 6.795.200	€ 285	26.048	€ 6.885.500	€ 264	26.276	€ 6.578.500	€ 250
M05BB05 Alendroninezuur met calcium en colecalciferol seq. prep. (Bonendro *)	-	-	-	1.245	€ 160.440	€ 129	2.089	€ 370.710	€ 177
Total M05BB (Bisphosphonate combination preparations)	41.384	€ 13.621.500	€ 329	43.558	€ 13.408.340	€ 308	42.266	€ 12.596.230	€ 298
M05BX03 Strontiumranelaat (Protelos *)	5.161	€ 1.320.100	€ 256	4.789	€ 1.357.000	€ 283	4.071	€ 1.228.900	€ 302
M05BX04 Denosumab (Prolia *)	-	-	-	-	-	-	3.577	€ 1.523.000	€ 426
Total M05BX (Other bone mineral density influencing medication)	5.161	€ 1.320.100	€ 256	4.789	€ 1.357.000	€ 283	7.648	€ 2.751.900	€ 360
H05AA02 Teriparatide (Forsteo *)	1.111	€ 4.045.200	€ 3.641	1.267	€ 5.142.400	€ 4.059	1.443	€ 6.082.300	€ 4.215
H05AA03 Parathyroidhormoon (Preolact *)	295	€ 1.189.200	€ 4.031	257	€ 976.690	€ 3.800	160	€ 539.530	€ 3.372
Total H05AA (Thyroid gland hormone)	1.406	€ 5.234.400	€ 3.723	1.524	€ 6.119.090	€ 4.015	1.603	€ 6.621.830	€ 4.131
G03XC01 Raloxifeen (Evista *)	2.717	€ 838.440	€ 309	2.462	€ 742.060	€ 301	2.154	€ 667.580	€ 310
G03XC02 Bazedoxifen	-	-	-	1	€ 50	€ 50	-	-	-
Total G03XC (Selective oestrogen receptor modulator)	2.717	€ 838.440	€ 309	2.463	€ 742.110	€ 301	2.154	€ 667.580	€ 310
Total osteoporosis medication according to GIP** database of CvZ	277.690	€ 59.251.867	€ 213	283.850	€ 59.873.274	€ 211	283.890	€ 50.435.640	€ 178



= medication is included in the calculation model

\*) CvZ = The Dutch college for health insurances ("College voor Zorgverzekeringen")

\*\*) GIP = The Dutch Pharmaceuticals and health appliances information project ("Genees- en hulpmiddelen Informatie Project")

Table 8, Osteoporosis medication use and costs in The Netherlands from 2009 until 2011. Source: GIP database (2012).<sup>84</sup>

According to the Osteoporosis patient association, it is correct that mean costs per anti-osteoporosis medication user per year have dropped by about 15% between 2010 and 2011. This could be explained by the influence of health care purchasing strategies of health insurers that affect medication prices. Also the influence of pharmaceutical patent expiring of medication which enables possibilities for generic pharmaceutical companies to produce this medication and sell it at lower prices compared to innovative pharmaceutical companies can play a role in this.

### 3.3.5. Prevention of subsequent fractures

This paragraph reveals the simple trick of the calculation model. In the model an estimate is made of the number of osteoporotic fractures that could have been prevented if (a certain share of) eligible osteoporosis patients would use certain anti-osteoporosis medication. Remember that the model calculates both "first fractures" and "subsequent fractures" to come to a total osteoporotic fracture incidence in a certain year. What the model does, with respect to medication, is that instead of adapting the absolute risk of fracture, it subtracts the preventable number of fractures from the total osteoporotic fracture estimate. The number of fractures that can be prevented depends on the factors scanning, medication admission, medication adherence and medication benefits. Altogether, the calculated number of eligible osteoporosis patients that gets medication and adheres to it, is multiplied by the relative risk reduction associated with the applicable medication. Latter is calculated by 1 minus the mean relative effect (of certain anti-osteoporosis medication from 2011

CBO osteoporosis guidelines) found in Table 9.<sup>19</sup> The outcome of the preventable osteoporotic fractures should be regarded an estimate, since the model input is also based on estimates.

### **Two models**

Two different models have been designed to provide estimates on absolute costs and savings associated with increasing the modeled availability of screening and treating osteoporosis by a certain percentage. The first model, the mainly discussed model in this thesis, provides estimates associated with preventing subsequent fragility fracture followed from first fracture by diagnosing and treating osteoporosis after first fracture. The second model should be regarded an optimal, unreal setting where both subsequent and first fracture can be prevented by having people at very high risk of fragility fracture administered anti-osteoporosis medication. Latter model is considered to be unreal because medication costs are based on people who are assessed to be at very high fracture risk but who can be helped by anti-osteoporosis medication. Hence those people's ten year fracture risk and their subsequent fracture risk will be reduced, while they would otherwise be certain of demonstrating with fragility fracture. Medication costs are therefore underestimated while the benefits are likely to be overestimated. Still I decided to consider this second model in the thesis, because fracture risk assessment tools are becoming of increasing importance. Hence, the true magnitude of the relation between preventing fragility fracture and mere repairing of fragility fracture will be somewhere in between the outcomes of model 1 and model 2.

As you can see in Figure 7 (model 1: schematic description of medication benefits effecting the subsequent fracture risk only), and Figure 8 (model 2: schematic description of medication benefits effecting the 10 year fracture risk and subsequent fracture risk), the share of patients that does not adhere to its medication as how it is prescribed and as long as it is prescribed has a negative effect on the number of preventable osteoporotic fractures. This factor has been built in into the model by an adaptable cell which contains the percentage of non-adhering osteoporosis patients that gets medication. The output has been estimated with non-adherence at 50%, according to Seeman et al. (2007) and Siris et al. (2009).<sup>85,86</sup> However, other findings on adherence are present among scientific literature on osteoporosis as well, like those of Netelenbos et al. (2010) for example, where the percentage of 50% non-adherence is regarded to be underestimated (they found a persistence percentage of only 43 among bisphosphonate users).<sup>17</sup>

According to both methods shown in Figure 7 and Figure 8, this method is designed to estimate the magnitude of the cost relation between the increase of screening and treating of osteoporosis after first fragility fracture and the decrease of subsequent fragility fracture. Section 4 (Results) will show an indication of whether this prevention will actually save or increase total costs on osteoporotic fractures to the Dutch society.

# Model 1: Prevention of subsequent fractures

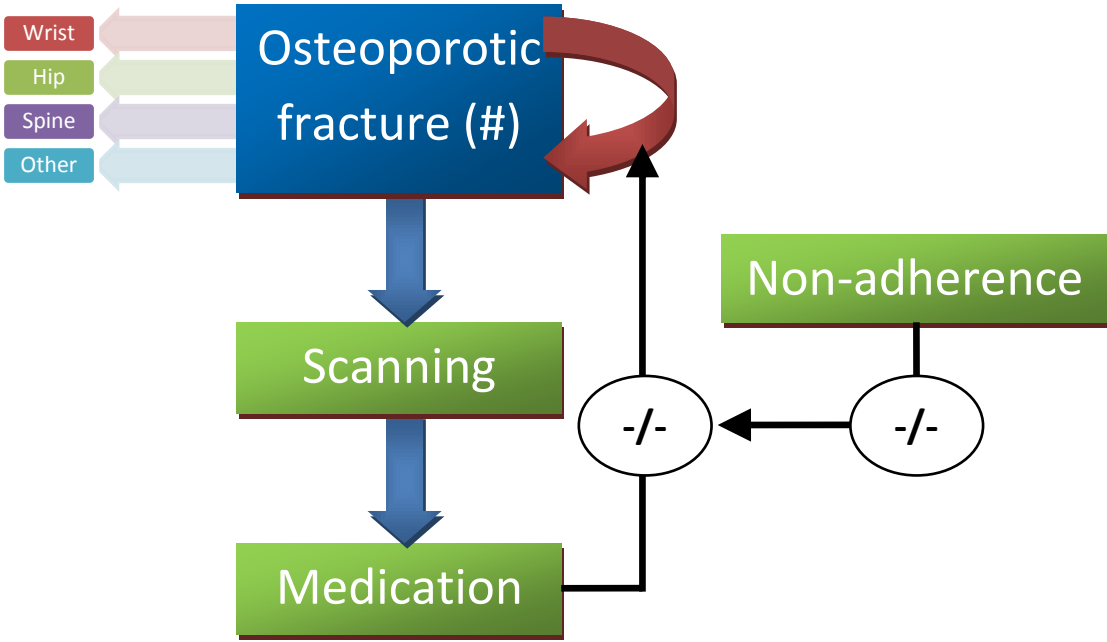


Figure 7, Schematic overview of the relation between medication and the number of osteoporotic fractures per year, if medication is considered to decrease the risk of subsequent fractures after a prior fracture. In this set up, medication is only used by every osteoporosis patient who has had a fracture, has been scanned for osteoporosis and has been prescribed anti-osteoporosis medication.



## Model 2: Prevention of first and subsequent fractures

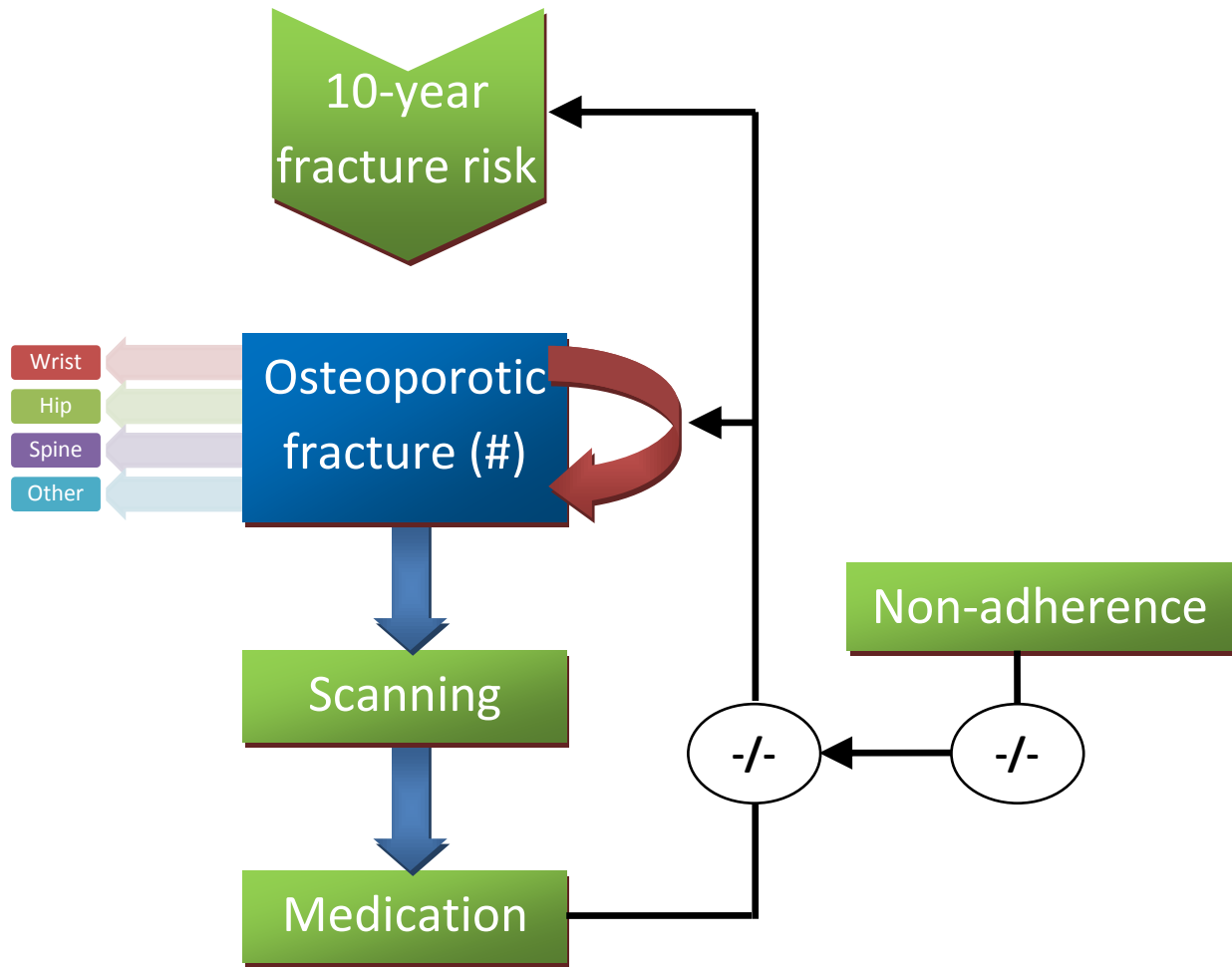


Figure 8, Schematic overview of the relation between medication and the number of osteoporotic fractures per year, if medication is considered to decrease the 10 year risk of osteoporosis patients. In this set up, medication is only used by every osteoporosis patient who has had a fracture, has been scanned for osteoporosis and has been prescribed anti-osteoporosis medication.

