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# The productivity gain by preventing first and subsequent hip fractures in osteoporotic patients as a result of optimal treatment

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# Abstract

**Background:** Preventing hip fractures could prevent patient disability and premature death, and lead to substantial societal savings in terms of productivity gains. However, the Norwegian government has decided against emphasizing productivity gains in prioritization decisions for financing pharmaceutical drugs. The question, however, remains whether including productivity gains could lead to better prioritizations. In our study we therefore aim to estimate the productivity gain by preventing first and subsequent hip fractures through optimal treatment of osteoporotic patients in Norway.

**Method:** A Markov cohort model was developed based on the incidence of hip fractures and deaths in Norway. All work-active 50-year old men and women in Norway were separately simulated through the model until retirement or death. A 30% RRR was applied to the model state transitions as a primary and secondary treatment intervention. Productivity gains were calculated based on averted sick leave, averted permanent disability, and averted hip fracture related death using the human capital approach (HCA) and a societal gain calculation.

**Results:** The total present productivity gain using the HCA was 122 million NOK. Averted permanent disability contributed with approximately 80% to the total estimate. Based on the 105 averted hip fractures due to the intervention, the average productivity gain per prevented hip fracture using the HCA was 1 167 000 NOK. The total productivity gain and the average productivity gain per prevented hip fracture was higher in men compared to women. The total societal gain and the average societal gain per prevented hip fracture was lower than the estimates obtained using the HCA in both sexes.

**Conclusion:** Optimal pharmacological treatment of osteoporosis in middle-aged patients had a positive impact on work productivity. The estimated total productivity gain was low relative to other findings, but the productivity gain per prevented hip fracture was substantial. In addition, the productivity gain in the entire work-active osteoporotic population in Norway can be significant if patients are treated optimally. Excluding these monetary gains from health economic evaluations of treatment interventions can lead to a reduced cost-effectiveness of interventions and the exclusion of major societal savings. The Norwegian government should acknowledge this while evaluating the drug politics and preparing a new priority message. Future inquiries could examine the productivity gain in a broader work-active population and incorporate other important fragility fracture types.

# Abbreviations and acronyms

| | |
|---|---|
| AOD | Anti-osteoporotic drug |
| BMD | Bone Mineral Density |
| COI | Cost of illness |
| DALY | Disability adjusted life year |
| DXA | Dual x-ray absorptiometry |
| EUR | Euro |
| FCA | Friction cost approach |
| FoF | Fear of Falling |
| FLS | Fracture Liaison Service |
| FRAX | Fracture Risk Assessment Tool |
| GDP | Gross domestic product |
| HCA | Human capital approach |
| NAV | Norwegian Labor and Welfare Organization |
| NOK | Norwegian kroners |
| OR | Odds Ratio |
| PTH | Parathyroid hormone |
| QALY | Quality adjusted life year |
| QoL | Quality of life |
| RR | Relative Risk |
| RRR | Relative risk reduction |
| RTW | Return to work |
| SD | Standard Deviation |
| SMR | Standard Mortality Ratio |
| UNN | University Hospital in Northern Norway |
| WHO | World Health Organization |

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# 1 Introduction

The 2015 public health message released by the Norwegian government in collaboration with the Ministry of Health and Care Services had a goal of reducing the number of hip fractures by 10% in Norway within 2018 (1). Unfortunately, numbers from the Norwegian National Hip fracture registry show that less than a one percent reduction was achieved (2). Although hip fracture rates have fallen, a high annual number of hip fractures persists as the population is ageing (3). In addition, several studies have reported suboptimal treatment and significant underdiagnosis of osteoporotic patients (4, 5). This can increase the risk of both first and subsequent fragility fractures (6). Of all fracture types, hip fractures are associated with the highest morbidity, mortality (7, 8) and costs to society (6). Therefore, preventing hip fractures could not only prevent patient disability and premature death but also lead to substantial societal savings in terms of productivity gains. However, the Norwegian government has decided to ignore productivity gains when prioritizing the financing of pharmaceuticals (9). They argue that emphasizing productivity gains could lead to the prioritization of treatments aimed at more productive patients over less productive patients. However, not accounting for these monetary gains could potentially lead to the exclusion of major societal savings and a reduced cost-effectiveness of interventions. The Norwegian health authorities' own ambitions of maximizing health services for the population given the constraint resources would not be met.

# 2 Background

## 2.1 Prioritization in the Norwegian health care sector

For the past 30 years, five governmental commissions have been tasked with preparing and evaluating priority setting principles for the Norwegian health care sector (10). The Lønning II commission in 1997, proposed three core criteria as the basis for prioritizing interventions: severity, expected benefits, and cost-effectiveness. These criteria were approved by the Norwegian parliament in the 1999 Priority message and has since formed the basis for what is believed to be an effective and just system for prioritization. Furthermore, in line with existing prioritization principles, the Norwegian parliament in the 2016 white paper on prioritization decided against emphasizing productivity gains in reimbursement decisions for pharmaceutical drugs (9). This was based on the assumption that the inclusion of productivity gains could lead to ethical challenges in prioritizations. However, the question remains whether including productivity gains could lead to better decisions.

As the new Norwegian government in 2021 aim to re-evaluate the drug politics and submit a new Prioritization message the highly controversial topic of productivity gains could once more be up for discussion.

## 2.2 Osteoporosis

Osteoporosis is characterized by a low bone mass and a gradual deterioration of the bone tissue and microarchitecture, compromising bone strength and increasing the risk of fragility fracture (11).

The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) of 2.5 standard deviations (SD) or more below the average value for young healthy females (BMD $\leq$-2.5 SD) (12). This definition has been widely accepted and provides a basis for diagnostic and interventional thresholds. The National Guidelines for Prevention and Treatment of Osteoporosis and Osteoporotic fractures in Norway from 2005 is largely based on the WHO definition of osteoporosis. The national guidelines further build on the WHO definition by stating that *"if a woman with low bone mass (osteoporosis) sustains a fracture, the condition is termed established osteoporosis"* (13). These guidelines have no operational definition for osteoporosis in men. Instead, a general definition is used: *"osteoporosis is a general change in the bone tissue that has led to a reduced bone mass and changes in the quality of the bone tissue with an increased risk of fracture"(13).*

Although the Norwegian national guidelines on osteoporosis incorporate important definitions, risk factors, diagnostic criteria, and treatment choices, it has not been updated since 2005. In the meantime, new drug treatments have been introduced and new insight into the disease development, treatment effects and diagnostics have surfaced. To keep up with these developments, several professional groups within different medical specialties developed their own treatment guidelines. The Norwegian Endocrinological, Rheumatological and Orthopedic associations have all created their own up-to-date treatment and diagnostic guidelines for osteoporosis and osteoporotic fractures (14-16).

Osteoporosis is a silent disease without obvious symptoms and is often not apparent until the occurrence of a low-energy fracture. A low-energy fracture is a fracture from standing height or less and implies that the fracture occurs at minimal impact (17). Relative to osteoporosis, fractures are of a more serious concern as they could result in substantial personal disability and mortality in patients as well as increased costs for society. The most common osteoporotic fractures are of the hip, wrist, and vertebra. Numerous studies have reported that of all types of osteoporotic fractures, hip fractures are associated with the greatest morbidity, mortality, and costs to society (6, 7, 12, 18, 19).

## 2.3 Hip fractures

The majority of hip fractures occur due to osteoporosis and a fall from standing or sitting height (a low-energy fracture) (20). Norway and Sweden have the highest reported incidence rates of hip fractures in the world (21). For largely unknown reasons, the risk of osteoporosis and fractures is significantly higher in these Nordic countries compared to the rest of the world (13). A study on the burden and management of fragility fractures in Europe estimated that the lifetime risk of sustaining a hip fracture in women and men at the age of 50 years in Sweden is 22.8% and 13.7%, respectively (6). A study on the population in Tromsø in Norway found that the estimated 10-year absolute risk of hip fractures at the age of 65 and 80 years was 4.2% and 18.6% in men, and 9.0% and 24.0% in women, respectively (22). In Norway approximately 9,000 adults sustain a hip fracture annually and 70% occur in women (23). On average, every hour one adult in Norway will have a hip fracture. Furthermore, the mean 1-year direct cost per hip fracture has been estimated to be over 500 000 Norwegian kroner (NOK) (19). This amounts to over 4.5 billion NOK in total costs per annum due to hip fractures.

Although nationwide data published in 2016 show a decline in hip fracture rates in Norwegian adults, the annual number of hip fracture cases has remained stable (3). This can be explained by the growing number of elderly persons, who are at the greatest risk of fracture (23).

Numerous studies report that sustaining an osteoporotic fracture increases the risk of subsequent fracture (23, 24). Available data suggest at least a doubled risk of sustaining a second fracture compared to the risk of the first (25). A study on hip fracture trends in Norway estimated that from 2006 to 2008 approximately 15% of the total hip fractures in women and 10% of the total hip fractures in men were subsequent hip fractures (23).

### 2.3.1 Hip fractures in the middle-aged population

Approximately 1 in 1000 Norwegian men and women at the age of 55 years will fracture their hip annually (19). In 2007, 110 individuals aged 50-69 years fractured their hip in the municipality of Oslo (26). A Danish study from 2018 estimated that between 2-11% of all hip fractures occur in persons below 60 years (27). In a study from Sweden on the long-term risks of osteoporotic fractures an estimated 20% of all fractures occurred at pre-retirement age (28).

It has previously been assumed that hip fractures in young adults are a result of high-energy trauma. However, a study conducted in Oslo in 2006 revealed that of 49 identified hip fractures in patients under 49 years, 65% of men and 67% of women had a history of low-energy trauma

(29). Furthermore, they found lower BMD values in these patients compared to the reference population regardless of trauma mechanism.

A hip fracture in middle age could have significant negative consequences for patients in terms of increased risk of death, disability, and the inability to participate in the labor market.

### 2.3.2 Morbidity

Patients with a hip fracture are almost always admitted to the hospital for surgery (20). Although many do recover, a large group become disabled with an increased need for care and health services. A systematic review conducted in 2014 on the outcomes in fracture patients after hospital discharge reported that hip fracture patients were the main users of informal care (7). Almost 70% of hip fracture patients reported using rehabilitation services after hospital discharge compared to 25% of vertebral fracture patients. A study from Oslo reported that among patients living at home prior to a hip fracture, 6% of those <75 years and 33% of those >85 years had moved to nursing homes after the fracture (30). In addition, approximately half of those who could walk without aid prior to the fracture were unable do so afterwards.

A review including 38 cohort studies on the long-term disability outcomes following hip fracture found that survivors of hip fracture had significantly worse health, mobility, functional independence, quality of life (QoL) and higher rates of institutionalization compared to their age-matched controls (31). Most of the included studies had reported outcomes in patients >60 years. Furthermore, most of the recovery, in terms of the ability to perform daily activities and the ability to walk, occurred within 6 months after fracture. However, between 40-60% of patients did not recover to their pre-fracture level of mobility and 30-60% had not regained their level of independence for basic daily activities. The study estimated that 10-20% of hip fracture patients in western nations are institutionalized.

In a study on the future burden of hip fractures in Norway it was estimated that the total health loss due to hip fractures would double from 32,850 Disability Adjusted Life Years (DALYs) in 2020 to 60,555 DALYs in 2040, assuming a medium population growth, an increasing proportion of elderly and a continued decline in hip fracture rates (32). In men the largest contributor to DALYs in the 2020 estimate was disability up until the mid-60s. In women, disability was the main contributor to DALYs up until the age of 80 years.

Data from the Norwegian Labor and Welfare Administration (NAV) reported that in 2016, 303 persons in Norway receiving unemployment benefits had the diagnosis of osteoporosis, both with and without previous fragility fracture(s) (33). Most (n=204) were in the age group 60-67

years and the majority were women (n=230). In this group, 236 received full unemployment benefits whilst the remainder received partial benefits. The data does not inform whether osteoporosis or low-energy fractures were the reason for the disability in these individuals. However, the abovementioned studies clearly suggest that an osteoporotic fracture markedly increases the likelihood of personal disability and the inability to participate in the labor market.

### 2.3.3 Mortality

Hip fractures are associated with a substantial short-term excess mortality. Patients may have as much as a 5-8 fold increased risk of death to all health causes the first 3 months after fracture (34). Although this excess mortality declines over time, returning to the level observed in the background population takes several years (8, 34). In a Norwegian study on the mortality following a first hip fracture, the highest excess mortality was observed the first two weeks after the fracture (8). Although declining over time, it remained higher compared to the background population for 12 years. Within the first year after fracture 33% of the men and 21% of the women had died. The 1-year mortality was almost three times as high in women and five times as high in men compared to the Norwegian background population. Furthermore, the highest excess mortality, in terms of standard mortality ratios (SMRs), was observed in the age group 50-64 years, at 0-3 months after fracture. The potential life-years lost due to hip fracture were also highest in this age group. The study estimated that approximately 5% of deaths in Norway among those ≥50 years could be attributed to hip fracture related death.

The high initial excess mortality after fracture could largely be related to infectious and cardiovascular complications (35). A study conducted in Denmark concluded that the post-fracture conditions such as infectious complications and not the pre-fracture conditions such as comorbidity were responsible for the excess mortality in hip fracture patients (36).

## 2.4 Fracture risk assessment

The clinical diagnosis of osteoporosis is based on the presence of a low-energy fracture and/or a T-score ≤ -2.5 SD in the lumbalcolumna, the femur or in the total hip measured using dual x-ray absorptiometry (DXA) (14). DXA is referred to as the "gold standard" method in measuring bone density (37). The T-score is the SD difference in BMD between the patient and that of a young healthy adult. Bone density and T-score values can be divided into four levels:

- Normal bone density: A T-score within 1 SD of the young adult mean
- Low bone density: A T-score of 1 to 2.5 SD below the young adult mean
- Osteoporosis: A T-score of 2.5 SD or more below the young adult mean
- Severe osteoporosis: A T-score of 3.5 SD or more below the young adult mean

The risk of fragility fractures doubles with every SD that the BMD falls below the young adult mean (37). Based on this information and BMD measurements patients with a high risk of fracture can be identified and treated.

As fracture risk is assessed individually and affected by numerous risk factors, risk assessment tools can be useful in identifying high-risk patients. The Fracture Risk Assessment Tool (FRAX®) is an online resource that estimates the 10-year risk of hip and major osteoporotic fractures based on nationality, sex, age, height, weight, previous low-energy fractures, parental hip fracture, smoking status, alcohol consumption, the presence of rheumatic arthritis and the use of glucocorticoids (16). The FRAX-score can be calculated with and without measured BMD-values and is therefore useful when DXA measurements are unavailable.

## 2.5 Treatment and follow-up services

The Norwegian orthopedic treatment guidelines for low-energy fractures in men and women ≥ 50 years state that all fracture patients should be offered (15):

- Optimal fracture treatment
- Blood tests
- Investigation of osteoporosis using DXA and/or FRAX with subsequent follow-up
- Treatment of osteoporosis
- Fall preventive measures

These prerequisites form the basis for a defined treatment algorithm for low-energy fractures (15). As patients with low-energy fractures have a high risk of subsequent fracture the guidelines emphasize the need for early treatment of osteoporosis. Treatment of osteoporosis includes lifestyle advice such as increased weight-bearing physical activity, a varied diet, smoking cessation and restrictions in alcohol consumption, treatment with calcium and vitamin D and treatment with anti-osteoporotic drugs (AODs).

In order to identify patients at high risk of recurrent fracture, treatment guidelines recommend that all Norwegian hospitals implement Fracture Liaison Services (FLS) (15). In the FLS model dedicated fracture coordinators identify fracture patients in orthopedic hospital departments and outpatient clinics and offer treatment for osteoporosis and follow-up services. FLS has documented effects on the prevention of recurrent fractures and fracture-related mortality in those ≥50 years. In Norway only 8 of 50 hospital departments that offer orthopedic services have implemented the FLS-model (38). In 2021 a proposal was presented to the Norwegian government in hopes of securing financial support for implementing FLS in all health authorities (38). In a hearing held by the Norwegian government 27$^{th}$ of May 2021 this proposal was rejected (39).

