Societal costs of vertebral compression fractures in Sweden

Date: November 2022
Available at: www.nordiq-analytics.com
Contact person: malin.nilsson@inossia.com

Abstract

Aim

The primary aim was to estimate the societal costs and quality of life of individuals who sought care for vertebral compression fractures, in Sweden, in 2019. The secondary aim was to conduct a scenario analysis of the potential cost-effectiveness of a bone cement softener solution developed by Inossia. The solution is used in the cement that is applied in vertebral augmentation surgery, and prevents consecutive fractures.

Methods

A cost of illness study was conducted, where resource use was estimated based on data from the Swedish National Board of Health and Welfare, the Swedish Association of Local Authorities and Regions and the Swedish Social Insurance Agency. A valuation of resource use was made based on cost data from the Swedish Association of Local Authorities and Regions and Statistics Sweden. Quality of life estimates were derived from the literature. Using effect estimations of Inossia's bone softener solution aimed at preventing consecutive vertebral compression fractures, net costs including cost of the solution were put in relation to the societal costs of vertebral compression fractures.

Result

In 2019, 8 187 individuals sought care for vertebral compression fractures within specialized outpatient and inpatient care in Sweden. Total costs related to the vertebral fracture were estimated at SEK 226.20 million. Direct costs related to healthcare amounted to SEK 125.75 million. Indirect costs related to sick leave and early retirement were estimated at SEK 100.45 million. The average quality of life retrieved from published literature for these patients was estimated to decrease by 16.4 % the first two years. Five people would need to be treated with Inossia´s product to avoid one recurrent fracture. 3 691 SEK would need to be invested to avoid one incident fracture within 3 months, which could lead to potential savings of 67 981 SEK due to avoiding one recurrent fracture. Net savings would therefore be 64 290 per avoided case. The cost benefits of Inossia´s product are 18 times larger than the investment made, compared to standard cement.

Conclusion

The disease burden and societal costs of vertebral compression fractures are significant, with a majority of costs related to direct healthcare costs. Treating patients with such fractures with augmentation surgery using a bone softener solution could be value for money. It is yet to be seen whether such a solution is as effective as hypothesized.

DISCLAIMER

This report was commissioned by Inossia AB and funded by Vinnova. The views expressed in this report are solely those of the authors and do not reflect the views of Inossia AB. Inossia AB had no influence on study design, data collection, statistical analyses, drafting the manuscript and drawing conclusions, which was solely done by the authors.

Preface

This report was produced by NordIQ Analytics on behalf of Inossia and through financial support from Vinnova. The primary aim was to estimate the societal costs and quality of life of patients with vertebral compression fractures, with costs relating to the burden on the healthcare and welfare sector. The secondary aim was to provide a scenario analysis estimating the potential cost-effectiveness of a bone softener solution aimed at preventing future vertebral compression fractures. An important part of this work stems from the lack of treatment provided to individuals who suffer from vertebral compression fractures.

Inossia did not have any influence on data collection, statistical analyses, drafting the manuscript or the conclusions of this report. However, we would like to thank Inossia for valuable discussions and feedback that improved and led the work towards the final product. Many thanks to Malin Nilsson, CEO and co-founder, Alejandro Lopez, product realization manager and Christina Lidén, business development manager.

Stockholm, November 2022

Filipa Sampaio, Richard Ssegonja, Camilla Nystrand
NordIQ Analytics

Table of contents

Figures and tables

Abbreviations

COI	Cost of illness
CPP	Cost per patient
HRQoL	Health-related quality of life
ICD-10	International Classification of Diseases 10th Revision
NBHW	The Swedish National Board of Health and Welfare
QALY	Quality-adjusted life-years
SIA	Swedish Social Insurance Agency
SKR	The Swedish Association of Local Authorities and Regions
VCF	Vertebral compression fractures

Summary

Osteoporosis is a disease characterized by weak bone and is considered a major public health problem, affecting over 30 million people in Europe and more than a hundred million people worldwide, predominantly postmenopausal women [1]. The main clinical consequence of the disease is bone fractures. Roughly 15% of these are vertebral fractures, some of which are causing vertebral compression (VCF). However, it is likely that these fractures are underestimated in the population as they are not recognized nor diagnosed at the first presentation. Treatment for VCF differs globally from conservatively to surgically. The common downside to conservative management is that eventually those patients need surgery. However, even after surgical treatment, re-operations and repeated fractures are a common occurrence. This report presents the cost burden of VCF in Sweden in 2019, as well as the impact of VCF on health-related quality of life. In addition, a scenario-based cost-effectiveness estimation reports on the potential cost savings of surgical management using a bone cement softener solution in comparison to standard cement.

The report follows a cost of illness design. Healthcare consumption consisting of inpatient, specialized outpatient and primary care, including medical diagnosis and treatment, were estimated using the Patent Register from the Swedish National Board of Health and Welfare and the Cost per Patient data in Sweden. Estimates of productivity loss related to sick leave and early retirement were based on statistics from the Swedish Social Insurance Agency and valued using cost estimates from Statistics Sweden. The burden of the disease related to VCF was estimated from the literature. The scenario-based cost-effectiveness analysis compares the effect of the two treatments regarding recurrent fractures in relation to the cost of the treatments, healthcare use and productivity losses.

The total cost of VCF in Sweden in 2019 amounted to approximately SEK 226 million. Direct costs related to inpatient care accounted for 50% of total costs. Productivity losses (indirect costs) amounted to 44% of total costs. Sick leave and early retirement cost approximately SEK 100 million. Roughly five individuals need to be treated with the bone cement softener solution to avoid one recurrent VCF, in comparison to standard cement. Considering the cost of the treatment as well as direct and indirect costs for the five initial fractures and the recurrent fracture, investing one SEK would yield about 18 SEK in return.

VCF is related to large morbidity, and consequently large societal costs. In order to avoid recurrent fractures, a bone cement softener could potentially yield large savings if proven as effective as assumed in the scenario analyses.

1. Introduction

Vertebral fractures can be broadly described as breaks in the bone continuity of the vertebral column, along the spine. That is the cervical, thoracic, lumbar and sacral regions of the vertebral column [2]. The fractures can be suspected based on clinical presentation and confirmed radiologically. They can also be further classified as burst fractures or not, stable (especially fractures involving the anterior column) or unstable. In this report, we will focus mainly on stable vertebral fractures as the product, a bone softener whose health economic aspects are being studied, is used in augmentation surgical management of stable vertebral fractures. The terms stable vertebral fractures, collapsed vertebrae, and vertebral compression fractures (VCF) are used interchangeably to mean the same in this report.

Vertebral compression fractures, especially due to osteoporosis, are a global public health concern [3], contributing considerably to the disability burden [4, 5]. In Europe, more than 30 million people are affected and more than a hundred million people worldwide. It is predominantly common in postmenopausal women [1]. However, it is likely underestimated as most of the fractures are not recognized or diagnosed at the first presentation [6, 7]. Most patients with VCF present or seek care at their primary healthcare centers. Patients initiate contact with care because of back or/and neck pain, neurological sequelae due to radiculopathies or myelopathies depending on which part of the spine is involved, and other related complications.

Vertebral compression fractures impact all dimensions of the patients' lives. That is, they pose an increased risk of repeated VCF and other fractures especially in osteoporosis patients [7, 8]. They may be associated with hospitalizations [9], chronic pain treatments, psychological distress, reduced quality of life [5, 10–13], surgical augmentation, long-term rehabilitation care [14], adjustments in the home employment (assignments and work time) [14], and long-term sick leave/work absence. With such broad impacts, VCF poses enormous cost implications. The cost burden of VCF has been previously documented in several scientific studies. Borgström and colleagues [15] estimated the annual direct cost after VCF at € 12 000 per patient in Sweden. These estimations are similar to figures reported by Coassy and colleagues [16]. Direct costs in Borgström and colleagues' estimates included medication, physical therapy, support costs, community care, informal care from relatives/friends and augmentation surgeries. However, estimates also vary considerably in the literature [16, 17], as different age groups are studied and different treatment modalities are used to treat these patients. For example, Eekman and colleagues quote the annual direct medical costs as € 689 [18]. The picture of the indirect costs is not any different, suffering from large variability in the literature. These are higher in younger individuals before retirement age as opposed to the elderly. Eekman and colleagues quote the indirect cost of VCF as € 12 500 annually per person [18]. These fractures also impact health related quality of life (HRQoL). The HRQoL has been estimated at 0.17 (1 denoting perfect health, and zero representing death) when an individual experiences a fracture [10], and literature demonstrates a rise over time to almost 0.70 over a period of 18

months [10]. Individuals seem to never attain their initial HRQoL, which has been observed as 0.83 [10]. There have been advancements in the management of these fractures with stipulated improvements in quality of life, cost savings and advocacies for research into the field.

Vertebral compression fractures are broadly managed conservatively and surgically with augmentation operations where indicated. Currently, the most commonly performed augmentation surgeries include balloon kyphoplasty and vertebroplasty. These procedures involve injection of cement into the vertebral body to increase its integrity [19]. Nonetheless, complications like re-operations, infections, cement emboli, cement leakage, radiculopathies, myelopathies and repeated fractures are a common occurrence and partly attributed to the cement used in the surgery. Thus, research into development of improved cement has been under way.

The primary aim of this report was to estimate the societal cost consequences and the HRQoL related to VCF for patients 50 years old and above in Sweden. The secondary aim was to provide a scenario analysis estimating the potential cost-effectiveness of a bone cement softener solution aimed at preventing subsequent VCF. The report focused on individuals with a VCF diagnosis in Sweden in 2019.

2. Methods

To answer the aims of the report, two types of approaches were used:
1) a cost-of-illness study design, where costs related to healthcare resource use and loss of productivity were estimated for the year 2019
2) a scenario-based cost-effectiveness analysis of a bone cement softener solution aimed at preventing future fractures

Due to Covid-19, which globally affected the tendency to hold physical face -to-face healthcare visits, it is likely that the statistics for healthcare visits in 2020-2021 have been affected by the pandemic. In this report, the year 2019 was used as the reference year to estimate healthcare consumption and productivity losses, to weed out the effect of the pandemic on the actual disease and cost burden.

2.1 Cost-of-illness study design

The prevalence method was used to estimate societal costs, since total costs were based on all ongoing cases of VCF in 2019, regardless of the year the individual was diagnosed. The method is explained in detail in Chapter 4.

