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FRAGILITY FRACTURES, SELF-RATED HEALTH AND TREATMENT WITH A SPINAL ORTHOSIS IN OLDER WOMEN IN PRIMARY HEALTH CARE

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Fragility Fractures, Self-Rated Health and Treatment with a Spinal Orthosis in Older Women in Primary Health Care

Thesis for Doctoral Degree (Ph.D.)

By

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To my family.

Popular science summary of the thesis

Osteoporosis is a condition where the structure and density of the bone is altered, and the bone becomes weaker and breaks more easily. Sometimes a fracture occurs after falling on the floor at home or after lifting a shopping bag. Osteoporosis is a silent disease and the fragility fracture is the first noticeable symptom. Except for the acute effects of pain and need for urgent care fragility fractures often lead to pain, reduced quality of life, loss of independence and increased mortality in the long term. It is mainly persons older than 50 years that are affected, especially women after menopause. Fragility fractures are common, and Sweden has the highest incidence in the world: half of all women and one in four of men over 50 years of age, will experience an osteoporotic fracture during their lifetime. The population of the world is getting older, estimates show that the number of osteoporotic fractures will increase. We have good medical treatments to prevent fractures or re-fractures. The problem is providing at-risk individuals with adequate and effective treatment. The WHO standard for the diagnosis of osteoporosis is measurement of bone density using Dual energy X-ray Absorptiometry (DXA). There is a general lack of awareness of osteoporosis both among health care professionals and patients. It would be highly beneficial if healthcare professionals could easily assess the risk of fragility fractures.

In Study I 350 women aged between 69 and 79 years were asked to assess their health by answering the question "How would you rate your health right now" by putting a mark on a line between "worst imaginable" to "best imaginable". We divided them into three groups according to how they rated their health: low, intermediate or high. After 10 years we investigated how many participants suffered a hip fracture or died. We found that those who had rated their health as low or intermediate 10 years ago had a three times higher risk of suffering a hip fracture compared to those who had rated their health as high. We did not find an association between self-rated health (SRH) and mortality. This indicates that SRH may be useful in identifying persons at risk of suffering a hip fracture in the next 10 years that who would benefit from further investigation with DXA.

In Study II we analysed blood samples that had been collected in the same women that participated in Study I. We analysed blood levels for parathyroid hormone (PTH) and insulin-like growth factor-binding protein 1 (IGFBP-1). We divided the women into four groups according to their levels of PTH and IGFBP-1: normal PTH and low IGFBP-1, normal PTH and

high IGFBP-1, elevated PTH and low IGFBP-1 or elevated PTH and high IGFBP-1. After 10 years we investigated how many of them had suffered a hip fracture or died. We found that those who had simultaneously elevated plasma levels of PTH and high IGFBP-1 had a two to three times higher risk of dying in the next 10 years compared to the other groups. We found no association with hip fractures indicating that a combination of elevated PTH and IGFBP-1 levels is not a factor that could be useful in identifying persons at risk of suffering a hip fracture in the next 10 years but may be considered as a fragility factor.

In Study III and IV the aim was to compare the effect of physiotherapy equipment training with an activating spinal orthosis. A total of 113 women were included in the study and randomly divided into either treatment with exercise or an activating orthosis, or neither (controls). In Study III we compared the effect of treatment in the different groups on back pain, back extensor strength and, kyphosis in older women with osteoporosis. We found no difference between the two methods regarding kyphosis, pain or back extensor strength. However, we could see that the back extensor strength increased in both the exercise group and the spinal orthosis group. This is important because there is a need for more treatment options in addition to medication and exercise. In Study IV we compared the effect between the groups regarding quality of life (QoL) and markers of pain in blood. We found no results that could clearly demonstrate a difference between exercise and using an activating spinal orthosis in terms of QoL. Regarding markers of pain we found that Interleukin-6 (IL-6) was significantly lower after six months in the group that was treated with the activating spinal orthosis. These results are interesting though we do not yet know how to interpret them. More research is needed.

Populärvetenskaplig sammanfattning

Osteoporos, eller benskörhet som det också kallas på svenska, är ett tillstånd med minskad täthet och försämrad struktur i skelettet vilket gör att skelettet blir svagare och bryts lättare. Man kan få en fraktur av sådant som normalt inte brukar ge frakturer, till exempel efter att man fallit på golvet hemma eller efter att ha lyft en matkasse.

Osteoporos ger inga symptom i sig och det är vanligt att man inte upptäcker att man har det förrän man får en fraktur. Förutom de akuta symptomen efter en fraktur, så leder osteoporosfrakturer ofta till kvarstående smärta, minskad självständighet, försämrad livskvalitet och ökad dödlighet på lång sikt. Risken för osteoporos ökar med åldern. Det är främst personer över 50 år som drabbas, särskilt kvinnor efter klimakteriet.

Fragilitetsfrakturer är vanliga och i Sverige är det vanligare med osteoporosfrakturer än i många andra länder. Av män och kvinnor över 50 år i Sverige kommer 1 av 2 kvinnor och 1 av 4 män drabbas av en osteoporosfraktur under sin återstående livstid. Världens befolkning blir allt äldre, vilket innebär att även antalet osteoporosfrakturer förväntas öka. Vi har effektiva läkemedelsbehandlingar för att förebygga osteoporosfrakturer. För att behandla osteoporos behöver man först hitta de personer som har sjukdomen. Enligt World Health Organization (WHO) diagnosticeras osteoporos genom en så kallad bentäthetsundersökning Dual-energy X-ray Absorptiometry (DXA). Tyvärr är osteoporos underdiagnostiserat och inte alla som skulle ha nytta av behandling får det. Enkla och lättbedömda riskfaktorer för osteoporos skulle hjälpa vårdpersonal att misstänka och utreda osteoporos. I Studie I fick 350 kvinnor i åldern 69 till 79 år svara på frågan: "Hur skulle du bedöma din hälsa just nu?" genom att sätta ett kryss på en linje mellan "sämsta tänkbara" och "bästa tänkbara". Vi delade sedan in kvinnorna i tre olika grupper baserat på hur de hade bedömt sin hälsa: låg, medel eller hög. Efter 10 år undersökte vi hur många av dem som hade drabbats av höftfraktur eller avlidit. Vi fann att de som för 10 år sedan hade bedömt sin hälsa som låg eller medel, hade tre gånger högre risk att ha drabbats av höftfraktur jämfört med dem som hade bedömt sin hälsa som hög. Vi fann däremot ingen koppling mellan självskattad hälsa (SRH) och dödlighet. Studien tyder på att SRH kan vara ett verktyg som kan hjälpa till att identifiera personer med risk att drabbas av höftfraktur inom de närmaste 10 åren. Dessa personer skulle behöva utredas vidare med bentäthetsundersökning. Då skulle man kunna behandla sjukdomen innan den har orsakat någon fraktur. I Studie II analyserade vi blodprover som hade samlats in från