## 2.6 Underdiagnosed and undertreated

A Danish nationwide study from 2005 estimated that the expected annual incidence of osteoporosis for persons ≥50 years in the population to be 58,658 per million inhabitants in women and 23,648 per million inhabitants in men (5). However, the observed annual incidence was only 4,823 per million inhabitants in women and 862 per million inhabitants in men. This corresponds to 8.2% of the expected annual incidence in women and 3.6% of the expected annual incidence in men, which indicates that osteoporotic patients are substantially underdiagnosed.

Osteoporotic patients both with and without previous fragility fracture are seldom offered treatment with AODs. A Norwegian population-based study from 2018 estimated that out of those with high risk of fracture, defined as a FRAX score for Major Osteoporotic Fracture ≥ 20%, only 25% of women and 17% of men were using AODs (4). In a subgroup of individuals who had BMD measurements, 24% of women and 16% of men who were defined as high-risk patients were treated with AODs. A Danish population-based study from 2008 found that only 4.1% of men and 9.2% of women received anti-osteoporotic drug therapy after hip fracture (40). A population study from Sweden in 2019 found that only 22% of elderly osteoporotic women eligible for treatment were prescribed AODs (41).

## 2.7 Governmental aims in hip fracture prevention

In the 2015 public health message the Norwegian government had a goal of intensifying measures aimed at the prevention of falls and reduce the number of hip fractures by 10 percent within the end of 2018 (1). However, the annual number of primary hip fracture surgeries only fell from 8411 in 2015 to 8334 in 2018, a reduction of 0,92% (2). Why the government chose a goal of reducing hip fractures by exactly 10% and whether this was based on scientific literature or on inputs from professional groups, is unknown. Furthermore, several professionals and researchers within the field of osteoporosis were never informed nor consulted with regard to the government's ambitious goal (42). The public health message had not included any measures aimed at increasing the follow-up and investigation of low-energy fractures in those ≥50 years as recommended by the professional groups.

In the 2018 public health message the Norwegian government introduced a new goal, a zero-vision for serious accidental falls at home (43). This was aimed at reducing the most serious consequence associated with falls, namely, hip fractures. The Norwegian parliament in collaboration with the Directorate of Health will prepare a cross-sectoral action plan for achieving this zero-vision. When published, the plan will include preventive measures such as home visits, physical activity measures, nutritional measures, medication review and follow-up services after fall. The public message, however, does not mention any measures aimed at identifying and treating the most serious underlying cause of fractures, that is, osteoporosis.

## 2.8 Productivity losses and gains

Productivity costs or productivity losses are the value of the lost productivity when individuals no longer can work as a result of illness, disability or death (44). Productivity costs are often measured in Cost-of-Illness (COI) studies where all costs associated with a specific disease are identified and measured, such as direct, indirect (productivity costs) and intangible costs (45). The aim is to estimate the total economic burden to society of a given disease. Productivity gains on the other hand, are the averted productivity losses due to a health intervention such as a drug treatment (46). Productivity gains are focused on measuring the economic benefits to society of a person's return to work due to their improved health. This term is more commonly found in health economic evaluations of health interventions, where the costs and effects/benefits of a new treatment are compared to that of an existing treatment for the same disease. Withing the cost-effectiveness framework of economic evaluations the monetarized production gains appear in the numerator of the cost-effectiveness ratio (CER) for a given intervention, as a cost saving to be subtracted (47):

$$CER = (C - PG)/H$$

*Where:*

$C = Program\ costs$

$PG = Production\ gains$

$H = Health\ effects$

It follows from the formula that the more production gains can be subtracted from the numerator the more favorable the cost-effectiveness ratio (47).

### 2.8.1 The economic benefits to society of a person's return to work

What are the economic benefits to society of a person's return to work due to their improved or recovered health? Table 1 illustrates what happens when a previously sick person returns to work (47). Firstly, the employer experiences a production gain (an increase in production) but must pay the employee a gross income. The net income that the employee experiences is the income after taxation. In addition, the employee loses his or her sickness benefits due to improved health. Lastly, the government receives tax revenues from the employee and gains in averted payments of sickness benefits. This allows a differentiation between the private and the collective gains. The private gains are the gains to the employee in terms of increased own consumption and the gains to the employer in terms of increased profit. The collective gains are the economic benefits to society because of increased taxes and saved sickness benefit payments. These gains increase the public budgets and allow for an increased expenditure on public goods and services. Furthermore, table 1 shows how transfer payments are nullified and only the actual increased productivity from improved or recovered health remains. In other words, these are the real economic changes from improved health. How are these changes then measured? For simplicity and to avoid having to measure the actual productivity of every worker, wage rates are often used as a proxy for measuring production gains.

*Table 1 - The consequences of an employee's return to work after sickness. The table is from J.A. Olsen's book Principles in Health Economics and Policy (47).*

| | Employer | Employee | Government |
|---|---|---|---|
| Production gains | +PG | | |
| Income and taxes | -I | +I -T | +T |
| Sickness benefits | | -SB | +SB |
| Net result | Increased profit | Increased own consumption | Increased public budget |
| | *Private gains* | *Private gains* | *Collective gains* |

PG: Production gains, I: Income, T: Income taxes, SB: Sickness benefit payments

### 2.8.2 Methods for measuring productivity gains

The two most common methods for measuring productivity losses and gains are the human capital approach (HCA) and the friction cost approach (FCA) (44). Both are recommended by national guidelines on economic evaluations of health interventions (48). However, there is an ongoing debate as to which of the two more appropriately measures work productivity.

In the HCA, productivity losses are calculated based on the present value of the future economic production lost due to illness, disability or premature death (44). Productivity losses in the HCA are valued as gross incomes. This method counts any hour not worked as an hour lost, which can lead to large estimates on productivity losses, especially in the case of long-term absence from work. The HCA is therefore often criticized for overestimating productivity losses associated with disease.

As opposed to the HCA, the FCA assumes that employees who are unable to work can be readily replaced by an already employed or unemployed person (44). This method assumes a productivity loss, in terms of a lost gross income, only in the period it takes to replace the ill or deceased worker and train a replacement. This period is called the friction period. FCA has been criticized for associated uncertainties, e.g., the duration of the friction period, at what time the friction period begins and if a previously sick person or internal labor reserves really can make up for lost productivity. In addition, the employment of a person who previously was employed can create a chain of vacancies, each with their own friction period. Some health economists argue that the productivity loss would need to be measured for all these periods that these vacancies create, further complicating the application of this method. As opposed to the HCA, studies that apply the FCA generally produce lower estimates on productivity losses.

In the 1990s the US Panel on Cost-effectiveness in Health criticized both methods. They instead proposed that productivity costs are and should be included as non-monetary effects rather than costs (or monetary gains) in health economic evaluations of interventions (49). The US Panel argued that respondents of health state questionnaires used for estimating non-monetary effects like the QALY would consider the effect of productivity and income when valuing health states. Implying that including productivity costs as costs (or monetary gains) in economic evaluations would lead to a double-counting. Since the US panel method was proposed, empirical studies have shown that generic instruments used in health state valuations are not visibly influenced by income effects, and can be used alongside monetary valuation methods like the FCA and the HCA for estimating productivity costs (49).

### 2.8.3 Productivity gains in health economic evaluations and drug decision-making

When conducting health economic evaluations of health interventions, the perspective taken decides which costs and monetary gains that are relevant to include. From a healthcare perspective the aim is to maximize health from a given healthcare budget (49). Therefore, costs and monetary gains that often fall outside this budget, such as productivity costs and gains, become less relevant to include. From a societal perspective all costs and monetary gains that are directly or indirectly induced by the implementation of the intervention are relevant to examine, including but not limited to productivity costs and gains (if productivity is in fact affected). The now outdated Norwegian guidelines on economic evaluations of health interventions from 2012 recommended that health economic analyses of health interventions take a societal perspective to "*think broadly with regard to consequences"*(50). However, in the 2016 whitepaper on the priority setting in the Norwegian health sector a broad healthcare or limited societal perspective was instead proposed (9). Implying that some consequences for resource use outside the health care sector can be emphasized in drug decision-making. However, as of 2016 productivity gains will not be emphasized in prioritization decisions for financing medicines in Norway.

### 2.8.4 A systematic inconsistency in the inclusion of productivity gains

In a report published by Menon economics in 2021, a comprehensive assessment of todays practice regarding socioeconomic evaluations of health interventions in Norway was conducted (51). The report underlined a systematic inconsistency in today's practice regarding the inclusion of productivity gains. Through several examples, the report illustrates that the choice between a broad healthcare and a societal perspective when conducting economic evaluations of health interventions, both inside and outside the healthcare sector, often is random and not clearly defined. The choice of perspective can have a large impact on the results of the economic analysis. In other words, whether productivity gains are included or not can greatly affect the cost-effectiveness of interventions. Furthermore, the report states that different valuations of the same health intervention can lead to a suboptimal allocation of societal resources. Interventions in the health sector will be due to the exclusion of productivity gains be worth less than interventions in other sectors were productivity gains are emphasized. This could ultimately lead to fewer appropriations to the health sector compared to other sectors. The report recommends to even out current differences in the methodological framework by adopting a

societal perspective in the healthcare sector and include productivity gains in economic evaluations of health interventions.

### 2.8.5 Potential equity issues in prioritization

The main concerns regarding the inclusion of productivity gains in prioritization decisions for treatment interventions in the healthcare sector is potential equity issues. Some drug treatments could have a greater potential for productivity gains than others (9), because they primarily are aimed at the young working population. Drugs with a larger potential for productivity gains could therefore be prioritized over other treatments with less or no potential productivity gains. This could be considered unjust as inclusion of these gains could lead to less resources being allocated to interventions aimed at those that are less productive, such as the retired and the disabled (49).

## 2.9 Productivity costs in fracture patients

In a COI study on the burden of osteoporotic fractures in Denmark productivity costs accounted for 13-14% of the total costs of fracture in all persons 50-90 years (52). A substantial portion of the total cost considering that productivity losses from work only occur in those under the age of retirement, and that the majority of fractures occur above the age of retirement. When looking at the cost-dependent fracture type, first and subsequent hip fractures accounted for 20-38% of the total costs of fractures.

In a prospective study from the Netherlands, direct and indirect costs associated with osteoporotic fractures in patients ≥50 years were collected through cost diaries (53). In this study, indirect costs accounted for approximately half of the total costs of fractures, of which 81% was due to sick leave in employed patients.

## 2.10 Markov models

The Markov model is an analytical framework frequently utilized in economic evaluations of healthcare interventions to estimate the costs and benefits of treatments and in health economic studies to estimate the economic burden of diseases (54). These models seek to incorporate the fact that disease status, resource utilization and treatment effects vary over time and between individuals (55).

In Markov models patients are moved between different disease states over time, representing the possible long-term trajectories of a given disease (54). Disease states are mutually exclusive and exhaustive, and individuals can only be in one state at any given time. Examples of general disease states that might be included in a simple Markov model are “healthy”, “sick”, “sicker” and “dead”. “Transitions” or movements between states is based on transition probabilities and transitions can only occur after a defined period of time, termed “a cycle”. Cycle lengths can vary depending on the disease being examined but are most often one year. The total length of the model simulation (the total number of cycles) is determined by the choice of treatment, the disease and the cohort being examined. However, when simulating chronic diseases, it is normal to adopt a lifetime perspective. A cohort of patients can for example be simulated through the model disease states until they reach a certain age or die. Time spent in each disease state in every cycle has associated costs and health outcomes. Costs and health outcomes can be aggregated over all consecutive cycles and compared to the costs and outcomes when a health intervention such as a drug treatment is applied to the model. Different health interventions for the same disease can be applied to the model and their costs and outcomes can be compared to one another.

### 2.10.1 Cohort simulations

There are two main types of Markov models, cohort simulations and microsimulations. In cohort simulations, the cohort that are simulated through the model are assumed to be homogenous (56). At any time in the simulation individuals within a certain state are assumed to have the same probabilities of transitioning to another health state. An inherent limitation to these simulations is that they have no memory of previous transitions or stays within states. Therefore, transition probabilities are solely based on the current health state occupied and not on the history of previous transitions. This memoryless function is often termed the Markov assumption or condition and can be relaxed by creating additional health states that capture the cohorts history. However, too many health states can result in difficult to manage models due

to “state explosion”. Furthermore, estimates on effects and costs in cohort simulations are given at group level (55). It is therefore impossible to follow the course of individual patients.

### 2.10.2 Microsimulations

In microsimulations, individuals in the cohort are assumed to be heterogeneous and therefore have individual trajectories and transition probabilities (56). Heterogeneity is based on the individual patient characteristics at the start of the simulation and the transitions to health states as the simulation progresses (55). Microsimulations can “track” individual patient courses and use the information on previous stays within states to calculate new transition probabilities for each individual. Microsimulation models therefore do not require the Markov assumption and thereby introduce a “memory” function to the model structure (56). Despite this, microsimulations are seldom used in health economic evaluations for drug decision-making. Perhaps due to their numerical complexity and extensive computational requirements (56).

## 2.11 Study aim

The aim of this study is to estimate the productivity gain by preventing first and subsequent hip fractures through optimal treatment of osteoporotic patients in Norway.

# 3 Method

## 3.1 Population, Intervention, Comparator and Outcome (PICO)

**Population:** The number of men and women aged 50 years in Norway in 2021 who are working full-time.

**Intervention:** Treatment with anti-osteoporotic drugs (AODs).

**Comparator:** A no-treatment or sub-optimal treatment scenario based on the incidence of hip fractures in the selected population.

**Outcome:** Averted first and subsequent hip fractures in the intervention model leads to a productivity gain by ensuring that patients can continue working.

## 3.2 The Markov model

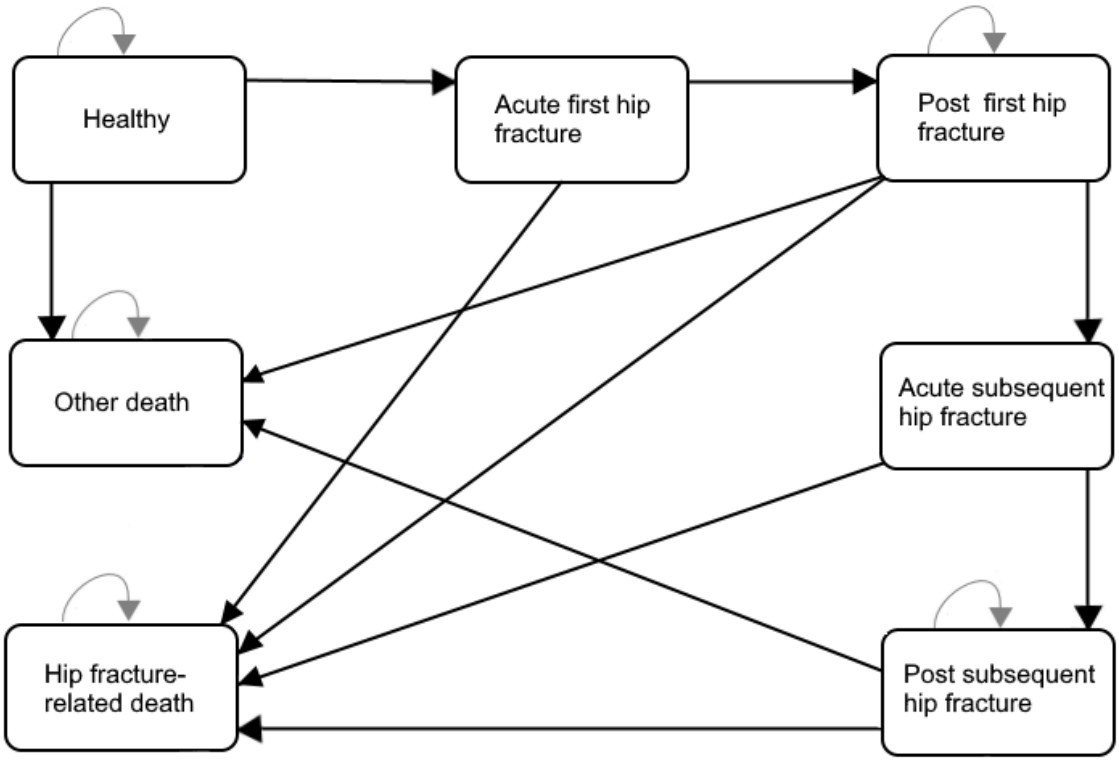



*Figure 1 - An illustration of the Markov model.*

R was used to develop a cohort simulation based on the number of men and women aged 50 years in Norway in 2021. A total of 36 795 women and 38 565 men were separately simulated through the model with their initial risks based on the age-specific hip fracture incidence in the Norwegian population (3). We chose 50 years as the starting age of the cohorts as data on hip fractures under the age of 50 in Norway were scarce. All hip fractures were assumed to be osteoporotic and caused by low-energy trauma. Simulations were run until individuals turned 70 years or died. 70 years was the assumed mean retirement age at which productivity from the labor market would cease. Cycle lengths were set to one year and transition probabilities varied with age, i.e., the time in the simulation. Twenty-one cycles were run as simulation outcomes were presented at the beginning of cycles.