The potential diagnoses included in VCF are presented in the table below, with associated disease codes according to the International Classification of Diseases 10th Revision (ICD-10). The number of individuals diagnosed with VCF throughout 2016-2019 was based on information from the patient register held at the Swedish National Board of Health and Welfare (NBHW), which is based on ICD-10 classifications. In this report, a decision was made only to include "Collapsed vertebra, not elsewhere classified" (ICD-10 disease code M48.5). The reason for this inclusion is the accuracy with which VCF can be captured. Diagnoses other than M48.5 may contain patients with VCF, but it is likely only a small proportion of these patients. Other ICD-10 codes may include patients with fractures of other bones, patients with a vertebral fracture due to falls related incidents, or patients with an underlying diagnosis that may not be eligible for treatment with a soft cement solution, such as cancer patients. The ICD-10 disease code M48.5 was used to collect data from the registers.

Table 1. Diagnoses of vertebral compression fractures

Disease code ICD-10	Disease group
M48.5	Collapsed vertebra, not elsewhere classified
M49.5	Collapsed vertebra in diseases classified elsewhere
M80.0	Age-related osteoporosis with current pathological fracture
M84.4	Pathological fracture, not elsewhere classified
T08	Fracture of spine, level unspecified

Direct costs, which include healthcare resource use, were calculated based on data from the National Board of Health and Welfare (NBHW) Patient Register and the Swedish

Association of Local Authorities and Regions (SKR), Cost Per Patient (CPP) database. These are explained in more detail later in this chapter.

Indirect costs, including the value of lost productivity, were estimated using the human capital approach, described in more detail later in this chapter. These costs were categorized into short and long-term sick leave and permanent sick leave (early retirement). The cost of sick leave was estimated based on statistics from the Swedish Social Insurance Agency (SIA) and national average estimates of gross income, estimated with data from Statistics Sweden. These calculations included social fees and holiday allowance and were estimated for women and men between the ages 50-65. Since information on an individual level was not available for this population, it was not possible to estimate the cost for lost household production.

Individuals with VCF also experience impaired functioning due to pain, suffering and discomfort associated with the condition, thereby affecting their HRQoL. The HRQoL for individuals diagnosed with VCF was estimated using published literature.

Some costs were not possible to estimate in this report. Health and social care outside of the hospital or primary care setting, such as municipal provided health care or help with daily activities at home could not be estimated. Additionally, care provided by family members or relatives were also not included.

2.2 Scenario-based cost-effectiveness

A scenario-based cost-effectiveness analysis was conducted, where the potential effect of vertebral augmentation with a softener added to the bone cement in comparison to bone cement alone, measured as avoided incident fracture, was analyzed in relation to the potential cost offsets due to preventing subsequent fractures. Costs for the two treatments/materials were provided by Inossia, as well as effect estimates for Inossia's bone cement softener solution. Effects related to surgical management using vertebral augmentation was sourced from the literature. Costs related to avoided fractures were based on data collected for the cost-of-illness study.

2.3 Resource use, productivity losses and disease burden

In order to estimate the frequency of healthcare resource use, data was collected from the NBHW [20] and the CPP database from SKR on inpatient and specialized outpatient care [21]. To estimate productivity losses, statistics from SIA [22] were used, and some assumptions made supported by evidence from the scientific literature. Disease burden was estimated from the literature.

2.3.1 Inpatient, specialized outpatient and primary care

Resources used in inpatient, specialized outpatient and primary care were retrieved from national statistics from the NBHW and the CPP database. After each completed healthcare visit, the care provider is obliged to report information regarding the patient,

including, for instance, age, gender, current diagnoses and surgeries. This means that there are reliable statistics for all patients who have been in contact with healthcare (inpatient and specialized outpatient) for patients with VCF. For primary care, data collection was only recently initiated, whereby frequency and costs related to healthcare visits in primary care was only reported by 12 regions (out of a total of 21) in 2019. The ICD-10 disease code used to collect data from the registers was M48.5.

2.3.2 Productivity losses

Indirect costs were based on data from the SIA, including financial compensation due to illness and early retirement. The SIA provides statistics on the number of days of financial compensation related to illness lasting longer than 14 days (long-term sick leave and early retirement). Compensation up to 14 days (short-term sick leave) is paid by the employer and is therefore not included in the SIA register. To a large extent, it is possible to obtain data on financial compensation distributed per diagnosis, but if there are fewer than 10 individuals in the sub-category, the SIA cannot disclose this information for reasons of confidentiality. Productivity losses were estimated for the proportion of ongoing cases of financial compensation due to M48 in 2019. This data was later adjusted to correspond to patients with M48.5, by estimating the proportion of patients with M48.5 within M48, using data from the NBHW.

The value of production was estimated according to the human capital method. In this method, the valuation of production is usually based on the assumption that production can be valued at a market price. This price may be set as the average gross income including social fees and holiday allowance, which refers to the costs that the employer would have incurred had the individual been in full employment. The result is a value of lost productivity, estimated from a societal perspective.

When an employee is ill and absent from work, the employer is obliged to pay for the sick leave to the employee for the first 2-14 days (short-term sick leave), corresponding to 80% of the salary. Day one is a qualifying deduction corresponding to 20% of the average weekly working time.

Since 2003, early retirement is not included in the pension system, but rather belongs to the universal social insurance coverage, and is categorized into activity compensation and sickness benefits. Both sickness benefits and activity compensation are paid to individuals who will probably never work full time again as a result of illness, where the difference is that the activity allowance applies to individuals between 19 and 30 years. Thus, only sickness benefits were included in the estimations in this report.

2.3.3 Health related quality of life and QALYs

HRQoL is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning. It goes beyond direct measures of population health, life expectancy, and causes of death, and focuses on the impact health status has on quality of life. HRQoL profiles or estimations can be used to produce utilities to calculate quality-adjusted life years (QALYs). QALYs are commonly used within

healthcare to estimate the individual health effects of interventions. It is a generic measure of disease burden, including both the quality and the quantity of life lived.

Calculating a QALY requires two inputs. One is the utility value (or utility weight) associated with a given state of health and the other is the number of years lived in that state. The underlying measure of utility is derived from clinical trials and studies that measure how people feel in these specific states of health or disease. In other words, utility is the HRQoL. The way they feel in a state of perfect health equates to a utility value of 1 (or 100%). Death is assigned a utility of 0 (or 0%), and in some circumstances it is possible to accrue negative QALYs to reflect health states deemed "worse than dead". The value people perceive in less than perfect states of health is expressed as a fraction between 0 and 1. The second input is the amount of time people live in various states of health. This information usually comes from clinical trials.

To calculate the QALY, the two measures are multiplied. For example, 1 year of life lived in a situation with utility 0.5 yields 0.5 QALYs—a person experiencing this state is getting only 50% of the possible value of that year. In other words, they value the experience of being in less than perfect health for a full year as much as they value living for half a year in perfect health (0.5 years × 1 Utility).

For the current study, a literature review was undertaken to identify published data on the quality of life changes due to a VCF. Only peer reviewed articles with observed data on Swedish patients 50+ years of age were included. Searches were made using appropriate search terms in PubMed in February 2022. See appendix A for details on the literature search terms and string.

2.4 Valuation of resource use and productivity losses

The use of healthcare resources and productivity losses were valued using the CPP-database for inpatient and specialized outpatient care [21] and salary estimates from Statistics Sweden [23].

2.4.1 Inpatient, specialized outpatient and primary care

The CPP-database contains data on the actual cost for each patient visit and is based on each individual's healthcare utilization. The CPP is an accounting system that is primarily used to monitor the volume of resources used in healthcare. The calculations in the CPP database are therefore based on costs recorded in connection with each visit within healthcare [24], registered with a so-called DRG code. Cost per visit was calculated by dividing the total cost for all visits by the total number of visits.

Today, most regions in Sweden are represented in the CPP-database regarding specialized outpatient and inpatient care [21]. In 2019, 1 265 033 somatic inpatient care cases were registered, which corresponds to approximately 93% of all somatic inpatient care in the NBHW Patient Register. The CPP-database for specialized outpatient care comprised, in 2019, a total of 13 million visits and includes visits to all types of medical professions within the public health care system, covering approximately 80% of all

specialized medical visits. About 3% of visits is estimated to occur within the private health care system, and not captured in the database. Average cost estimates from the CPP-database can therefore be considered a reliable estimate of the actual costs related to healthcare visits in Sweden within specialized outpatient and inpatient care [28], although not all types of visits within healthcare are registered in the CPP-database. For primary care, data collection was only recently initiated, and only reported by 12 regions (out of a total of 21) in 2019, comprising a total of 6.95 million visits in 2020 (no data for 2019 available). However, region Stockholm which is the largest region in terms of population size, was not one of the reporting regions. Since fewer regions deliver data to CPP for primary care visits, the average estimates have lower reliability.

2.4.2 Productivity losses

The cost related to individuals´ inability to work (until the age of retirement) due to illness was estimated based on the average gross income in Sweden in 2019 for men and women between 50 and 65 years. This information was retrieved from Statistics Sweden [23]. The estimate included social fees estimated at 44.1% [25]and holiday allowance.

3. Vertebral compression fractures

3.1 Prevalence

The number of individuals who sought care for VCF, based on the ICD-10 code M48.5, has been stable throughout 2016-2019. Roughly, 70% of all cases of VCF are women.

Table 2. Number of diagnosed cases in years 2016-2019

M48.5	2016	2017	2018	2019
Men	2 468	2 468	2 439	2 546
Women	5 841	5 912	5 717	5 641
Total	**8 309**	**8 393**	**8 156**	**8 187**

Source: The Swedish National Board of Health and Welfare

3.2 Age distributions

The graph below depicts the age distribution for patients diagnosed with VCF within specialized outpatient and inpatient care in Sweden in 2019. There is a clear rightward skewness to the data, showing that these types of fractures occur more frequently in the older population. For patients older than 75 years, there are about twice as many women as men being diagnosed with VCF.