Medication	Follow-up	Spinal fractures		Non-spinal fractures		Hip fractures	
		Relative effect	Quality of evidence	Relative effect	Quality of evidence	Relative effect	Quality of evidence
Alendronate	1-4 years	0.55 (0.43 – 0.69)	High	0.77 (0.64 - 0.92)	High	0.47 (0.26 – 0.85)	High
Risedronate	2-3 years	0.63 (0.51 – 0.77)	High	0.80 (0.72 – 0.90)	High	0.74 (0.59 – 0.94)	High
Etidronate	2-4 years	0.59 (0.36 - 0.96)	High	1.07 (0.72 – 1.06)	Moderate	1.20 (0.37 – 3.88)	Moderate
Zoledronic acid	3 years	0.30 (0.24 – 0.38)	High	0.75 (0.64 – 0.87)	High	0.59 (0.42 – 0.83)	High
Ibandronate	3 years	0.50 (0.34 – 0.74)	High	N/A (Indeterminate)	N/A	N/A (Indeterminate)	N/A
Raloxifene	3 years	0.60 (0.50 – 0.70)	High	0.91 (0.79 – 1.06)	Moderate	N/A (Indeterminate)	N/A
Strontium ranelate	3 years	0.63 (0.56 – 0.71)	High	0.86 (0.75 – 0.98)	High	N/A (Indeterminate)	N/A
Teriparatide *	1.5 years	0.36 (0.28 – 0.47)	High	0.62 (0.48 – 0.82)	High	N/A (Indeterminate)	N/A
PTH *	1.5 years	0.42 (0.24 – 0.72)	High	N/A (Indeterminate)	N/A	N/A (Indeterminate)	N/A
Denosumab	3 years	0.32 (0.26 – 0.41)	High	0.80 (0.67 – 0.95)	High	0.60 (0.37 – 0.96)	High

Table 9, Overview of effects of different anti-osteoporosis medication on the prevention of fractures in the primary analyses of RCTs with fracture prevention as outcome. Based on CBO's GRADE analysis on post-menopausal women with a high fracture risk. No separate meta-analyses about anti-osteoporosis effect are known for the medication with an asterisk (\*). Where quality of evidence is high, the background has been colored green, orange for moderate and red for not applicable (N/A). Source: CBO's osteoporosis guideline (2011).<sup>19</sup>

### 3.3.6. Deterministic sensitivity analysis

To assess the robustness of the model's estimates on a cost or savings factor between costs on prevention of osteoporosis (subsequent osteoporotic fracture) and the costs of treatment of osteoporotic fracture, a sensitivity analysis has been performed by separately increasing and decreasing the model determinants by 25%. Modeled parameters are analyzed for their sensitivity by holding the other parameters at their original values. This should provide insight in the separate effects of the determinants on the model outcomes. Next to model parameters like in-hospital costs of fracture treatment and anti-osteoporosis medication costs per user per year, the sensitivity analysis also includes model parameters which are less obvious with respect to the model outcomes. It has been regarded to be common sense that when costs of osteoporotic fracture *treatment* rise and/or the costs of *preventing* the latter costs fall, the calculation model will tend to show results in favor of fragility fracture prevention instead of having fragility fractures run their course due to osteoporosis. Other model parameters, like non-adherence, fracture risk and BMD distribution over population, are less obvious to the model outcomes however. Therefore, analyzing changes in these parameters probably are more interesting compared to only regarding cost factors. Hence, these parameters are also included in the sensitivity analysis, to compare the relative importance of all model parameters.

## 4. Results

In this section, the outcomes of model 1, where subsequent fractures are prevented by screening for and treating of osteoporosis patients after first fracture (like described in section 3.3.5), will be presented. The outcomes of model 2 will not extensively be regarded since these outcomes cannot be substantiated by real-world founded arguments. To come to *difference-in-difference* estimates, scenario 2 (10% additional scanning compared to scenario 1) will be compared to the base case scenario (scenario 1). Everything else but the percentage of 50+ people that will be scanned for osteoporosis after a fracture will be held equal, so that the difference between the scenario's can only be attributable to the usage of DEXA scanning (*ceteris paribus*). Table 10 shows an overview of the scenario's determinants, being the model input.

		Base case scenario (scenario 1)	New scenario (scenario 2)
% scanned for osteoporosis after fracture	50+ men	10%	20%
	50+ women	10%	20%
% decrease in mortality per decade	50+ men	2%	2%
	50+ women	2%	2%
% that gets medication after diagnosis of osteoporosis	50+ men	100%	100%
	50+ women	100%	100%
% decrease in medication costs per 10 years	Men and women	0%	0%
% non adherence	Men and women	50%	50%
# years that patients are prescribed medication	Men and women	5 years	5 years
# years that are taken into account in determining in-hospital costs	Men and women	3 years	3 years
# years that are taken into account in determining out-hospital costs	Men and women	Lifetime	Lifetime

Table 10, Overview of differences in model determinants per scenario.

### 4.1. Osteoporotic prevalence and incidence

By using the estimated BMD distribution by Schuit et al. (2004) over the Dutch population over the coming decades, the model estimates that the prevalence of osteoporosis by the WHO criteria will be over 1.3 million by the year 2020.<sup>71</sup> As from then, it is estimated to grow tremendously. By the year 2050 the osteoporosis prevalence among the Dutch is estimated to have reached 1.7 million [see Figure 9]. To put this into perspective, Figure 10 has been included to provide with estimates of all health states concerning BMD among 50+ people in the Netherlands. Both the share of 50+ people as well as the share of osteoporosis patients is expected to increase. From the osteoporosis health care burden perspective, especially the share of osteoporosis patients is worrying. This share is expected to grow from 5.3% in 1990 to 9.8% in 2050, see Table 11.

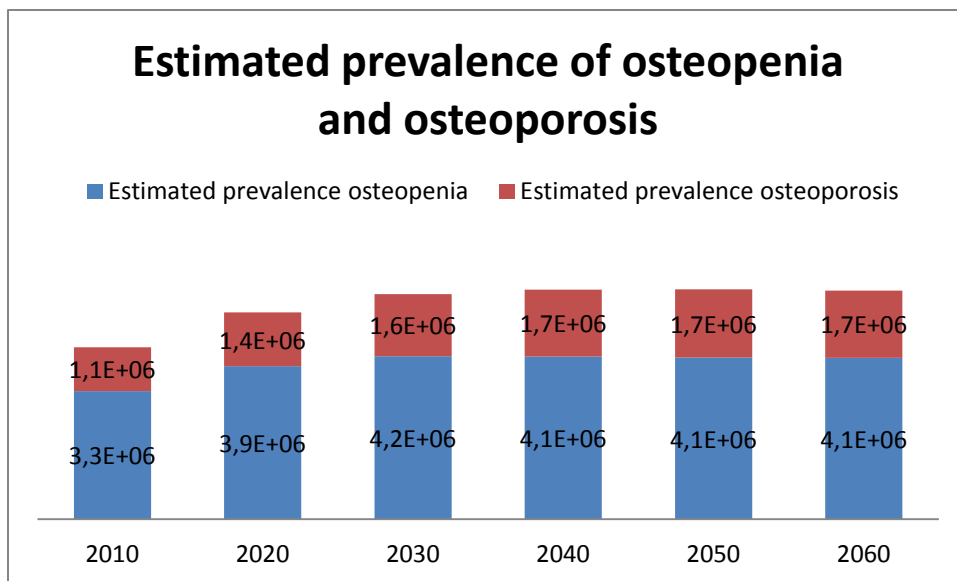


Figure 9, Estimated prevalence osteopenia and osteoporosis in The Netherlands over decades. Based on the Dutch demography.

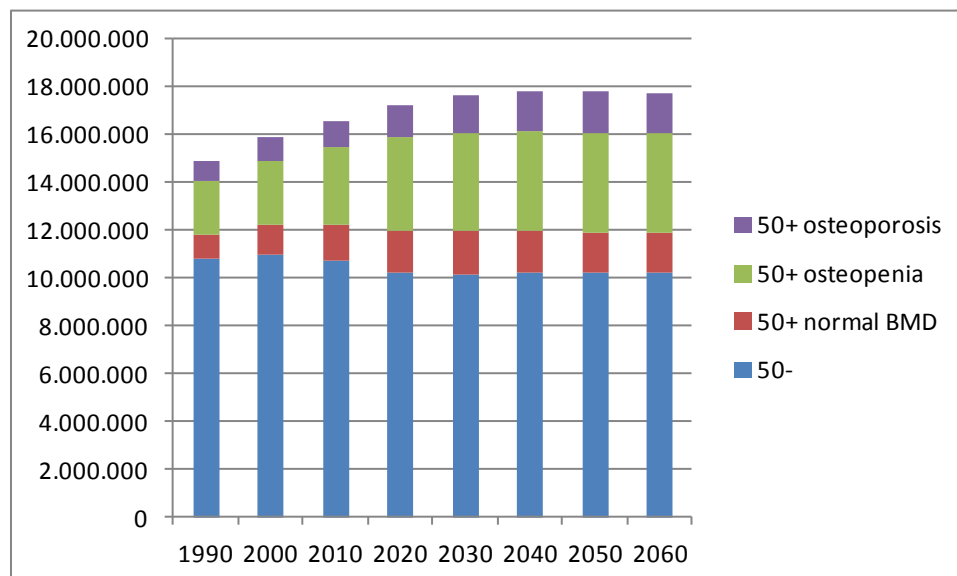


Figure 10, (Predicted) development of osteoporotic prevalence (in numbers of people) among the Dutch demography between 1990 and 2060.

Prevalence (as a % of total population)	1990	2000	2010	2020	2030	2040	2050	2060
Osteoporosis	5,3%	5,9%	6,7%	7,9%	9,0%	9,6%	9,8%	9,6%
Osteopenia	15,2%	17,1%	19,7%	22,6%	23,5%	23,2%	23,2%	23,2%

Table 11, (Predicted) prevalence of 50+ people with osteoporosis and osteopenia as a percentage of the total Dutch population throughout past and coming decades.

The prevalence of osteoporotic fracture is estimated to be over 72,000 in 2010 and to be almost 118,000 by the year of 2050; an increase of over 60%. In the years in between, the number of osteoporotic fracture shows a concave relationship over time, meaning that as from 2010 the number will highly increase compared to the rate of increase reaching the year 2050. After 2050 the number is believed to decrease, since the number of 70+ people is likely to decrease from then. In

the estimated number of osteoporotic fractures, wrist fracture and hip fracture take the most important roles [see Figure 11].

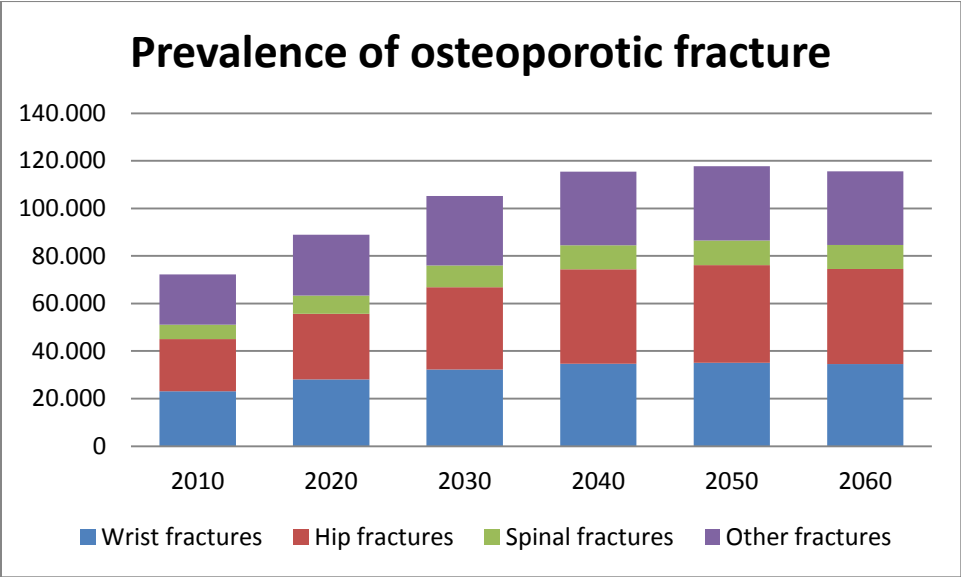


Figure 11, Estimated prevalence of osteoporotic fracture throughout future decades. These estimates only include fractures: in people >50 years old, within people with osteopenia or osteoporosis and with an osteoporotic nature.

By 2020, both wrist and hip fractures are estimated to amount (almost) up to 28,000 in numbers. According to the model estimates, hip fractures are likely to gain on the wrist fractures. By 2040 the first will almost count 40,000 and the latter will almost reach 35,000. Within the hip fracture estimates, the largest part can be attributed to the female gender. For example, females attribute for 87% to the total estimated number of osteoporotic hip fractures in 2020 [see Figure 12].

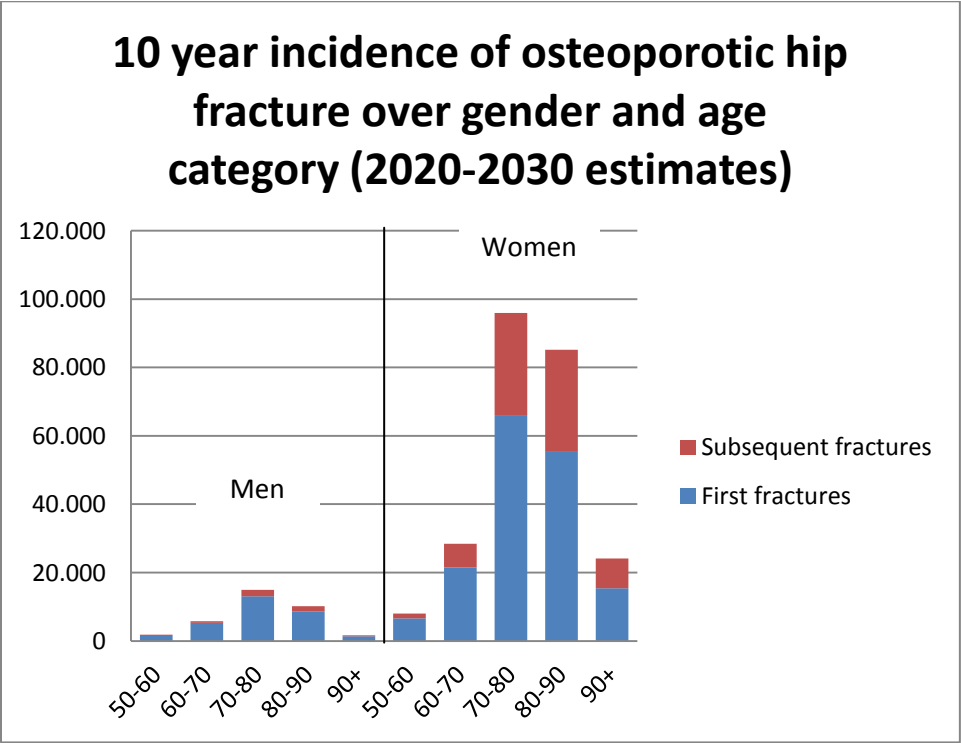


Figure 12, Incidence of osteoporotic hip fracture in 2020, divided into first and subsequent fracture, over gender and age category.

As you can see, the age group between 70 and 90 years old accounts for the most osteoporotic fractures. This is the case both in women and in men, but women are far more likely to experience a fragility fracture [see Figure 13].