All individuals started in the "Healthy" state at the beginning of the simulation. It was assumed that none had sustained a hip fracture prior to the start of the simulation. From the "Healthy" state individuals could either remain in this state, transition to the state "Other death", or experience a first hip fracture. Individuals who experienced a first hip fracture remained in the "Acute first hip fracture" state for one cycle. Those who survived the acute phase and thus did not transition to the "Hip-fracture related death" state were moved to the "Post first hip fracture"

state in the subsequent cycle. In this state individuals either remained there, died, or experienced a subsequent hip fracture. Individuals who experienced a subsequent hip fracture remained in the "Acute subsequent hip fracture" state for one cycle. Those who survived transitioned to the "Post subsequent hip fracture" state. From here individuals could either die or remain there for the rest of the simulation.

"Other death" and "Hip fracture-related death" were absorbing states. "Other death" reflects the background mortality in Norway whilst "Hip fracture-related death" reflects the mortality attributed to hip fractures. Due to the high acute mortality after hip fracture, it was assumed that individuals who died in the acute phases died of a hip fracture related reason and thus could not transition to the "Other death" state. Acute and post states were implemented to differentiate between the high acute mortality associated with the hip fracture and the mortality in the subsequent years (8). The subsequent hip fracture states were implemented to observe the proportion of individuals sustaining a second hip fracture. Table 2 gives an overview and a description of the different model states.

*Table 2 - An overview and description of the different model states.*

| State | Description |
|---|---|
| Healthy | Individuals without a prior hip fracture |
| Other death | Background mortality |
| Hip fracture-related death | Mortality attributed to hip fracture |
| Acute first hip fracture | First year after a first hip fracture |
| Post first hip fracture | Subsequent year(s) after a first hip fracture |
| Acute subsequent hip fracture | First year after a subsequent hip fracture |
| Post subsequent hip fracture | Subsequent year(s) after a subsequent hip fracture |

## 3.3 Transition probabilities

Transition probabilities were primarily based on incidence rates extracted from Norwegian and Swedish population-based studies and Statistics Norway. Due to a lack of transparency in terms of reporting study outcomes, several studies containing relevant data could not be selected for inclusion to the model. Therefore, where data was unavailable assumptions were made. For all transition probabilities utilized in the model see appendix 2.

### 3.3.1 Healthy to Acute first hip fracture

The transition probabilities from Healthy to Acute first hip fracture were based on the age-specific hip fracture incidence in men and women in Norway reported by Søgaard et al (3). As incidence rates were reported in 5-year age groups it was chosen to equally distribute the rate across the different ages in the same 5-year age interval in the model. Annual state transition probabilities were derived using the following formula:

$$P = 1 - e^{-rt}$$

*Where:*

$P = transition\ probability$
$e = base\ of\ the\ natural\ logarithm$
$r = event\ rate$
$t = time$

### 3.3.2 Healthy to Other death

Transition probabilities from Healthy to Other death were based on the age- and gender specific background death rates in the Norwegian population in 2020 from Statistics Norway (57). As incidence rates were reported in 5-year age groups it was chosen to equally distribute the rate across the different ages in the same 5-year age interval in the model. Annual state transition probabilities were derived using the formula illustrated in 3.3.1.

### 3.3.3 Acute first hip fracture to Post first hip fracture

The Acute first hip fracture state was a temporary state, lasting for one cycle. Individuals who did not transition to Hip fracture-related death from the Acute first hip fracture state after one

cycle were moved to the Post first hip fracture state. Therefore, the probability of transitioning to the Post first hip fracture state after once cycle was:

$$p(PFH) = 1 - p(HRD)$$

*Where:*

*p(PFH) = the probability of transitioning to the Post first hip fracture state*

*p(HRD) = the probability of transitioning to the Hip fracture related death state*

### 3.3.4 Acute first hip fracture to Hip fracture-related death

The probabilities of transitioning to Hip fracture-related death in the Acute first hip fracture state were based on a Swedish population based study by Kanis et al (58). The study reported mortality rates in 5-year age groups in men and women at 6 months and at 5 years after hip fracture. The mortality rates at 6 months after fracture were selected and equally distributed across the different ages in the same 5-year age interval in model. Using the formula in 3.3.1 the annual state transition probabilities were derived.

### 3.3.5 Post first hip fracture to Hip fracture-related death

The probabilities of transitioning to Hip fracture-related death in the Post first hip fracture state were based on the study by Kanis et al (58). The mortalities attributed to hip fracture were derived by subtracting the age- and gender specific background mortalities in Norway from the reported age- and gender specific mortalities at 5 years after fracture. As mortality rates were reported in 5-year age groups it was chosen to equally distribute the rate across the different ages in the same 5-year age interval in the model. Using the formula in 3.3.1 the annual state transition probabilities were derived.

### 3.3.6 Post first hip fracture to Other death

The probabilities of transitioning from Post first hip fracture to Other death were based on the age- and gender specific background death rates in Norway (see 3.3.2) (57). It was assumed that hip fracture patients had the same background mortality as the general population.

### 3.3.7 Post first hip fracture to Acute subsequent hip fracture

The probabilities of transitioning from the Post first hip fracture state to the Acute subsequent hip fracture state were based on an observational study from the UK (59). The study reported the incidence rates of subsequent hip fractures one year after the first in men and women in two age groups, 55-64 and 65-74. The incidence rate in those 55-64 years was equally distributed across the different ages in this age interval and these rates were then applied to those 50-64 years in the model. The rate in those 65-74 years was equally distributed across the different ages in this interval and these rates were then applied to those 65-70 years in the model. The annual state transition probabilities were derived using the formula in 3.3.1 and assumed to be the same regardless of the time at which the second hip fracture occurred in the simulation.

### 3.3.8 Acute subsequent hip fracture to Post subsequent hip fracture

Like the state described in 3.3.3 the Acute subsequent hip fracture state was a temporary state. Individuals who survived the acute state and thus did not transition to Hip fracture-related death after one cycle were moved to the Post-subsequent hip fracture state. Using the same formula as in 3.3.3 the probabilities of transitioning to the Post subsequent hip fracture state were derived.

### 3.3.9 Acute subsequent hip fracture to Hip fracture-related death

The probabilities of transitioning to Hip fracture-related death in the Acute subsequent hip fracture state were assumed to be the same as the probabilities in 3.3.4. This was based on the age- and gender specific mortality rates at 6 months after hip fracture from the study by Kanis et al (58).

### 3.3.10 Post subsequent hip fracture to Hip fracture related death

The probabilities of transitioning to Hip fracture-related death in the Post subsequent hip fracture state were assumed to be the same as in 3.3.5. This was based on the age- and gender specific mortality rates at 5 years after hip fracture reported in the study by Kanis et al (58).

### 3.3.11 Post-subsequent hip fracture to Other death

The probabilities of transitioning from Post subsequent hip fracture to Other death were based on the background death rates in Norway (see 3.3.2) (57). Table 3 summarizes the annual state transition probabilities used in the model.

*Table 3 - An overview and description of the annual state transition probabilities.*

| Transition probability: | Based on: |
|---|---|
| From Healthy to Acute first hip fracture | Hip fracture incidence in Norway |
| From Healthy to Other death | Background mortality in Norway |
| From Acute first hip fracture to Post first hip fracture | Those who survive the acute phase |
| From Acute first hip fracture to Hip fracture related death | Mortality at 6 months after hip fracture |
| From Post first hip fracture to Hip fracture related death | Mortality attributed to hip fracture at 5 years after fracture |
| From Post first hip fracture to Other death | Background mortality in Norway |
| From Post first hip fracture to Acute subsequent hip fracture | Incidence of second hip fracture in the UK |
| From Acute subsequent hip fracture to Post subsequent hip fracture | Those who survive the acute phase |
| From Acute subsequent hip fracture to Hip fracture related death | Mortality at 6 months after hip fracture |
| From Post subsequent hip fracture to Hip fracture related death | Mortality attributed to hip fracture at 5 years after fracture |
| From Post subsequent hip fracture to Other death | Background mortality in Norway. |

## 3.4 Intervention and comparator

The comparator model, which was based on the incidence of hip fractures and deaths in the population, was assumed to represent a no-treatment or sub-optimal treatment scenario. The intervention, which represented an optimal treatment scenario, was based on a systematic review of clinical trials data on the comparative effectiveness of AODs in the treatment of osteoporosis and prevention of fractures (60). The study found high-strength evidence that bisphosphonates (alendronate, ibandronate, risendronate, and zoledronic acid), denosumab, and teriparatide reduce fractures in postmenopausal women with osteoporosis compared to placebo with relative risk reductions (RRRs) of 20-40% (relative risks of 0.60-0.80) for non-vertebral fractures (fractures not occurring in the vertebra). A RRR of 30% was chosen as the base-case intervention in the model and applied as a risk reduction in all cycles and in both gender cohorts. As data on the comparative effectiveness of AODs in the treatment of osteoporosis in men was scarce the RRR was assumed to be the same in both sexes. The intervention was applied as both a primary and secondary prevention in the model. Risk reduction was applied to the state transition from healthy to acute first hip fracture and from the post first hip fracture to the acute subsequent hip fracture state. The table below summarizes the relative risk reductions that were applied to the model state transitions.

*Table 4 - Relative Risk Reductions from the treatment intervention.*

| State transition: | RRR: |
|---|---|
| From Healthy to Acute first hip fracture | 30% |
| From Post-first hip fracture to Acute subsequent hip fracture | 30% |

## 3.5 Calculation of productivity gains

To estimate the productivity gain, the number of first and subsequent hip fractures and hip fracture-related deaths in the intervention model were subtracted from the comparator model. These are the number of averted hip fractures and hip fracture related deaths due to the intervention. Productivity gains were then calculated based on averted sick leave, averted permanent disability, and averted hip fracture-related death using the HCA and a societal gain calculation. Productivity gains were estimated for each cycle (at each age) in the simulation.

Below are some important model assumptions related to the calculation of productivity gains, which are summarized in table 5:

**I.** All individuals were working full-time prior to the start of the simulation and would continue to do so when in the Healthy state.

**II.** All individuals who sustained a hip fracture experienced a fixed number of sick leave days within the first year of fracture.

**III.** A fixed proportion of patients who survived the acute phases would experience disability. It was assumed that individuals experiencing disability were 100% disabled to work the remaining time in the model.

**IV.** Individuals who did not experience disability to work were assumed to continue working full-time.

*Table 5 - A summary of the assumptions related to the calculation of productivity gains.*

| Health state: | Assumption: |
|---|---|
| Healthy | All persons working full-time |
| Acute first hip fracture | All persons experience sick leave days |
| Post first hip fracture | A proportion permanently disabled; rest are working full-time |
| Acute subsequent hip fracture | All persons experience sick leave days |
| Post subsequent hip fracture | A proportion permanently disabled; rest are working full-time |

### 3.5.1 Human capital approach

The time absent from the labor market due to hip fracture and thus the potential production gain from optimal treatment was valued as the mean age- and sex specific gross incomes in Norway. Absence from the labor market due to hip fracture was accounted for in sick leave days, years in permanent disability, and years lost due to premature hip fracture related death. For simplicity, productivity was not adjusted to account for labor force participation and unemployment. Gains were calculated based on averted absenteeism (physical absence from work) and not presenteeism (reduced work performance) and unpaid production. Multiplier effects and compensation mechanisms were not accounted for in our study. The table below illustrates how productivity gains were calculated using the HCA.

*Table 6 - Calculation of productivity gains using the HCA.*

| Productivity gain due to: | Formula: |
|---|---|
| Averted hip fracture related death | Gross income * expected remaining years in the labor market |
| Averted permanent disability | Gross income * expected remaining years in the labor market |
| Averted sick leave | Gross income * averted sick leave days |

### 3.5.2 Societal gain

To identify the production gain to society of optimal treatment, time away from the labor market was valued as the potential gained income taxes and potential averted sickness benefit payments. These are the collective gains to society (see table 1). This method was originally prepared and utilized in the thesis by Mikkelborg on the productivity gain by preventing major cardiovascular events (61). For averted hip fracture related death, the societal gain was the age- and gender specific income taxes for the potential remaining years left in the labor market. For averted permanent disability, this was the age- and gender specific income taxes and avoided net disability pension payments for the potential remaining years left in the labor market. Lastly, averted sick leave was measured in the age- and gender specific gross incomes. The table below illustrates how the societal gain was calculated.

*Table 7 - Calculation of the societal gain.*

| Productivity gain due to: | Formula: |
|---|---|
| Averted hip fracture related death | Income tax * expected remaining years in the labor market |
| Averted permanent disability | (Income tax + avoided net disability pension payments) * expected remaining years in the labor market |
| Averted sick leave | Gross income * averted sick leave days |

### 3.5.3 Gross incomes, tax rates and disability pension payments

Mean monthly gross income estimates for full-time employees were retrieved from Statistics Norway (62). Estimates were reported in 5-year age groups in men and women with the last group being those ≥60 years. It was chosen to apply the same mean gross income to all ages within the same 5-year age interval. For those ≥60 years the same mean gross income was applied to all ages within this last age interval until 70 years. Daily gross income estimates were derived by dividing monthly gross incomes by the average number of working days per month in Norway (63). Annual gross income estimates were calculated by multiplying monthly gross incomes by 12.

Mean income tax rates were retrieved from Statistics Norway and reported in 5-year age groups in both men and women (64). It was chosen to apply the same tax rate to all ages within the same 5-year age interval.

In Norway disability pension payments consist of 66 % of an individual's annual gross income up to six times the National Insurance basic amount (65). Per May 2021 this amount was six times 106, 399 NOK (66). To calculate the annual gross disability pension payments, gross incomes that were below six times this amount were multiplied by 0.66. For gross incomes above six times the National Insurance basic amount, 638 394 was multiplied by 0.66. Annual net disability pension payments were then calculated by subtracting an income tax of 21%. For all income, tax rate and disability pension estimates utilized in the calculations see appendix 4.

### 3.5.4 Sick leave days

As data on the observed number of sick leave days from work after hip fracture in Norway was unavailable, we relied on expert clinician opinion. One orthopedic clinician from the University hospital in Northern Norway (UNN) stated that for persons with office jobs, sick leave for 4-6 weeks would normally be sufficient. For those with physically demanding jobs, a sick leave of a minimum of 12 weeks would be necessary. An average of 8 weeks (56 days) was chosen as a fixed number of sick leave days from work in the calculation of productivity gains.

### 3.5.5 Permanent disability

The proportion of patients permanently disabled to work was based on a prospective cohort study by Ekegren et al (67). The study reported the 12-month work-related outcomes following hip fracture in patients ≤65 years. Of those who worked prior to hip fracture and survived to 12 months after fracture, 35% had not returned to work. The study differentiated between trauma mechanisms and in those with low-energy trauma and who were working prior to fracture (68 persons), 34% (23 persons) had not returned to work at 12 months. Although the study reported sex- and age specific 12-month Return to work (RTW) rates, for simplicity, the overall proportion of persons not returning to work (35%) was chosen in the calculation of production gains. It was assumed that those who did not return to work at 12 months were permanently disabled to work. This assumption was supported by two previous studies showing little change in RTW rates from 12 to 24 months in general trauma populations (from 64% to 68%) (68) and in patients with major limb trauma (from 42% to 51%) (69). The table below summarizes some important elements in calculating productivity gains.