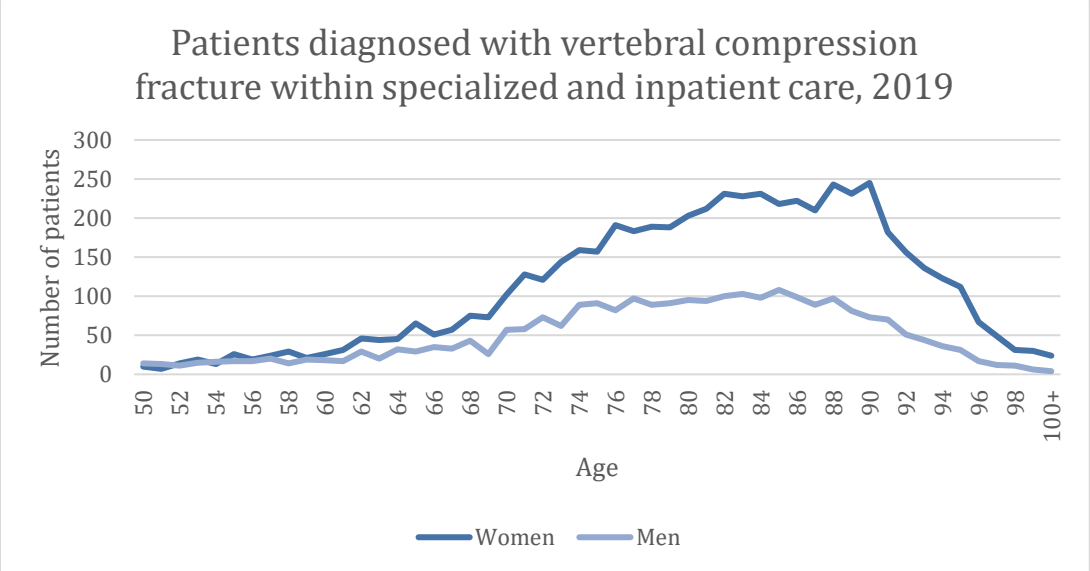


Figure 1. Age distribution of vertebral compression fractures in Sweden, 2019

3.3 Risk factors

The incidence of VCF is on the rise globally [26, 27]. This can be partially related to the aging population [26] and other risk factors including osteoporosis, malignancies/tumors, trauma, cancer therapy, glucocorticoids use, infections and other

bone degenerative disorders such as Paget's disease [27]. Osteoporosis is by far the most common risk factor. Osteoporosis primarily leads to decreased bone mineral density and hence increased bone fragility [27, 28].

3.4 Treatment

VCF are broadly managed conservatively with analgesics, osteoporosis specific treatment when deemed necessary, calcitonin, braces, physical/physiotherapy, walking aids, and home help [29–32]. Alternatively, patients can be managed surgically with minimally invasive augmentation operations [29–31]. Patients that are candidates for surgery include those that have continued deterioration despite conservative treatment. Currently, most augmentation surgeries are vertebroplasty (VP) and balloon kyphoplasty (BKP). VP involves minimal access surgery and injection of cement into the vertebral body to increase its integrity [19]. BKP on the other hand, involves minimal access surgery where a cavity for more safe injection of the cement is created in the vertebral body using a balloon, then the created space is filled with a bone cement to hold together the integrity of the vertebral body [19]. There is accumulating evidence regarding the effectiveness [19, 33–36] and cost-effectiveness [35, 37–40] of these interventions. These surgical interventions have been demonstrated to be cost-effective in different geographical and healthcare settings [37, 41]. The common downside to conservative management is that eventually those patients need surgery. However, even after surgical treatment, re-operations and repeated fractures are a common occurrence. Although the evidence supporting the increased risk of repeated fractures after vertebral augmentation surgery is contradicting, the mentioned increased risk of subsequent fractures has been partly attributed to the type of cement used in the procedure.

Inossia AB has attempted to improve the cement used in surgical procedures by a softener (Inossia™ Cement Softener) to add to conventional bone cements. It makes the cement softer, matches the characteristics of trabecular bone and can reduce the rate of further painful fractures by up to 75%. The new cement has been verified in mechanical studies, cell studies and large animal trials in sheep. Altogether, the material was found to be safe to use clinically. The cement softener is currently being tested for its effectiveness in a randomized controlled trial.

4. Cost of illness

This chapter gives an overview of the theoretical underpinnings of the methodology used in the costing analysis in this report, and in a more detailed manner, describes the assumptions behind the cost estimates.

The fundamental goal with cost of illness (COI) studies is to estimate the economic burden that illness imposes on society. Estimates from COI studies serve different purposes. They can be used to inform decision-makers and stakeholders of the magnitude of a certain disease by describing all medical and societal costs related to that disease. COI can help argue that policies targeting certain diseases should be given high priority in a policy agenda setting. Additionally, COI estimates can drive stakeholders towards a need to investigate the cost-effectiveness of new healthcare programs, technologies, or drugs. Estimates of societal costs can also facilitate cross-national comparisons of disease consequences and various approaches that are available to confront those consequences. COI studies do not, however, provide guidance on what or how we should optimally allocate societal resources. They rather show the potential (economic) benefits that can be achieved by a certain intervention or policy if it can successfully prevent the use of societal resources related to a certain disease, given the intervention is cheaper than status quo. In this vein, COI studies generally include a metric of 'health loss' and try to measure the resource costs incurred in treating a specific disease. It is important, however, that costs are estimated using similar methodology across medical areas to allow for fair comparisons of economic burden of illnesses and strategies to combat them [42, 43].

COI studies are based on the assumption that every resource has an alternative use. This may imply that all types of resources can be measured, even if not in monetary terms. There are three steps in a cost analysis: (1) *identification,* (2) *quantification* and (3) *valuation*.

4.1 Identification

The first step in a cost analysis is to identify all the relevant resources that will be consumed in relation to a particular disease or health condition. This requires deep knowledge about the condition being investigated to ensure validity, as well as clear and well-defined diagnosis codes to ensure transparency.

COI studies may be carried out from a variety of perspectives, each including slightly different cost items, which may lead to different results for the same illness. These perspectives may measure costs to a particular society, the healthcare system, third-party payers, the government, and the patients and their families. It is, therefore, important to define the perspective from which costs will be estimated.

In general, the broader societal perspective is preferred, because it reflects the full range of opportunity costs attributable to a disease regardless of which sector they

occur in. A third-party payer perspective, for instance a region's or municipality's perspective, takes a narrower financial perspective, and would only include the costs that would influence their own budget.

The definition of a societal cost can be divided into three different aspects [43]. The first aspect (1) requires that a cost cannot be incurred as an income in another sector of society. Redistributions or transfer costs can therefore not be seen as a cost, for instance, rehabilitation benefits. Such may be a cost for the SIA, but an income to the individual. In the second aspect (2), only external costs constitute a societal cost, not internal costs. An internal cost is what a consumer pays for a good or a service. This cost only affects the consumer, whereas an external cost has a wider impact. This is because an internal cost is usually offset against the value of the good or the service being consumed, and the cost would not have arisen had the consumer refrained from consumption. The third aspect (3) says that sometimes one can refrain from the second aspect if the consumer does not consume the goods or services voluntarily or deliberately. Discomfort and deterioration of one's standard of living due to illness can therefore be regarded as a cost to society.

Economic costs fall into three categories: direct, indirect and intangible costs. *Direct costs* are tangible, monetary costs that can be determined by observing immediate expenditure on health services, social care and other services. They consist of both medical and non-medical costs. Medical costs are those related to medical care expenses for diagnosis, treatment and rehabilitation, such as outpatient and inpatient care and medication. If we were to estimate costs from the healthcare payer perspective, only medical costs would be included. Non-medical costs relate to the consumption of other resources by patients and families, including transportation costs and informal care (often given by relatives).

Indirect costs are opportunity costs that represent societal output forgone as a consequence of a disease or illness and are measured in terms of lost productivity. These can, for instance, include short and long-term sick leave and early retirement. Indirect costs therefore include resources that are not produced by individuals due to reduced work capacity because of their illness. Indirect costs include sectors other than the healthcare sector, such as the educational sector. An example would be costs for additional support in school due to a disability or disease. These costs would only be relevant from a societal perspective.

Intangible costs are not resources *per se,* rather a valuation of the wider impacts associated with early mortality or pain and suffering. These are usually considered subjective, as they are not associated with any real cost, and their value is usually determined or estimated by a decision-maker.

4.2 Quantification

Upon identification of the relevant cost items from the costing perspective chosen, the extent of resource consumption must be assessed. Resource use can be estimated

quantifying, for instance, number of days of care, time spent on each healthcare visit, medication used or number of days of sick leave. When quantifying the resources used, the level of detail will depend on the availability of information. Costs can be obtained by means of micro-costing or simply using a gross cost. When micro-costing, every component of a larger cost, such as hospitalization, transportation or overheads should be estimated. This is, however, time-consuming, especially when dealing with complex data. Importantly, resource use between individuals differs, thus generalizing estimates based on a few individuals to a larger population inevitably carries large bias. Additionally, it is usually difficult to have access to individual-level data pertaining to different sectors of society. Gross-costing is generally easier, where aggregated costs are usually obtained from a single source such as electronic databases or the medical literature. For instance, hospitalization costs can be obtained for specific diagnosis codes from registers, and averaged across the relevant patients.

Two different methodological approaches can be used to estimate costs in COI studies - the *prevalence-based* and the *incidence-based* approach [42]. In the *prevalence-based* approach, all resource use related to the disease under study is identified and quantified over a specific year. Productivity losses related to, for instance, early mortality, are summed and attributed to the year in which the deaths occurred. The prevalence-based approach thus constitutes a combination of actual resource use over a year and future expected resource use attributed to a particular year.

The *incidence-based* approach estimates the number of cases of death or hospitalization in a given year and applies a lifetime cost estimate to these new cases. The choice of method depends on data availability and the purpose of the study, and can be combined to strengthen the results.
Two methods can be used when quantifying resource consumption, a 'top-down' and a 'bottom-up' approach, based on what type of data is available. In the 'top-down' approach, all relevant expenditure is added and then divided by the corresponding unit of activity. This approach is simple to apply, often using routinely collected data for the whole population, and is most appropriate where an average cost, such as the average cost per person receiving treatment for VCF, is required. However, this approach does not allow analysis of variation in costs, for example for patients requiring additional support beyond a standard intervention or variation by patient characteristics. In contrast, in the 'bottom-up' approach, all resources required to provide a specific intervention or service are described and quantified. One departs from a sub-group of individuals from a population of interest, for instance a sub-group of women with a diagnosis of VCF, and estimates the resource use for every individual in that sample. The average estimates are later applied to all individuals in the population studied. The monetary value of those resources is linked to the specific resource item. This approach tends to be more accurate and versatile, as it can be linked to individuals, thus retaining variability between patients and between sites [36].