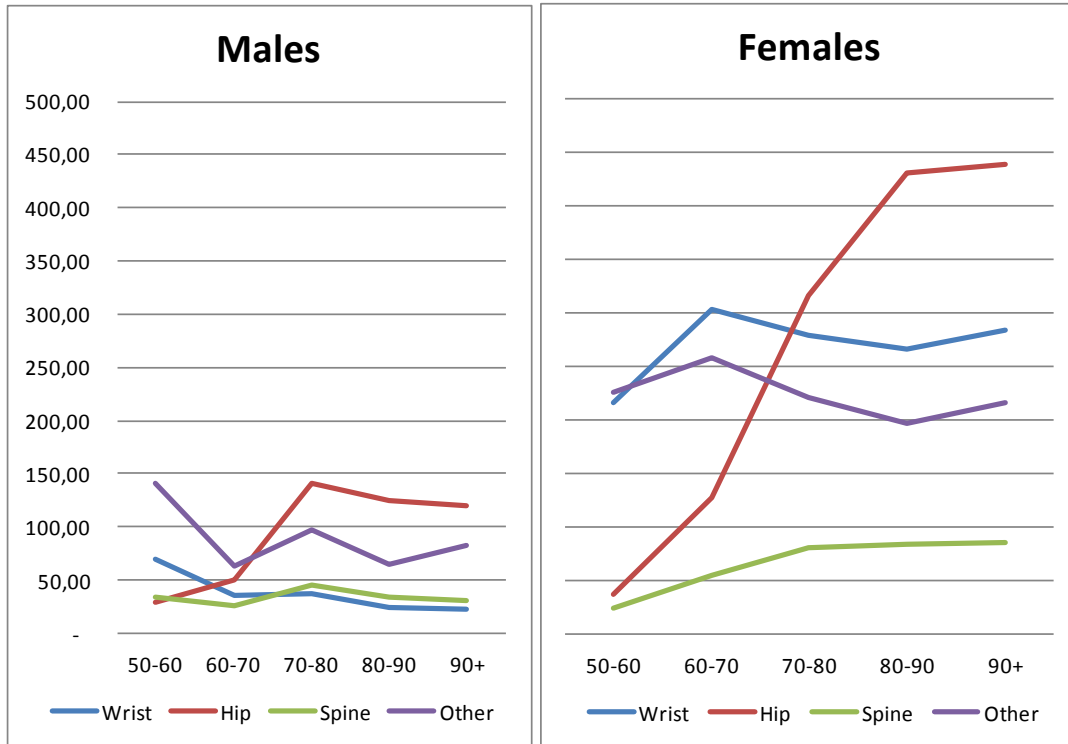


Figure 13, Incidence of osteoporotic fracture per 10,000 patients per year. Estimates for the year 2010. This has been derived from 10 year fracture risk estimates from Van Staa et al. (2001) in combination with estimates of Melton et al. (1997) on the osteoporotic nature of fractures and was used as input for the calculation model.

According to the calculations of the model, this relation in number of fractures experienced by men and women respectively will manifest in a 90% proportion assigned to women and only 10% to men. Together, men and women account for an estimated approximately 200 osteoporotic fractures in the wrist, in the hip and in other sites per 10,000 osteoporosis patients in the year 2010. Spinal fractures stop at only about 55 fractures a year in 2010. Those numbers, which work as the calculation input for the model estimates, stay approximately equal over the decades, except for hip fractures which show a slight increase between the years 2020 and 2040 [see Figure 14]. This can be explained by not changing the 10 year fracture risk by Van Staa et al. (2001) over the years.<sup>74</sup>

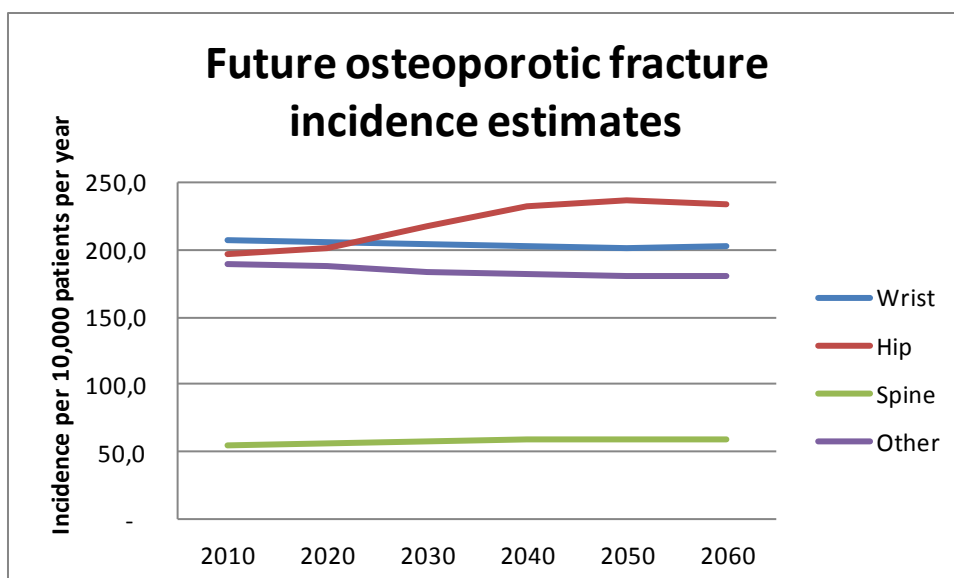


Figure 14, Estimated incidence of osteoporotic fracture per 10,000 osteoporosis patients per year. The model is hence based on osteoporotic incidence staying approximately equal over the years, except for the incidence of hip fracture which is estimated to slightly increase from 2020 to 2040.

#### 4.2. Costs associated with fragility fracture

The calculation model makes estimates on mean costs per fracture site of repair and rehabilitation of osteoporotic fracture in the in- and outhospital scene. These entail approximately € 3,400 per wrist fracture, € 24,400 per hip fracture, € 4,800 per spinal fracture and € 2,700 for other fractures [see Table 12].

Costs of fracture treatment, per site	2010	2020	2030	2040	2050	2060
Wrist	€ 3.416	€ 3.418	€ 3.422	€ 3.427	€ 3.429	€ 3.429
Hip	€ 24.406	€ 26.019	€ 26.238	€ 26.685	€ 27.010	€ 27.264
Spine	€ 4.812	€ 4.722	€ 4.738	€ 4.768	€ 4.777	€ 4.771
Other	€ 2.724	€ 2.726	€ 2.733	€ 2.739	€ 2.742	€ 2.742
Mean weighted costs per fracture	€ 9.688	€ 10.339	€ 10.841	€ 11.357	€ 11.598	€ 11.595

Table 12, Costs of fracture treatment if no preventive interventions are implemented; repair and rehabilitation of fracture only, in- and outhospital costs.

Based on these estimates the total financial burden of osteoporosis and its consequences have been estimated to approach € 700 million in 2010 and to exponentially increase between 2010 and 2040 [see Figure 15]. This increase can only be attributed to ageing Dutch population, since this is the single most important determinant of the calculation model. The estimate does not include costs on anti-osteoporosis medication made by the osteoporosis population that already takes this medication. Therefore the total burden of osteoporosis would be even greater.

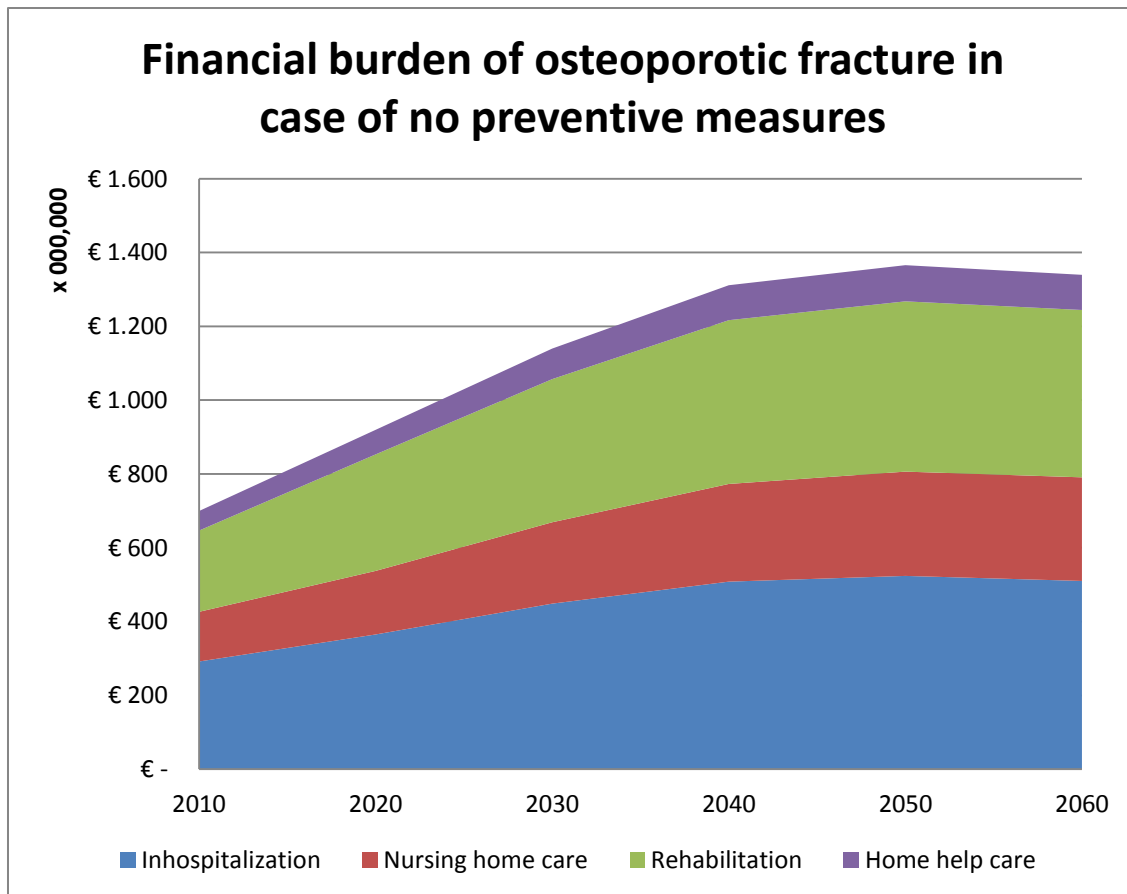


Figure 15, Estimated financial burden of osteoporosis and its consequences, in case of only treating fracture instead of treating osteoporosis.

A rough estimate of the total osteoporotic financial burden *including anti-osteoporosis medication costs of current users* would take the yearly burden to be more closer to € 800 million per year and still rising rapidly. The costs to anti-osteoporosis medication has shown to stay about equal over the years.<sup>84</sup> They will, however, increase if osteoporosis prevention and treatment will get more attention. If the prescribing and persistence rate will not change, and hence approximately € 100 million can be added to the yearly osteoporosis costs to society, the total financial burden of osteoporosis associated costs is estimated to account for € 1.4 billion of the health care budget by the year of 2040. Considering that this estimate is based on a health care perspective, according to Zethraeus et al. (2006) roughly 10% of total health care costs can be added to estimate the total costs to society, hence including indirect costs like production loss as well.<sup>35</sup> This would mean that the calculation spreadsheets used for writing this thesis estimate the current societal burden of osteoporosis to approximate roughly € 880 million per year, rising to roughly € 1.55 billion per year around 2040. Which part of this can be prevented by treating osteoporosis after first fragility fracture will be presented in section 4.2.3.

#### 4.2.1. Inhospital treatment

Solely based on demographic prognoses, the incremental in-hospital costs following from osteoporotic fracture will tremendously increase until the year 2050. Compared to the estimates of 2005, in the baseline scenario the costs in 2050 would have almost doubled if the trend sets on without preventive measures. In-hospital costs alone are estimated to contribute to a financial burden of about € 290 million in 2010 and are expected to rise to € 365 million by 2020. Of these



costs, some 75% is due to in-hospital treatment of hip fractures. This share is likely to grow to 79% in 2050, according to the model estimates [see Figure 16]. In-hospital costs are estimated to contribute to about 40% of total treatment costs associated with osteoporosis [see Table 13].

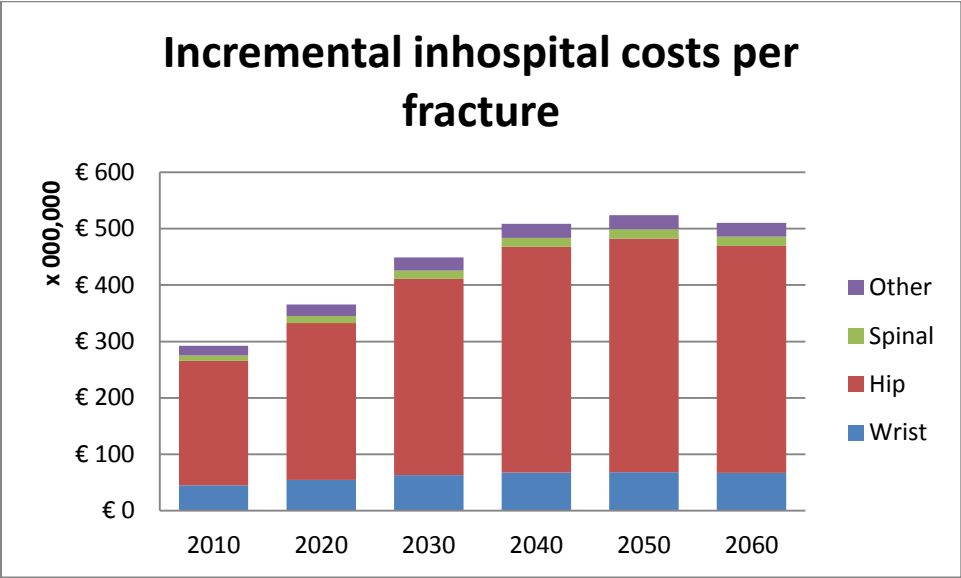


Figure 16, Share of fracture kind of the total incremental in-hospital costs over the coming decades.

Fragility fracture related health care costs (%)	2010	2020	2030	2040	2050	2060
In-hospitalization costs of osteoporotic fractures	41,7%	39,7%	39,4%	38,8%	38,4%	38,1%
Costs of institutionalization in nursing homes	19,2%	18,7%	19,3%	20,2%	20,7%	21,0%
Rehabilitation costs due to osteoporotic fractures	31,5%	34,3%	34,0%	33,8%	33,8%	33,8%
Costs of home (help) care from osteoporosis	7,6%	7,2%	7,3%	7,2%	7,2%	7,1%

Table 13, Estimated fragility fracture related health care costs per cost driver over the coming decades.