samma kvinnor som deltog i studie I. Vi analyserade två hormoner i blodproverna: parathormon (PTH) och insulin-like growth factor-binding protein 1 (IGFBP-1). Vi delade in kvinnorna i fyra grupper baserat på deras nivåer av PTH och IGFBP-1: normalt PTH och lågt IGFBP-1, normalt PTH och högt IGFBP-1, förhöjt PTH och lågt IGFBP-1 eller förhöjt PTH och högt IGFBP-1. Efter 10 år undersökte vi hur många av dem som hade drabbats av höftfraktur eller avlidit. Vi fann att de som samtidigt hade förhöjda plasmanivåer av PTH och högt IGFBP-1 hade två till tre gånger högre risk att dö inom de närmaste 10 åren jämfört med de andra grupperna. Vi fann ingen koppling till höftfrakturer, vilket tyder på att kombinerade nivåer av PTH och IGFBP-1 inte är användbart för att identifiera personer med risk att drabbas av höftfraktur. Däremot verkar samtidigt förhöjda nivåer av PTH och IGFBP-1 tyda på en ökad skörhet. I Studie III och IV var syftet att jämföra effekten av handledd redskapsträning i grupp och behandling med en aktiverade ryggkorsett. 113 kvinnor deltog i studien och delades slumpmässigt in i 3 i grupper: redskapsträning, behandling med en aktiverande ryggkorsett eller en kontrollgrupp (som inte fick någon särskild behandling). Vi jämförde sedan ryggsmärta, ryggmuskelstyrka, kyfosgrad (kuttryggighet), självskattad hälsa och om man kunde se en skillnad i smärtmarkörer i blodprov mellan de olika grupperna. Vi fann ingen skillnad mellan grupperna när det gäller ryggsmärta, ryggmuskelstyrka eller kuttryggighet. Däremot kunde vi se att ryggmuskelstyrkan ökade i både träningsgruppen och korsettgruppen. Detta är viktigt eftersom det finns ett behov av fler behandlingsalternativ utöver medicinering och träning. Vi fann inte heller några skillnader mellan träning och användning av en aktiverande ryggkorsett när det gäller självskattad hälsa. När det gäller smärtmarkörer fann vi att interleukin 6 (IL-6), en signalmolekyl i kroppen som spelar en viktig roll i kroppens immunförsvar, var lägre efter sex månader i gruppen som behandlades med den aktiverande ryggkorsetten. Det är ett intressant resultat, men som vi ännu inte riktigt vet hur vi ska tolka. Mer forskning behövs.

Abstract

Fragility fractures, particularly hip fractures and vertebral fractures, are associated with significant morbidity, reduced functional status, and increased mortality in older adults. Identifying reliable predictors of fracture risk and mortality, as well as effective management strategies, is critical for improving outcomes in older adults. This research investigated whether self-rated health (SRH) or combined blood levels of parathyroid hormone (PTH) and insulin-like growth factor-binding protein 1 (IGFBP-1) may provide additional prognostic value. We also evaluated the effects of non-pharmacological interventions, exercise and wearing an activating spinal orthosis, on osteoporosis-related symptoms.

In Study I a cohort of 350 community-dwelling women aged 69–79 years (median 72.4) assessed their SRH by answering the question “How would you rate your health right now?” using a visual analogue scale (0–100 mm) at baseline. They were followed for 10 years and data on hip fractures and all-cause mortality were retrieved from healthcare registers. SRH was categorised as low, intermediate, or high (reference). Associations with the 10-year risks of hip fractures and all-cause mortality were analysed using Cox proportional hazards regression model. During the 10-year follow-up, 40 hip fractures and 72 deaths occurred. Women with low and intermediate SRH had a significantly higher risk of hip fracture (HR: 3.17, 95% CI: 1.25–8.01 and HR: 2.75, 95% CI: 1.08–7.04, respectively) compared to those with high SRH. The association remained significant after adjusting for bone mineral density. No association was observed between SRH and all-cause mortality.

In Study II the same cohort as in Study I was studied, but this time we investigated whether baseline blood levels of PTH in combination with IGFBP-1 were associated with a 10-year risk of hip fractures and all-cause mortality. Blood samples were collected from 338 women. Participants were divided into four groups: (A) normal PTH and low IGFBP-1, (B) normal PTH and high IGFBP-1, (C) elevated PTH and low IGFBP-1, and (D) elevated PTH and high IGFBP-1 (reference). Ten-year data on hip fractures and all-cause mortality were retrieved from healthcare registers. Associations with a 10-year risks of hip fractures and all-cause mortality were analysed using age-adjusted Cox proportional hazards regression models. Women with elevated PTH and high IGFBP-1 (D) had a two- to threefold increased risk of all-cause mortality compared to the other groups. No association was found between PTH and IGFBP-1 levels and hip fracture risk.

Studies III and IV are based on the same randomised controlled trial including 113 women aged ≥ 60 years with back pain and osteoporosis, with or without vertebral fractures. The participants were randomised into three groups: spinal orthosis, equipment training, and control. Assessments were performed at baseline, after 3 months and after 6 months. In Study III we analysed the difference between the three groups regarding back pain, back extensor strength, and kyphosis index. Statistical analyses were conducted using mixed models for repeated measures according to intention-to-treat (ITT) and per-protocol (PP) principles. The change in extensor strength in each group was analysed with paired *t*-test.

In Study IV, we analysed differences between the three groups regarding health-related quality of life (HRQoL), which was measured by using the quality of life questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41) and the Short Form health survey (SF-36). Statistical analyses were conducted using mixed models for repeated measures according to ITT and PP principles. We also used Wilcoxon signed-rank test to compare HRQoL values at baseline, 3 months, and 6 months within groups and Mann-Whitney test to compare controls to intervention groups regarding change of CGRP, IL-6, and SP from baseline to 6 months.

A total of 96 participants completed the study. In Study III, no significant differences were observed between groups for back pain, kyphosis index, or back extensor strength after 6 months. However, back extensor strength increased within groups: 26.9% in the spinal orthosis group, 22.1% in the training group, and 9.9% in the control group. In Study IV no significant improvement in quality of life (QoL) was observed. No changes were detected in the levels of calcitonin gene-related peptide (CGRP) or substance P (SP). Interleukin-6 (IL-6) levels were significantly lower at six months in the spinal orthosis group compared to the other groups.

In conclusion our findings suggest that SRH may serve as an independent risk marker for hip fractures, complementing assessments based on BMD. Simultaneously elevated PTH and IGFBP-1 levels are associated with increased mortality (all-cause and cardiovascular) but not fracture risk. Non-pharmacological interventions, such as activating spinal orthoses and equipment training, may improve back extensor strength, though their impact on pain, kyphosis and HRQoL remains unclear. Spinal orthosis may be an alternative treatment method in osteoporosis, though further studies are needed.