4.3 Valuation

Upon the selection of costing perspective, and thereby the identification and quantification of the relevant resources, these should be valued in monetary terms. According to economic theory, resources should be valued according to their 'opportunity cost' – the benefit forgone from not investing in the next best alternative. Under the assumption of perfect markets, market prices may reflect opportunity costs. Perfect markets are free from competition, there is full information on goods and services for consumers and sellers, and there are no external effects that can affect pricing or trading. Since we usually do not trade in perfect markets, resource use must be valued in a different manner other than through market prices.

Direct medical costs, i.e. healthcare related costs, are usually not considered to come from perfect markets, therefore different tariffs and standard prices are used to value such costs, including price lists for different healthcare visits or treatments. Such established price lists are usually based on time spent during visits, resources used (materials, etc.) and overheads (rent, administration, etc.).

Indirect costs can be valued using a human capital approach [44] or a friction cost approach [45]. The human capital approach is most often used to value indirect costs in Sweden. This method assumes that markets are perfect, that there are free movement of goods and people, and that there is no unemployment, which means that nobody can replace a person who is unable to work. In short, this method places a value on lost output by calculating the sum of discounted expected future income, which equals the individual´s gross income including social fees. On the other hand, the friction cost approach considers unemployment, and the fact that people can be replaced after a certain number of months or years depending on the type of work. However, information at the individual level is required to perform a friction cost analysis, thus the human capital method is most often used.

Estimating the value of intangible costs is complicated because they are not valued within a market, but usually by decision-makers. Most COI studies report the prevalence of disease burden, but refrain from quantifying it. Within healthcare, there has long been an unwillingness to quantify human suffering in monetary terms, which has contributed to the use of generic measures of health-related quality of life, such as QALYs [43]. The use of QALYs in the evaluation of different treatments across different medical areas allows for the possibility of comparing alternatives and relative cost-effectiveness, since disease-specific measures cannot be compared outside their specific medical areas. It also enables decision-makers to put a price tag on a QALY, and therefore make a monetary assessment of the burden of disease and quality of life.

5. Societal costs of vertebral compression fractures

This chapter presents the societal costs and quality of life of patients diagnosed with VCF. The first part of the chapter presents the societal costs, which are categorized into direct and indirect costs. The second part of the chapter presents a brief description of the quality of life loss associated with VCF. All costs are expressed in 2019 Swedish krona (SEK).

5.1 Direct costs

Direct costs pertain to costs related to the use of healthcare resources including primary care, inpatient and specialized outpatient care.

5.1.1 Primary care

The CPP-database contains information on patients who have received primary care in Sweden in 12 out of 21 regions. In 2019, the number of primary care visits due to VCF amounted to 1 501 (Table 3).

Table 3. Number of primary care visits for patients 50+ years, 2019

Vertebral compression fracture	2019
Men	437
Women	1 064
Total	**1 501**

The number of primary care visits was multiplied by the average cost per visit for VCF to estimate the total cost of primary care. This was estimated at nearly SEK 2.33 million (see Table 4). Primary care costs amongst men with VCF amounted to SEK 669 087, and costs among women amounted to roughly SEK 1.66 million.

Table 4. Primary care cost of patients 50+ years with VCF in 2019

Vertebral compression fracture	Number of visits [a]	Cost per visit (SEK)	Total (SEK)
Men	437	1 565	1 665 636
Women	1 064	1 531	669 087
Total	**1 501**	**1 555**	**2 334 723**

[a] The Swedish Association of Local Authorities and Regions' Cost Per Patient-database

5.1.2 Inpatient care

The NBHW Patient register contains information on the number of patients with a specific diagnosis within the inpatient public healthcare system in Sweden. The CPP-database holds additional information on inpatient care, including completed episodes, average length of care, number of days of care, and number of patients, reported per main diagnosis. The number of patients in inpatient care with a VCF diagnosis amounted to 5 474 in 2019 (Table 5). The number of episodes of inpatient care due to VCF amounted to 2 063 in 2019 (Table 6). The number of episodes of inpatient care decreased by 8,4% between 2016 and 2019.

Table 5. Number of patients 50+ years with a VCF diagnosis in inpatient care, 2016-2019

Vertebral compression fracture [a]	2016	2017	2018	2019
Men	1 727	1 675	1 627	1 753
Women	4 099	4 088	3 923	3 721
Total	**5 826**	**5 763**	**5 550**	**5 474**

[a] The National Board of Health and Welfare's Patient Register

Table 6. Number of inpatient care episodes for patients 50+ years, 2016-2019

Vertebral compression fracture	2016	2017	2018	2019
Men	653	684	597	682
Women	1 599	1 710	1 429	1 381
Total	**2 252**	**2 394**	**2 026**	**2 063**

Table 7 summarizes the average costs per inpatient care episode for all patients with VCF. The average cost per inpatient care episode for patients with a VCF diagnosis was SEK 54 351, which was based on 2 063 episodes in the CPP database.

The total cost of inpatient care for VCF was estimated by multiplying the number of episodes by the average cost per episode for VCF. The total cost of inpatient care was estimated at SEK 112.13 million (see table 7).

Table 7. Inpatient care cost of patients 50+ years with VCF in 2019

Vertebral compression fracture	Number of episodes[a]	Cost per episode(SEK)	Total (SEK)
Men	682	54 503	37 171 374
Women	1 381	54 276	74 955 276
Total	**2 063**	**54 351**	**112 126 650**

[a] The Swedish Association of Local Authorities and Regions' Cost Per Patient-database

5.1.3 Specialized outpatient care

The NBHW Patient register also contains information on the number of patients with a specific diagnosis within the specialized outpatient public healthcare system in Sweden. The CPP-database also contains information on patients who have received specialized outpatient care. Outpatient care refers to the type of care that does not require overnight hospitalization. Specialized outpatient care can include both less resource-intensive services such as visits to clinics and more resource-intensive services such as day surgery.

The number of cases with a VCF diagnosis in specialized outpatient care in Sweden, in 2019, amounted to 3 939 (Table 8). The number of specialized outpatient care visits related to VCF amounted to 2 763, in 2019 (Table 9). The number of visits to outpatient care related to VCF increased by 11,7% between 2016 and 2019.

Table 8. Number of patients 50+ years with a VCF diagnosis in specialized outpatient care, 2016-2019

Vertebral compression fracture	2016	2017	2018	2019
Men	1 146	1 202	1 211	1 193
Women	2 630	2 714	2 652	2 746
Total	**3 776**	**3 916**	**3 863**	**3 939**

Table 9. Number of specialized outpatient care visits by patients 50+ years, 2016-2019

Vertebral compression fracture	2016	2017	2018	2019
Men	772	905	858	925
Women	1 701	1 813	1 747	1 838
Total	**2 473**	**2 718**	**2 605**	**2 763**

Note: The number of visits in outpatient care are fewer than the number of patients 50+ years with a VCF diagnosis as denoted in table 8. The difference is due to table 8 reporting on prevalent cases, and table 9 is likely only to pick-up incident fractures.

The number of specialized outpatient care visits was multiplied by the average cost per visit for VCF to estimate the total cost of specialized outpatient care. This was estimated at around SEK 11.29 million (see Table 10). Specialized outpatient care costs amongst men with VCF amounted to SEK 3.61 million, and costs among women amounted to roughly SEK 7.68 million.

Table 10. Specialized outpatient care cost of patients 50+ years with VCF in 2019

Vertebral compression fracture	Number of visits[a]	Cost per visit (SEK)	Total (SEK)
Men	925	3 906	3 613 359
Women	1 838	4 176	7 675 673
Total	**2 763**	**4 086**	**11 289 032**

[a] The Swedish Association of Local Authorities and Regions' Cost Per Patient-database

5.2 Indirect costs

Indirect costs included illness-related productivity losses that are borne by the community at large, such as for instance, costs of reduced working capacity due to morbidity. In this report, productivity losses have been divided into those accruing due to short- and long-term sick leave and early retirement. Productivity losses were estimated based on the human capital approach.

The average annual gross income in Sweden in 2019 among individuals aged between 50-64 years old was SEK 353 450 for women and SEK 441 600 for men, according to Statistics Sweden [23]. Including 44,1% social charges [25], the average societal cost of one year of lost productivity amounts to SEK 509 321 for women and SEK 636 346 for men. Since sickness and rehabilitation benefits are calendar-day allowances, individuals receive allowance seven days a week. Therefore, one year of lost productivity corresponds to 365 days of sick leave.

Since short- and long-term sickness benefits as well as disability pension are transfer costs (state allowances), the actual transfer cost estimates were not included in the present analysis. Including such costs would involve a double count of costs when considering the loss of production that occurs due to the individual's absence from work. However, the extra cost that arises when processing these payments could be costly. Such costs vary widely between individuals, and we have therefore chosen to exclude it from the analysis.

5.2.1 Productivity loss due to short-term sick leave

Short-term sick leave refers to sickness absence that is shorter than 14 days, hence qualifying for sickness benefits paid by the employer. Under the simplified assumption that the number of individuals of VCF-related short-term sick leave is the same as for long-term sick leave within the first 14 days of leave (14 days of total 36.28 days of sick leave estimated from the literature [17]), the number of sick days as a result of VCF was 5 443, which corresponded to a total of 14,9 lost years of productivity for the population patients with VCF, in 2019. The cost related to short-term sick leave due to VCF was therefore estimated at SEK 6.52 million (Table 11).

Table 11. Short-term sick leave and productivity losses in 2019

Diagnosis	Number of cases in progress	Sickness benefits (in days)	Sickness benefits (in years)	Total productivity loss (SEK)
Men	180	2 515	6,9	3 447 705
Women	209	2 928	8,0	3 075 544
Total	**389**	**5 443**	**14,9**	**6 523 249**

5.2.2 Productivity loss due to long-term sick leave

Long-term sick leave refers to the sick leave from work that lasts longer than 14 days, and thus entails sickness and rehabilitation allowance from the SIA. According to

statistics from the SIA, the number of recipients for sickness and rehabilitation benefits in Sweden, in December 2019, amounted to 680 000 [46].

According to data from SIA, the number of ongoing cases with a diagnosis of M48 amounted to 1 080 individuals. Using data from the patient register from the NBHW, the proportion of individuals with a diagnosis code of M48.5 was estimated (36%). This proportion was then used to estimate the proportion of cases receiving benefits with a diagnosis code of M48 that corresponded to the diagnosis code of M48.5. A total number of ongoing cases related to VCF (with a diagnosis of M48.5) in Sweden, in 2019, was estimated at 389 individuals, Information on the number of net days related to specific diagnoses is not included in the public statistics, hence this data was not available.