Looking at in-hospital treatment costs per fracture site, it would make sense to give priority to possible preventable subsequent fractures of a certain fracture site. After all, it might be clear that a hip(-like) fracture is more costly than any other random fracture. Based on research on the risk of fracture following from prior fracture by Klotzbuecher et al. (2000) and Johnell et al. (2003), the calculation model estimates provide insight in the likelihood of occurrence of subsequent hip fracture due to prior fracture.<sup>11,41</sup> It turns out that approximately half of the subsequent hip fracture estimates originates from prior hip fracture (49% in 2020).

**4.2.2. Outhospital treatment**

Regarding that a lifetime perspective has been taken for outhospital care, since it has been assumed that all rehabilitation will be executed in an outhospital setting and because only 50+ men and women are regarded in the model, outhospital costs take account of the lion’s share of the total costs associated with osteoporotic fracture. Together they form 58% of the costs attributable to osteoporotic fracture. This estimated percentage stays about the same over the next decades. For 2010, it has been estimated that institutionalization into nursing homes and rehabilitation clinics together with the home help care costs for people returning home after a fracture are believed to account for over € 400 million in 2010 and for over € 550 million in 2020. Without intervening measures, the model estimates that by the year 2050, more than € 800 million will have to be spend on outpatient care following from osteoporotic fracture.

Like the in-hospital costs, the same problem child is applicable to out-hospital care costs. The model estimates that 60% of costs to rehabilitation care can be attributed to osteoporotic hip fractures. This number will grow to more than 70% over the coming decades. The share of incremental health care costs of hip fractures to nursing home care is even more striking. Since other fractures than hip fractures have been regarded to be just a trigger to institutionalization rather than the actual direct cause of admission, hip fractures are the only cost estimates in this section. Still the model has calculated an incremental head of expenditure of over € 130 million in 2010 and € 170 million by the year of 2020. For home help costs associated with care after osteoporotic fracture, estimated to only be good for approximately 7% of total in- and out-hospital costs throughout the coming decades, also counts that hip fractures consume the most financial resources. Over the years, these fractures are estimated to contribute to home help care costs for a constant 85%, while wrist fractures only account for 1% for example. Altogether home help care costs are estimated to have amounted more than € 50 million in 2010 and are expected to almost amount up to € 100 million by 2050.

#### **4.2.3. Costs and savings from preventing interventions**

This section is the key to the estimation of the savings factor between preventing osteoporotic fracture by treating osteoporosis on the one hand and just treating fractures which are the direct consequence of osteoporosis on the other. The admission of anti-osteoporosis medication after a first fracture is investigated and believed to have a significant effect on the relative risk of (subsequent) fracture.<sup>10,27,30,53,73,87,88</sup> The effect differs over medication types. In the category of bone mineral density increasing medicine, the effect ranges from a relative risk of fracture of only 0.32 compared to no medication by using Denosumab (in preventing spinal fractures), to a mean negligible or undefined effect of Etidronate (in the prevention of hip fractures and other non-spinal fractures).<sup>19</sup>

All anti-osteoporosis medication described in the 2011 CBO guidelines have been incorporated in the calculation model separately. However, because of uncertainty concerning the relative fracture risk decrease indebted to the medication, both effects and costs have been weighted over the number of medication users so that one mean weighted medicine has been created which reflects real practice current Dutch society's medication use in the year 2011.<sup>84</sup> With these integrated costs and benefits the model has estimated that about 450 osteoporotic fractures (2020 estimate) can be prevented per year per additional 10% scanning of 50+ people for osteoporosis after first fracture. This number increases over the years, along with the demography.

Having scanned an extra 10% of 50+ people with first fracture is estimated to reveal more than 5,300 new osteoporosis patients who were otherwise not known to be suffering from the disease. If instead of only 10%, the pool of fracture patients that gets DEXA scanned will increase to 30%, almost 11,000 new osteoporosis patients are estimated to be found. Apart from being treated, only being diagnosed properly might be worth a lot to some people. Especially when the fact has been taken into account that a full bone densitometrics research by the use of DEXA devices is regarded a non-aggravating intervention that only costs a little more than € 100 per scan.<sup>78,79</sup> Altogether, an additional 10% scanning percentage would imply about 5,300 newly identified osteoporosis cases by about 10,500 additional DEXA scans which account for approximately 1.1 million Euros on incremental costs see [Table 14].

Full bone densitometrics research	2010	2020	2030	2040	2050	2060
DEXA scans performed due to wrist fracture	2.358	2.834	3.167	3.306	3.323	3.288
DEXA scans performed due to hip fracture	1.932	2.432	3.004	3.390	3.479	3.380
DEXA scans performed due to spinal fracture	558	689	807	871	879	863
DEXA scans performed due to other fracture	3.844	4.599	5.006	5.134	5.167	5.129
<i>Total DEXA scans performed due to fractures</i>	<i>8.691</i>	<i>10.554</i>	<i>11.985</i>	<i>12.702</i>	<i>12.850</i>	<i>12.660</i>
DEXA scanning costs from wrist fracture	€ 251.397	€ 302.215	€ 337.740	€ 352.499	€ 354.356	€ 350.591
DEXA scanning costs from hip fracture	€ 206.041	€ 259.370	€ 320.287	€ 361.525	€ 371.013	€ 360.423
DEXA scanning costs from spinal fracture	€ 59.464	€ 73.427	€ 86.099	€ 92.909	€ 93.767	€ 92.063
DEXA scanning costs from other fracture	€ 409.836	€ 490.347	€ 533.791	€ 547.433	€ 551.008	€ 546.869
<i>Total DEXA scanning costs from all fractures</i>	<i>€ 926.738</i>	<i>€ 1.125.359</i>	<i>€ 1.277.917</i>	<i>€ 1.354.366</i>	<i>€ 1.370.145</i>	<i>€ 1.349.946</i>
Diagnosis after wrist fracture through scan	1.207	1.471	1.708	1.846	1.873	1.841
Diagnosis after hip fracture through scan	1.136	1.433	1.809	2.092	2.181	2.113
Diagnosis after spinal fracture through scan	291	363	442	493	504	492
Diagnosis after other fracture through scan	1.700	2.071	2.372	2.530	2.568	2.531
<i>Total osteoporosis cases identified</i>	<i>4.334</i>	<i>5.339</i>	<i>6.331</i>	<i>6.961</i>	<i>7.126</i>	<i>6.977</i>

**Table 14, Incremental costs and benefits from additional 10% DEXA scanning after fracture in 50+ fracture patients.**

Of these new cases it is predicted that the most will be found from densitometrics research after 'other' fractures (~ 8%), probably because this is the subgroup containing the most fractures [see Table 15].

Full bone densitometrics research	2010	2020	2030	2040	2050	2060
Diagnosed wrist fracture as % of total	5,26%	5,28%	5,33%	5,38%	5,40%	5,38%
Diagnosed hip fracture as % of total	5,27%	5,27%	5,31%	5,34%	5,38%	5,37%
Diagnosed spinal fracture as % of total	4,82%	4,82%	4,87%	4,91%	4,94%	4,94%
Diagnosed other fracture as % of total	8,11%	8,13%	8,21%	8,23%	8,27%	8,24%
<i>Total diagnosed as % of total fractures</i>	<i>6,06%</i>	<i>6,06%</i>	<i>6,08%</i>	<i>6,09%</i>	<i>6,12%</i>	<i>6,11%</i>

**Table 15, Newly identified osteoporosis cases per fracture site as a percentage of total osteoporotic fractures, with adding an extra 10% to total DEXA scanning likelihood (% DEXA scanning is increased by 10% for both males and females).**

Assuming that everyone suffering from a fracture with an osteoporotic nature will be prescribed medication once being diagnosed with osteoporosis according to the WHO standards, this means that approximately 7,000 additional osteoporosis patients (compared to already medication receiving patients whose number is not estimated by the model) will be eligible for medication administering by the year of 2020 when the total DEXA scanning percentage will be increased from 10% to 20%. Based on the mean weighted 5 year cost of medication of € 938 these 7,000 patients are estimated to cost € 6.5 million on medication. This comes down to about € 7,200 on medication costs to society in order to have one osteoporotic fracture prevented in 2020 [see Table 16].

Medication costs per prevented fracture	2010	2020	2030	2040	2050	2060
Wrist	€ 8.357	€ 8.252	€ 7.939	€ 7.682	€ 7.606	€ 7.663
Hip	€ 6.187	€ 6.225	€ 6.152	€ 6.057	€ 5.981	€ 5.985
Spine	€ 5.971	€ 5.966	€ 5.823	€ 5.668	€ 5.595	€ 5.616
Other	€ 8.790	€ 8.741	€ 8.505	€ 8.346	€ 8.315	€ 8.373
<i>Overall</i>	<i>€ 7.287</i>	<i>€ 7.254</i>	<i>€ 7.044</i>	<i>€ 6.862</i>	<i>€ 6.781</i>	<i>€ 6.816</i>

**Table 16, Mean estimated societal costs on medication (excluding vitamin D and calcium supplements) which on average have to be made before prevention one fracture within that specific fracture site.**

Together with the € 1.1 million additional costs of DEXA scanning compared to the baseline scenario of only scanning 10% of 50+ fracture patients, this comes down to a mean cost of € 1,260 per treated osteoporosis patient.<sup>v</sup> This might seem a high price, considering that the benefits of anti-

<sup>v</sup> [ € 2,250,718 (DEXA) + € 6,536,948 (treatment) ] / 6,972 (eligible for medication in 2020) = € 1,260.

osteoporosis medication are not everlasting and there is no guarantee of preventing osteoporotic fracture by treating osteoporosis patients. However, the calculation model estimates that by treating 3,500 extra osteoporosis patients, through increasing the scanning percentage by 10%, approximately 400 osteoporotic fractures will be prevented. Calculating that the mean cost per fracture is about € 9,000 and the mean weighted cost per fracture is even about € 10,000 by the year 2020, those incremental 3,500 osteoporosis patients who are identified and treated at the cost of about € 1,260 per patient are less costly than what their fractures would have costed if no preventive measures would have been taken. In means of prevented fractures, one prevented osteoporotic fracture is estimated to save approximately 3,500 Euros in 2020 [see Table 17]. This is where the savings factor from preventing subsequent fragility fracture originates from.

Prevention costs per prevented fracture	2010	2020	2030	2040	2050	2060
DEXA scans	€ 2.561	€ 2.497	€ 2.290	€ 2.113	€ 2.054	€ 2.077
Medication	€ 7.287	€ 7.254	€ 7.044	€ 6.862	€ 6.781	€ 6.816
<b>Total</b>	<b>€ 9.848</b>	<b>€ 9.751</b>	<b>€ 9.334</b>	<b>€ 8.975</b>	<b>€ 8.835</b>	<b>€ 8.893</b>
Treatment costs per prevented fracture	2010	2020	2030	2040	2050	2060
Inhospital	€ -5.043	€ -5.074	€ -5.199	€ -5.308	€ -5.372	€ -5.351
NH	€ -2.778	€ -2.839	€ -2.972	€ -3.178	€ -3.321	€ -3.403
Rehab.	€ -3.657	€ -4.409	€ -4.524	€ -4.676	€ -4.779	€ -4.819
Home care	€ -979	€ -986	€ -1.017	€ -1.044	€ -1.060	€ -1.056
<b>Total</b>	<b>€ -12.456</b>	<b>€ -13.308</b>	<b>€ -13.711</b>	<b>€ -14.206</b>	<b>€ -14.532</b>	<b>€ -14.630</b>
<b>Difference prevention &amp; treatment</b>	<b>€ -2.609</b>	<b>€ -3.557</b>	<b>€ -4.377</b>	<b>€ -5.231</b>	<b>€ -5.697</b>	<b>€ -5.737</b>

**Table 17, Mean estimated incremental health care costs/savings on preventive and curative care per prevented fracture.**

That is where the savings factor of the model originates from. While costs per treated osteoporosis patient are calculated to be € 1,260 per patient, the model estimates their corresponding prevented costs are € 1,720 per newly identified and treated osteoporosis patient since the estimated prevented costs amount up to almost € 6 million by 2020. Net saved in- and outhospital costs would hence be over € 1.6 million, resulting in a savings factor of 1.36 in favor of treating osteoporosis instead of treating its consequences. This means that every invested Euro will be worth € 1.36 afterwards, if spend on interventions to treat osteoporosis. Due to the demographic developments in The Netherlands, this *lever* is expected to grow, to 1.65 in 2060, implying a possibility for a net saving of about 3.73 million Euros per year per 10% additional screening and treating. Table 18 provides an overview.

Savings factor and cost savings	2010	2020	2030	2040	2050	2060
Savings factor of prevention	1,26	1,36	1,47	1,58	1,64	1,65
Absolute cost savings per year	€ 944.000	€ 1.603.000	€ 2.443.000	€ 3.352.000	€ 3.800.000	€ 3.729.000

**Table 18, Predicted point estimates of the savings factors per year between the treatment of osteoporosis after first fracture to prevent subsequent osteoporotic fracture versus merely treating subsequent osteoporotic fracture (model 1) and predicted absolute cost savings (rounded to 1,000 Euros) associated with a 10% increase of combined diagnosis and treatment of osteoporosis after first fragility fracture.**

If will be assumed that the medication benefits will affect the ten year risk of fracture (called *model 2* in section 3.3.5), instead of only the risk of subsequent fracture, the savings factor of prevention versus treatment will be significantly larger. In that case, model estimates will comprise a factor of 4.11 and 4.85 by the year 2020 and 2050 respectively [see Table 19]. This kind of savings magnitudes can only be attained, however, if people at high risk of osteoporosis are being scanned and treated upfront their first fracture. Hence this is regarded an unreal scenario since one cannot predict

fragility fracture with 100% certainty. In order to attain this, too much variables are applicable to real world settings.