List of scientific papers

- I. **Uzunel E, Lundin H, Wändell P, Salminen H. Association between self-rated health and the risk of hip fracture and mortality in a cohort of older women during a 10-year follow-up.** Blank RD, redaktör. PLoS ONE. 05 mars 2021;16(3):e0247924.
- II. **Uzunel E, Ranch Lundin H, Grahn Kronhed AC, Wändell P, Salminen H. Levels of parathyroid hormone and IGF binding protein 1 and associations with mortality and hip fractures in older women.** Sci Rep. 26 november 2024;14(1):29399.
- III. Kaijser Alin C, **Uzunel E**, Grahn Kronhed AC, Alinaghizadeh H, Salminen H. **Effect of treatment on back pain and back extensor strength with a spinal orthosis in older women with osteoporosis: a randomized controlled trial.** Arch Osteoporos. december 2019;14(1):5
- IV. **Uzunel E**, Grahn Kronhed AC, Kaijser Alin CK, Ahmed AS, Wändell P, Salminen H. **The Effect of Group Training or Spinal Orthosis on Quality of Life and Potential Plasma Markers of Pain in Older Women With Osteoporosis. A Randomized Controlled Trial.** Archives of Rehabilitation Research and Clinical Translation. december 2023;5(4):100297.

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List of abbreviations

BMD	Bone mineral density
BMI	Body mass index
BTM	Bone turnover markers
CaSR	Calcium receptors
CGRP	Calcitonin gene-regulating peptide
COPD	Chronic obstructive pulmonary disease
CTX	C-terminal cross-linked telopeptide of type I collagen
RI	Downton fall risk index
DXA	Dual X-ray absorptiometry
EU	European union
FRAX	Fracture risk assessment tool
GH	Growth hormone
IGF-I	Insulin-like growth factor 1
IGFBP-1	Insulin-like growth factor binding protein 1
IL-6	Interleukin 6
PINP	Procollagen type I N-terminal propeptide
PRIMOS	Primary health care and osteoporosis project
PTH	Parathyroid hormone
QALY	Quality adjusted life year
QoL	Quality of life
QUALEFFO-41	Quality of life questionnaire of the European foundation for osteoporosis - 41 items
RA	Rheumatoid arthritis
RCT	Randomised Controlled Trial
SF-36	Short form-36
SP	Substance P
SRH	Self-rated health
VAS	Visual analogue scale
WHO	World health organization

Introduction

Osteoporosis is a disease that negatively affects the quality of the bone. The cortical and the trabecular bone gets thinner and the trabecular structure is altered, which increases the risk of fractures [1, 7]. Osteoporosis is a silent disease, and there are no symptoms before the fracture occurs [1]. Fractures in individuals with osteoporosis may be caused by minor trauma, typically a fall from standing height or lower, which would not normally result in a fracture [8, 9]. The risk of osteoporosis increases with age, and the condition is more common in individuals older than 50 years. After menopause, women have an increased risk of osteoporosis and fragility fractures. Common locations of fragility fractures are the hip, spine, proximal humerus and distal forearm. Fragility fractures are associated with increased mortality and loss of independence, disability, pain and reduced quality of life [2–4]. Vertebral fracture is the most common fragility fracture, and they often lead to chronic back pain, reduced mobility and loss of independence, which negatively affects health-related quality of life [3, 10–12]. Worldwide, there are more than 9 million osteoporotic fractures every year. In the European Union (EU), there were 3.5 million new fragility fractures in 2010, and the numbers are estimated to be increasing [5, 13, 14]. The incidence varies between countries, and Sweden has one of the highest lifetime incidences of fragility fractures in the world (47.3% for women and 23.8% for men) [2]. There is effective medical treatment to prevent fractures, but since osteoporosis is a silent disease, it is underdiagnosed and undertreated, even in those who have already suffered a fracture [6, 15, 16]. In primary health care, we often meet individuals at high risk of fragility fractures, but the awareness of patients and healthcare providers needs to be improved. The diagnosis must be considered during the doctor's appointment, which is usually booked due to another reason [17, 18]. The definition of osteoporosis relies on bone mineral density (BMD), which is measured by Dual-energy X-ray Absorptiometry (DXA). There are also algorithms and tools that consider risk factors, sometimes in combination with bone mineral density, to identify at-risk individuals, but they are not always easy to interpret and are not always suitable for all patient groups [1, 19]. Another challenge is to relieve the pain that often follows a vertebral fracture [20]. Exercise programmes are recommended after fragility fractures and have been shown to have an effect on BMD pain and health-related quality of life [21–26]. The use of spinal orthoses or braces in patients with vertebral fractures has been debated. There are also different types of orthoses, and opinions and results differ in terms of whether and when they should be used. Sub-acute use has been

suggested to improve back extensor muscular strength, pain and functioning after 6 months, but not at 12 months [27–29]. This thesis addresses potential new early indicators for the future risk of hip fractures in older women in primary health care and whether long term use of an activating spinal orthosis may be an alternative to exercise regarding the effect of back extensor strength and pain and health-related quality of life.

1 Background

1.1 Osteoporosis

Osteoporosis is a global public health issue that leads to great suffering for those affected and high costs to society. In a study exploring osteoporosis in 27 countries in the European Union (EU), it was estimated that 22 million women and 5.5 million men suffered from osteoporosis in 2010. There were 3.5 million new fragility fractures (610,00 hip fractures, 560,000 forearm fractures, 520,000 vertebral fractures and 1,800,000 other fractures) that occurred, and women accounted for two thirds of the fractures. The estimated number of deaths related to fractures was 43,000. The estimated cost for incident and prior fragility fractures in 2010 was EUR 37 billion. Quality-adjusted life years lost were estimated at 1,180,000 in 2010 [14]. In a more recent study of six countries in the EU, including Sweden, it was estimated that fragility fractures will rise by 23.3% from 2017 to 2030 [5]. The incidence of fragility fractures varies in the world for unclear reasons. The variation cannot solely be explained by differences in bone mineral density (BMD) but may depend on how many elderly people there are in the population, as well as genetic and ethnic factors, variations in diet, physical activity, exposure to sunlight and socioeconomic status [30, 31]. The ageing of the global population and the increasing population, as well as urbanisation and lifestyle changes, may contribute to the overall increase of fragility fractures [32].

Osteoporosis can be considered as primary or secondary. Primary osteoporosis is a condition that can be attributed to menopause or high age. Secondary osteoporosis is when the bone loss is caused by other diseases or medications. Examples of such diseases are hyperparathyroidism, thyrotoxicosis, hypogonadism, vitamin D

deficiency, inflammatory diseases or kidney failure. One example of substances that cause osteoporosis are corticosteroids [33].