It was assumed that patients with VCF were absent from work due to the disease for an average of 36,3 days, based on scientific literature [17]. Based on the number of ongoing cases due to VCF, the number of net days with sickness benefits was calculated, which corresponded to 8 662. The total number of years with sickness benefits due to VCF in Sweden was estimated at 23,7 years. The monetary value of productivity loss due to long-term sick leave amounted to just over SEK 13.48 million (presented in Table 12). Women with VCF accounted for just over 48% of the costs related to loss of productivity due to long-term sick leave.

Table 12. Number of paid sickness benefits and productivity losses in 2019

Diagnosis	Number of cases in progress	Sickness benefits (in days)	Sickness benefits (in years)	Total productivity loss (SEK)
Men	180	4 002	11,0	6 977 798
Women	209	4 660	12,8	6 502 688
Total	**389**	**8 662**	**23,7**	**13 480 486**

5.2.3 Productivity loss due to early retirement

Early retirement due to sickness refers to those individuals who receive financial disability benefits. To be eligible for disability benefits, the individual's ability to work must be reduced by at least a quarter for at least one year.

In 2019, according to the SIA, 253 individuals with VCF were granted disability benefits. Disability benefits can be granted to varying degrees (25, 50, 75 and 100%) depending on how much work capacity is considered to be reduced. The number of individuals with different degree of benefits could not be ascertained due to data confidentiality; hence, it was assumed that a quarter of the individuals with a VCF received 25%, 50%, 75% and 100 % of the full amount of disability compensation respectively. In 2019, the cost of early retirement due VCF amounted to just over SEK 80.44 million (Table 13).

Table 13. Productivity losses due to early retirement in 2019

Diagnosis	Number of people receiving benefits	Productivity loss (SEK)
Men	138	43 776 179
Women	115	36 671 144
Total	**253**	**80 447 323**

5.3 Total societal costs for VCF

Table 14 and Figures 2 and 3 show the total societal costs of VCF. Total societal costs amounted to SEK 226.20 million. Direct healthcare costs including both primary, specialized outpatient and inpatient care, diagnosis and treatment amounted to approximately SEK 125.75 million. The largest cost items were those linked to inpatient care, which accounted for over 89% of the direct costs related to VCF. Overall, direct healthcare costs accounted for nearly 56% of total societal costs.

Indirect costs amounted to SEK 100.45 million, in 2019. The largest indirect costs were productivity losses due to early retirement, which accounted for about 80% of the total indirect costs of VCF. Overall, indirect costs accounted for over 44% of total societal costs.

Table 14. Total societal costs of patients 50+ years with VCF in 2019, SEK

	Men	Women	Total
Direct costs	**41 453 820**	**84 296 585**	**125 750 405**
Primary care [a]	669 087	1 665 636	2 334 723
Inpatient care	37 171 374	74 955 276	112 126 650
Specialized outpatient care	3 613 359	7 675 673	11 289 032
Indirect costs	**54 201 682**	**46 249 376**	**100 451 058**
Morbidity			
Short-term sick leave	3 447 705	3 075 544	6 523 249
Long-term sick leave	6 977 798	6 502 688	13 480 486
Early retirement	43 776 179	36 671 144	80 447 323
Total costs	**95 655 502**	**130 545 961**	**226 201 463**

[a] These estimates are largely underestimated due to the fact that only 12 out of the 21 regions in Sweden report data on primary healthcare consumption in 2019.

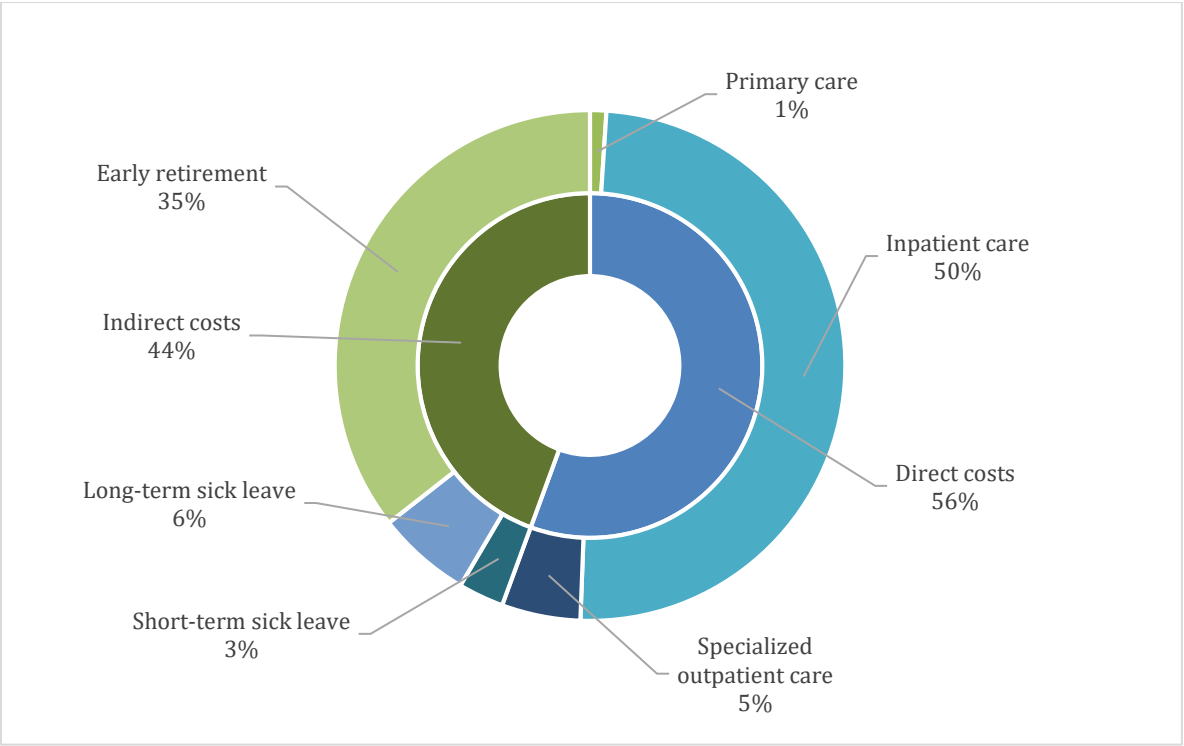


Figure 2. Distribution of total costs of vertebral compression fractures

VCF in women accounted for the largest societal costs, approximately SEK 130.55 million, which corresponded to nearly 58% of the total societal costs for VCF. Costs related to early retirement and inpatient care primarily contributed to this financial burden.

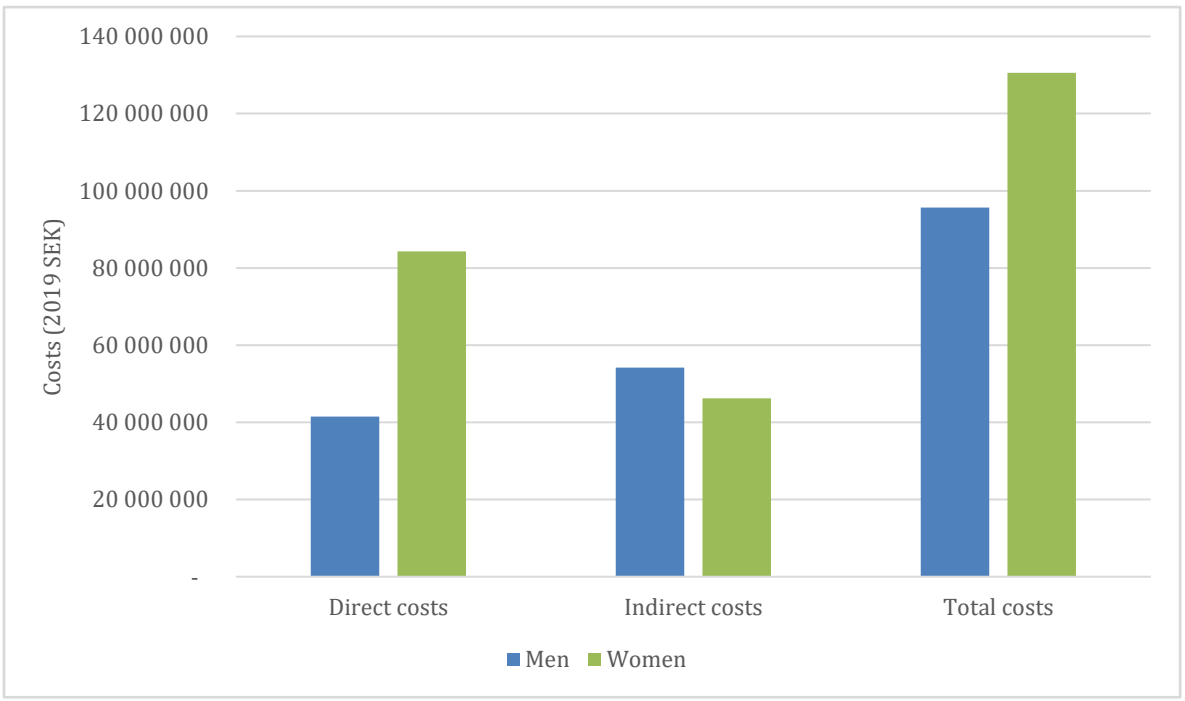


Figure 3. Distribution of costs related to vertebral compression fractures by sex

5.4 Health-related quality of life

The literature review resulted in 64 peer-reviewed articles, whereby titles and abstracts were reviewed by three people. Twenty-two articles were selected for full text screening. Based on these, four articles [12, 15, 47, 48] were deemed relevant for the inclusion criteria, with data on quality of life changes for individuals with a VCF. Two of the included studies [47, 48] were included in a meta-analysis to calculate pooled estimates of quality of life at different time points.

Table 15 shows the quality of life changes for an average patient with VCF throughout 2 year after the compression fracture, based on the four selected articles. As depicted, quality of life decreases by 16.4% directly after a VCF, and slowly increases thereafter. Up to two years after the VCF, patients have still not regained the quality of life they had before the compression fracture. Information related to the search can be found in Appendix A.