<b>Savings factor and cost savings</b>	<b>2010</b>	<b>2020</b>	<b>2030</b>	<b>2040</b>	<b>2050</b>	<b>2060</b>
Savings factor of prevention	3,80	4,11	4,40	4,70	4,85	4,85
Absolute cost savings per year	€ 9.963.000	€ 13.659.000	€ 17.699.000	€ 21.275.000	€ 22.694.000	€ 22.260.000

**Table 19, Predicted point estimates of the savings factors per year between the treatment of osteoporosis before first fragility fracture and subsequent fracture versus merely treating osteoporotic fracture (model 2) and predicted absolute cost savings (rounded to 1,000 Euros) associated with a 10% increase of combined diagnosis and treatment of osteoporosis before first fragility fracture such that relative fracture risk is reduced by administering medication to osteoporosis patients at 100% risk of fracture.**

As the cost-effectiveness of anti-osteoporosis medication is regarded to play a big role in the estimation of a savings factor between preventing and treating (subsequent) fragility fracture, the assumption that the cost-effectiveness of this medication will get even better over the years will enlarge the lever as well. If all used medication would have the cost-effectiveness of the bisphosphonate *Alendronate*, the savings factor in the model where only subsequent risk will be decreased will grow to 3.45 (in 2020) and 4.33 (in 2050), while where both first fracture risk and subsequent risk will be decreased, the savings factor will even grow to 10.44 (in 2020) and 12.82 (in 2050). Table 20 serves as an overview of the savings factors for the two different models in case every new osteoporosis patient will be provided with anti-osteoporosis medication that is as cost-effective as Alendronate.

<b>Savings factor from preventing</b>	<b>2010</b>	<b>2020</b>	<b>2030</b>	<b>2040</b>	<b>2050</b>	<b>2060</b>
Subsequent fracture only	3,17	3,45	3,78	4,14	4,33	4,32
First fracture and subsequent fracture	9,58	10,44	11,38	12,36	12,82	12,80

**Table 20, Predicted savings factors between prevention of subsequent fragility fracture and mere repairing of subsequent fragility fracture for the two models regarded in the thesis in case of the most cost effective anti-osteoporosis medication will be prescribed to and used by all newly identified osteoporosis patients. Subsequent fracture only equals model 1 in combination with Alendronate. First fracture and subsequent fracture equals model 2 in combination with Alendronate.**

Moreover, preventing fragility fracture is estimated to avert QALY loss.<sup>vi</sup> This is deemed even more important than saving costs. Now that the model estimates the character of osteoporotic fracture prevention by osteoporosis treatment to be actually cost saving, the health effects of treating osteoporosis prior to first fracture are not just a fortuitous coincidence. As it happens, the model values the result of every additional 10% DEXA scanning after fracture, combined with proper medication to prevent subsequent fracture, as a prevention of 276 QALYs lost for the year of 2020. Compared to the total health burden of fragility fractures in the Netherlands [see Table 21] this does not seem a lot (~0.54%), but considering that this figure can still be improved by a 9 fold (if combined DEXA scanning and treating of osteoporosis patients would become 100%) this is of genuine matter.

<sup>vi</sup> Quality Adjusted Life Year: 1 QALY equals 1 year of life in 100% health.

Estimated number of QALYs lost per year	2010	2020	2030	2040	2050	2060
Due to osteoporotic wrist fracture	4.267	5.150	5.811	6.036	5.945	5.835
Due to osteoporotic hip fracture	25.458	32.105	38.557	42.098	41.224	39.662
Due to osteoporotic spinal fracture	7.784	9.620	10.945	11.351	10.911	10.695
Due to other osteoporotic fracture	3.292	3.899	4.509	4.724	4.690	4.612
<i>Total</i>	<i>40.800</i>	<i>50.774</i>	<i>59.822</i>	<i>64.209</i>	<i>62.770</i>	<i>60.804</i>

Table 21, Estimated number of QALYs lost on fragility fractures per year.

Figure 17 and Figure 18 show the input and output framework of the front of *model 1*, the version where only the subsequent fractures are prevented by anti-osteoporosis medication. Figure 17 shows the results of only a slight increase in scanning and treating fracture patients for osteoporosis, while Figure 18 shows attainable future outcomes in case almost every fracture patient will be scanned, treated by the most cost-effective medication and adheres to the medication better.

# Osteoporosis in The Netherlands

## Model variables

Reset

Scenario 1 Scenario 2

DEXA scanning % of 50+ men	10%	20%
DEXA scanning % of 50+ women	10%	20%

Treating % of 50+ men after fragility fracture	100%	100%
Treating % of 50+ women after fragility fracture	100%	100%

Non-adherence % of treated patients	50%	50%
-------------------------------------	-----	-----

Year **2020**

Population	17.228.781	
50+ population (% of total population)	7.013.789	40,7%
50+ osteopenia population (% of 50+ population)	3.902.306	55,6%
50+ osteoporosis population (% of 50+ population)	1.369.553	19,5%

DEXA scanning % of 50+ men  
 DEXA scanning % of 50+ women  
 Treating % of 50+ men after fragility fracture  
 Treating % of 50+ women after fragility fracture  
 Non-adherence % of treated patients

Fragility fractures (#)		
Scenario 1	Scenario 2	Difference
88.974	88.523	-451

DEXA scans (#)		
Scenario 1	Scenario 2	Difference
10.554	21.108	10.554

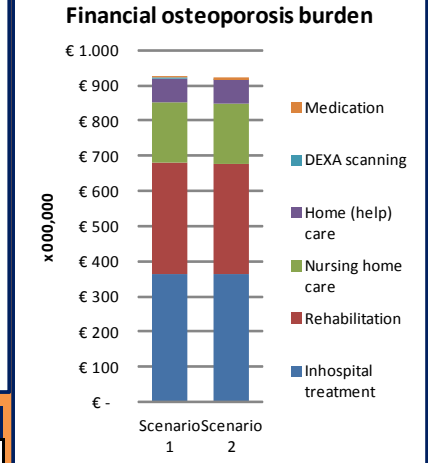
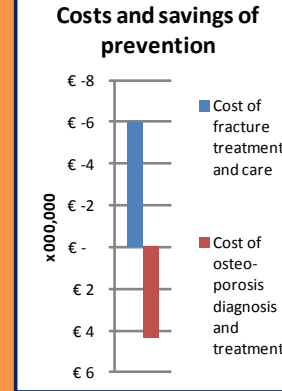
Identified osteoporosis patients (#)		
Scenario 1	Scenario 2	Difference
5.339	10.679	5.339

New patients starting with medication (#)		
Scenario 1	Scenario 2	Difference
3.486	6.972	3.486

Direct and indirect cost of fragility fracture (€)			
	Scenario 1	Scenario 2	Difference
Inhospital treatment	€ 365.373.260	€ 363.087.053	€ -2.286.207
Rehabilitation	€ 315.701.608	€ 313.714.893	€ -1.986.716
Nursing home care	€ 172.242.032	€ 170.962.890	€ -1.279.142
Home (help) care	€ 66.609.453	€ 66.164.942	€ -444.511
<b>Total</b>	<b>€ 919.926.354</b>	<b>€ 913.929.777</b>	<b>€ -5.996.576</b>

Costs of subsequent fracture prevention (€)			
	Scenario 1	Scenario 2	Difference
DEXA scanning	€ 1.125.359	€ 2.250.718	€ 1.125.359
Medication	€ 3.268.474	€ 6.536.948	€ 3.268.474
<b>Total</b>	<b>€ 4.393.833</b>	<b>€ 8.787.666</b>	<b>€ 4.393.833</b>

Absolute osteoporosis burden in The Netherlands (€ and QALYs)			
	Scenario 1	Scenario 2	Difference
Treatment and care	€ 924.320.186	€ 922.717.443	€ -1.602.743
QALY loss	50.774	50.498	-276



**Cost-effectiveness**  
 'Leverage' factor: **1,36**  
 Every invested €1 on prevention of subsequent fragility fracture yields € 1,36 in prevention of fragility fracture treatment and care

Figure 17, Input and output framework of the calculation model. Base year = 2020. Difference DEXA scanning scenario 1 and 2 = 10%. Difference treating scenario 1 and 2 = 0%. Difference non-adherence scenario 1 and 2 = 0%. Medication costs and benefits applied = weighted average of model included medication.

# Osteoporosis in The Netherlands

## Model variables

Reset

Scenario 1 Scenario 2

DEXA scanning % of 50+ men	10%	90%
DEXA scanning % of 50+ women	10%	90%

Treating % of 50+ men after fragility fracture	100%	100%
Treating % of 50+ women after fragility fracture	100%	100%

Non-adherence % of treated patients	50%	30%
-------------------------------------	-----	-----

Year

2050

Population

17.781.688	
7.595.634	42,7%
4.127.758	54,3%
1.738.479	22,9%

50+ population (% of total population)

50+ osteopenia population (% of 50+ population)

50+ osteoporosis population (% of 50+ population)

DEXA scanning % of 50+ men

DEXA scanning % of 50+ women

Treating % of 50+ men after fragility fracture

Treating % of 50+ women after fragility fracture

Non-adherence % of treated patients

Fragility fractures (#)		
Scenario 1	Scenario 2	Difference
117.709	110.863	-6.846

DEXA scans (#)		
Scenario 1	Scenario 2	Difference
12.850	115.646	102.796

Identified osteoporosis patients (#)		
Scenario 1	Scenario 2	Difference
7.126	64.132	57.006

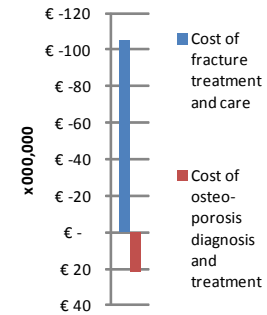
New patients starting with medication (#)		
Scenario 1	Scenario 2	Difference
4.824	43.420	38.595

Direct and indirect cost of fragility fracture (€)			
	Scenario 1	Scenario 2	Difference
Inhospital treatment	€ 523.419.094	€ 484.661.436	€ -38.757.657
Rehabilitation	€ 460.989.305	€ 426.763.599	€ -34.225.706
Nursing home care	€ 282.132.865	€ 257.709.376	€ -24.423.489
Home (help) care	€ 97.857.068	€ 90.182.767	€ -7.674.302
<b>Total</b>	<b>€ 1.364.398.332</b>	<b>€ 1.259.317.177</b>	<b>€ -105.081.154</b>

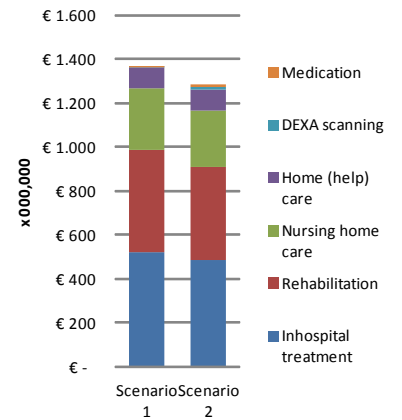
Costs of subsequent fracture prevention (€)			
	Scenario 1	Scenario 2	Difference
DEXA scanning	€ 1.370.145	€ 12.331.301	€ 10.961.157
Medication	€ 1.269.599	€ 11.426.391	€ 10.156.792
<b>Total</b>	<b>€ 2.639.744</b>	<b>€ 23.757.692</b>	<b>€ 21.117.949</b>

Absolute osteoporosis burden in The Netherlands (€ and QALYs)			
	Scenario 1	Scenario 2	Difference
Treatment and care	€ 1.367.038.075	€ 1.283.074.870	€ -83.963.206
QALY loss	62.713	58.752	-3.961

### Costs and savings of prevention



### Financial osteoporosis burden



### Cost-effectiveness

'Leverage' factor: 4,98

Every invested €1 on prevention of subsequent fragility fracture yields € 4,98 in prevention of fragility fracture treatment and care

Figure 18, Input and output framework of the calculation model. Base year = 2050. Difference DEXA scanning scenario 1 and 2 = 80%. Difference treating scenario 1 and 2 = 0%. Difference non-adherence scenario 1 and 2 = 20%. Medication costs and benefits applied = all medication is as cost-effectiveness as Alendronate.



### 4.3. Osteoporosis treating outcomes over different variables

According to the literature, there are three important variables where health care in the osteoporosis scene can be improved. These are scale of diagnosis (scanning), scale of treatment (medication) and compliance with medication (non-adherence). To determine what the separate effects are per variable, these variables have separately been analyzed to come to a difference-in-difference framework where the possible improvements, in money terms, have been estimated.

		Scanning	Medication	Non-adherence
Scanning (%)	Scenario 1	10%	100%	50%
	Scenario 2	20%	100%	50%
Medication (%)	Scenario 1	10%	90%	50%
	Scenario 2	10%	100%	50%
Non-adherence (%)	Scenario 1	10%	100%	50%
	Scenario 2	10%	100%	40%
2020	Δ treatment costs of osteoporosis	€ 4,394,000	€ 327,000	€ 0
	Δ treatment costs of osteoporotic fracture averted	€ 5,997,000	€ 600,000	€ 400,000
	Absolute cost savings	€ 1,603,000	€ 273,000	€ 400,000
	Cost savings factor	1,36	1,83	N/A *
	Averted QALY loss	276	28	18
2040	Δ treatment costs of osteoporosis	€ 5,752,000	€ 440,000	€ 0
	Δ treatment costs of osteoporotic fracture averted	€ 9,104,000	€ 910,000	€ 607,000
	Absolute cost savings	€ 3,352,000	€ 471,000	€ 607,000
	Cost savings factor	1,58	2,07	N/A *
	Averted QALY loss	376	38	25

Table 22, Schematic overview of associated costs and benefits of the separate effects of three different model parameters. Scanning and medication have been increased by 10% and non-adherence has been decreased by 10% to look at the effects. Costs and benefits are defined per year. Cost savings factor can be read as the return on investment from investing € 1. Treatment costs of osteoporosis contain DEXA scanning and anti-osteoporosis medication costs. Treatment costs of osteoporotic fracture contain in and out hospital costs associated with fragility fracture repair, rehabilitation and care. Figures indicated in red imply incremental costs of the new scenario (compared to the base case scenario) and figures in green imply averted costs. For the parameter *non-adherence*, no cost savings factor is present because no investments have been associated with decreasing the non-adherence percentage among anti-osteoporosis medication users. The estimates are rounded to 1,000 Euros.