1.1.1 Definition of osteoporosis

The World Health Organization's (WHO) definition of osteoporosis is as follows:

"Osteoporosis is a systemic skeletal disease with decreased bone density and degraded skeletal microstructure that leads to an increased risk of fragility fractures" [1]. The WHO's definition of osteoporosis is based on BMD measurement with DXA. If T-score is ≤ -2.5 SD below the average BMD value of young white women, it is considered as osteoporosis. A T-score value ≤ -1.0 but > -2.5 is classified as osteopenia. The term "established osteoporosis" means a T-score ≤ -2.5 and a fragility fracture [1, 4]. Although BMD measurement is a reliable method with high specificity, fractures also occur in persons with low estimated risk according to their BMD value alone [34]. While DXA remains the clinical standard for osteoporosis diagnosis, advanced techniques like High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) provide 3D assessment of bone microarchitecture and differentiation between trabecular and cortical bone, crucial for evaluating bone strength. However, HR-pQCT is not widely used in clinical practice due to its limited availability, high cost, longer scanning time, and lack of standardized diagnostic thresholds [153, 154].

1.2 Fragility fractures

The clinical consequence of osteoporosis is a fracture. The most common sites of fragility fractures are the hip, spine, distal forearm and proximal humerus [2]. All fragility fractures significantly increase the risk of future fragility fractures, particularly within the first year. Especially strong associations have been observed between prior and subsequent vertebral fractures, with an approximately four times higher risk in women with a previous vertebral fracture [35, 36]. The risk of a second non-vertebral fracture varies, but may be about three times higher than that of the general at-risk population [37, 38]. Fragility fractures of the hip and spine are associated with increased mortality [39–42]. They are also associated with pain, disability, impaired functioning and deterioration in quality of life [4, 13, 43, 44].

Vertebral fracture is the most common fragility fracture. Two thirds of vertebral fractures may go undetected because they sometimes lack severe symptoms and have subtle radiographic signs. It can also be difficult to know how to manage these fractures clinically [10, 45]. However, they often lead to chronic back pain, reduced mobility, loss of height and kyphosis, which in turn can affect lung function negatively. Social and physical function may be affected, with a loss of independence as a result. Health-related quality of life is often decreased [3, 11, 12, 20, 43].

Hip fractures lead to excess mortality rates (often above 20%), especially in the first year [41, 46–48]. Many survivors do not regain their pre-fracture functional status, and some may need long time nursing care [42, 44, 48, 49]. Reduced mobility and weakness are common, often leading to a decline in overall physical activity and loss of independence, which can negatively affect mental health and health-related quality of life [12, 43, 47–51].

1.3 Treatment of osteoporosis and prevention of fragility fractures

Both pharmacological and non-pharmacological strategies are recommended for the treatment of osteoporosis and fragility fractures in healthcare programmes [52–54].

1.3.1 Bone specific drugs

Bone specific treatments (antiresorptive or anabolic agents) improve BMD and decrease the risk of re-fracture [52, 53, 55, 56].

1.3.2 Non-pharmacological treatment

Physiotherapeutic rehabilitation, focusing on muscle strengthening, posture correction and mobility improvement, is important after fractures. It is also an important intervention to prevent falls and new fractures [52–54, 57].

1.3.2.1 Exercise programmes

Supervised multicomponent exercise programmes are recommended and have been associated with beneficial effects, including the prevention of falls, maintenance of bone mineral density and maintenance of daily function in older women with osteoporosis (with and without fractures). These programmes also have positive effects on HRQoL. The exercise should include progressive resistance training, balance training, mobility training,

posture exercises (back extensor muscles) and functional exercises adapted to activities of daily living to reduce falls risk. The exercise programmes should be individually tailored and are recommended two to three times a week [21–24, 26, 54].

1.3.2.2 Spinal orthoses

The use of spinal orthoses after vertebral fractures has been debated, and because of the diversity in the studies conducted, there are difficulties in drawing clear conclusions and there is no consensus [27, 28]. Different types of spinal orthoses have been studied, many of which serve distinct purposes across different phases of recovery. This includes rigid, semi-rigid and flexible orthoses. They have been studied for acute, subacute and longer term rehabilitation. In the acute phase, the function is to stabilise the vertebrae in order to facilitate healing and reduce deformity, alleviate pain and improve posture and balance. One of the main concerns, especially when using rigid orthoses, is muscle atrophy after extended use [27]. In the subacute phase, where mainly semi-rigid or flexible orthoses are used, there is also evidence of reduced kyphosis, increased muscle strength, improved postural stability and better function. A special form of semi-rigid orthosis is the activating spinal orthosis Spinomed®. It has a steel rail in the back, which reaches from the seventh cervical vertebra to the sacrum and is adapted to the spinal curvature to keep an upright position. When the back is flexed, the rail and straps around the shoulders provide feedback to continuously activate the back extensor muscles [29]. It has shown positive effects on back extensor muscular strength, pain, quality of life and functioning at 6 months, but not at 12 months. In a qualitative study, patients perceived that the activation spinal orthoses were supportive in their daily lives. They saw it as a "close friend" that reminded them to maintain good posture, which in turn reduced pain and allowed for more independence [58]. There is a need for more studies on the long-term use of spinal orthoses, where it is important to balance pain relief and functional support with the risks of muscle atrophy and psychological dependence [27, 28].

1.4 Risk factor identification for osteoporosis and fragility fractures

In addition to BMD, other risk factors, such as prior fractures, high age, history of falls, smoking, high alcohol intake, being female, early menopause, certain medications (i.e. corticosteroids), low body mass index, sedentary lifestyle, hip fracture in parent and comorbidities (endocrine disorders, rheumatological disorders), have been consistently linked to an increased risk of fragility fractures [31, 38, 59–61]. Tools that use algorithms to

consider both BMD values and known risk factors to predict the probability of future fractures have been developed to support clinical decisions [e.g. the fracture risk assessment tool (FRAX) and Garvan fracture risk calculators] [59, 62]. However, there is no global consensus on which fracture risk assessment tools have the best prediction performance, because the predictive accuracy of these tools may vary across populations [19].