Table 15. Health-related quality of life changes due to vertebral compression fractures

Time	Utility
Right before VCF	0.73
Directly after VCF	0.19
4 months after VCF	0.47
6 months after VCF	0.49
9 months after VCF	0.51
12 months after VCF	0.50
18 months after VCF	0.54
24 months after VCF	0.61

6. Scenario-based cost-effectiveness analysis

6.1 Effects and costs of surgical management

Treatment of vertebral compression fractures through intravertebral injection of bone cement, so called vertebral augmentation surgeries, for example vertebroplasty (VP) and balloon kyphoplasty (BKP), result in an immediate pain relief. Of approximately 300,000 inpatient vertebral augmentation procedures performed in the United States between 2005 and 2010, 73% were kyphoplasty, using standard bone cement [49]. The American Academy of Orthopedic Surgeons recommends against the use of vertebroplasty. Thus, all the scenario-based cost-effectiveness analysis will be a comparison between surgical management of vertebral fractures using standard bone cement and the Inossia bone cement softener.

In a literature review and meta-analysis from 2017, electronic databases were searched for literature published until March 2016 for randomized and quasi-randomized controlled trials comparing different treatment regiments for VCF, including BKP with VP. Outcomes included back pain, back disability, quality of life, new VCF, and adverse events [50]. In the study, 14 reports of 10 unique studies that met eligibility criteria and were included for analysis.

The study found that the risk of incident radiographic VCF occurring within 3 months of intervention after BKP was 23.3% (number of studies = 1). This risk increased with time. In addition, the study looked at adjacent vertebral fractures and clinical vertebral fractures, however, no information was reported relating to such fractures occurring within 3 months of intervention.

Inossia has estimated that the risk of incident VCF occurring within three months of intervention with their bone cement softener solution is 5%.

Inossia has provided information regarding the cost of the two treatment regimens. While the surgical procedure and after-care are similar, the price of the two bone cements differ. While the standard cement without softener comes at a cost of 675 SEK (65 Euro), Inossia´s product cost 1 350 SEK (130 Euro).

6.2 Costs related to an incident case of vertebral compression fracture

6.2.1 Healthcare costs

The costs estimated and reported previously in this report are based on one-year prevalence estimates of VCF in Sweden. From the data gathered, it is not possible to estimate the cost per incident fracture. We therefore use two different care pathway scenarios (Figures 3 and 4) for patients with VCF to estimate the healthcare costs related to one fracture. The pathways were confirmed by expert opinion and data from Region Uppsala. These pathways only apply to a patient that is a candidate for surgical management:

Figure 4. Healthcare pathway 1

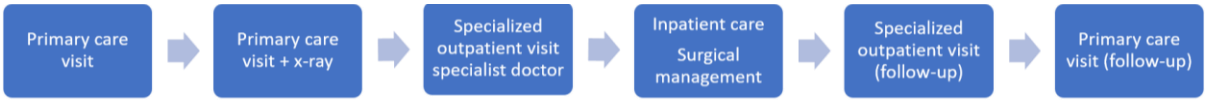


Figure 5. Healthcare pathway 2

The costs for each care pathway are based on the costs per visit in primary, specialized outpatient and inpatient care, and reported in Tables 4, 7 and 10. The cost of an x-ray was sourced from the most recent price list for imaging and functional medicine from Region Uppsala [51]. Pathway costs pertain to the costs of treatment of one fracture per person. The total for each care pathway is presented in Table 16 below.

Table 16. Average costs per person for two different care pathways for patients with VCF in 2019, SEK.

Pathways	Men	Women	Total
Care pathway 1			
Primary care visit 1	1 531	1 565	1 576
Primary care visit 2	1 531	1 565	1 576
X-ray	949	949	949
Specialized outpatient visit (specialist doctor)	3 906	4 176	4 086
Inpatient care (surgical management)	54 503	54 276	54 351
Specialized outpatient visit (follow-up)	3 906	4 176	4 086
Primary care visit (follow-up)	1 531	1 565	1 576
Total	**67 857**	**68 272**	**68 200**

Care pathway 2			
Specialized outpatient visit (emergency) + x-ray	4 855	5 125	5 035
Inpatient care (surgical management)	54 503	54 276	54 351
Specialized outpatient visit (follow-up)	3 906	4 176	4 086
Primary care visit (follow-up)	1 531	1 565	1 576
Total	**64 795**	**65 142**	**65 058**

6.2.2 Indirect costs

As with the healthcare costs, with the data available, it was not feasible to estimate indirect costs related to incident cases of VCF. The report presents results for prevalent cases of VCF. We therefore assume that individuals receiving sickness and early retirement benefits represent a proportion of the prevalent cases. Since short- and long-term sickness is likely directly after an incident fracture, and not related to a prevalent case since more than one year back, our estimates are probably underestimated. It is more likely that incident cases are fewer than prevalent cases, hence the proportion receiving sickness benefits are larger.

In Table 2 of this report (page 16), the number of patients diagnosed with VCF in 2019 within inpatient and specialized outpatient care in 2019 was reported to be 8 187, including 2 546 men and 5 641 women. Note that these are prevalent cases, and not incident for 2019. In addition, it does not include potential cases that visit primary healthcare only. As shown in Tables 11 and 12, the number of ongoing cases receiving short- and long-term sick leave benefits was 389. Out of the prevalent population, it means that almost 5% receive short-term sick leave. As shown in Table 13, the number of individuals on early retirement was 253. Out of the prevalent population, about 3% therefore retire early.

Costs for short-term sick leave

Table 11 reports that the total cost for short-term sick leave in 2019 amounts to 6 523 249 SEK. With a prevalent population of 8 187, the average cost per person for short-term sick leave is therefore 797 SEK. For women, the average cost is 545 SEK and for men 1 354 SEK.

Costs for long-term sick leave

Table 12 reports that the total cost for long-term sick leave in 2019 amounts to 13 480 486 SEK. With a prevalent population of 8 187, the average cost per person for long-term sick leave is therefore 1 647 SEK. For women, the average cost is 1 153 SEK and for men 2 741 SEK.

Costs for early retirement

Costs for early retirement were not included in these total cost estimates for the cost-effectiveness analysis, since these considered the risk of a recurrent fracture within three months of surgical management using either standard cement or Inossia´s soft cement. This inherently excludes any costs that may incur beyond time period. Costs

related to early retirement were assumed to incur much later due to standard lengthier processual and administrative bureaucracies.

The total costs for an incident case of VCF in 2019 is presented in Table 17 below. Care pathways are in the cost range for the total population of 67 491 to 70 643 SEK.

Table 17. Total average costs for different care pathways including indirect costs for patients with VCF in 2019, SEK

Pathways	Men	Women	Total
Care pathway 1	71 952	69 970	70 643
Care pathway 2	68 890	66 840	67 491

6.3 Scenario-based cost-effectiveness

The cost-effectiveness estimates are based on the two different care pathways. It is assumed that an individual move through the first care pathway at their first occurrence of VCF, and that the recurrent fracture is treated as depicted in the second care pathway. Using information regarding effect of the two treatment options, Inossia's bone cement softener vs. standard cement, the effect difference is 18.3% in risk of new incident fracture. From this effect difference, we estimated the number needed to treat (NNT) with Inossia´s product to get one avoided recurrent fracture. The NNT was estimated by dividing the unity by the effect difference (1/18.3%), and resulted in an NNT of 5.46. This can be interpreted as roughly five people need to be treated with Inossia´s product compared to standard cement to avoid one recurrent fracture.

The NNT was used to estimate the amount needed to invest to avoid one recurrent fracture (the cost of Inossia's product times the NNT), depicted in Table 19. If treating 5.46 people, assuming they would go through care pathway 1, it would cost 393,406 SEK with Inossia's product or 389,715 SEK with standard cement. This is presented in Table 18. As fewer individuals have recurrent fractures after treatment with Inossia's product, (0.27 vs. 1.27 individuals with the standard cement), the cost of recurrent fractures amounts to 18,809 SEK for Inossia's product vs. 86,790 SEK for standard treatment. This is assuming an individual move through care pathway 2. The total costs for NNT and recurrent fractures are smaller for Inossia's treatment than with standard cement. If treating 5.46 individuals and thus avoiding 1 recurrent fracture with Inossia's product, it would lead to 67,981 SEK in potential savings, compared to standard cement. These results are shown in Table 19. The ratio between investment costs to avoid on recurrent fracture and the potential savings is 18.42. This means that for one SEK invested, you could get 18.42 SEK back in potential savings from a societal perspective. This includes healthcare costs and indirect costs due to short- and- long-term sick leave.

Table 18. Cost per avoided recurrent incident VCF in 2019, SEK

	Inossia			Standard cement		
	Men	**Women**	**Total**	**Men**	**Women**	**Total**
NNT	5.46	5.46	5.46	5.46	5.46	5.46
N. recurrent fractures	0.27	0.27	0.27	1.27	1.27	1.27
Cost cement	1 350	1 350	1 350	675	675	675
Cost pathway 1	71 952	69 970	70 643	71 952	69 970	70 643
Cost pathway 2	68 890	66 840	67 491	68 890	66 840	67 491
Total cost NNT	400 557	389 727	**393 406**	396 865	386 035	**389 715**
Total cost recurrent fractures	19 191	18 631	**18 809**	88 571	85 961	**86 790**
Total cost NNT + recurrent fractures	419 748	408 358	**412 215**	485 436	471 996	**476 505**

Table 19. Results from the scenario-based cost-effectiveness analysis, 2019 SEK

	Inossia vs. standard cement
What we need to invest to avoid one incident fracture within 3 months *(total population)* [a]	3 691
Potential savings if investment above avoids one recurrent fracture *(total population)* [b]	67 981
Net savings [c]	64 290
Cost-benefit ratio [d]	18.42

a Corresponds to the difference in total cost for NNT between Inossia´s product and standard cement.
b Corresponds to the difference in total cost for recurrent fractures between Inossia´s product and standard cement.
c Corresponds to the difference between potential savings if investment above avoids one recurrent fracture and what we need to invest to avoid one incident fracture within 3 months.
d Corresponds to the ratio between potential savings if investment above avoids one recurrent fracture and what we need to invest to avoid one incident fracture within 3 months.