The three variables are all linked to each other when it comes to presenting absolute figures. The absolute cost savings from increasing the treating percentage of fracture patients that has been diagnosed with osteoporosis by 10% could for example have been higher if the screening percentage would have been increased at the same time. Therefore Table 22 better suits considering the cost savings factor as a return on investment from increasing or decreasing a variable by 10%.

### 4.4. Sensitivity analysis

In Figure 19 below, the outcomes of the sensitivity analysis are presented. The outcomes are presented in a so-called *tornado diagram*. This implies that the model parameters which are most sensitive to relative changes appear at the top (a change of +25% in the parameter has a positive effect on the savings factor of the preventive intervention) and bottom (a change of +25% in the parameter has a negative effect on the savings factor of the preventive intervention) of the chart.

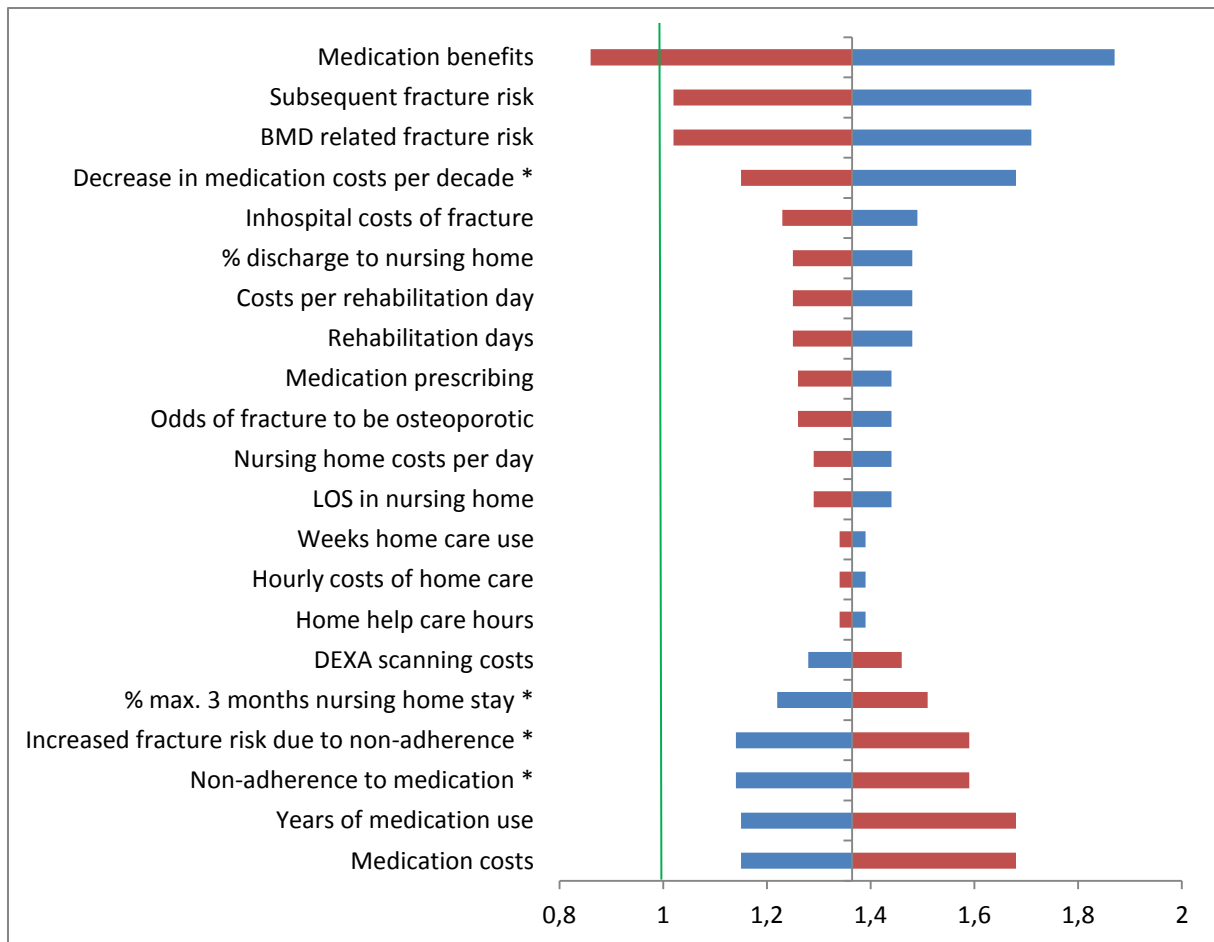


Figure 19, Sensitivity analysis outcomes per model parameter for the year 2020 displayed in a so-called tornado chart. Every model parameter has been increased by 25% (blue bars) and decreased by 25% (red bars) to determine the magnitude of the separate effects of the parameters on the calculated savings factor. The outcomes after changing the model parameters have been compared to the savings factor of 1.36, resulting from the model input of Table 10. The green vertical line (at 1) indicates the boundary of the intervention being cost-saving or not. Left from the green line would mean that a change in this particular model parameter will undermine the cost-saving character of prevention of subsequent fractures. The parameters with an asterisk (\*) are instead of being multiplied by 1.25 and 0.75 to increase and decrease them respectively, being added up and subtracted with 25%.

Figure 19 suggests that only one model parameter is able to undermine the cost saving character of treating osteoporosis patients after their first fracture to prevent subsequent fracture. This concerning parameter is *medication benefits*. If the parameter *BMD related fracture risk* is further divided into fracture risk for people with normal BMD, osteopenia or osteoporosis however, a decrease in fracture risk of people with osteoporosis (*ceteris paribus*) will also decrease the cost savings factor to below 1. This can be explained by a relatively high fracture risk of normal BMD people and osteopenia patients compared to osteoporosis patients, which means that relatively high screening costs have to be made on normal BMD people and osteopenia patients while only a relatively low number of osteoporosis patients will be found and can be treated.

The sensitivity analysis implies that when the medication benefits of anti-osteoporosis medication are reduced by 25%, compared to the base line input for scenario 1 and 2 as discussed in Table 10, the savings factor between prevention and treatment of osteoporotic (subsequent) fracture would drop below 1. This would mean that an investment of € 1 would not be earned back (hence the term savings factor would not be applicable anymore), while it would still save (quality adjusted) life years.

That is when cost-effectiveness would come around, next to an according threshold for costs per QALY gained. As long as prevention is deemed to be cost saving, decision makers would not have to worry about intervention thresholds since every invested Euro will save money and (quality adjusted) lives.

## 5. Validation

As Mandelblatt et al. (1996) claimed: “A prospective model is only as good as its ability to represent reality at the appropriate level, which depends on the model’s structure and on the assumptions made”.<sup>89</sup> Unreal model assumptions or determinants will hence question the usefulness of the model’s conclusions. Direct validation of the model’s input and output is however not always possible, because often a primary motivation for modeling is the unavailability of comparable literature material.<sup>2,90</sup> Besides, even if a subject has already been investigated the context of the research or the investigated population could be too different from the data or group that has to be scrutinized. To validate the results derived from the calculation spreadsheet comparing the results with other Dutch research in the field of osteoporosis and its consequences is preferred because costs related to osteoporotic fractures are very likely to vary a lot over countries. For example, daily hospital admission costs are substantially lower in The Netherlands compared to the US and Sweden.<sup>24</sup> Even within Europe the ranges of fracture unit costs among countries are wide. Wrist fracture unit costs, for example, vary from € 809 in Spain to € 2,022 in Italy (in 2002 Euros).<sup>76</sup>

### 5.1. Validation of model determinants (model input)

#### Distribution of osteoporosis over the Dutch population

In validating the distribution of BMD within the Dutch population, the model input which uses estimates of Schuit et al. (2004) have been compared with estimates of De Laet (1996).<sup>43,71</sup> In Table 23 and Table 24 below, it is shown that the estimates that have been incorporated by the calculation model are higher than those of De Laet which are based on The Rotterdam study (ERGO research). However, if the estimates of Schuit et al. have been replaced by the estimates of De Laet in the calculation model, it appears that the savings factor, as discussed in section 4.2.3, only drops by 0,02. Hence, even then the savings factor is still positive, i.e. € 1.34 per invested € 1 in 2020.

Males										
	50-60		60-70		70-80		80-90		90+	
	Schuit	DeLaet	Schuit	DeLaet	Schuit	DeLaet	Schuit	DeLaet	Schuit	DeLaet
Normal BMD	32%	65%	25%	58%	23%	51%	17%	43%	14%	41%
Osteopenia	63%	32%	64%	37%	63%	42%	54%	47%	50%	48%
Osteoporosis	5%	3%	11%	5%	14%	7%	29%	10%	36%	11%

Table 23, Distribution of BMD over the Dutch male population according to Schuit et al. and according to De Laet. Where De Laet’s estimates are lower than those of Schuit et al. have been indicated in red.

Females										
	50-60		60-70		70-80		80-90		90+	
	Schuit	DeLaet	Schuit	DeLaet	Schuit	DeLaet	Schuit	DeLaet	Schuit	DeLaet
Normal BMD	35%	51%	23%	40%	15%	26%	10%	15%	8%	13%
Osteopenia	48%	42%	56%	48%	48%	53%	42%	52%	38%	50%
Osteoporosis	17%	7%	21%	12%	37%	21%	48%	33%	54%	37%

Table 24, Distribution of BMD over the Dutch female population according to Schuit et al. and according to De Laet. Where De Laet's estimates are lower than those of Schuit et al. have been indicated in red.

### In and outhospital costs

To be sure that the model input from somewhat older research about in and outhospital costs, which has been used as the basis for their estimates which have been used for our model input, is based on reasonable up-to-date figures, beneath, in Table 25, a quick comparison has been performed. While the estimates used in the model could be overestimated for in-hospital costs and underestimated for outhospital costs, the sensitivity analysis has shown that even a 25% reduction of in-hospital costs will not dramatically change the estimated savings factor. A 25% reduction of *all* in-hospital costs for model input, will make the savings factor 1.26, which is still not less than 1 and hence positive. Compared with estimates from Hartholt et al. (2012), outhospital costs might be underestimated, meaning that the savings factor would even increase.

Cost unit	Source	Amount	Base year	= Amount in 2010 Euros
Hospital admission (per day)	De Laet et al. (1999)	Fl. 773 ~ € 350	1993	€ 508
	Meerding et al. (2006)	€ 382	1999	€ 485
	Hartholt et al. (2012)	€ 439	2009	€ 444
Nursing home admission (per day)	De Laet et al. (1999)	Fl. 209 ~ € 95	1993	€ 138
	Meerding et al. (2006)	€ 138	1999	€ 175
	Hartholt et al. (2012)	€ 253	2009	€ 256
GP visit (per day)	De Laet et al. (1999)	Fl. 30 ~ € 14	1993	€ 20
	Meerding et al. (2006)	€ 16	1999	€ 20
	Hartholt et al. (2012)	€ 40	2009	€ 40

Table 25, Cross comparison of used unit costs in osteoporosis or falls literature to put the original unit costs, where the incremental in-hospital costs are based on, in perspective.

### Outhospital stay after in-hospital stay

To validate cost estimates associated with the discharge to care institutions or with home help care due to fragility fracture, Table 3, Table 5, Table 6 and Table 7 should be compared by similar formats. Especially the source for home help care of Pasco et al. (2005) should be critically reviewed because its sample, where the results are based on, is considered to be very small. Similar formats on the Dutch osteoporosis population have not been found however. When research on national or international fragility data has been found it did not satisfy the same criteria used in this model. Comparing with i.e. estimates by Tarride et al. (2012) [see Figure 20] which have indicated that while 65% of fracture patients entering the hospital lived at home only 38% of them could have returned to their homes after being released from the hospital, or by Gilbert et al. (2009) has hence not been made possible, because our model calculates with mean estimates over the whole population

instead of dividing the population into groups by discharge percentage or by resource intensity weights with respect to costs.<sup>91, 92</sup>

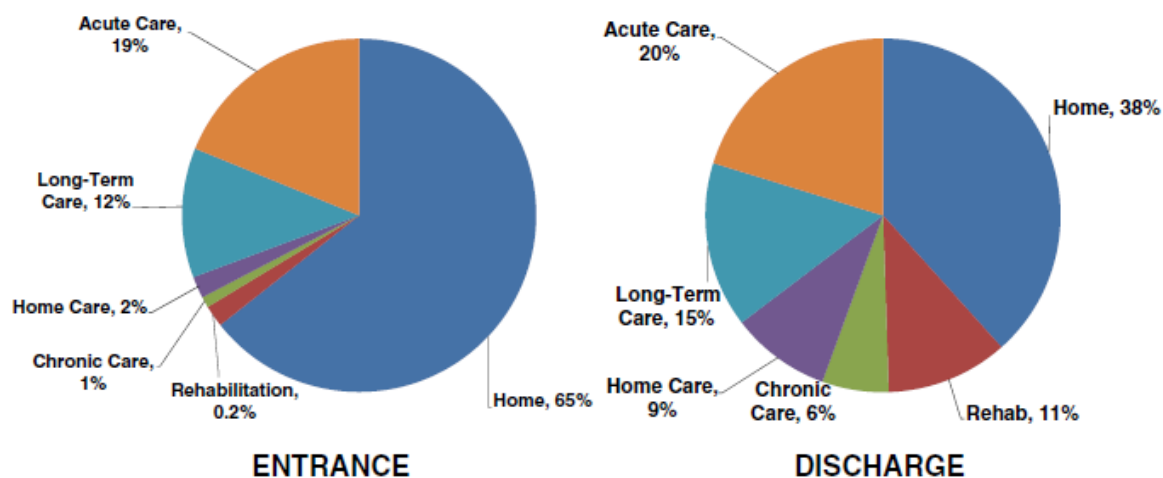


Figure 20, Pie charts of entrance and discharge respectively in and to institutions following from hospitalization for osteoporosis-related fracture (N = 57,433 Canadians). Reprinted from Tarride et. al. 2012. The burden of illness of osteoporosis in Canada.