*Table 8 - Important elements in calculating productivity gains:*

| Productivity gain due to: | Calculated based on the: |
|---|---|
| Averted hip fracture related death | Difference in the number of hip fracture-related deaths between the comparator and intervention model |
| Averted permanent disability | Difference in the number of individuals surviving the acute phases of fracture between the comparator and intervention model. 35% of these individuals would have been permanently disabled to work |
| Averted sick leave | Difference in the number of individuals sustaining first and subsequent hip fractures between the comparator and intervention model. All these individuals would have experienced 56 days of sick leave |

## 3.6 Sensitivity analysis

One-way sensitivity analysis was conducted on the effect of the intervention in reducing hip fractures. RRRs used in sensitivity analysis were obtained from the same study as the applied base-case intervention (60).

*Table 9 - Base-case and RRRs applied in sensitivity analysis.*

| | Low | Base-case | High |
|---|---|---|---|
| RRR | 20% | 30% | 40% |

## 3.7 Discounting

Productivity gains were discounted to the present value by a 4% annual standard rate as recommended in the Norwegian National guidelines on health economic evaluations (50) and by the Norwegian Ministry of Finance (70).

# 4 Results

## 4.1 Productivity gain using HCA in the Norwegian population

The total discounted productivity gain using the HCA in a Norwegian population of 50-year-old men and women simulated over a 20-year period was 122 563 806 NOK. Table 10 presents the productivity gain in men and women in 5 year age intervals. In both men and women, the age interval from 55-59 years contributed the most to the total estimated productivity gain, 41% and 55%, respectively. The number of individuals the calculations were based on were largest in the last age interval, from 65-70 years, in both sexes. In men, however, the productivity gain was in fact lowest in this age interval. In women, the productivity gain was lowest from 50-54 years. The total productivity gain due to the intervention was greatest in men.

*Table 10 - The discounted productivity gain using the HCA and the percent contribution to the total estimates, in men and women in 5-year age intervals.*

| Age interval | Individuals* | | Discounted HCA** and %-contribution | | | |
|---|---|---|---|---|---|---|
| | Women | Men | Women | % | Men | % |
| 50-54 | 5 | 5 | 0.62 | 1 | 12.6 | 18 |
| 55-59 | 10 | 5 | 28.9 | 55 | 28.4 | 41 |
| 60-64 | 15 | 15 | 12.3 | 23 | 19.4 | 28 |
| 65-70 | 30 | 20 | 11.1 | 21 | 9.2 | 13 |
| **Total** | **60** | **45** | **52.9** | **100** | **69.6** | **100** |

**The number of individuals the calculations are based on. These are all the averted hip fractures as a result of the intervention.*

***Productivity gains are in the million NOK.*

## 4.2 Productivity gain per prevented hip fracture

Table 11 presents the average productivity gain per prevented hip fracture in 5 year age intervals in men and women. Based on the 105 averted hip fractures due to the intervention, the average productivity gain per prevented fracture was ~1 167 000 NOK. In men the average productivity gain per prevented fracture was ~1 550 000 NOK, almost double that of the women (~880 000 NOK). The age interval from 55-59 years had the largest productivity gain per prevented hip fracture, at approximately 2 890 000 NOK in women and 5 680 000 NOK in men. The productivity gain per prevented hip fracture was lowest in the first age interval in women (~120 000 NOK) and in the last age interval in men (~460 000 NOK).

*Table 11 - The average discounted productivity gain per prevented hip fracture using the HCA, in 5 year age intervals in men and women.*

| Age interval | Individuals* | | Average productivity gain per prevented hip fracture** | |
|---|---|---|---|---|
| | Women | Men | Women | Men |
| 50-54 | 5 | 5 | 0.12 | 2.52 |
| 55-59 | 10 | 5 | 2.89 | 5.68 |
| 60-64 | 15 | 15 | 0.82 | 1.29 |
| 65-70 | 30 | 20 | 0.37 | 0.46 |
| **Total** | **60** | **45** | **0.88** | **1.55** |

**The number of individuals the calculations are based on. These are all the averted hip fractures as a result of the intervention.*

***Productivity gains are in the million NOK.*

## 4.3 Productivity gain distribution

Table 12 presents the discounted productivity gain in men and women distributed on averted sick leave, averted permanent disability, and averted hip fracture related death. In both men and women, averted permanent disability contributed the most to the total estimated productivity gain, 81% and 79%, respectively.

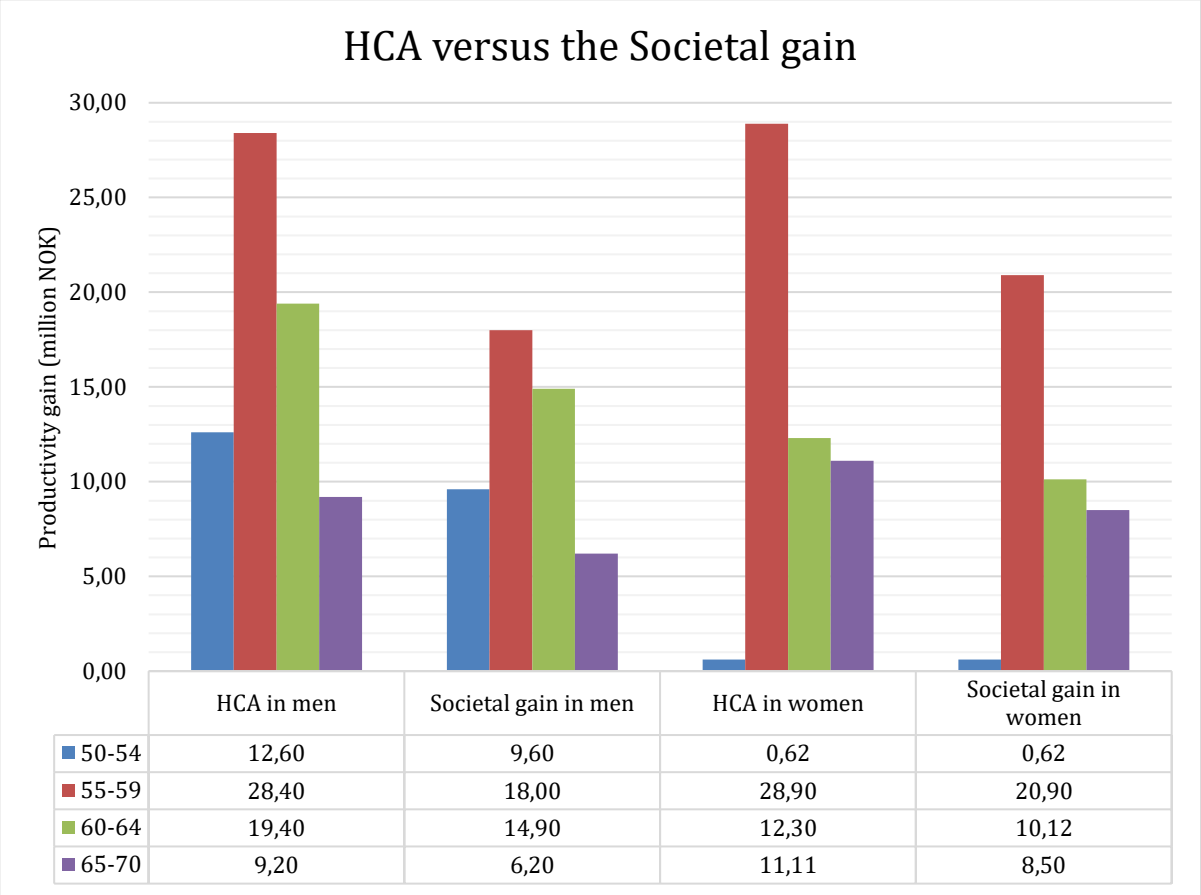
*Table 12 - Productivity gain distribution in men and women.*

| Productivity gain due to: | Discounted HCA* and %-contribution | | | |
|---|---|---|---|---|
| | Women | % | Men | % |
| Averted sick leave | 4.8 | 9 | 4.3 | 6 |
| Averted permanent disability | 42 | 79 | 56.2 | 81 |
| Averted hip fracture related death | 6.1 | 12 | 9.1 | 13 |
| **Total** | **52.9** | **100** | **69.6** | **100** |

**Productivity gains are in the million NOK.*

## 4.4 HCA versus societal gain

The total discounted societal gain was 88.7 million NOK, 48.7 million NOK in men and 40 million NOK in women. Based on the 105 averted hip fractures, the average societal gain per prevented fracture was approximately 845 000 NOK. Figure 2 compares the productivity gain using the HCA to the societal gain, in men and women, in 5-year age intervals. The societal gain was lower than the productivity gain obtained using the HCA, in both sexes. For the remaining societal gain calculations see appendix 3.




| | HCA in men | Societal gain in men | HCA in women | Societal gain in women |
|---|---|---|---|---|
| 50-54 | 12,60 | 9,60 | 0,62 | 0,62 |
| 55-59 | 28,40 | 18,00 | 28,90 | 20,90 |
| 60-64 | 19,40 | 14,90 | 12,30 | 10,12 |
| 65-70 | 9,20 | 6,20 | 11,11 | 8,50 |

*Figure 2 – Discounted HCA versus the discounted societal gain in men and women in 5-year age intervals.*

## 4.5 Results of sensitivity analysis

One way sensitivity analysis was conducted by varying the effect of the intervention in reducing fractures. Table 12 illustrates the productivity gain with the different applied RRRs in men and women. Sensitivity analysis with a -10% RRR from base-case resulted in a reduced gain by 37.4 million NOK in men and by 17.2 million NOK in women. A +10% RRR from base-case resulted in an increased gain by 28.3 million NOK in men and by 23.9 million NOK in women.

*Table 13 - The discounted productivity gain using the HCA with the different applied RRRs, in men and women, in 5-year age intervals.*

| Age interval | Low* | | Base-case* | | High* | |
|---|---|---|---|---|---|---|
| | Women | Men | Women | Men | Women | Men |
| 50-54 | 0.62 | 0.71 | 0.62 | 12.6 | 10 | 24.3 |
| 55-59 | 18 | 13.2 | 28.9 | 28.4 | 29.4 | 36.1 |
| 60-64 | 9.8 | 11.7 | 12.3 | 19.4 | 22.8 | 23.5 |
| 65-70 | 7.3 | 6.6 | 11.1 | 9.2 | 14.6 | 14 |
| **Total** | **35.7** | **32.2** | **52.9** | **69.6** | **76.8** | **97.9** |

**The productivity gains are in the million NOK.*

## 4.6 Population movement

The figures below illustrate the population movement in the different model health states over the course of the simulation, with the different applied RRRs. For illustrative purposes we chose to exclude the "Other death" and "Healthy" states. The temporary states "Acute first hip fracture" and "Acute subsequent hip fracture" were excluded as state membership only lasted for one cycle. As none sustained a second hip fracture during the course of the simulation, the "Post subsequent hip fracture" state was also excluded. In the figures, the dotted lines illustrate the health state membership with the applied intervention (int), and the solid lines illustrate the health state membership without the applied intervention (comp).

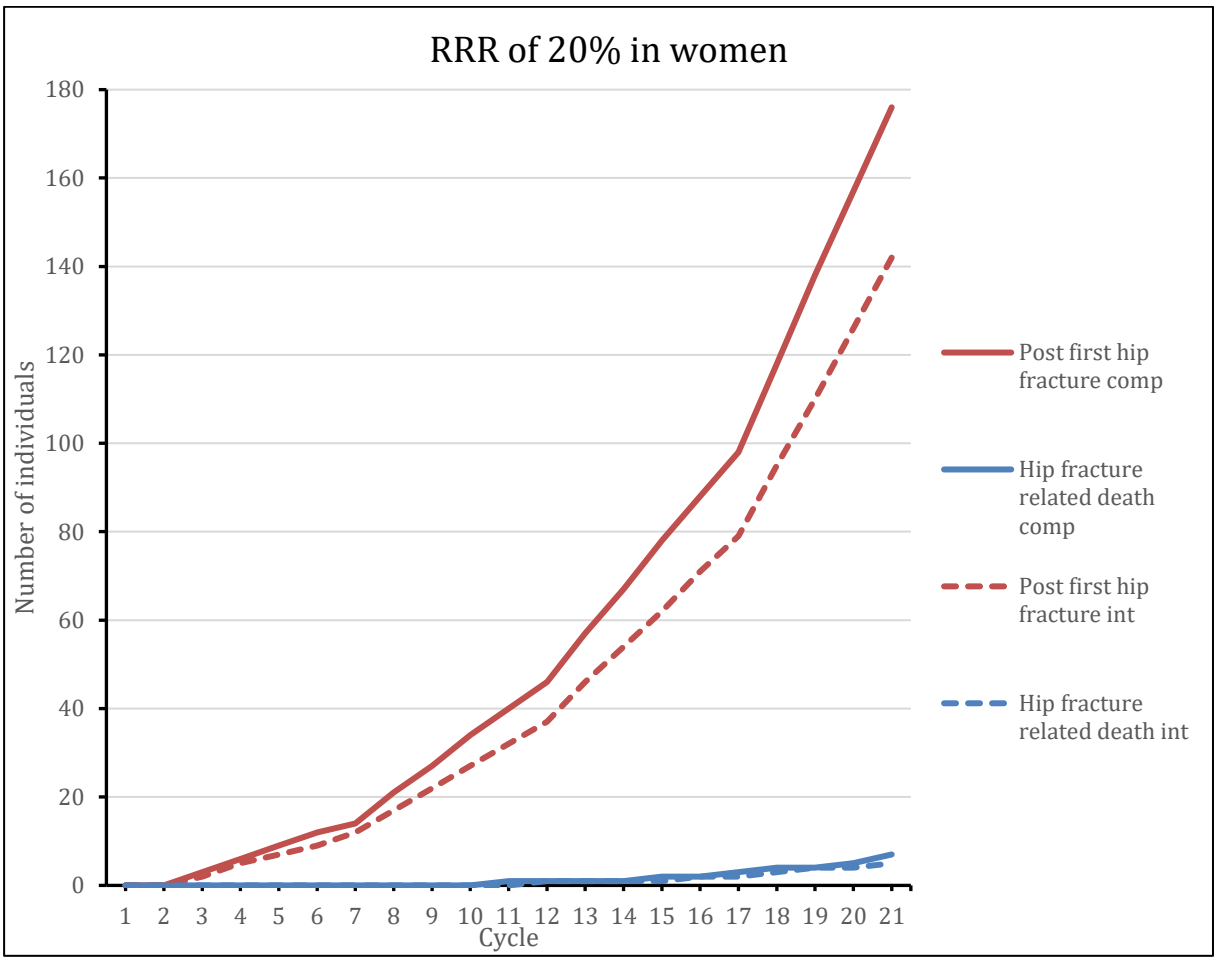



*Figure 3 - Population movement in women, with and without a RRR of 20%.*

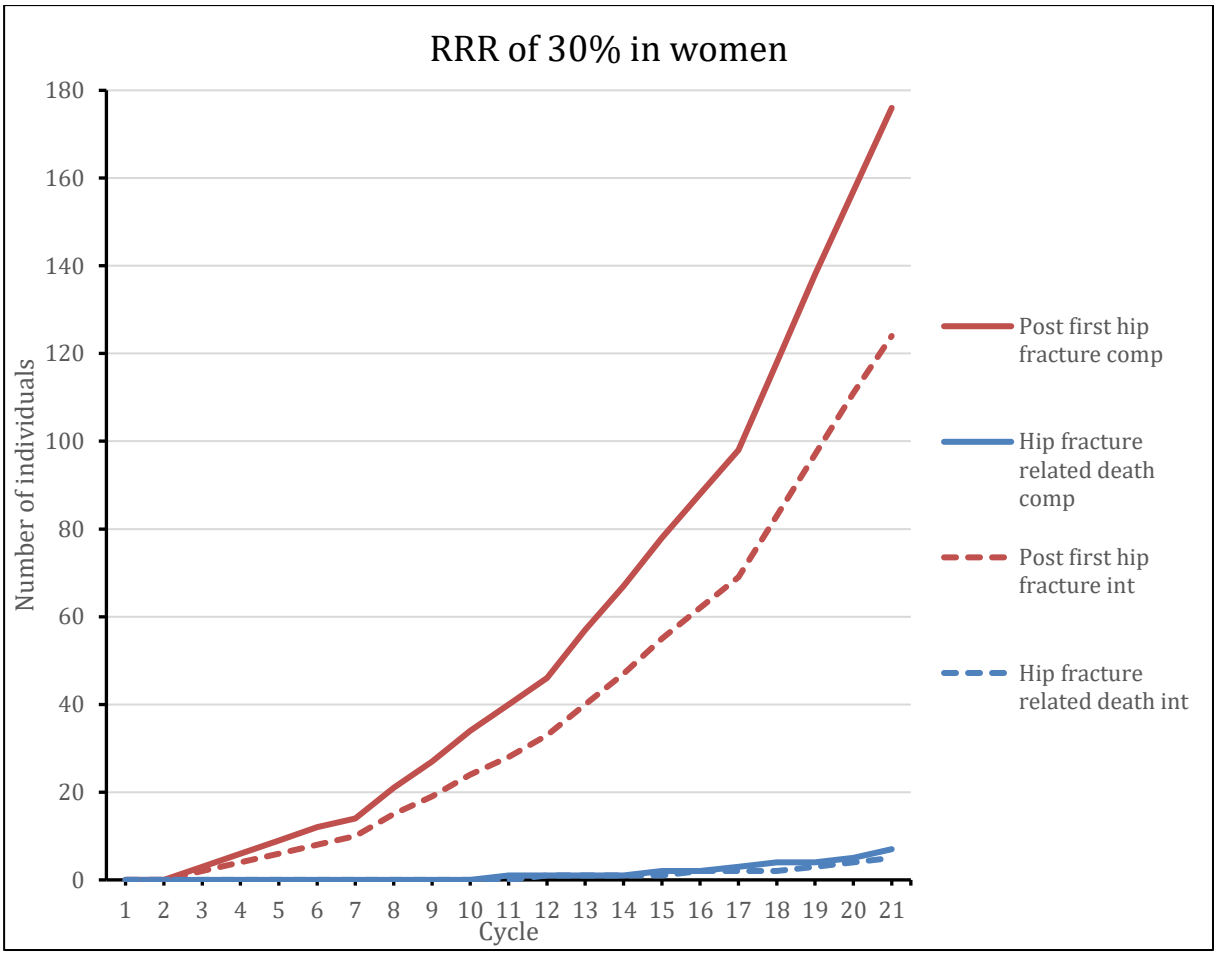



*Figure 4 - Population movement in women, with and without the base-case intervention.*