1.4.1 Self-rated health

In early studies of osteoporosis, self-rated health (SRH) was one of several variables evaluated as a positive prognostic marker. SRH refers to how a person evaluates their own health by answering a single question. It is a stable marker of health and a predictor of mortality [63–66]. Another concept used to describe an individual's subjective perception of their well-being and health are quality of life (QoL) and health-related quality of life (HRQoL). The definition of these concepts varies to some extent. QoL has a broader definition and covers satisfaction with health status and other aspects of life [43, 50, 67]. HRQoL is a subset of QoL and may be defined as QoL in relation to health status and health care [50, 67–69]. SRH is a simple way of assessing HRQoL. All concepts are considered to contribute complementary information that medical and epidemiological data may not detect [43, 67–69]. QoL can be measured in a generic or a disease-specific way. Generic instruments assess a broad range of dimensions relevant to QoL. It can be used in different populations and conditions and to compare the impact of different disorders and conditions with each other. There are two types of generic instruments: health indexes (utility) and health profiles. Health indexes (utility) assess QoL as a single number from a continuum, usually between 0 (death) and 1.0 (best health). This is done either by asking the person to rate all aspects of QoL in a single number or asking questions that make it possible for the examiner to classify the person into one of several predetermined categories. Health profiles may contain different categories/dimensions, and the results may be divided into dimension-specific scores or aggregated to a single overall score. Specific QoL instruments focus on certain aspects of QoL that are important for a predefined population (having the same symptom, condition, disease or age, etc.). These instruments can be used to follow a population with a certain condition over time or after different treatments. All instruments have their limitations and advantages, and there is no gold standard that works well in all settings. The type of instrument or method that is best suited to a particular study has to be

carefully thought out for that particular population or endpoint [43, 67, 68, 70, 71]. QoL is negatively affected after fragility fracture, and an association with low bone density (with or without fractures) has been described [72–75]. Most studies have described the decline in QoL after a hip fracture or vertebral fracture. Regarding hip fractures, some evidence suggests that the decline in QoL starts years before the fracture, and this makes it interesting as a potential marker [43, 49, 50, 76]. Even in the absence of fractures, awareness of osteoporosis may impair QoL due to concerns about future fractures [73, 74]. There are also studies that suggest that participating in a study itself may lead to better QoL, but it may also be the other way around, that is, that those with higher QoL are more likely to participate in a study [77].

1.4.2 Bone metabolism and the role of calcium regulating hormones, the growth factor Insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein 1 (IGFBP-1)

Another context in which potential risk markers for fragility fractures could be found is the complex control of bone metabolism. A delicate homeostasis must be sustained when the bone tissue is continuously replaced in a process called remodelling. The main players are the osteoblasts (bone-forming) and the osteoclasts (bone-resorbing). Bone turnover markers (BTM) are biochemical markers of bone turnover (for example PINP, CTX) and can be measured in urine and/or blood, but the variability due to biological and technical factors remains a challenge. BTMs reflect osteoclast and osteoblast activity in osteoporosis and other bone metabolic diseases. BTMs have been suggested to be able to predict fragility fractures and to determine whether a person would benefit from treatment, as well as a tool to monitor treatment. At present BTMs have limited value in predicting fractures in the clinical setting. There is also insufficient data on whether they can be used to determine the future benefit from treatment or to monitor treatment in the clinical practice [78, 79]. Local bone modelling as in fracture healing and adaption in bone mass in response to different conditions is regulated by inflammatory actors such as cytokines, prostaglandins and growth factors. There is also evidence that the peripheral nervous system plays an important role. Substance P (SP) and calcitonin gene-regulating peptide (CGRP) are sensory neuropeptides involved in pain, inflammation and vascular permeability and have also been demonstrated to be able to stimulate bone cells via specific receptors in fracture healing and early skeletal development [80, 81]. Pain mechanisms in osteoporosis are not sufficiently

known. The acute pain correlated with fractures seems to be nociceptive and is influenced by inflammatory cytokines such as prostaglandins and interleukin-6 (IL-6). Pain may develop into chronic pain through peripheral and central sensitisation, which involves neuropeptides such as SP and CGRP as well as proinflammatory cytokines [82–84]. Vitamin D and calcium are important factors in bone metabolism. Both vitamin D and calcium are important for the mineralisation process of the extracellular matrix produced by the osteoblasts. Vitamin D also affects the reabsorption of calcium and phosphate from the bowel. Phosphate is important for the mineralisation as well. Calcium levels are regulated by parathyroid hormone (PTH). Calcium receptors (CaSR) on the parathyroid cells starts the release of PTH at low levels of calcium and increases calcium levels by activating osteoclasts and the resorption of bone. They also trigger release of calcium to facilitate the activation of vitamin D in the kidney to increase the reabsorption of calcium and phosphate from the duodenum and to increase the reabsorption of calcium but not phosphate in the urine [85]. If PTH is constantly raised, as in hyperparathyroidism, it leads to increased bone resorption. Insulin-like growth factors (IGF-I and IGF-II) and the Insulin-like growth factor binding proteins (IGFBP1-6) that IGFs are bound to in serum, are important in the development and growth of the skeleton and the maintenance of bone mass in adult life. IGF-I is released from the liver through the stimulation of growth hormone (GH). The GH/IGF axis acts in an endocrine and autocrine/paracrine way and IGF-I is also secreted from many other organs as well as bone [86]. IGF-I increases bone formation by enhancing the differentiation of the osteoblasts and by recruiting premature osteoclasts as a coupling agent in the remodelling process. Bone is also a major reservoir for IGF-I. There is a decline in IGF-I during aging. Insulin-like growth factor binding proteins (IGFBPs) are also produced by bone cells. They take part in the regulation of IGFs by binding to them and inhibiting their function, prolonging the half-life or enhancing their effect by targeting them to certain cell types. There is also evidence suggesting that some IGFBPs might have effect by themselves at bone and other tissues [87]. Most of the research studying IGFBPs and markers for bone growth show negative associations for IGFBP-1, -2 and -4 and possibly IGFBP-6, whereas IGFBP-3 and -5 were associated with markers for bone growth [87]. The correlation between BMD and serum IGF-I has been described, but the cause and effect are not totally understood [88].

1.5 Pain in osteoporosis

Fragility fractures often lead to pain. Acute pain at the time of injury caused by mechanical, inflammatory and neuropathic components is common in both vertebral and non-vertebral fractures. The acute pain may be chronic through sensitisation of the peripheral and central nervous system, which is most common in vertebral fractures [83, 84, 89]. The acute pain in vertebral fractures may vary from mild/absent to severe [11, 20, 90]. The chronic pain may develop due to structural and biomechanical changes as a result of the fracture. Decrease in bone density and changes in micro-architecture may also lead to mechanical stress on the bones, leading to microfractures that chronically stimulate the pain receptors and lead to the release of inflammatory mediators. Both the sensitisation of the peripheral and central nervous system may result in the development of chronic pain [82–84, 89, 91]. Non-vertebral fractures, such as those of the hip or wrist, typically cause acute pain. While they can lead to chronic pain in some cases, this is less common than the persistent pain observed with vertebral fractures [43]. Vertebral fractures, in particular, are linked to decreased quality of life due to the combined burden of pain, reduced mobility and reduced social activities [11, 20, 43, 82, 83]. The mechanisms of pain in osteoporosis are not fully understood. The acute pain in osteoporosis is mainly nociceptive. Pain in osteoporosis involves neuropeptides such as Substance P, CGRP and proinflammatory cytokines (IL-6, IL-1 and TNF- α), which induce nociceptor sensitisation, central sensitisation and chronic pain [83, 89, 91].

2 Research aims

2.1 Overall aim

To explore associations that could contribute to identifying individuals at risk of fragility fractures and all-cause mortality and to evaluate the effect of non-pharmaceutical treatment of backpain in osteoporosis in older women in primary health care.