### Medication prescription and non-adherence

The base case scenario of the model is based on a 10% screening and medication prescribing percentage after first fracture. Although the Dutch GP guidelines suggest that treatment for osteoporosis should be considered for all patients suffering from an osteoporotic fracture, according to previous research only 5% of the patients seemed to be newly detected and treated after fracture.<sup>55</sup> Of the people who have been investigated to be treated, at least half of them discontinued treatment.<sup>55</sup> Because the estimation of the number of preventable fractures commonly depends on a lot of parameters, instead of validating this number the source could rather be validated. The source used for the model is, however, regarded to be highly reliable since it is based on various literature.<sup>19</sup>

## 5.2. Validation of model results

### Prevalence and incidence

The Dutch osteoporosis prevalence has been estimated to amount 800,000 patients in 2002.<sup>20,93</sup> The calculation model described in this study estimates more than 900,000 around that year, however. While this comparison shows an overestimate of the model, the estimated number of osteoporotic fractures can as well be underestimated by the other analyses because 2002 CBO guidelines on osteoporosis provide estimates on osteoporotic fracture that were over 83,000 while the model estimates over 72,000 cases in 2010 for the base case scenario.<sup>12</sup> Furthermore, other previous research for osteoporotic prevalence estimated that the prevalence will increase by 38% between 2007 and 2025 and by about 60% between 2007 and 2040.<sup>36,94</sup> In this thesis' model, the osteoporosis prevalence is estimated to increase by 23% between 2010 and 2020, and by 53% between 2010 and 2040.

### **Hip fracture**

Being regarded the most important osteoporotic consequence with regard to financial and health burden, hip fractures deserve a closer look. This model estimates almost 40,000 hip fractures with an osteoporotic nature by the year 2040. A previous estimate found in the literature stopped at 30,000 for 2040 however.<sup>24</sup> Estimates considering osteoporotic hip fracture vary widely, however. More recent sources estimate the osteoporotic hip fracture burden to be higher, varying from about 19,000 in 2002 to 17,000 by 2011.<sup>20,95</sup> These estimates are more in line with the calculation model's estimates of approximately 18,400 in the year 2000, ranging to 22,000 in 2010. A trend analysis has shown that the in-hospitalization due to hip fracture has increased by 16%, which is more likely to be attributable to demographic changes in the population than to increase in the prevalence of osteoporosis.<sup>95,96</sup>

### **Wrist, spinal and other fracture**

RIVM estimates dating back to 2002 allow comparison with Dutch data on other (osteoporotic) fracture than hip fracture.<sup>20</sup> They estimate the fracture burden of wrist and spinal fracture to amount up to 42,000 and 16,000 respectively, whereas my calculations only estimate about 23,000 and 6,000 respectively. Total osteoporotic fracture has been discussed in the second CBO guideline of 2002.<sup>12</sup> Here they estimate a total of 83,000 osteoporotic fractures to yearly occur, while this calculation model stops at the estimate of 72,000 for 2010.

### **Associated costs**

In 2005, the Dutch societal burden of health care expenses amounted up to about € 68.5 billion. Of this, about € 4.2 billion (6.2%) was spent on skeletal related and connective tissue related diseases, the category where osteoporosis is part of.<sup>36</sup> Within this category, hospital care and specialists take care of 43% of costs, whereas in the discussed model in-hospital costs account for 42%. Estimates on costs on osteoporosis in the Dutch society show great variety: where some papers estimate the disease's costs to be only € 120 million per year, other researchers' estimates amount over 600 million per year (corrected by inflation).<sup>20,94</sup> Still, the latter estimate could be low if looking at estimated care costs associated with falling, which shows correlation with osteoporosis. Fall-related annual costs are namely estimated to reach about € 674 million, based on research over the years 2007-2009.<sup>42</sup> This variety can probably be explained by the assumption made in the calculations and by the in and exclusion of specific costs. It is, however, not always transparent where the estimates are based on. Either way, the estimate of 800 million for 2010, which includes all kinds of care and medication, seems to be rather high.

The comparison of total costs associated with in and out-hospital care after fracture has proven to be more difficult. While these have intensively been investigated over the years by several authors from different countries, these seem to depend a lot on the nation's health care structure. Even while the most fracture sites are easy to define and case finding does not seem to be hard, cost estimates for site specific fractures vary widely. For instance, De Laet (1999) claims that for the relatively easy diagnosed hip fractures, costs per fracture vary from under € 5,500 to over € 36,000, depending upon country and timeframe of interest. A recent research on costs per fracture estimates that, averaged over men and women, hip, wrist and other fractures would cost about € 21,505, € 3,420 and € 5,710 per fracture, respectively.<sup>42</sup> The osteoporotic fracture costs modeled in our study come close to these estimates, except for other fractures, with about € 24,400 per hip fracture, € 3,460 per wrist fracture and € 2,780 per other fracture.

## DEXA scans

Estimated costs on DEXA scans could not be validated since the Dutch information system<sup>vii</sup> management on diagnosis-treatment combinations to be declared says that the codes, like in Table 26, and associated numbers on DEXA scans are never provided to them.

Declaration codes of (poly)clinical research or treatment	
140042	General medical science, polyclinical
140135	Orthopedics, polyclinical
140282	Internal medical science, polyclinical
140301	Internal medical science, clinical
140302	Internal medical science, clinical
140500	Reumatology, day treatment
140502	Reumatology, day treatment
140505	Reumatology, polyclinical
140506	Reumatology, polyclinical
140508	Reumatology, polyclinical
140511	Reumatology, clinical
140512	Reumatology, clinical
140602	Clinical geriatry, clinical
140603	Clinical geriatry, clinical
140606	Clinical geriatry, polyclinical
140607	Clinical geriatry, polyclinical
140608	Clinical geriatry, day treatment
140609	Clinical geriatry, day treatment
140610	Clinical geriatry, polyclinical
140611	Clinical geriatry, polyclinical
140612	Clinical geriatry, day treatment
140613	Clinical geriatry, day treatment
140614	Clinical geriatry, clinical
140615	Clinical geriatry, clinical
140702	General medical science, polyclinical
140704	Orthopedics, polyclinical
140709	Internal medical science, polyclinical
140713	Reumatology, polyclinical
160502	Reumatology, day treatment
160503	Reumatology, polyclinical

Table 26, Short definition of declaration codes of (poly)clinical research or treatment associated with osteoporosis within the Dutch Health Authorities DTC/DCG tariff application.

## Savings factor

Previous research about a savings factor or a lever between prevention and treatment of (subsequent) fragility fracture has not been found. Previous research is more concentrated on the effect of preventive interventions on the decrease of relative fracture risk. Zethraeus et al. (2006), however, provided a reference model for the assessment of the cost-effectiveness of the treatment and prevention of osteoporosis. This model was based on the Swedish population and is very dependent on the used model parameters, concluding from their sensitivity analysis.<sup>35</sup> In their base case scenario, Zethraeus et al. (2006) provided evidence for a cost-effectiveness ratio of treating osteoporosis in 70 year old women which amounted about € 28,200 per QALY gained. However, if by changing some model parameters the investigated intervention could as well dominate the *no*

<sup>vii</sup> DIS. In Dutch: DBC informatie systeem.

*intervention* alternative. Aside from discrepancies between this reference model and the calculation model for this thesis, like the methodology and country-based costs, uncertainty around the cost-effectiveness of prevention of fragility fracture by the treatment of osteoporosis remains high.

## 6. Discussion

### 6.1. Discussion of the model design

#### **Cost-effectiveness estimation by a *return on investments ratio***

The calculation model consisting of spreadsheets, built for this thesis, is not regarded ideal when measured up to for example Markov health state models on the burden of osteoporosis. Rather, it serves the purpose of providing a quick idea of the effect of changing model parameters on the return on investments ratio with respect to prevention of subsequent fragility fracture. It is more a collection of data and assumptions which have been put together to estimate the cost-effectiveness of preventing subsequent fragility fracture. The model is more likely to underestimate the savings factor than to overestimate the savings factor, since I have been conservative in translating research outcomes of earlier research into the model framework of this study. Where, for example, estimates for the age category of 90+ were not available, the estimates of the lower age category have been used for this category. On the other hand, compared to previous models from the literature on treating osteoporosis, the cost saving outcome is rare. This might be explained by different settings or methodologies.

#### **Uncertain explaining power of the model**

The explaining power of the model, with respect to putting its estimations in a real world perspective, is reduced by the fact that empirical findings on anti-osteoporosis medication benefits could not have been obtained for males. Instead, data from research on women has been used. There is evidence, however, that the magnitude of the medication effect will be different for men. The same issue applies for the multiplying factor to convert ten year fracture risk estimates of osteopenia to osteoporosis. Besides, using average costs and benefits over the entire 50+ population does not come close to real world figures because costs and benefits seem to vary a lot over gender and age groups.<sup>14</sup>

#### ***Fragility fractures with osteoporotic nature: pleonasm or extra filter?***

In calculating the number of osteoporosis patients eligible for medication, the assumption has been made that only people with a fracture with an osteoporotic nature will be administered medication for five years in a row. It has also been assumed that only these people will take advantage of the medication benefits. This means that if the 'filter' of fractures being of osteoporotic nature will be removed because it is argued that this will underestimate the number of osteoporotic fractures since a BMD distribution has already been implemented in the model, more theoretical patients will be eligible for medication. This will even increase the savings factor between prevention of osteoporosis and sole repairing of osteoporotic fracture.



## 6.2. Discussion of the results

### 6.2.1. Underestimation of the lever

#### Fragility fracture incidence over age

Compared to the incidence rates of Harvey et al. (2010) [see Figure 21], the incidence rates calculated by the model [see Figure 13] are rather low.<sup>97</sup> This can be explained by using the 10 year fracture risk of Van Staa et al. (2001) which did almost not show an increase in fracture probability by age.<sup>74</sup> Hence, the real problem of an ageing population could be underestimated. Especially compared to life time risk.

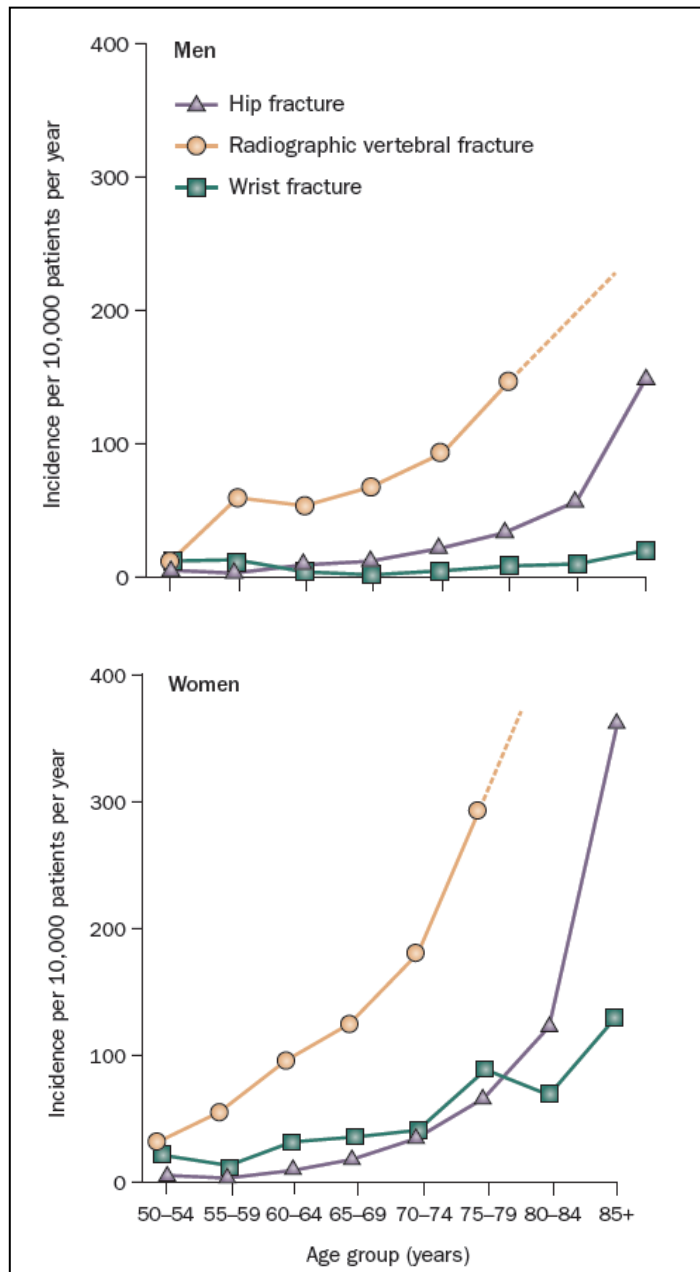


Figure 21, The incidence of radiographically determined vertebral, hip and wrist fracture by age and gender. Reprinted from Harvey et al. (2010).

#### Preventability of first and subsequent fracture

In the method of the calculation model, benefits of medication are calculated by their ability to

decrease fracture risk. The model (*model 1*) is designed to subtract medication benefits, in terms of prevented fractures, from the estimated osteoporotic subsequent fractures. Instead of the ability of having effect on the ten year risk of fracture when the medication will be taken upfront first fracture, the model only calculates the benefits from preventing subsequent fracture. Since fracture risk assessment tools are assumed to be used more often, high risk patients are more likely to get medication before they actually experience a fracture (*model 2*). Hence, the main model's estimates (*model 1*) could be underestimated and the savings factor might be higher in favor of the preventive intervention compared to fracture treatment only.

### **Medication effect**

What could also be reason for underestimation of the lever is that in the model it has been assumed that osteoporosis patients that are prescribed anti-osteoporosis drugs are using these drugs for 5 years in order to experience the effects of it while, for most medication, research has shown that fracture risk is already significantly reduced after only 1 year of therapy.<sup>10</sup> Hence, related medication costs could as well drop which would enlarge the discussed savings factor.

### **Average costs per fragility fracture**

Considering that among the cost estimates with respect to fragility fracture, costs like ambulance rides and additional GP visits following from fragility fracture are not included in the calculations, the cost per fracture estimates might be underestimated. Even more costs which have not yet been taken into account might need to be added to the average cost of fracture to catch up on real-life estimates. Some of them are unlikely to be measured well, like people who suffer the consequences of a fracture and hence need incremental in- or outhospital care but of whom the fracture has never actually been diagnosed. They will have returning complaints and returning costs (think of irreparable damage to the nerve system for example) since the fracture has never been properly treated like it should have been. This phenomenon is known to occur among patients suffering from spinal fractures. Others might not fit into present clinical pathways of normal fracture repair and will get stuck into AWBZ<sup>viii</sup> care with invalidity and nursing, becoming very expensive to society.<sup>98</sup> Such costs are not included into the model because cost estimates on this are lacking. Also costs following from spinal fractures are likely to be underestimated in the model since they often stay undiagnosed.