7. Discussion

This report aimed to identify, quantify and value the socioeconomic consequences related to vertebral compression fractures, as well as to estimate the quality-of-life changes in patients with these fractures. Additionally, a scenario-based cost-effectiveness calculation was performed to estimate the amount needed to invest to avoid one recurrent fracture, as well as potential cost savings. The total societal costs related to VCF amounted to approximately SEK 226.20 million, in 2019. Direct healthcare costs amounted to SEK 125.75 million. The largest direct cost items were those related to inpatient care, which accounted for 89% of the direct costs of VCF. Indirect costs related to loss of production due to sick leave and early retirement amounted to SEK 100.45 million. Estimates of quality of life from the literature in patients with VCF are large, and patients usually do not regain their quality of life two years after the fracture as compared to before the fracture. Five people would need to be treated with Inossia´s product to avoid one recurrent fracture. The total sum we would need to invest to avoid one incident fracture within 3 months is 3 691 SEK, which could lead to potential savings of 67 981 SEK due to avoiding one recurrent fracture, and net savings of 64 290 SEK. Benefits of Inossia´s product are more than 18 times larger than the investment made, compared to standard cement.

The estimated costs for VCF in this report are considerably lower in relation to what has been reported for other countries for vertebral fractures. For instance, a recent multi-country study by Willers and colleagues [1] estimated the societal costs of fragility fractures in 2019. All countries in the European Union plus Switzerland and the UK were included. The study reported estimates of annual direct costs related to incident fractures ranging from 1.4 billion EUR for Sweden to 10.2 billion EUR for Germany. Assuming that 15% of osteoporosis related fractures corresponds to vertebral fractures (as reported in the same study), direct costs ranged from 222 million EUR for Sweden to 1.58 billion EUR for Germany. Approximately 840 million EUR was the corresponding amount for Italy and 280 million EUR for Spain. These estimates cannot be directly comparable to the estimates from the current report for several reasons. The estimates rest on different methodological assumptions as well as include different cost components. In regards to the methodology used, Willers and colleagues based their incidence rates of vertebral fractures on a Swedish study from 2000, using a population from one of Sweden's 21 regions. In the current report, the number of individuals with VCF was based on national registers. In addition, cost estimates in Willers and colleagues paper were assumed from the literature, whereas in the current report we have estimated costs based on the number and cost of episodes of care based on national registers.

The current practice in Sweden for patients with VCF is conservative treatment (only primary care). The bone cement softener introduced by Inossia can potentially be economically beneficial, when applying an incremental effect of 18.3%, when compared to standard cement

The results of the present report should be interpreted with caution, as they are based on multiple assumptions. First, data limitations made it challenging to fully quantify medical related resource use. The CPP-database does not have 100% coverage of all healthcare visits in the country, nor are all contacts with the healthcare services recorded in this database by healthcare professionals. In 2019, only 12 out of 21 regions in Sweden were reporting primary care data to CPP, with region Stockholm not included in the group of 12. Cost per visit, which is an estimate based on the total number of care visits, is likely to be largely underestimated.

Importantly, the prevalence-based approach was used to estimate societal costs related to VCF. The prevalence-based approach means that all those who received treatment based on a VCF diagnosis in 2019 were captured, not the number of cases diagnosed that year. The report therefore estimates the annual cost of diagnosed cases, rather than the cost of those diagnosed in 2019. This can have an impact on the magnitude of costs related to treatment of VCF, since the most costly interventions are those immediately after the fracture occurs.

The identification of prevalent cases from the patient register relied solely on one ICD-code, M48.5. Although patients with VCF may be coded with other diagnosis codes, this is likely only a small proportion. To make sure we captured VCF as accurately as possible, a decision was made to restrict analysis to this code only. Other ICD-10 codes may include patients who were not eligible for this analysis, such as patients with fractures elsewhere in the body, patients with a vertebral fracture due to a fall related incident, or patients with cancer.

Another limitation pertained to the estimation of indirect costs. Short-term sick leave (up to 14 days) was calculated based on several assumptions (the same number of individuals registered for long-term sick leave was assumed in this estimation). Although this estimate is conservative, it should be interpreted with caution. Additionally, no information was available on the number of days individuals with VCF were on long-term sick leave (which affected sickness benefits beyond the first 14 days). An average estimate was sourced from the published literature. However, the study this estimate was sourced from was not based on a Swedish sample of patients, hence the impact of this assumption on the results is difficult to assess.

8. Conclusion

Total societal costs of VCF amounted to approximately SEK 226.20 million, with direct healthcare costs estimated at SEK 125.75 million and indirect costs related to productivity losses amounting to SEK 100.45 million. A bone cement softener to reduce the probability of consecutive fractures has the potential to be value for money and incur savings, if effects are as large as those used in the scenario-based cost-effectiveness analysis employed in this report. Despite limitations in finding reliable data regarding resource use for individuals with VCF, the quality of life decrements and its related societal costs are undeniably significant. Priority should be given to resource allocation towards better treatment for individuals with VCF, especially to prevent subsequent fractures.

9. References

1. Willers C, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, McCloskey E V, Borgström F, Kanis JA (2022) Osteoporosis in Europe: a compendium of country-specific reports. Arch Osteoporos 17:23
2. Alastra. EWAJ Vertebral Fracture - StatPearls - NCBI Bookshelf.
3. Ballane G, Cauley JA, Luckey MM, El-Hajj Fuleihan G (2017) Worldwide prevalence and incidence of osteoporotic vertebral fractures. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 28:1531–1542
4. Johnell O, Kanis JA (2006) An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 17:1726–1733
5. Borgström F, Karlsson L, Ortsäter G, et al (2020) Fragility fractures in Europe: burden, management and opportunities. Arch Osteoporos 15:59
6. Fink HA, Milavetz DL, Palermo L, Nevitt MC, Cauley JA, Genant HK, Black DM, Ensrud KE (2005) What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? J bone Miner Res Off J Am Soc Bone Miner Res 20:1216–1222
7. Kendler DL, Bauer DC, Davison KS, et al (2016) Vertebral Fractures: Clinical Importance and Management. Am J Med 129:221.e1-10
8. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA 3rd, Berger M (2000) Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J bone Miner Res Off J Am Soc Bone Miner Res 15:721–739
9. Baaj AA, Downes K, Vaccaro AR, Uribe JS, Vale FL (2011) Trends in the treatment of lumbar spine fractures in the United States: a socioeconomics perspective: clinical article. J Neurosurg Spine 15:367–370
10. Svedbom A, Borgstöm F, Hernlund E, et al (2018) Quality of life for up to 18 months after low-energy hip, vertebral, and distal forearm fractures-results from the ICUROS. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 29:557–566
11. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey E V, Jönsson B, Kanis JA (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8:136
12. Johansson L, Sundh D, Nilsson M, Mellström D, Lorentzon M (2018) Vertebral fractures and their association with health-related quality of life, back pain and physical function in older women. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 29:89–99
13. Hallberg I, Bachrach-Lindström M, Hammerby S, Toss G, Ek A-C (2009) Health-related quality of life after vertebral or hip fracture: a seven-year follow-up study.

BMC Musculoskelet Disord 10:135
14. Pasco JA, Sanders KM, Hoekstra FM, Henry MJ, Nicholson GC, Kotowicz MA (2005) The human cost of fracture. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 16:2046–2052
15. Borgström F, Zethraeus N, Johnell O, et al (2006) Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 17:637–650
16. Coassy A, Svedbom A, Locrelle H, et al (2022) Costs of patient management over 18 months following a hip, clinical vertebral, distal forearm, or proximal humerus fragility fracture in France-results from the ICUROS study. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 33:625–635
17. Tran O, Silverman S, Xu X, Bonafede M, Fox K, McDermott M, Gandra S (2021) Long-term direct and indirect economic burden associated with osteoporotic fracture in US postmenopausal women. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 32:1195–1205
18. Eekman DA, ter Wee MM, Coupé VMH, Erisek-Demirtas S, Kramer MH, Lems WF (2014) Indirect costs account for half of the total costs of an osteoporotic fracture: a prospective evaluation. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 25:195–204
19. Garfin SR, Yuan HA, Reiley MA (2001) New technologies in spine: kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures. Spine (Phila Pa 1976) 26:1511–1515
20. Socialstyrelsen [The National Board of Health and Welfare] Statistikdatabaser - Diagnoser i sluten vård - Val.
21. Sveriges Kommuner och Regioner [Swedish Association of Local Authorities and Regions] KPP Databas | SKR.
22. Försäkringskassan [Swedish Social Insurance Agency] Statistik och analys.
23. Statistics Sweden [Statistiska centralbyrån] Sammanräknad förvärvsinkomst för boende i Sverige hela året efter region, utbildningsnivå, kön och ålder. År 2000 - 2020. PxWeb.
24. Sveriges Kommuner och Regioner [Swedish Association of Local Authorities and Regions] Nationella KPP-principer, version 4 | SKR.
25. Ekonomifakta (2019) Sociala avgifter över tid. https://www.ekonomifakta.se/fakta/skatter/skatt-pa-arbete/sociala-avgifter-over-tid/. Accessed 22 Dec 2019
26. Felsenberg D, Silman AJ, Lunt M, et al (2002) Incidence of vertebral fracture in europe: results from the European Prospective Osteoporosis Study (EPOS). J bone Miner Res Off J Am Soc Bone Miner Res 17:716–724
27. Pisani P, Renna MD, Conversano F, Casciaro E, Di Paola M, Quarta E, Muratore M, Casciaro S (2016) Major osteoporotic fragility fractures: Risk factor updates and societal impact. World J Orthop 7:171–181
28. Johnell O, Kanis J (2005) Epidemiology of osteoporotic fractures. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 16 Suppl 2:S3-7