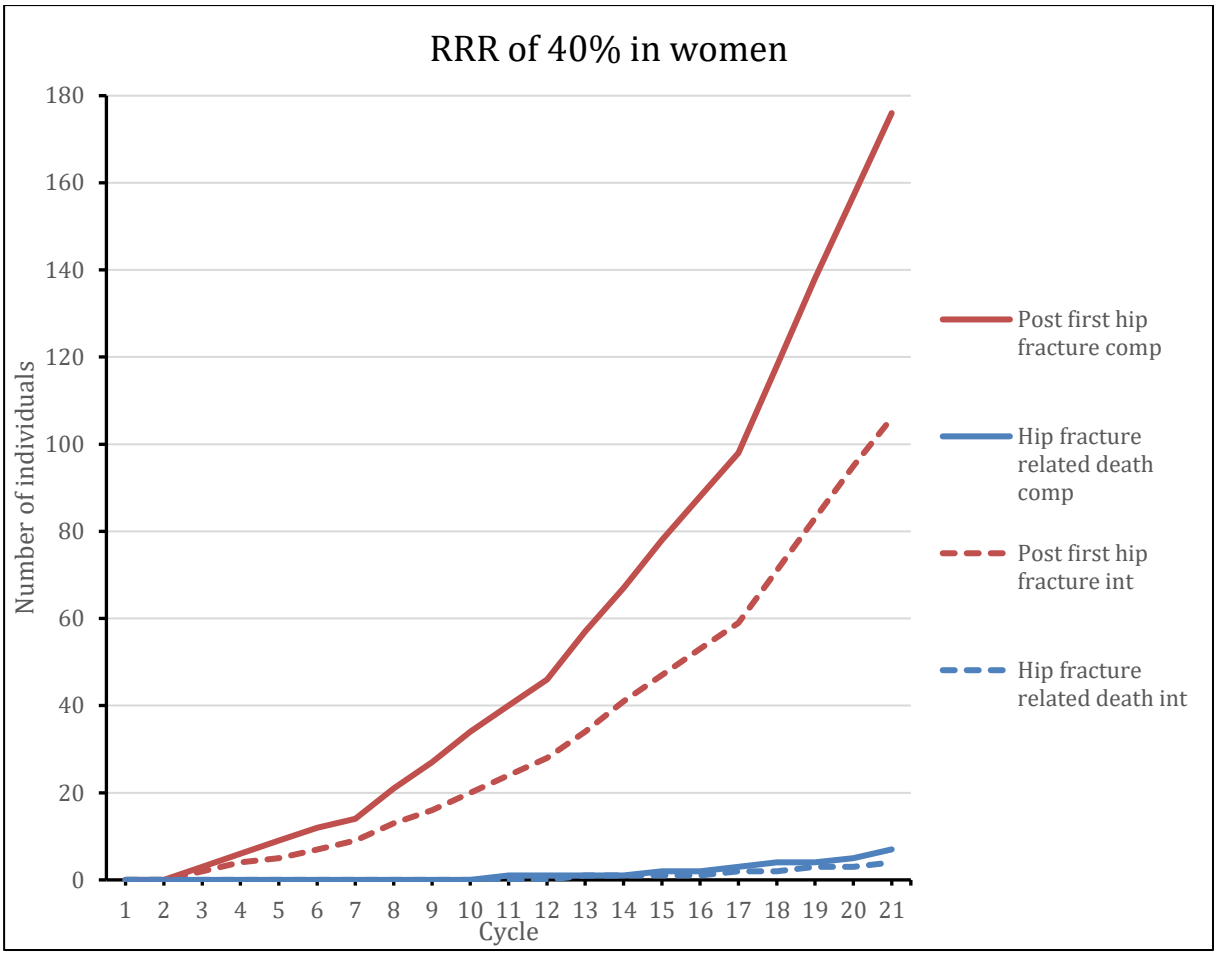



*Figure 5 - Population movement in women, with and without a RRR of 40%.*

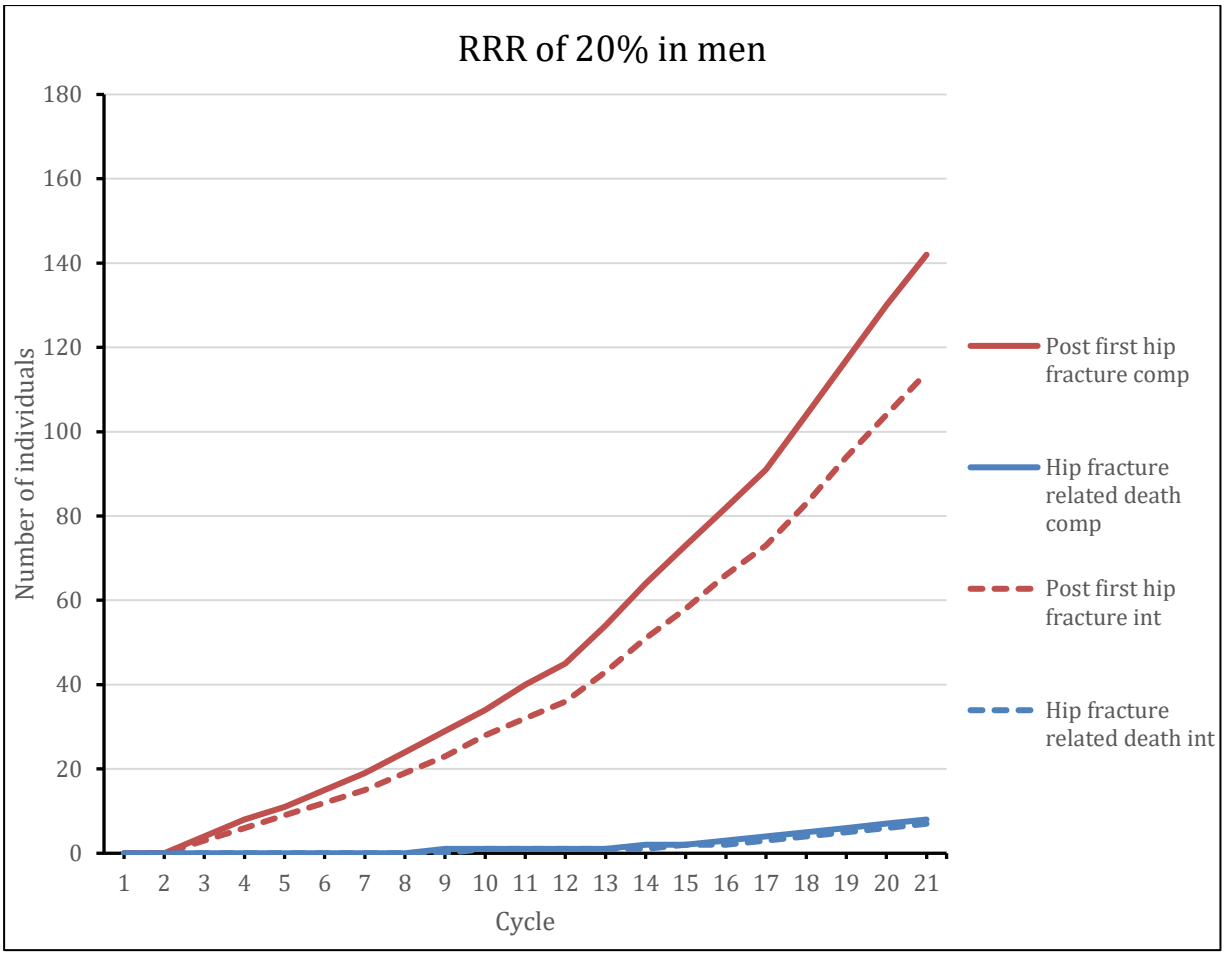



*Figure 6 - Population movement in men, with and without a RRR of 20%.*

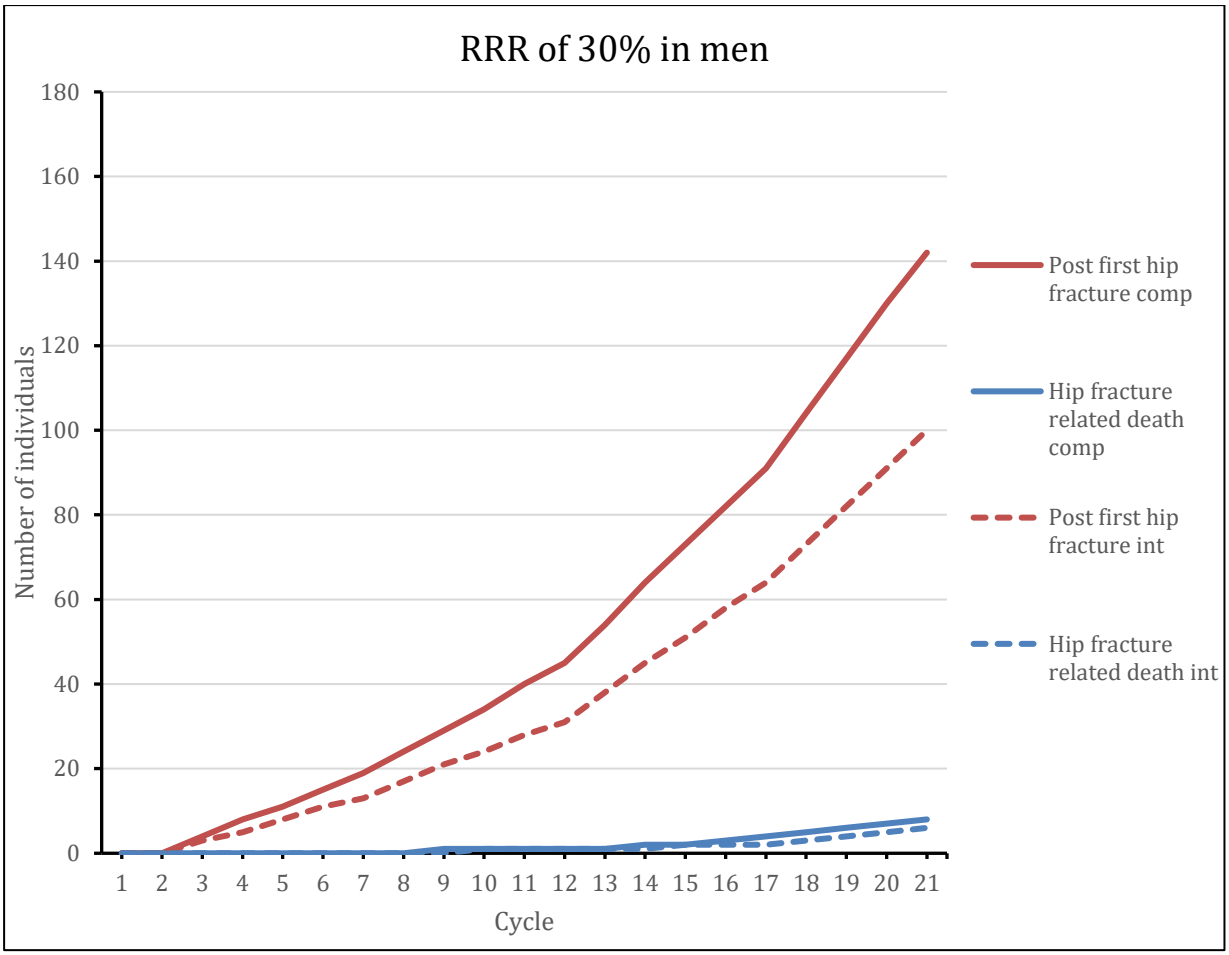



*Figure 7 - Population movement in men, with and without the base-case intervention.*

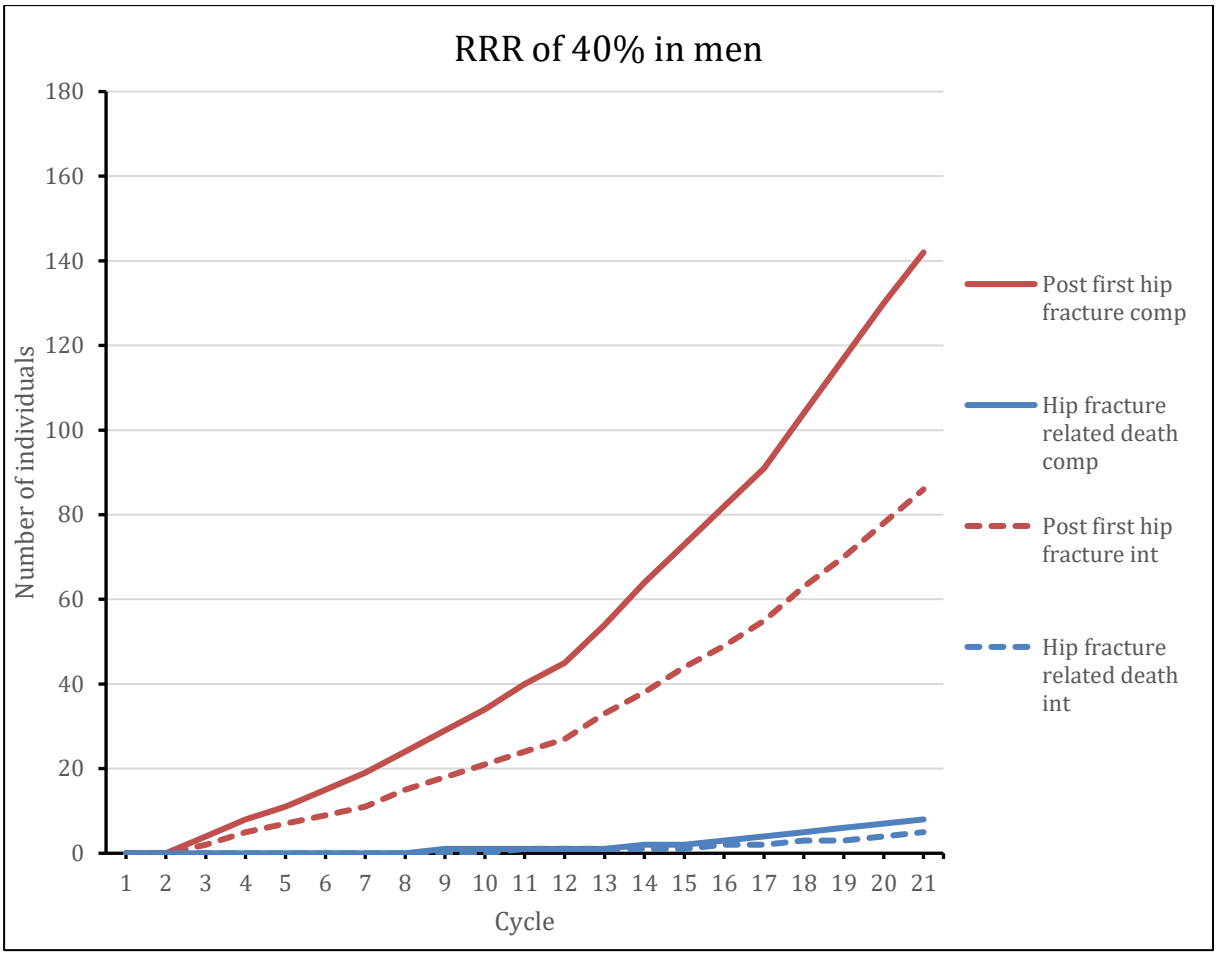



*Figure 8 - Population movement in men, with and without a RRR of 40%.*

# 5 Discussion

To our knowledge this is the only study conducted on the productivity gain from averted hip fractures in the Norwegian population. Our model predicts the present productivity gain from averted absenteeism as a result of optimal pharmacological treatment of osteoporosis, independent of treatment type, in the middle-aged Norwegian population.