2.2 Specific aims

Study I: To explore the association between the assessment of self-rated health in older women and the 10-year risk of suffering from a hip fracture or all-cause mortality.

Study II: To explore the effect of simultaneously elevated plasma levels of PTH and IGFBP-1 on the 10-year risk of suffering from a hip fracture and all-cause mortality.

Study III: To compare the effect of physiotherapy equipment training and the use of an activating spinal orthosis to controls on back pain, back extensor strength, and kyphotic index in older women with osteoporosis.

Study IV: To compare the effect of physiotherapy equipment training and the use of an activating spinal orthosis to controls on QoL, and whether such an effect could be associated to plasma levels of biomarkers of pain (substance P, CGRP and IL6).

3 Materials and methods

This thesis includes four studies. It is based on two different study populations, but all participants are older women. Studies I and II are prospective cohort studies and Studies III and IV are randomised controlled trials (RCT). For an overview of the studies included in this thesis, see table 1.

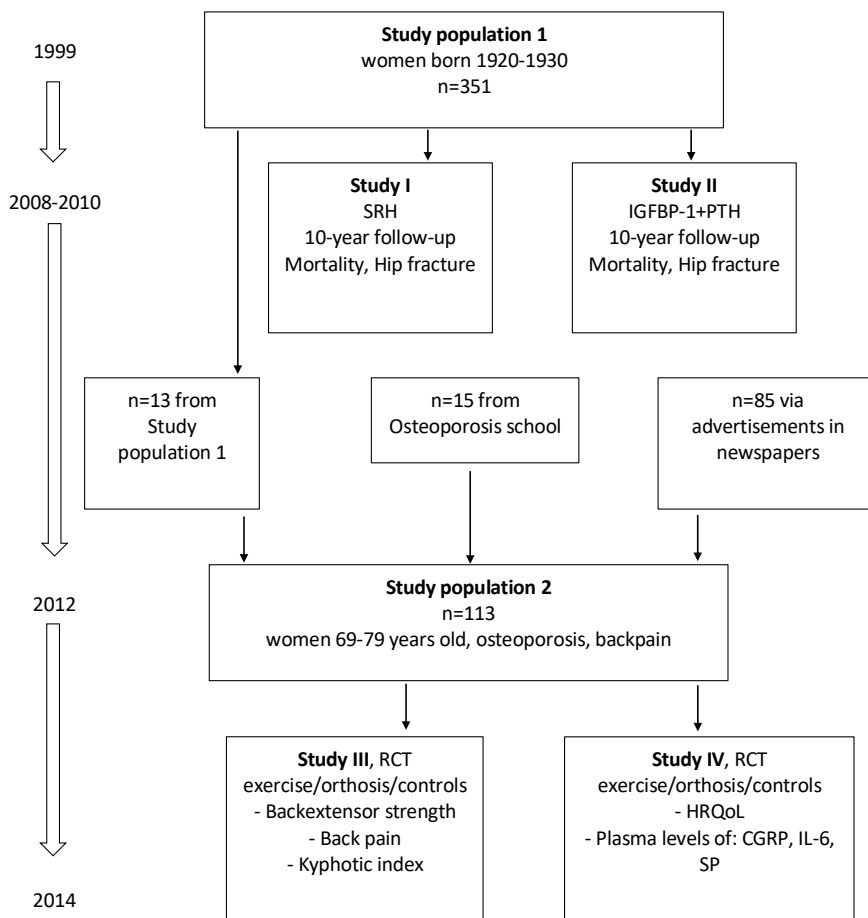
Table 1 Overview of the four studies

Study	Participants	Design	Data	Analysis
I	Study population 1 n=350	Prospective cohort study	<ul style="list-style-type: none">• Baseline Self-rated health by a single question• 10-year data on mortality and hip fractures	Cox proportional hazards regression model
II	Study population 1 n=338	Prospective cohort study	<ul style="list-style-type: none">• Baseline data of levels of PTH and IGFBP-1• 10-year data on mortality and hip fractures	Cox proportional hazards regression model
III	Study population 2 n=113	RCT: -Controls -Exercise -Orthosis	<ul style="list-style-type: none">• Baseline, 3 and 6 months data• pain, back extensor strength, kyphotic index	A mixed model for repeated measures according to intention to treat and per-protocol paired t-test
IV	Study population 2 n=113	RCT: -Controls -Exercise -Orthosis	<ul style="list-style-type: none">• Baseline, 3 and 6 months data• HRQoL QUALEFFO-41, SF-36, levels of CGRP, SP, IL-6	A mixed model for repeated measures according to intention to treat Mann-Whitney test Wilcoxon signed-rank test

3.1 Study populations

The participants who have been included in the studies that form the basis of this thesis come from two different study populations, which overlap to some extent, see flowchart 1.

Flowchart 1 Overview of study populations and studies

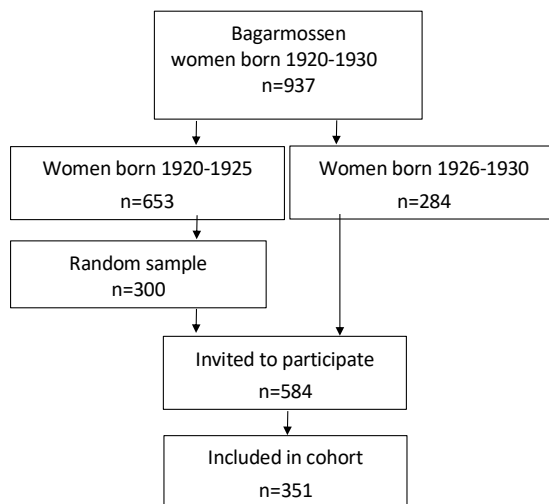


3.1.1 Study population 1 (Studies I and II)

A cohort gathered in 1999 as a part of the Primary Health Care and Osteoporosis (PRIMOS) project to study different aspect of osteoporosis in elderly women [92–95]. The cohort was selected in two steps. At the time of inclusion 957 women born between 1920 and 1930 lived in Bagarmossen (a suburb of Stockholm). An invitation letter was sent randomly to 300 of the women and 179 accepted. In order to recruit more participants the invitation was randomly sent to another 284 women from the same area who were born between 1926

and 1930. This resulted in another 174 participants (total of 351 female participants). The women had to be community dwelling and physically able to transport themselves to the health care centre for examinations. A total of 351 participants were included out of 584 invited (60%). The most common reasons for declining participation were frail health status or insufficient mobility to visit the primary healthcare center. See flowchart 2.