### **Supplements next to medication**

The model only makes estimates on incremental scanning and medication costs. The total financial burden of these subjects has not been regarded in the estimation on the total financial burden of osteoporosis in The Netherlands. Table 8 shows that the total costs on anti-osteoporosis medication for 2010 will account for about € 60 million.<sup>84</sup> This does not include costs on calcium and vitamin D supplements however. Such supplements are likely to provide another significant cost factor because of their widespread use along with anti-osteoporosis medication. In 2009, calcium supplements as medication took account of more than € 35 million.<sup>84</sup>

### **Costs per fracture and fracture risk**

The costs per fracture are likely to be even higher since in the cost estimations several factors have not been assessed. For example, the journey to the hospital by ambulance and GP visits after a fracture have not been included in the calculations for direct medical costs. Besides, most costs input integrated into the model only regard the costs of fracture within one year after the fracture, while it

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<sup>viii</sup> General Act on Special Medical Expenses.

has been proven that osteoporotic fracture leads to incremental costs even in later years.<sup>12,24</sup> What strikes more is that not only the costs per fracture might be higher. Also the fracture risk should be increasing in the model to reflect practice based data since the incidence of fall-related cases is known to be increasing as from 2001 up to date.<sup>95</sup>

### **Vertebral fractures**

With regard to the estimation of vertebral (spinal) fractures it has been argued that only about one-third of these fractures actually come to clinical attention because they often remain asymptomatic.<sup>55</sup> This could explain our low estimates for vertebral fractures. Their real incidence is poorly known, and their real prevalence is likely to be much higher. There is evidence that it increases with age in about the same way as investigated for hip fractures.<sup>43</sup> Hence, it is indicated (in population studies that use radiographic screening) that vertebral fractures play a more important role than previously assumed. It has been shown that the loss in quality of life (QoL) in the year after a hospitalized vertebral fracture is the same or even greater than the loss in QoL that is caused by a hip fracture, while our model input is based on the QoL reduction after vertebral fracture to be only half the reduction associated with the years after hip fracture.<sup>97</sup>

### **Medication and cost-effectiveness**

The model is only designed to calculate with one sort of anti-osteoporotic medication at the time. Society, of course, is however much more complicating in the sense that one sort of medication will not be suitable for all osteoporosis patients. Hence, conclusions should not be drawn according to the model's calculations with the most cost-effective outcomes only, but rather according to the trend that every sort of medication becomes more cost-effective over years because of developments in the demography, innovation, patent expiry and because of decreasing costs of existing medication. Hence, in the model, the costs and effects of the most often prescribed anti-osteoporosis medication in The Netherlands has been weighted over its usage. This employs the base case savings factor of 1.36 (2020 estimate). When, for cost containment purposes for example, only the most cost-effective medication will be prescribed, the savings factor will be increased to as much as 3.45 in 2020. Recent literature has indicated that, in the next decade, new possibilities in the osteoporosis diagnostics and treatment framework will emerge. These are likely to offer better cost-effectiveness results than are already available.<sup>3</sup>

### **Real practice osteoporosis screening and treating**

Instead of the assumption incorporated in the model that 10% of fragility fracture people will be screened and treated for osteoporosis, in reality only 5% will be.<sup>19</sup> Taking this into account, reality is likely to be worse off compared to the model estimates. This, too, counts for the percentage of people that is prescribed anti-osteoporosis medication after first fracture, without regarding the screening percentage. The model presumes a percentage of 100% in both scenario's, resulting in a combined percentage of screening and treating of 10% because screening has been set at 10%, while real world practice has been found less collaborative according to the osteoporosis care gap phenomenon discussed in section 2.3.

## **6.2.2. Overestimation of the lever**

### **Time horizon and double counting**

The time horizon used in the study has been set at 10 years, while the average length of stay (LOS) estimates within nursing homes after osteoporotic fracture are life time based. This could bring

about discrepancy between the model and real world practice. Nursing home costs could also be overestimated by double counting of fracture patients who are institutionalized following from hip fractures while they were already nursing home occupants. It is, as well, likely that hip fracture patients will use less care than the calculation model currently estimates since the model has merged different studies on usage of different health care resources after hip fracture into one study. For example, it is not likely that 12% of hip fracture patients in age category 50-60 years old have to go to a nursing home, while all of them will receive rehabilitation therapy (calculated by an average duration) and 44.9% will be in need of home help care. Such issues could be prohibited by designing a more complicated calculation model that incorporates a life table method or by designing a Markov model with transition probabilities. For the purpose of this thesis a more simple design has been employed however. Besides, in real practice settings, nursing home, rehabilitation and home help care can exhibit overlap as well.

### **Calculations based on averages**

The model considers every fracture patient to be average. Hence every patient is multiplied by the average rehabilitation days. However, especially among the relatively young age categories within the 50+ population it is likely that they will not need rehabilitation at all and that the in-hospital costs are lower than that of their relatively old colleagues. There will, on the other hand, also be exceptions that need relatively many rehabilitation which might compensate for this.

### **Additional costs associated with treating osteoporosis**

*Treating costs* of osteoporosis are likely to be underestimated since these only include scanning and medication costs while probably more cost factors should be included here. Think of additional GP visits, up taking of vitamin D and calcium supplements and more than one extra DEXA scan to check the osteoporosis progression after a period of drug taking. This is likely to overestimate the savings factor. Besides, the model calculates with a direct effect of medication, while in reality first costs have to be made without having (full) benefits. Thereby, medication costs in the model do not include the yearly costs of non-adherence expressed in money while research shows that about 77% of bisphosphonate users ceases medication uptake within a year. Apart from the clinical consequence of low compliance resulting in increased risk of fracture, too costs of wasted drugs are clear. The yearly additional costs of non-adherence, early stopping and other forms of wasting anti-osteoporosis drugs have been estimated to approximate 5 to 10 million Euros.<sup>17,86,99,100,101,102</sup> Finally, by treating osteoporosis not only the patient's quality of life will increase. Indirectly, also the mortality risk will decrease by confining excess mortality due to fragility fractures. This means that treated patients are likely to live longer which might entail incremental health care costs. These costs from added life years have not been regarded in the model, while these might just make the difference in the discussed intervention being cost saving or not.

## **6.2.3. Discussion of findings**

### **Cost containment and transparency**

In short, the most important risk factors for osteoporotic fracture justify the following statement: When age increases, bone mass decreases, the frequency of falling increases which eventually leads to increasing odds of breaking bones. Since this study, among others, has shown that the demographic *evolution* in the Netherland of the years to come could become a demographic *burden* if no measures are taken to prevent falls among the elderly at high risk of fragility fracture, cost-effectiveness will play a crucial role in the cost containment of elderly care due to osteoporosis.

Already, the national budget spent on falls exceeded the budgets of diabetes and heart failure for people of over 65 years old.<sup>103</sup> Thereby, transparency within cost-building of osteoporosis will still have to increase. Total costs on DEXA scanning in the Netherlands, for example, are said to be unknown at the Dutch central management system for declaring codes (DIS<sup>vii</sup>). A number of performed DEXA scans in the Netherlands could not have been validated since this intervention has been labeled a 'supportive product' and information about this is hence not delivered to the Dutch information system on Diagnosis-combination groups<sup>ix</sup>. This phenomenon asks for further research because numbers and costs on 'supportive products' will too have to be monitored somewhere.

### **Sex discrimination**

Playing with the model's input variables revealed a remarkable outcome. The model has calculated that treating male osteoporosis patients after first fragility fracture with anti-osteoporosis medication to prevent subsequent fracture is not cost-saving, while concerning women it is. This finding originates from the difference between men and women in fracture risk, odds of a fracture being of osteoporotic nature and associated cost of fragility fracture through sex characteristics.

### **Postponing intervening**

Notice that the savings factor between treating osteoporosis and treating subsequent osteoporotic fracture has been estimated to grow according to the calculation model [see Table 18]. This might suggest that waiting for the savings factor to grow is profitable, since this would imply more return on investment. This, however, conflicts with the financial mechanism of discounting. If an intervention is already cost-saving, decision makers should be eager to make use of that intervention as soon as possible since it is profitable to save costs as soon as possible. Cost-saving *now* should be preferred over cost-saving *in the future*. Besides, prospective research from and on the Netherlands has indicated that investing in health stays possible and desirable for the Dutch health index and even indispensable for the Dutch economy.<sup>104</sup>

### **Learning from other countries**

The demographic evolution, as the Netherlands is about to undergo, has already happened in other European countries. Therefore, it is likely that they have too struggled with an increasing osteoporosis burden. Perhaps Dutch policy makers could learn from the developments with respect to facing an ageing population in these other countries. It might as well be the case that some countries already have come up with a solution to the burden of osteoporosis or fragility fracture. This could provide a challenge for further research.

## **7. Conclusion**

Osteoporosis currently is a much-discussed disease since it is closely connected with ageing. Methodological issues like perspective, time horizon and discounting lead to a wide variation in estimations on the osteoporosis burden, so too in the Netherlands. The inclusion or exclusion of different health care costs in these estimations are reason for discussion as well. Thereby, uncertainty increases by the lack of transparency in the health care scene in determining actual absolute costs. Over the ages, transparency has actually proven to grow as a result of cost containment and getting value for money in the health care sector. However, with growing transparency within the osteoporosis costs column, also the cost estimations on total health care and

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<sup>ix</sup> DCG, or in Dutch: Diagnose-behandel combinaties, DBC.

societal costs of osteoporotic consequences in the Netherlands are ever rated higher throughout the ages. Since cost containment in the health care sector tends to get more important, not only should be looked at cost-effectiveness as a criterion in economic evaluation of osteoporosis confining interventions. Instead, prognoses on future costs and their budget impact should also be taken into account. Preventive measures will get more interesting compared to mere treatment of fragility fractures, as previous research showed cost-effectiveness in treating high-risk patients with anti-resorptive drugs, particularly if administered as soon as possible after a first fragility fracture. The health and financial burden of osteoporosis and its consequences in the Netherlands is estimated to double between 2010 and 2050. This means that by 2050, it is estimated that 62,770 QALYs will be lost due to fractures with an osteoporotic nature and that these will account for about 1.4 billion (health)care-related Euros per year. This statement is not likely to be overestimated since osteoporotic fracture is known to be highly correlated with age and the calculation model is primarily based on the evolving Dutch demography. Keeping this in mind, focus should be shifted from osteoporosis *care* to osteoporosis *cure* in order to prevent osteoporotic fracture. Especially since this study has shown that the treatment of osteoporosis, as it prevents osteoporotic fracture, can actually be cost saving. Even when anti-osteoporosis medication will be prescribed after *first* fragility fracture, the saved costs on repair and care of *subsequent* fragility fracture exceed the costs of diagnosis and treatment of the newly detected osteoporosis patients. Every 10% increase in combined screening and treating of osteoporosis after first fragility fracture is estimated to generate a net saving on the financial osteoporosis burden in the Netherlands between € 1.6 million and € 13.6 million per year around the year 2020. This magnitude primarily depends on the cost-effectiveness of prescribed anti-osteoporosis medication, fracture risk associated with osteoporosis and osteopenia and on possibilities in preventing first fracture as well. Latter could be employed through early detection of people at high risk by i.e. fracture risk assessment tools. These tools and other strategies for targeting high fracture risk people have already been developed, but combining them with increased diagnostics and treatment to prevent (subsequent) fracture will be a necessary challenge to reduce the osteoporosis burden in the future. Fortunately, the future is likely to offer even better diagnostics and medication to improve available possibilities.

The calculation model, designed on behalf of this study, has provided proof for the existence of a positive savings factor between *the prevention of subsequent fracture by treating osteoporosis after first fracture* and *merely fracture repairing*, to the advantage of prevention. This factor, which can be seen to work as a lever for minimizing the cost burden of osteoporosis to society for its relatively low investments compared to its returns, is very likely to grow when fracture risk will already be assessed before first fracture. The model design is, however, not perfect and its outcomes should be regarded to give direction rather than to give robust predictions. Nevertheless its results provide reason for further exploration of the cost saving character of combined screening and treating osteoporosis to prevent the costly consequences of osteoporotic fracture. New exploration then should be based on real-world practice settings instead of on an economic model to be certain about the preventability of the clinical and economic burden of osteoporosis and its consequences. Without intervening, the health and financial burden due to osteoporosis in the Netherlands will dramatically increase in the coming decades. Therefore, this study should provide challenge for further research.

## Summary

Due to demographic developments within the Dutch society in the coming decades, the burden of osteoporosis associated health care costs is increasing and very likely to increase a lot in the near future. The model designed for this study estimates that, compared to 2010, the financial burden of osteoporosis will double to about € 1.4 billion. With fragility fractures, clinically being the most important consequence of osteoporosis, looming over the scarce health care resources, therefore preventing them becomes ever more important. By the comparison of two spreadsheets, containing the cost estimates of preventing and only treating osteoporotic fracture, it has been estimated that preventing subsequent fractures by treating osteoporosis after first fracture is cost saving. For the year 2020, every € 1 invested in preventing subsequent fractures by administering anti-osteoporosis medication after first fracture is estimated to prevent € 1.36 on treatment and care costs of subsequent fracture. This lever (savings factor) will grow as fracture risk assessment tools will be implemented to enable the prevention of first fracture as well. The maximum savings factor has been estimated to amount up to 4.11 by 2020 in the case that taking medication affects the ten year risk on prior and subsequent fracture, which would mean that every osteoporosis patient would have been identified before first fracture. Every 10% increase in screening and treating osteoporosis, to prevent subsequent osteoporotic fracture, is estimated to be associated with a net saving of € 1.6 to € 13.6 million of total osteoporotic costs to society. Latter estimate is considered to be unrealistic however, since this is associated with 100% predictability of fragility fracture linked to osteoporosis. Because fracture risk assessment tools are advancing, real world practice is thought to be somewhere in between both estimates. Apart from the assumption that the cost-effectiveness of anti-osteoporosis medication is likely to increase in the future which would make prevention of both first and subsequent fragility fracture even more interesting, the outcomes of the research should already provide reason for the better implementation of osteoporosis guidelines with respect to screening for osteoporosis after fracture accompanied by prescribing of anti-osteoporosis medication.

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