## 5.1 Discussion of results

### 5.1.1 Productivity gain using HCA

Our study yielded a total present productivity gain of around 120 million NOK. The greatest contribution to this was in the age interval from 55-59 years, in both gender cohorts. This was because these individuals still had many expected work years left. In women, the productivity gain was lowest from 50-54 years as none in this age interval had experienced disability or died from a hip fracture related reason. In men, the productivity gain was lowest in the last age interval, from 65-70 years, as these individuals had few expected work years left. The average productivity gain per prevented hip fracture was 1 167 000 NOK. This is over double the estimated average 1-year direct cost per hip fracture in Norway (19). Therefore, although the total productivity gain in our study was low due to a low incidence of hip fracture, the productivity gain per prevented hip fracture was substantial. In addition, although the number of averted hip fractures were greatest in the female cohort (n=60), both the total productivity gain and the average productivity gain per prevented hip fracture was greatest in men due to higher gross incomes. As reported by Statistics Norway, annual gross income estimates were approximately 100 000 NOK higher in men compared to women in all age groups (62). Our findings are therefore in line with the current literature criticizing the HCA for being subject to biases in earning patterns (48). As women on average earn less than men, their lost productive time is valued lower.

### 5.1.2 Productivity gain distribution using HCA

Averted permanent disability contributed substantially more to the total estimated productivity gain compared to averted sick leave and averted hip fracture related death. Contributing approximately 80% to the total estimated productivity gain, in both sexes. This was because the probability of becoming permanently disabled to work in our model was significantly higher than the probability of dying. In addition, sick leave was only measured in 56 lost days as opposed to lost years due to disability.

### 5.1.3 HCA as the primary method

The HCA is by far the most utilized method for measuring productivity costs, included in more than 90% of COI studies (44). To enable broader comparisons to previous findings we therefore chose this method as the primary method for estimating productivity gains. Although the HCA is the predominant method, todays country-specific pharmaeconomic guidelines vary in their recommendations on which method(s) to use (48). Some guidelines suggest that both the FCA and the HCA should be used to estimate productivity gains/losses. Ideally, in order to be fully transparent in terms of the possible magnitude of productivity gains, our study would also have used the FCA. However, with uncertainties such as the length of the friction period and how it is affected by the unemployment level, application of this method to our study would have been difficult. The FCA is arguably more applicable when unemployment levels are high, making it easier to replace sick workers (44, 49, 71). As the unemployment level in Norway is low (72), this further supports our use of the HCA. Estimates on the productivity gain using the FCA would likely have been lower than those we obtained using the HCA. Especially, considering the long time horizon and high probability of permanent disability to work in our model.

### 5.1.4 Societal gain

The societal gain calculation was implemented to observe how public budgets are impacted by interventions in the healthcare sector. In other words, what are the monetary gains from averted hip fractures to the rest of society. This is of particular interest to policymakers, who want an estimate on the potential savings to society from preventing chronic illnesses. Large savings could assist in prioritizing the implementation of fracture preventive measures and facilitate increased post-fracture care. In addition, they may be used to identify incorrect prioritizations and inefficient use of societal resources.

### 5.1.5 Societal gain distribution

The total present societal gain was over 80 million NOK. Societal gain estimates from averted sick leave were the same as the estimates obtained using the HCA. We assumed that individuals would be fully compensated with their gross incomes in this time period. For premature hip fracture related death, the potential gain to society were the income taxes. For permanent disability, the potential gain to society were the income taxes and the avoided net disability pension payments. As the potential monetary gain per prevented disability was greatest, it was expected that averted permanent disability would contribute the most to the total estimated societal gain. In addition, as previously mentioned, the probability of becoming permanently disabled to work in our model was significantly higher than the probability of dying.

### 5.1.6 Societal gain compared to HCA

The total societal gain and the average societal gain per prevented hip fracture was lower than the estimates obtained using the HCA. This was because both the income taxes and the avoided net disability pension payments used in the calculation of the societal gain were lower than the gross incomes used in the HCA. Our findings are therefore in line with the current criticism directed at the HCA for overestimating the societal productivity gain (44).

### 5.1.7 Comparison to other findings

#### Challenges

Few studies have been conducted on the productivity gain/loss in the middle-aged osteoporotic population. Finding relevant and comparable studies was therefore challenging. Those relevant for comparisons had utilized different models and methods, populations and population sizes, and time horizons. Comparisons were further complicated by the universal lack of standardization of the methods used for measuring productivity costs, with some studies having only estimated the productivity loss as a result of short-term sick leave. Furthermore, all the selected studies had measured the productivity loss as a result of fracture as opposed to the productivity gain from a health intervention. However, as the productivity gain simply is the averted productivity loss due to a treatment intervention these findings are still comparable to ours. For better comparisons productivity costs in the selected studies were converted from euro (EUR) to April 2022 NOK, not adjusted to account for inflation (73).

#### Comparison

*Denmark*

One COI study on the burden of osteoporotic fractures in Denmark estimated productivity losses using a Markov model (52). They used the HCA to value the time away from the labor market as average sex- and age-specific daily wages. Losses were then calculated based on the number of days absent from work due to hospitalization, rehabilitation, nursing home care and premature death. They estimated the total costs based on fractures occurring between 2001 to 2010 in Denmark to be EUR 1.563 billion (~14.9 billion NOK), of which 13-14% (~2 billion NOK) were productivity costs. The productivity costs per person were ~5000 EUR (~48 000 NOK) in men and ~3400 EUR (~32 400 NOK) in women. This is substantially lower than our estimated productivity gain per prevented fracture using the HCA. However, the authors of the study admit that their findings are very conservative and in the lower end compared to other findings. Furthermore, as they examined a much larger population than us their total estimated productivity cost was significantly higher than our total estimated productivity gain using the HCA. Given the high productivity cost in this study one can only imagine the positive effect even a modest health intervention could have on productivity.

*Netherlands*

In a study on the economic burden of injury in the Netherlands in 2012 the annual productivity costs due to hip fracture were estimated to be EUR 76 512 00 (~738 million NOK), using the FCA with a 6 month friction period (74). Hip fractures had the highest productivity cost per case at EUR 34,518 (~330 000 NOK per case). This estimate is lower than our estimated average productivity gain per prevented hip fracture using the HCA, which can be explained by the fact that the FCA generally produces lower estimates than the HCA when examining chronic conditions like osteoporosis. Furthermore, as the authors examined a much larger population than we did their total estimated productivity cost was significantly higher than our total estimated productivity gain.

*Austria*

In a study on the economic burden of osteoporotic fractures in Austria in 2008, the annual productivity cost due to fractures was estimated to be EUR 59.4 million (~563 million NOK) (75). Of the total estimate, EUR 40.1 million (~373 million NOK) was due to sick leave days from work, valued as the average daily income in men and women using the HCA. The remaining amount, EUR 19.3 million (~180 million NOK), were disability pensions from osteoporosis-related conditions. Like the above-mentioned studies, this study had also examined a much larger population than us.

*Italy*

In a study on the direct and indirect costs associated with surgically treated pelvic fractures in Italy the median total costs per patient were estimated to 29,425 EUR, of which 60% or 17,719 EUR (~174 000 NOK) was attributed to work absence (76). The monetary value of one lost productive day was considered the gross domestic product (GDP) per capita per day and productivity costs were estimated based on the time from trauma to resumption of work. However, the study did not account for productivity costs as a result of permanent loss of productivity such as permanent disability or premature death. Although pelvic fractures are most commonly caused by high-energy trauma these results illustrate how productivity costs can account for a large portion of the total costs of lower extremity injuries.

*Norway*

Although no studies have been conducted on the productivity gain/loss in the Norwegian osteoporotic population, a study from 2015 estimated the future economic burden of hip fractures in Norway (77). The study projected a future cost increase from 2014 to 2040 to be between 14%-121%, with a 65% increase as the most likely outcome. Illustrating the need for fracture preventive measures if cost increases associated with hip fractures are to be contained.

*A systematic review of the indirect cost studies on fragility fractures*

In a systematic review of the indirect and social cost studies on fragility fractures the authors noted that the direct costs of fractures have been extensively analyzed, while the indirect costs have not (71). Furthermore, the included studies did not allow for direct comparisons. Although all studies estimated the costs associated with lost labor productivity, many covered different concepts. Some had only taken into account the number of workdays lost due to hospitalization whilst others had included the indirect costs associated with both early retirement, lost leisure time and premature death. The authors argued that the availability of data and the ease with which patients could be followed up may have been the reason why some studies explored more concepts than others. Lastly, they point out that the scarcity of studies linking indirect costs with the effects of treatments and adherence is striking, especially, when many of them emphasize the positive cost-effectiveness of treatments.

## 5.2 Discussion of method

### 5.2.1 Discussion of Markov model

#### Model assumptions and uncertainty

In the process of building our Markov model, we had to make several assumptions with regard to the model structure and transition probabilities. Model outcomes are therefore associated with uncertainties. Thus, we cannot be certain that the estimated productivity gain in this population is accurate. However, the purpose of this thesis was not to obtain the most accurate estimate on the potential productivity gain from treatment. On the contrary, we wanted to investigate how the productivity in the middle-aged osteoporotic population can be affected while acknowledging the low incidence of hip fractures.

#### Data collection

Input data for the Markov model was extracted from population-based studies collected through literature searches (see appendix 1 for MeSH terms). Studies were subjectively chosen based on the relevance to the Norwegian population and their overall strengths and limitations. However, due to a lack of transparency, in terms of reporting study outcomes, many studies could not be selected for inclusion to the model. Studies that reported outcomes in Odds Ratios (OR) and/or Relative Risks (RR) but did not report probabilities in the unexposed/control groups could not be selected. This is because it is impossible to calculate transition probabilities from ORs and RRs without probabilities in the unexposed/control groups (78).

#### Cohorts

We chose the entire population of 50-year-old men and women in Norway as the starting cohorts. This entire population was chosen because incidence data from the literature was only available on population-level. In addition, we did not have data on the number of middle-aged osteoporotic patients in Norway. Due to a substantial underdiagnosis, obtaining a correct estimate on the number of osteoporotic patients would have been difficult, if not impossible. Furthermore, 50 years was chosen as the starting age of the cohorts because data on hip fractures in those <50 years was scarce. Although the incidence of osteoporotic hip fractures in those <50 years likely is very low, excluding them may have led to a slight underestimation of the productivity gain. Furthermore, although the typical retirement age in Norway is 67 years (79), we chose 70 years because pensions in Norway are adjusted according to the life expectancy in the population (80). As the life expectancy is continuously increasing, younger persons today will have to work longer than older persons to maintain the same pension level.

## Health states and transitions

*Assumptions related to the healthy state and transitions*

We assumed that none had sustained a hip fracture prior to the start of the simulation in the "Healthy" state. This is likely inaccurate, as some individuals may previously have sustained a hip fracture, leading to an underestimation of the number of hip fractures in our model. Furthermore, we assumed that all hip fractures were the result of osteoporosis and low-energy trauma. The proportion with osteoporosis and would need treatment with AODs in the two gender cohorts is unknown. Regardless, the RRR from the intervention would only apply to those at risk of fracture.

*Assumptions related to the acute hip fracture states and transitions*

For simplicity, we assumed that individuals could not sustain a subsequent hip fracture within the acute phase of the first hip fracture. This may have led to an underestimation of the total number of hip fractures. Previous studies have found that the risk of sustaining a subsequent fracture is greatest within the first year after the first fracture (81-83). A Danish nationwide population-based study estimated that the risk of sustaining a subsequent hip fracture was increased 12-fold at 30-days and 2-fold at 1 year after the first hip fracture (81). A population study from Malmo in Sweden found that the risk of subsequent fracture was highest immediately after the first fracture (83). Furthermore, we assumed that individuals who died in the acute states, died from a hip fracture related reason, and could not transition to the "Other death" state. This assumption is supported by a Norwegian population-based study that estimated the 1-year excess hip fracture mortality to be fivefold higher in men, and threefold higher in women compared to the general population (8). We therefore chose not to subtract the background mortality in the population from the reported acute mortality after hip fracture to obtain the mortality attributed to hip fracture. This may have led to an overestimation of the number of hip fracture related deaths. However, as only 15 individuals (7 women and 8 men) died from a hip fracture related reason in our model, hip fracture related deaths are likely underestimated. Possibly, this can partly be explained by the fact that we, due to a lack of mortality data, had to choose the 6-month rather than the 30-day mortality as the acute mortality after fracture. As reported by the above-mentioned population-based study, the 30-day mortality is higher than the 6-month mortality after fracture (8). Diamantopoulos et al found a mortality OR of 8.6 at 0-3 months after hip fracture compared to 2.7 at 3-6 months after hip fracture (84).

*Assumptions related to the post hip fracture states and transitions*

The transition probabilities in the model varied with age, i.e., the probabilities of dying or sustaining a fracture increased as individuals in the cohorts got older. However, the model did not allow for transition probabilities to vary with the time after fracture. In other words, we could not account for the variation in risk of sustaining a subsequent hip fracture or dying at different times after the first hip fracture. We therefore had to choose a fixed hip fracture related mortality in the post hip fracture states. For simplicity, we chose the mortality at 5 years after fracture as the post-hip fracture mortality, taken from the same study as the reported acute mortality (58).

## Comparator

The comparator model, which was based on the incidence of hip fractures in the population, was assumed to represent a sub-optimal or no treatment scenario, as both treatment rates with AODs and adherence to oral alendronate (which is the most commonly prescribed AOD) in the Norwegian population is low (4, 85). Furthermore, this assumption implies that the incidence and risk of hip fracture is the same in these two scenarios, which is supported by a Belgian article that found that low adherence to AODs fails to lower the burden of disease (86). Low adherence to treatment significantly decreases the benefit on BMD and fails to decrease the risk of vertebral and femoral fractures.

## Intervention

*Constant risk reduction and complex treatment variations*

We applied the intervention for the entirety of the simulation to represent an optimal treatment and adherence. All those at risk of sustaining a first and subsequent hip fracture were therefore treated for the entirety of the simulation through a constant RRR, or at least benefited from residual treatment effects. In reality, different AODs have different recommended treatment durations and treatment effects that vary over time. In addition, some AODs like alendronate have documented residual effects that persist for several years after treatment discontinuation (87). We did not have the capacity to account for these complex variations in our model.

*Effectiveness in men and primary versus secondary treatment effects*

Data on the effectiveness of AODs in the prevention of fractures in men is scarce, and we assumed that the treatment effect was the same in both men and women (88). Data on the effect of AODs in women are often extrapolated to the male populations. Furthermore, we assumed that the effect of the treatment was the same in both primary and secondary prevention of

fractures. The study on the comparative effectiveness of AODs did not clearly differentiate between the effects of treatments in reducing the risk of first and second fractures (60).