Flowchart 2 Study population 1

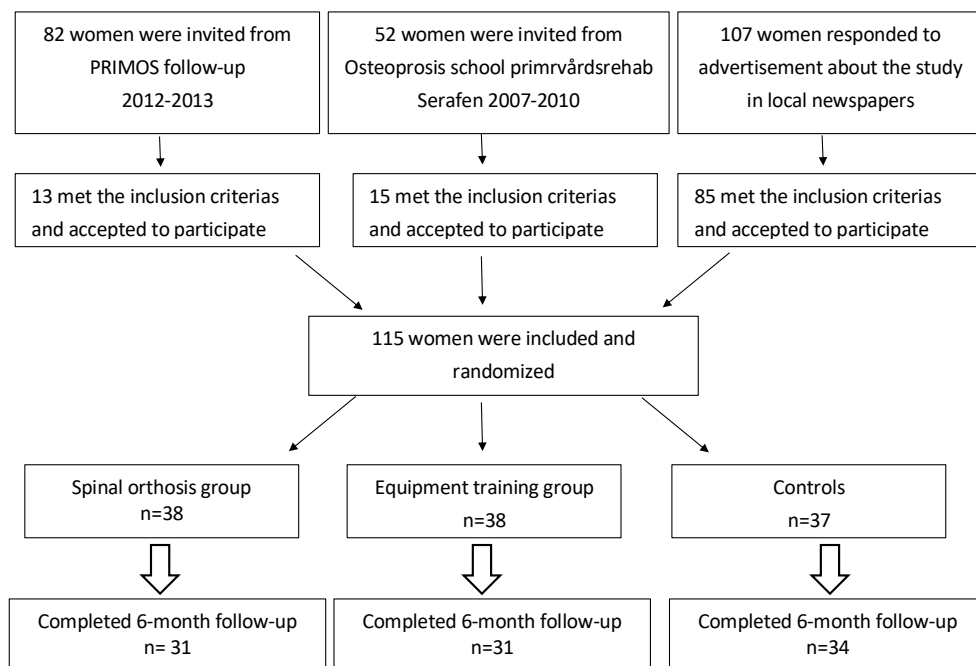


3.1.2 Study population 2 (Studies III-IV)

An invitation to participate in study population 2 was sent to 82 of the women who participated in study population 1. Participants were also recruited from two other sources: i) former attendants in an osteoporosis school at Primärvårdsrehab Serafen 2007-2010 and ii) advertisements in four local newspapers and an osteoporosis patient association magazine [96]. Out of the 82 women from study population 1 that were invited, a total of 13 were interested and eligible. Out of all women who had attended the osteoporosis school, 52 were invited and 15 were interested and met the inclusion criteria. The advertisement yielded 107 candidates for the study, and 85 were eligible and willing to participate. This resulted in a total of 113 participants. Inclusion criteria were osteoporosis diagnosis, suffering from back pain, 60 years of age or older and to be sufficiently good at the Swedish language. Drop-outs varied across groups: in the spinal orthosis group, five withdrew before three months (two due to illness, one diagnosed with spinal stenosis) and four before six months (two due to illness, two declined further participation). In the equipment training group, six withdrew before three months (two due to illness, four declined further

participation) and one before six months (due to illness). In the control group, one withdrew before three months (due to illness) and one before six months (declined further participation). See flowchart 3.

Flowchart 3 Study population 2



3.2 Variables

3.2.1 Variables in Studies I and II

Baseline examination (Studies I and II):

Data on age, weight and height were collected. Data were collected from self-reported questionnaires or medical records regarding lifestyle factors (outdoor activities more than 30 minutes/day, smoking, medications (loop-diuretic, bisphosphonates, calcium and vitamin D3, insulin and oral anti diabetics), diseases/comorbidities (asthma/COPD, diabetes, earlier/present cancer, cardiovascular disease) and self-reported fractures (before inclusion and after the age of 50).

DXA and FRAX (Studies I and II):

DXA was performed during 1999 and 2001. Measurements were conducted using Hologic QDR 4500 DXA equipment (Hologic, Marlborough, MA, USA). The measurements were expressed as T-scores, for the hip calculated according to the NHANES-III reference population. T-score was used as a continuous variable and a dichotomized variable if the T-score was ≤ -2.5 or not. BMD at the femoral neck was used as a continuous variable (g/cm^2). FRAX (Fracture risk assessment tool) was used to calculate the 10-year probability of fragility fractures with BMD in the algorithm. The FRAX calculations were done in 2013.

Self-rated health (SRH) (Study I):

Self-rated health (SRH) was assessed at baseline: The participants answered the question “How would you rate your health right now” by putting a mark along a visual -analogue scale (VAS) ranging from “worst imaginable” to “best imaginable”. The distance between “worst imaginable” to the mark was measured in millimetres (0 mm to a maximum of 100 mm). This variable was further divided into tertiles: low SRH (5-51 mm), intermediate SRH (52-73 mm), and high SRH (74-99 mm).

Balance tests performed at baseline (Study I):

Chair-rise test without using the armrests, timed gait speed (i.e. how many seconds it took to walk back and forth 15 m x 2, including a 180-degree turn as fast as possible with shoes on a well-lit even floor) and timed one-leg stand test (OLST) the longest time (maximum 30 seconds) they managed to stand on one leg with eyes open, barefoot, and arms alongside the body out of four attempts. We also created a combination variable of those who were unable to rise from a chair without support and had a gait speed less than 0.8 meter per second (mps) (Unable to rise from chair and slow gait speed).

Biochemical analyses including PTH and IGFBP-1 (Study II):

Fasting blood samples were collected at baseline and analysed on an ongoing basis or frozen at -70°C until analysed. Levels of Intact PTH in plasma (reference range 10–65 ng/L) was analysed and IGFBP-1 concentrations in serum were determined by a method using radioimmunoassay [97]. Levels of ionized calcium in serum (reference range 1.17–1.29 mmol/L), 25 hydroxy vitamin D in serum (nmol/L), creatinine in plasma (reference range $< 110 \mu\text{mol}/\text{L}$ for women and $< 120 \mu\text{mol}/\text{L}$ for men) and albumin in plasma

(reference range 37–48 g/L) were analysed routinely. Estimated glomerular filtration rate (GFR) was calculated by using the Cockcroft-Gault formula. The levels of PTH and IGFBP1 was used to divide the participants in four groups: (A) normal levels of PTH and low IGFBP-1; (B) normal levels of PTH and high IGFBP-1; (C) elevated levels of PTH and low IGFBP-1; and (D) elevated levels of PTH and high IGFBP-1.

Follow up data (Studies I and II):

Follow-up data was obtained from the Swedish Cause of Death Registry and data on inpatients and outpatients from the National Patient Register, both of which are kept by the National Board of Health and Welfare.

3.2.2 Variables in Studies III and IV

Demographic/ lifestyle data and anthropometric measures collected at baseline (Studies III and IV):

Data on age, height, weight, body mass index (BMI), marital status, self-reported medical history, present diagnoses including osteoporosis, fracture history, medications (for example: bone-specific drugs, vitamin D, painkillers, corticosteroids), need for community or home health care, use of walking aids, time spent outdoors/physical activity and smoking status.