29. Alexandru D, So W (2012) Evaluation and management of vertebral compression fractures. Perm J 16:46–51
30. Esses SI, McGuire R, Jenkins J, et al (2011) The treatment of symptomatic osteoporotic spinal compression fractures. J Am Acad Orthop Surg 19:176–182
31. Luthman S, Widén J, Borgström F (2018) Appropriateness criteria for treatment of osteoporotic vertebral compression fractures. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 29:793–804
32. Bornemann R, Koch EMW, Wollny M, Pflugmacher R (2014) Treatment options for vertebral fractures an overview of different philosophies and techniques for vertebral augmentation. Eur J Orthop Surg Traumatol 24 Suppl 1:S131-43
33. McGirt MJ, Parker SL, Wolinsky J-P, Witham TF, Bydon A, Gokaslan ZL (2009) Vertebroplasty and kyphoplasty for the treatment of vertebral compression fractures: an evidenced-based review of the literature. Spine J 9:501–508
34. Felder-Puig R, Piso B, Guba B, Gartlehner G (2009) Kyphoplastie und Vertebroplastie bei osteoporotischen Wirbelkörperkompressionsfrakturen. Orthopade 38:606–615
35. Stevenson M, Gomersall T, Lloyd Jones M, Rawdin A, Hernández M, Dias S, Wilson D, Rees A (2014) Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. Health Technol Assess 18:1–290
36. Wang B, Zhao C-P, Song L-X, Zhu L (2018) Balloon kyphoplasty versus percutaneous vertebroplasty for osteoporotic vertebral compression fracture: a meta-analysis and systematic review. J Orthop Surg Res 13:264
37. Pron G, Hwang M, Smith R, Cheung A, Murphy K (2022) Cost-effectiveness studies of vertebral augmentation for osteoporotic vertebral fractures: a systematic review. Spine J. https://doi.org/10.1016/j.spinee.2022.02.013
38. Borgström F, Beall DP, Berven S, Boonen S, Christie S, Kallmes DF, Kanis JA, Olafsson G, Singer AJ, Åkesson K (2015) Health economic aspects of vertebral augmentation procedures. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 26:1239–1249
39. Svedbom A, Alvares L, Cooper C, Marsh D, Ström O (2013) Balloon kyphoplasty compared to vertebroplasty and nonsurgical management in patients hospitalised with acute osteoporotic vertebral compression fracture: a UK cost-effectiveness analysis. Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 24:355–367
40. SBU – Swedish Agency for Health Technology Assessment and Assessment of Social Services Percutaneous Vertebroplasty and Balloon Kyphoplasty in Treating Painful Osteoporotic Vertebral Compression Fractures.
41. Hopkins TJ, Eggington S, Quinn M, Nichols-Ricker CI (2020) Cost-effectiveness of balloon kyphoplasty and vertebroplasty versus conservative medical management in the USA. Osteoporos Int 31:2461–2471
42. Ament, A., Evers S (1993) Cost of illness studies in health care: a comparison of two cases. Health Policy (New York) 26:39–42
43. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW (2015) Methods for the Economic Evaluation of Health Care Programmes, 4th ed. Oxford University press, New York

44. Weisbrod B (1961) The valuation of human capital. J Polit Econ 69:425–436
45. Brouwer WB, Koopmanschap MA (2005) The friction-cost method : replacement for nothing and leisure for free? Pharmacoeconomics 23:105–111
46. Försäkringskassan [Swedish Social Insurance Agency] Socialförsäkringen i siffror 2020.
47. Ström O, Borgstrom F, Zethraeus N, et al (2008) Long-term cost and effect on quality of life of osteoporosis-related fractures in Sweden. Acta Orthop 79:269–280
48. Zethraeus, Niklas & Borgström, Fredrik & Johnell, Olof & Kanis, John & Önnby, Karin & Jönsson, Bengt Costs and quality of life associated with osteoporosis related fractures - Results from a Swedish survey.
49. Goz V, Errico TJ, Weinreb JH, Koehler SM, Hecht AC, Lafage V, Qureshi SA (2015) Vertebroplasty and kyphoplasty: national outcomes and trends in utilization from 2005 through 2010. Spine J 15:959–965
50. Rodriguez AJ, Fink HA, Mirigian L, Guañabens N, Eastell R, Akesson K, Bauer DC, Ebeling PR (2017) Pain, Quality of Life, and Safety Outcomes of Kyphoplasty for Vertebral Compression Fractures: Report of a Task Force of the American Society for Bone and Mineral Research. J bone Miner Res Off J Am Soc Bone Miner Res 32:1935–1944
51. Region Uppsala Imaging and functional medicine at Uppsala´s University Hospital [Bild- och funktionsmedicinskt centrum på Akademiska sjukhuset | Akademiska].

Appendix A.

Aim: To estimate the HRQoL for patients with vertebral fractures

Method: Systematic review

Topic breakdown and search terms:

Population: Swedish, males and females aged 50+.

Intervention and comparator: not applicable

Outcome: HRQoL → quality of life, health related quality of life, EQ5D.

Vertebral fractures: fractures, vertebra, osteoporosis, postmenopausal, spine fractures, compression fractures, osteoporotic fractures, fragility fractures.

Filters:
Geographical area: limited to Sweden (incorporated in the search terms)
Language: English/Swedish and available in full text
Year of publication: 2010+

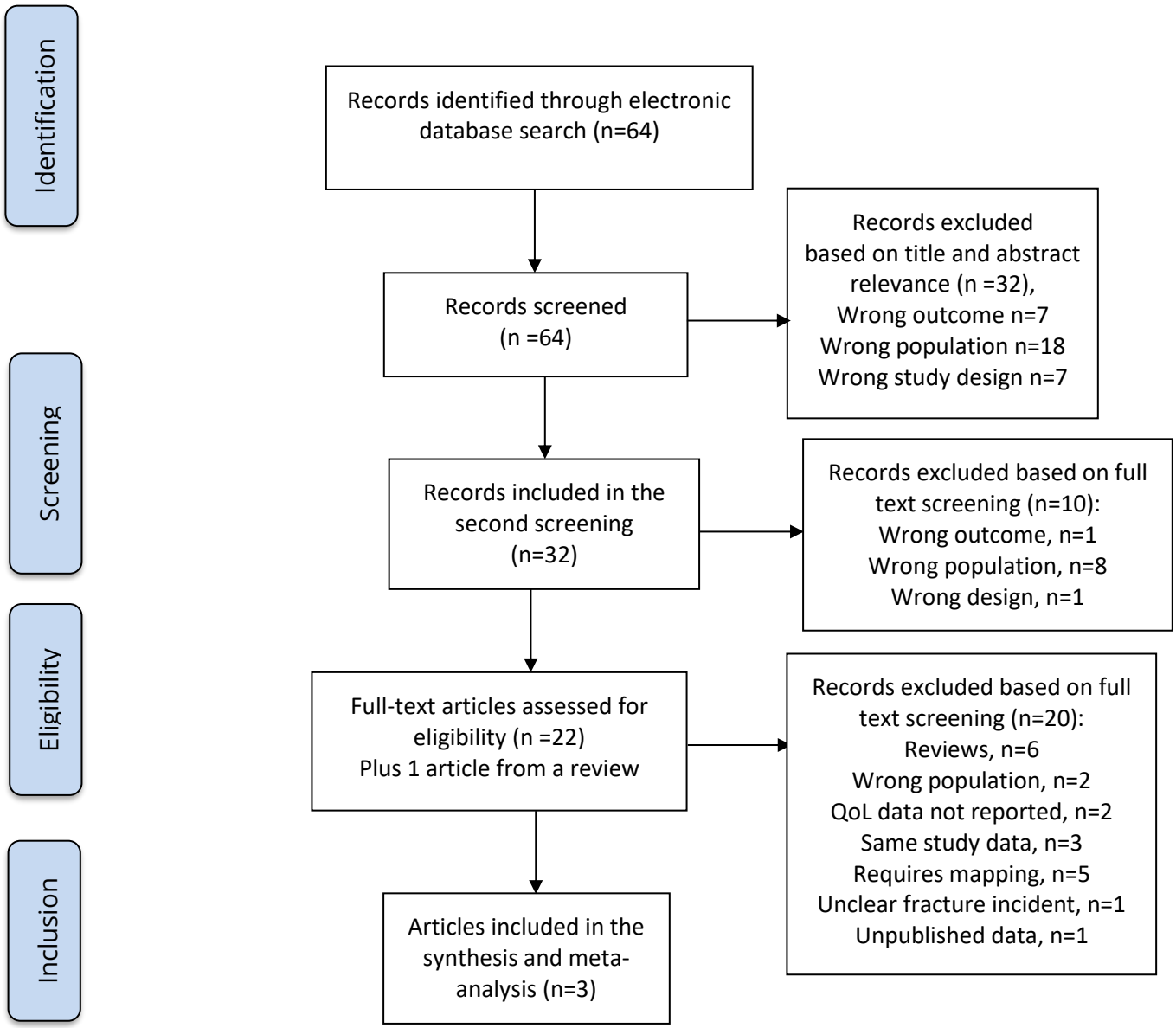
Database search:

PubMed

Search: (("compression fractures" OR "vertebral fractures" OR "spinal fractures" OR "osteoporotic fractures" OR "fragility fractures") AND ("quality of life" OR "Health related quality of life")) AND (Sweden)
("compression fractures"[All Fields] OR "vertebral fractures"[All Fields] OR "spinal fractures"[All Fields] OR "osteoporotic fractures"[All Fields] OR "fragility fractures"[All Fields]) AND ("quality of life"[All Fields] OR "Health related quality of life"[All Fields]) AND ("sweden"[MeSH Terms] OR "sweden"[All Fields] OR "sweden s"[All Fields])

64 hits

Figure 1. Flow chart showing the selection of studies



*Wrong design: refers to protocol papers, guidelines, technical reports and the like.

Table 1. Summary of included studies

Authors	Year	Country	Sample	Age/years	Gender	Duration/months	Study design	Utility tool
Ström et al. (2)	2008	Sweden	76	(50–93)	86% Female	0, 4, 12, 18	Prospective observational	EQ-5D
Borgström et al. (3)	2006	Sweden	81	(50–96)	84% Female	0, 4, 12	Prospective observational	EQ-5D
Zethraeus et al. (1)	2002	Sweden	16	75 (56–90) [a]	94% Female	2 weeks, 6, 9, 12	Longitudinal	EQ-5D, SF-12

[a] Mean age and confidence intervals. The rest of the age values are ranges

References:

1. Zethraeus, Niklas & Borgström, Fredrik & Johnell, Olof & Kanis, John & Önnby, Karin & Jönsson, Bengt (2002) Costs and quality of life associated with osteoporosis related fractures - Results from a Swedish survey. *SSE/EFI Working Paper Series in Economics and Finance* 512, Stockholm School of Economics.
2. Ström Oskar, Fredrik Borgström, Niklas Zethraeus, Olof Johnell, Lars Lidgren, Sari Ponzer, Olle Svensson, Peter Abdon, Ewald Ornstein, Leif Ceder, Karl Göran Thorngren, Ingemar Sernbo & Bengt Jönsson (2008) Long-term cost and effect on quality of life of osteoporosis-related fractures in Sweden, *Acta Orthopaedica*, 79:2, 269-280, DOI: 10.1080/17453670710015094
3. Borgström F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, Svensson O, Abdon P, Ornstein E, Lunsjö K, Thorngren KG, Sernbo I, Rehnberg C, Jönsson B. (2006) Costs and quality of life associated with osteoporosis-related fractures in Sweden. *Osteoporos Int*. 17(5):637-50. doi: 10.1007/s00198-005-0015-8. Epub 2005 Nov 9. PMID: 16283064.