*Base-case effect estimate*

The applied base-case intervention of a 30% RRR may have been a conservative effect estimate. One study on the effect of alendronate in the prevention of osteoporotic fractures in postmenopausal women estimated a RRR of 40% in the primary and 53% in the secondary prevention of hip fractures (89). A systematic review from 2017 on the effectiveness of AODs in the prevention of secondary fragility fractures found that bisphosphonates and parathyroid hormone (PTH) significantly reduces the risk of secondary non-vertebral fractures with RR 0.59 (RRR of 41%) and 0.64 (RRR of 36%) (90). A study from Italy estimated the RRR for hip fractures from meta-analysis and pivotal trials to be 40% for alendronate, denosumab and zoledronate (91). A study on zoledronic acid for treatment of postmenopausal osteoporosis found that annual infusions with this drug over a three-year period reduced the risk of hip fracture by 41% (92). In addition, studies have shown that zoledronic acid reduces mortality in hip fracture patients (93). Relative risk reductions as a result of the intervention could therefore have been applied to the transitions to the "Hip fracture related death" state.

## Sensitivity analysis

We determined that variations in the effect of the intervention would likely have the greatest impact on fracture outcomes and on the estimated productivity gain. One way sensitivity analysis was therefore conducted on the effect of the intervention in reducing first hip fractures in both men and women. As none sustained a second hip fracture in the comparator model, sensitivity analysis was not conducted on the effect of the intervention in reducing subsequent fracture. We chose the upper and lower estimates of the applied base-case intervention for sensitivity analysis (60). One way sensitivity analysis was therefore conducted with a 20% and 40% RRR. In men, a ±10% RRR from base-case resulted in approximately ±30 million NOK. In women, a ±10% RRR from base-case resulted in approximately ±15-20 million NOK. It is difficult to make any conclusions regarding the robustness of our calculations, as sensitivity analysis was only conducted on one variable. Variables other than the intervention would likely have had an equally great if not greater impact on our estimates. As permanent disability contributed ~80% to the total estimates in both sexes, sensitivity analysis on this variable would likely have impacted the productivity gain greatly. Unfortunately, due to time constraints we were unable to conduct sensitivity analysis on other relevant variables.

### 5.2.2 Estimation of productivity gains

#### Unemployment

We assumed that everyone worked prior to the start of the simulation, and we did not adjust for the unemployment rate in our calculations. The unemployment rate in Norway was, as of January 2022, 3,2% of the workforce (72). Given the low level of unemployment, this likely would not have had an impact on our calculations.

#### Gross incomes and tax rates

We assumed a fixed gross income and income tax rate for individuals when estimating productivity gains. This may have led to an underestimation of the productivity gain as it is normal for salaries and taxes to increase with the time spent in the labor market.

#### Sick leave days

We assumed a fixed amount of sick leave days (56 days) in the calculation of productivity gains. In reality, sick leave days may vary greatly. The recommendations by the Norwegian Directorate of Health, state that sick leave can vary from 2-16 weeks depending on the type of work and the outcome in the patient (94). For patients with an uncomplicated fracture course and a well-organized work environment, 2 weeks of sick leave may be sufficient. For patients with physically demanding jobs and difficulties organizing a suitable work environment, sick leave up to 16 weeks may be necessary. The previously mentioned COI study on the burden of osteoporotic fractures in Denmark estimated the sick leave from work after fracture to be 3 months (52). In a report on the burden of fragility fractures in Europe average sick leave days from work in the first year after hip fracture was estimated to be 42 days (6). Furthermore, when sick days due to fragility fractures were expressed per 1000 people per year in those aged 50-65 years, Sweden had the highest average estimate at 161 sick days.

We assumed that gross incomes would be an appropriate estimate on the societal gain from averted sick leave. When individuals become sick from work in the short-term, the economic loss to society are the lost income taxes and the net sickness benefits payments. This equals the lost gross incomes if persons are fully compensated in this time period. However, sick leave payments may in fact vary. In Norway, the employer pays for the first 16 days of sick leave and can chose whether or not to fully compensate their employees (95). From the 17$^{th}$ day, The Norwegian Labor and Welfare Organization (NAV) pay for individuals' sick leave. NAV pays a maximum of six times the National Insurance basic amount in sickness benefits.

### Permanent disability

We assumed a fixed proportion of permanent disabilities after hip fracture (35%). However, disability rates may vary depending on fracture outcomes and patient characteristics like age and comorbidity. In addition, rehabilitative measures could have increased RTW rates over time, with some partially back to work and others fully back to work. Disability pension payments would therefore have decreased over time as patients began returning to work. Furthermore, a 35% permanent disability to work may at first glance seem high. However, a study on the long-term disability associated with hip fractures found that burden of disease studies grossly underestimate the long-term disability from hip fractures (96). The study estimated that 29% of hip fracture patients ≥60 years become disabled in the long-term. A study on proximal femur fractures in patients <50 years reported that outcomes in young hip fracture patients may have long term effects on the function of the hip joint, leading to disability and long-term absence from work (97). In addition, the psycho-social impact of sustaining a hip fracture, such as the Fear of Falling (FoF) may contribute to negative disability outcomes in patients. A systematic review on the fear of falling after hip fracture estimated that 50% or more of hip fracture patients suffer from FoF, and that FoF was associated with many negative rehabilitation outcomes (98). As the literature predominantly focuses on disability outcomes in the elderly (99) it was difficult to find studies on the disability outcomes in the middle-aged hip fracture population.

### Mortality in hip fracture patients

For simplicity we assumed that hip fracture patients had the same background mortality as the general population. Studies have found that the prevalence of comorbidity in osteoporotic patients is higher than in the general population (100, 101). The total mortality in our study may therefore have been underestimated. Furthermore, we assumed that those with a second hip fracture had the same mortality as those with a first hip fracture. A prospective population-based cohort study from Tromsø in Norway found that subjects with a subsequent hip fracture had a higher probability of dying compared to those with a single hip fracture (a multivariable adjusted hazard ratio of 3 versus 2) (18). One population-based study from Taiwan found that the 1-year mortality rate was significantly higher after second hip fracture (18.8%) compared to the first (14.1%) (102). Therefore, deaths after second hip fracture in our study could, in theory, have been underestimated. This, however, is not the case as none sustained a second hip fracture during the course of the simulation.

### Unpaid production

Productivity costs not only include those related to paid production, but also those related to unpaid production (49). These are considered all activities outside the labor market by individuals for themselves or for others. Some examples are volunteer work, caring for family members and household work. From a societal perspective, productivity costs from unpaid work are important. We did not examine these changes in our study as sufficient knowledge on how to properly measure them is lacking. In addition, distinguishing leisure time from time spent on unpaid labor can, in many cases, be challenging.

### Presenteeism

Presenteeism is the reduced productivity or efficiency at work due to illness, which can occur both before and after absenteeism (physical absence from work) (49). The costs related to presenteeism can be important, especially, in disease areas where partial recovery allows for persons to return to work and in countries where sickness benefits are limited. We did not examine the potential monetary gain from averted presenteeism in our study as we had no way of measuring diminished productivity at work.

### Multiplier effects

Multiplier effects are when individuals productivity loss negatively impacts their co-workers productivity at work (49). Although the costs and monetary gains related to multiplier effects can be of significance, little is known of how to measure them. These effects were therefore not accounted for in our study.

### Compensation mechanisms

Compensation mechanisms are those mechanisms in the labor market that compensate for lost productivity when workers become ill (49). For example, ill workers can compensate for their own lost productivity when they return to work and/or colleagues may take over some of the ill workers tasks. Like multiplier effects, little is known about the costs associated with compensation mechanisms. These were therefore not included in our study.

## 5.3 Generalizability

As we only examined the productivity gain in one cohort of patients, those 50 years old in Norway today, our results cannot be generalized to the broader work-active Norwegian population. To obtain an estimate on the total productivity gain in the entire work-active Norwegian population >50 years we would have had to simulate all age cohorts 50-69 years until retirement or death. The resultant productivity gain would be significantly higher than what was found in this study. For example, if we assume an average productivity gain per cycle (per year) of 5.8 million NOK (the total productivity gain divided by the number of cycles) and an equal population size in all age cohorts, the total productivity gain from simulating all age cohorts 50-69 years in Norway until retirement or death would be 1.34 billion NOK. Although this calculation is a simplification it illustrates how large the productivity gain potentially could be from optimally treating all work-active osteoporotic persons >50 years in the population.

## 5.4 Strengths and limitations

The current health policy and health economic literature is almost exclusively focused on the elderly osteoporotic population, rendering the younger osteoporotic patients under-explored and inadvertently marginalized. Thus, this study's main strength is that it explores the impact of health interventions in a silent sub-set of osteoporotic patients. In addition, this study is unique as it examines an indirect monetary gain that typically has been regarded as negligible in this population due to a low incidence of fracture.

The main limitations to this study are related to the model parameter and productivity gain assumptions. Although sensitivity analysis was conducted to attempt to assess outcome robustness and assumptions made were supported by findings in the literature, productivity gain estimates are associated with uncertainty. Furthermore, as we did not have access to population databases, we relied solely on incidence data published in a limited set of studies. This may have led to the inclusion of lower quality data to the model.

## 5.5 Productivity gain in the Norwegian priority setting

Our study illustrates the potential importance of productivity gains in a healthcare priority setting. Choosing not to include these monetary gains in health economic evaluations of treatment interventions can render treatments aimed at the young working population less cost-effective. Interventions that potentially could lead to a substantial monetary saving to society would be completely overlooked. On the other hand, choosing to include these monetary gains in economic evaluations in the health sector could lead to ethical issues in prioritization. Prioritizing treatments aimed at more productive persons over less productive persons would violate with the basic healthcare principle of *"equal access for equal need"*(46). Which, in this context, implies that a health benefit has an equal social value regardless of one's income. However, the argument for completely excluding productivity gains solely based on equity issues is hard to defend. Especially, considering how we already indirectly prioritize based on age through the severity-criteria in the healthcare sector, and that productivity gains to a large degree are based on age. One possible solution to the equity issue is to present cost-effectiveness results both with and without productivity gains (49). Health care decision makers would then have to attempt to balance the desirable effect of freeing resources due to a production gain with the equity issues of including them. However, there is no easy solution to this issue. In addition, if productivity gains are to be a part of health economic evaluations of health interventions, issues related to how to properly value, measure and include them must be thoroughly addressed.

As the Norwegian government are tasked with evaluating the drug-politics and prepare a new priority message, they should acknowledge the potential impact productivity gains can have on the cost-effectiveness of interventions and on the public budgets. The decision must then be made as to whether these monetary gains are to be given weight in prioritization decisions or if they are to, once more, be disregarded.

## 5.6 Future research

This study was limited to one cohort of individuals in Norway, those 50 years old today. Future inquiries could explore the productivity gain in a broader population, including all work-active persons >50 years. Study models could include higher quality data extracted directly from primary sources like population registries and incorporate other commonly occurring fragility fractures, like those of the vertebra and forearm, as these too can have significant impacts on work absenteeism.

# 6 Conclusion

Despite model uncertainties, our results show that optimal treatment of the middle-aged osteoporotic population in Norway can have a positive impact on work productivity, regardless of a low incidence of fragility hip fracture. The estimated total productivity gain in our study was low relative to other findings, but the productivity gain per prevented hip fracture was substantial. In addition, the productivity gain in the entire work-active osteoporotic population in Norway can potentially be significant if patients are treated optimally. Excluding these monetary gains from health economic evaluations of treatment interventions in the Norwegian healthcare sector can lead to a reduced cost-effectiveness of interventions and the exclusion of major societal savings. The Norwegian government should acknowledge this as they are tasked with evaluating the drug politics and prepare a new priority message. To strengthen our findings, future inquiries could examine the productivity gain in a broader population and incorporate other important fragility fracture types.

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# Appendix

## A.1. MeSH terms

Hip Fractures / rehabilitation*

Hip Fractures* / prevention & control

Hip Fractures* / epidemiology

Hip Fractures / etiology

Hip Fractures / economics

Hip Fractures / mortality*

Hip Fractures / therapy

Fractures, Bone / economics*

Fractures, Bone / epidemiology

Osteoporotic Fractures / prevention & control*

Osteoporotic Fractures / economics

Osteoporotic Fractures / epidemiology

Osteoporosis / diagnosis*

Osteoporosis / drug therapy*

Osteoporosis, Postmenopausal*

Osteoporosis, Postmenopausal / complications

Osteoporosis, Postmenopausal / epidemiology

Osteoporosis, Postmenopausal / drug therapy*

Osteoporosis / complications

Diphosphonates / therapeutic use

Alendronate / therapeutic use*

Denosumab / therapeutic use

Teriparatide / therapeutic use

Comparative Effectiveness Research

Bone Density Conservation Agents / therapeutic use*

Bone Density Conservation Agents / administration & dosage*

Bone Density / physiology

Norway / epidemiology

Sweden / epidemiology

Denmark / epidemiology

Direct Service Costs*

Cost of Illness*

Costs and Cost Analysis / methods*

Health Care Costs* / statistics & numerical data

Employment / economics

Employment / statistics & numerical data

Sick Leave / economics

Health Planning / economics

Health Expenditures / statistics & numerical data*

Decision Support Techniques

Disease / economics*

Absenteeism

Technology Assessment, Biomedical / economics*

Resource Allocation

Markov Chains*

Models, Economic

Health Policy / economics

Hospitalization* / economics

## A.2. Health state transition probabilities

### Annual state transition probabilities in women

| Transitions | Cycles | | | |
|---|---|---|---|---|
| | 1 to 5 | 6 to 10 | 11 to 15 | 16 to 21 |
| Healthy to Other death | 0.000351938 | 0.000523863 | 0.000917579 | 0.001500873 |
| Healthy to Acute first hip fracture | 0.000079996 | 0.000179984 | 0.000299955 | 0.000579832 |
| Healthy to Healthy | 0.999568065 | 0.999296153 | 0.998782466 | 0.997919296 |
| Acute first hip fracture to Hip fracture related death | 0.002995504 | 0.004171276 | 0.005803097 | 0.008087122 |
| Acute first hip fracture to Post first hip fracture | 0.997004496 | 0.995828724 | 0.994196903 | 0.991912878 |
| Post first hip fracture to Other death | 0.000351938 | 0.000523863 | 0.000917579 | 0.001500873 |
| Post first hip fracture to Hip fracture related death | 0.002425055 | 0.003330442 | 0.00445206 | 0.005980048 |
| Post first hip fracture to Acute subsequent hip fracture | 0.00228738 | 0.00228738 | 0.00228738 | 0.002414081 |
| Post first hip fracture to Post first hip fracture | 0.994935627 | 0.993858316 | 0.992342981 | 0.990104998 |
| Acute subsequent hip fracture to Hip fracture related death | 0.002995504 | 0.004171276 | 0.005803097 | 0.008087122 |
| Acute subsequent hip fracture to Post subsequent hip fracture | 0.997004496 | 0.995828724 | 0.994196903 | 0.991912878 |
| Post subsequent hip fracture to Other death | 0.000351938 | 0.000523863 | 0.000917579 | 0.001500873 |
| Post subsequent hip fracture to Hip fracture related death | 0.002425055 | 0.003330442 | 0.00445206 | 0.005980048 |
| Post subsequent hip fracture to Post subsequent hip fracture | 0.997223007 | 0.996145696 | 0.994630361 | 0.99251908 |

## Annual state transition probabilities in men

| Transitions | Cycles | | | |
|---|---|---|---|---|
| | 1 to 5 | 6 to 10 | 11 to 15 | 16 to 21 |
| Healthy to Other death | 0.000471889 | 0.000841646 | 0.001345095 | 0.00234325 |
| Healthy to Acute first hip fracture | 0.000099995 | 0.00013999 | 0.000259966 | 0.000379928 |
| Healthy to Healthy | 0.999428116 | 0.999018364 | 0.998394939 | 0.997276822 |
| Acute first hip fracture to Hip fracture related death | 0.005385446 | 0.007670431 | 0.010939721 | 0.015577397 |
| Acute first hip fracture to Post first hip fracture | 0.994614554 | 0.992329569 | 0.989060279 | 0.984422603 |
| Post first hip fracture to Other death | 0.000471889 | 0.000841646 | 0.001345095 | 0.00234325 |
| Post first hip fracture to Hip fracture related death | 0.003362335 | 0.004627261 | 0.004464007 | 0.008795095 |
| Post first hip fracture to Acute subsequent hip fracture | 0.001098396 | 0.001098396 | 0.001098396 | 0.001080416 |
| Post first hip fracture to Post first hip fracture | 0.99506738 | 0.993432697 | 0.993092503 | 0.987781239 |
| Acute subsequent hip fracture to Hip fracture related death | 0.005385446 | 0.007670431 | 0.010939721 | 0.015577397 |
| Acute subsequent hip fracture to Post subsequent hip fracture | 0.994614554 | 0.992329569 | 0.989060279 | 0.984422603 |
| Post subsequent hip fracture to Other death | 0.000471889 | 0.000841646 | 0.001345095 | 0.00234325 |
| Post subsequent hip fracture to Hip fracture related death | 0.003362335 | 0.004627261 | 0.004464007 | 0.008795095 |
| Post subsequent hip fracture to Post subsequent hip fracture | 0.996165777 | 0.994531093 | 0.994190899 | 0.988861655 |

## A.3. Societal productivity gain in the Norwegian population

*Table 14 - The discounted societal gain in men and women in 5-year age intervals.*

| Age interval | Individuals* | | Discounted societal gain** and %-contribution | | | |
|---|---|---|---|---|---|---|
| | Women | Men | Women | % | Men | % |
| 50-54 | 5 | 5 | 0.62 | 2 | 9.6 | 20 |
| 55-59 | 10 | 5 | 20.9 | 52 | 18 | 37 |
| 60-64 | 15 | 15 | 10.1 | 25 | 14.9 | 30 |
| 65-70 | 30 | 20 | 8.5 | 21 | 6.2 | 13 |
| **Total** | **60** | **45** | **40.1** | **100** | **48.7** | **100** |

**The number of individuals the calculations are based on. These are all the averted hip fractures as a result of the intervention.*

***Productivity gains are in the million NOK.*

*Table 15 - The average discounted societal gain per prevented hip fracture in 5 year age intervals in men and women.*

| Age interval | Individuals* | | Average societal gain per prevented hip fracture** | |
|---|---|---|---|---|
| | Women | Men | Women | Men |
| 50-54 | 5 | 5 | 0.12 | 1.92 |
| 55-59 | 10 | 5 | 2.09 | 3.60 |
| 60-64 | 15 | 15 | 0.67 | 0.99 |
| 65-70 | 30 | 20 | 0.28 | 0.31 |
| **Total** | **60** | **45** | **0.67** | **1.08** |

**The number of individuals the calculations are based on. These are all the averted hip fractures as a result of the intervention.*

***Productivity gains are in the million NOK.*

*Table 16 – Societal gain distribution in men and women.*

| Gain due to | Societal gain in men | Societal gain in women |
|---|---|---|
| Averted sick leave | 4 317 532 | 4 837 895 |
| Averted permanent disability | 41 820 593 | 33 512 635 |
| Averted hip fracture related death | 2 540 308 | 1 693 737 |
| **Total** | **48 678 434** | **40 044 267** |

## A.4. Gross incomes, taxes, and disability benefits

| | Monthly gross incomes (NOK) | | Annual gross incomes (NOK) | | Daily gross incomes (NOK) | | Income taxes (%) | | Annual income taxes (NOK) | | Annual gross disability benefit payments (NOK) | | Income taxes on disability benefits (%) | | Annual net disability benefit payments (NOK) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age groups | Men | Women | Men | Women | Men | Women | Men | Women | Men | Women | Men | Women | Men | Women | Men | Women |
| 50-54 | 59 680 | 51 780 | 716 160 | 621 360 | 2754 | 2389 | 28 | 28 | 200 525 | 173 981 | 421 340 | 410 098 | 21 | 21 | 332 859 | 323 977 |
| 55-59 | 59 860 | 51 400 | 718 320 | 616 800 | 2762 | 2372 | 28 | 28 | 201 130 | 172 704 | 421 340 | 407 088 | 21 | 21 | 332 859 | 321 600 |
| ≥60, 67-70 | 59 320 | 50 030 | 711 840 | 600 360 | 2737 | 2309 | 28, 23 | 28, 23 | 199 315, 163 723 | 168 101, 138 083 | 421 340 | 396 238 | 21 | 21 | 332 859 | 313 028 |

# A.5. Syntax

## Women without intervention

```
n_t <- 21
n_s <- 7
n_c <- 36795

v_state_names <- c("Healthy", "Acute first hip fracture", "Post first hip fracture", "Acute subsequent hip fracture", "Post subsequent hip fracture", "Hip fracture-related death", "Other death")

trans_mat <- array(NA_real_,
                   dim = c(n_s, n_s, n_t),
                   dimnames = list(from  = v_state_names,
                                   to    = v_state_names,
                                   cycle = 1:n_t))
trans_mat[1, 3, ] <- 0
trans_mat[1, 4, ] <- 0
trans_mat[1, 5, ] <- 0
trans_mat[1, 6, ] <- 0

trans_mat[2, 1, ] <- 0
trans_mat[2, 4, ] <- 0
trans_mat[2, 5, ] <- 0
trans_mat[2, 7, ] <- 0

trans_mat[3, 1, ] <- 0
trans_mat[3, 2, ] <- 0
trans_mat[3, 5, ] <- 0

trans_mat[4, 1, ] <- 0
trans_mat[4, 2, ] <- 0
trans_mat[4, 3, ] <- 0
trans_mat[4, 7, ] <- 0

trans_mat[5, 1, ] <- 0
trans_mat[5, 2, ] <- 0
trans_mat[5, 3, ] <- 0
trans_mat[5, 4, ] <- 0

trans_mat[6, 1, ] <- 0
trans_mat[6, 2, ] <- 0
trans_mat[6, 3, ] <- 0
trans_mat[6, 4, ] <- 0
trans_mat[6, 5, ] <- 0
trans_mat[6, 7, ] <- 0
trans_mat[6, 6, ] <- 1

trans_mat[7, 1, ] <- 0
trans_mat[7, 2, ] <- 0
trans_mat[7, 3, ] <- 0
trans_mat[7, 4, ] <- 0
trans_mat[7, 5, ] <- 0
trans_mat[7, 6, ] <- 0
trans_mat[7, 7, ] <- 1

trans_mat[2, 2, ] <- 0
trans_mat[4, 4, ] <- 0

trans_mat[1, 7,  1:5]  <- 0.000351938
trans_mat[1, 7,  6:10] <- 0.000523863
trans_mat[1, 7, 11:15] <- 0.000917579
trans_mat[1, 7, 16:21] <- 0.001500873

trans_mat[1, 2,  1:5]  <- 0.0000799968
trans_mat[1, 2,  6:10] <- 0.000179984
trans_mat[1, 2, 11:15] <- 0.000299955
trans_mat[1, 2, 16:21] <- 0.000579832

trans_mat[1, 1,  1:5]  <- 0.999568065
trans_mat[1, 1,  6:10] <- 0.999296153
trans_mat[1, 1, 11:15] <- 0.998782466
trans_mat[1, 1, 16:21] <- 0.997919296

trans_mat[2, 6,  1:5]  <- 0.002995504
trans_mat[2, 6,  6:10] <- 0.004171276
trans_mat[2, 6, 11:15] <- 0.005803097
trans_mat[2, 6, 16:21] <- 0.008087122

trans_mat[2, 3,  1:5]  <- 0.997004496
trans_mat[2, 3,  6:10] <- 0.995828724
trans_mat[2, 3, 11:15] <- 0.994196903
trans_mat[2, 3, 16:21] <- 0.991912878

trans_mat[3, 7,  1:5]  <- 0.000351938
trans_mat[3, 7,  6:10] <- 0.000523863
trans_mat[3, 7, 11:15] <- 0.000917579
trans_mat[3, 7, 16:21] <- 0.001500873

trans_mat[3, 6,  1:5]  <- 0.002425055
trans_mat[3, 6,  6:10] <- 0.003330442
trans_mat[3, 6, 11:15] <- 0.00445206
trans_mat[3, 6, 16:21] <- 0.005980048


trans_mat[3, 4,  1:5]  <- 0.00228738
trans_mat[3, 4,  6:10] <- 0.00228738
trans_mat[3, 4, 11:15] <- 0.00228738
trans_mat[3, 4, 16:21] <- 0.002414081

trans_mat[3, 3,  1:5]  <- 0.994935627
trans_mat[3, 3,  6:10] <- 0.993858316
trans_mat[3, 3, 11:15] <- 0.992342981
trans_mat[3, 3, 16:21] <- 0.990104998

trans_mat[4, 6,  1:5]  <- 0.002995504
trans_mat[4, 6,  6:10] <- 0.004171276
trans_mat[4, 6, 11:15] <- 0.005803097
trans_mat[4, 6, 16:21] <- 0.008087122
```

```r

trans_mat[4, 5,  1:5]  <- 0.997004496
trans_mat[4, 5,  6:10] <- 0.995828724
trans_mat[4, 5, 11:15] <- 0.994196903
trans_mat[4, 5, 16:21] <- 0.991912878

trans_mat[5, 7,  1:5]  <- 0.000351938
trans_mat[5, 7,  6:10] <- 0.000523863
trans_mat[5, 7, 11:15] <- 0.000917579
trans_mat[5, 7, 16:21] <- 0.001500873

trans_mat[5, 6,  1:5]  <- 0.002425055
trans_mat[5, 6,  6:10] <- 0.003330442
trans_mat[5, 6, 11:15] <- 0.00445206
trans_mat[5, 6, 16:21] <- 0.005980048

trans_mat[5, 5,  1:5]  <- 0.997223007
trans_mat[5, 5,  6:10] <- 0.996145696
trans_mat[5, 5, 11:15] <- 0.994630361
trans_mat[5, 5, 16:21] <- 0.99251908

trans_mat

state_membership <- array(NA_real_,
                          dim = c(n_t, n_s),
                          dimnames = list(cycle = 1:n_t,
                                          state = v_state_names))

state_membership[1, ] <- c(n_c, 0, 0, 0, 0, 0, 0)

for (i in 2:n_t) {
  state_membership[i, ] <- state_membership[i - 1, ] %*% trans_mat[, , i - 1]
}

state_membership
```

## Men without intervention

```r
n_t <- 21
n_s <- 7
n_c <- 38565

v_state_names <- c("Healthy", "Acute first hip fracture", "Post first hip fracture", "Acute subsequent hip fracture", "Post subsequent hip fracture", "Hip fracture-related death", "Other death")

trans_mat <- array(NA_real_,
                   dim = c(n_s, n_s, n_t),
                   dimnames = list(from  = v_state_names,
                                   to    = v_state_names,
                                   cycle = 1:n_t))
trans_mat[1, 3, ] <- 0
trans_mat[1, 4, ] <- 0
trans_mat[1, 5, ] <- 0
trans_mat[1, 6, ] <- 0

trans_mat[2, 1, ] <- 0
trans_mat[2, 4, ] <- 0
trans_mat[2, 5, ] <- 0
trans_mat[2, 7, ] <- 0

trans_mat[3, 1, ] <- 0
trans_mat[3, 2, ] <- 0
trans_mat[3, 5, ] <- 0

trans_mat[4, 1, ] <- 0
trans_mat[4, 2, ] <- 0
trans_mat[4, 3, ] <- 0
trans_mat[4, 7, ] <- 0

trans_mat[5, 1, ] <- 0
trans_mat[5, 2, ] <- 0
trans_mat[5, 3, ] <- 0
trans_mat[5, 4, ] <- 0

trans_mat[6, 1, ] <- 0
trans_mat[6, 2, ] <- 0
trans_mat[6, 3, ] <- 0
trans_mat[6, 4, ] <- 0
trans_mat[6, 5, ] <- 0
trans_mat[6, 7, ] <- 0
trans_mat[6, 6, ] <- 1

trans_mat[7, 1, ] <- 0
trans_mat[7, 2, ] <- 0
trans_mat[7, 3, ] <- 0
trans_mat[7, 4, ] <- 0
trans_mat[7, 5, ] <- 0
trans_mat[7, 6, ] <- 0
trans_mat[7, 7, ] <- 1

trans_mat[2, 2, ] <- 0
trans_mat[4, 4, ] <- 0
```

```r

trans_mat[1, 7,  1:5]  <- 0.000471889
trans_mat[1, 7,  6:10] <- 0.000841646
trans_mat[1, 7, 11:15] <- 0.001345095
trans_mat[1, 7, 16:21] <- 0.00234325

trans_mat[1, 2,  1:5]  <- 0.000099995
trans_mat[1, 2,  6:10] <- 0.00013999
trans_mat[1, 2, 11:15] <- 0.000259966
trans_mat[1, 2, 16:21] <- 0.000379928

trans_mat[1, 1,  1:5]  <- 0.999428116
trans_mat[1, 1,  6:10] <- 0.999018364
trans_mat[1, 1, 11:15] <- 0.998394939
trans_mat[1, 1, 16:21] <- 0.997276822

trans_mat[2, 6,  1:5]  <- 0.005385446
trans_mat[2, 6,  6:10] <- 0.007670431
trans_mat[2, 6, 11:15] <- 0.010939721
trans_mat[2, 6, 16:21] <- 0.015577397

trans_mat[2, 3,  1:5]  <- 0.994614554
trans_mat[2, 3,  6:10] <- 0.992329569
trans_mat[2, 3, 11:15] <- 0.989060279
trans_mat[2, 3, 16:21] <- 0.984422603

trans_mat[3, 7,  1:5]  <- 0.000471889
trans_mat[3, 7,  6:10] <- 0.000841646
trans_mat[3, 7, 11:15] <- 0.001345095
trans_mat[3, 7, 16:21] <- 0.00234325

trans_mat[3, 6,  1:5]  <- 0.003362335
trans_mat[3, 6,  6:10] <- 0.004627261
trans_mat[3, 6, 11:15] <- 0.004464007
trans_mat[3, 6, 16:21] <- 0.008795095

trans_mat[3, 4,  1:5]  <- 0.001098396
trans_mat[3, 4,  6:10] <- 0.001098396
trans_mat[3, 4, 11:15] <- 0.001098396
trans_mat[3, 4, 16:21] <- 0.001080416

trans_mat[3, 3,  1:5]  <- 0.99506738
trans_mat[3, 3,  6:10] <- 0.993432697
trans_mat[3, 3, 11:15] <- 0.993092503
trans_mat[3, 3, 16:21] <- 0.987781239

trans_mat[4, 6,  1:5]  <- 0.005385446
trans_mat[4, 6,  6:10] <- 0.007670431
trans_mat[4, 6, 11:15] <- 0.010939721
trans_mat[4, 6, 16:21] <- 0.015577397

trans_mat[4, 5,  1:5]  <- 0.994614554
trans_mat[4, 5,  6:10] <- 0.992329569
trans_mat[4, 5, 11:15] <- 0.989060279
trans_mat[4, 5, 16:21] <- 0.984422603

trans_mat[5, 7,  1:5]  <- 0.000471889
trans_mat[5, 7,  6:10] <- 0.000841646
trans_mat[5, 7, 11:15] <- 0.001345095
trans_mat[5, 7, 16:21] <- 0.00234325

trans_mat[5, 6,  1:5]  <- 0.003362335
trans_mat[5, 6,  6:10] <- 0.004627261
trans_mat[5, 6, 11:15] <- 0.004464007
trans_mat[5, 6, 16:21] <- 0.008795095

trans_mat[5, 5,  1:5]  <- 0.996165777
trans_mat[5, 5,  6:10] <- 0.994531093
trans_mat[5, 5, 11:15] <- 0.994190899
trans_mat[5, 5, 16:21] <- 0.988861655

trans_mat

state_membership <- array(NA_real_,
                          dim = c(n_t, n_s),
                          dimnames = list(cycle = 1:n_t,
                                          state = v_state_names))

state_membership[1, ] <- c(n_c, 0, 0, 0, 0, 0, 0)

for (i in 2:n_t) {
  state_membership[i, ] <- state_membership[i - 1, ] %*% trans_mat[, , i - 1]
}

state_membership
```