Risk of falls performed at baseline (Study IV):

Assessed using the Downton Fall Risk Index (DFRI) where a score of ≥ 3 indicates high fall risk.

Pain performed at baseline, 3 months and 6 months (Studies III and IV):

- Visual Analog Scale (VAS): Present pain and pain during the last week. Rating on a 100 mm scale (0 = no pain, 100 = worst pain).
- Borg CR-10 scale: Present pain and pain during the last week. Rating from 0 (no pain) to 10 (extremely strong pain).

HRQoL (baseline, 3 months and at 6 months, Study IV)

- SF-36, Generic instrument assessing 8 domains (vitality, social function, physical function, bodily pain, general health, mental health, role physical, and role emotional) and 2 summary scores (physical and mental components). Scale: 0 (worst) to 100 (best) QoL.
- QUALEFFO-41 (Quality of Life Questionnaire of the European Foundation for Osteoporosis - 41 items) Disease-specific instrument for osteoporosis with vertebral fractures, assessing 7 domains (pain, activities of daily living, jobs around the house, mobility, social function, general health perception, mental functioning) and a total score. Scale: 0 (best) to 100 (worst) QoL.
- EQ-VAS score, part of the standardised instrument for measuring generic health status EQ5D. The participants were asked “how good or bad your own health is today in your opinion” by drawing a line towards a VAS scale (0-100 mm) ranging from “worst imaginable health state” to “best imaginable health state” [152].

Isometric Back Extensor Strength (baseline, 3 months and 6 months, Studies III and IV)

Digi-Max, results reported as mean and maximum force in Newton (N) over 6 seconds.

Hand Grip Strength (baseline, Study IV)

JAMAR dynamometer for dominant and non-dominant hand reported in kilograms.

Spinal X-Ray (baseline, Studies III and IV)

Thoracic and lumbar X-rays taken to investigate vertebral fractures in those who had not recently been X-rayed. Vertebral fractures were evaluated using the Genant classification.

Plasma Biomarkers (baseline and at 6 months, Study IV)

Venous blood was collected for SP, CGRP, and IL-6 levels. They were centrifuged and stored at -70°C until analysis. Enzyme-linked immunosorbent assay (ELISA) kits were used for analysis.

Spinal Curvature (baseline and 6 months, Study III):

Flexicurve ruler. Kyphotic index and angle calculated from the width and length of spinal curves. Hyperkyphosis defined as kyphotic index ≥ 13 .

3.3 Statistical methods

3.3.1 Statistical analysis- Studies I and II

Baseline characteristics for continuous variables were reported as mean (M), standard deviations (SD) and 95% confidence intervals (95% CI) if normally distributed and median and interquartile range (IQR) if skewed. Normality was tested using Q-Q plots. Categorical data were presented as frequencies and percentages. Comparisons of baseline characteristics across groups were conducted using the Kruskal–Wallis test for skewed variables and one-way ANOVA for normally distributed variables, provided Bartlett's test confirmed homogeneity of variance. For dichotomous variables, the Chi-square test was applied when expected cell frequencies were five or greater; otherwise, Fisher's exact test was used. In Study II, Spearman's correlation coefficient was employed to evaluate potential correlations between IGFBP-1 and PTH. In study I and II associations with all-cause mortality and hip fractures across the four groups with different PTH/IGFBP-levels and between tertiles of SRH were analysed using the Cox proportional hazards regression model (HR). The proportional hazards assumption was tested, with the global test yielding insignificant results, and covariates were checked for collinearity and possible confounders were identified as variables altering age-adjusted hazard ratios by $\geq 10\%$. P-values < 0.05 were deemed statistically significant in the Cox regression model and for baseline group comparisons. All analyses were conducted using Stata statistical software version 14.2 (StataCorp. LLC, College Station, TX, USA).

3.3.2 Statistical analysis- Studies III and IV

Baseline characteristics was reported as means and standard deviations for normally distributed continuous variables and as median with interquartile range for skewed variables. Frequencies and numbers were used if the variables were dichotomous. One-way ANOVA was used for comparisons of differences in variables between the three treatment groups at baseline for continuous variables and Chi-square test for categorical variables. In Study IV comparisons between groups also were analysed with the Kruskal–Wallis test for

skewed variables and Fisher's exact test was used for dichotomous variables, if the frequency in one of the groups was lower than five. P values ≤ 0.05 were considered significant for baseline characteristics. In Study III we used paired t test to analyse change between baseline and 6-month follow-up in each group. These analyses were performed with STATA version 14.2 (StataCorp LP, Texas, USA). In Studies III and IV differences in changes of HRQoL, back pain, back extensor strength and spinal curvature between the interventions were analysed by comparing the difference in group mean between baseline, 3 months and 6 months. A mixed model for repeated measures according to intention to treat adjusted for age (Study IV) and age, vertebral fractures and FVC (Study III) was used and results were presented as least squares means (LS means). In study IV, the HRQoL scores was considered missing if $\geq 30\%$ of the items in QUALEFFO-41 or $\geq 50\%$ of the items in SF36 were absent. Analyses were performed with SAS version 14 (SAS Institute, Cary, NC, USA) in study III and SAS version 9.4.46 (SAS Institute, Cary, NC, USA) in Study IV. P values ≤ 0.05 were considered significant. In Study IV Wilcoxon signed-rank test was used to compare HRQoL values at baseline, 3 months, and 6 months within groups. P values ≤ 0.01 were considered significant regarding HRQoL. Also, Mann-Whitney test was used to compare controls to intervention groups regarding change of CGRP, IL-6, and SP from baseline to 6 months. P values ≤ 0.05 were considered significant. Power calculations were performed in relation to the primary endpoints of the RCT: back extensor strength, pain and spinal curvature, but not in relation to the secondary endpoints: HRQoL or changes in markers of pain.

3.4 Ethical considerations

Both Studies I and II, which are follow-up studies on the PRIMOS cohort, were approved by the Regional Ethical Review Board in Stockholm (Ref. Nos. 145/98, 2007/188 – 31/3 and 2011/1743-32) and the Radiation Protection Committee at Karolinska University Hospital. Afterwards we completed with a request (DNR 2011/1743-32) to calculate FRAX risk. Ethical approval for Studies III and IV was obtained from the Ethical Review Board of Stockholm (Registration No. 2011/142-31/3). An additional request on permission to analyse IL-6 was also approved (registration No. 2016_187-32). Informed consent was obtained from all participants before enrolment at baseline. Participants received both verbal and detailed written information regarding the purpose of the study. All participant

was informed that their participation was voluntarily and could be withdraw at any time without consequences. The studies were performed in accordance with the ethical standards of the Declaration of Helsinki.

The data is kept in a safe way. A possible ethical dilemma is that the people participating in the studies receive information about their health status that they did not ask for, for example that they had osteoporosis. That could give cause for worries. On the other hand, all participants are offered follow-up and treatment. The risks of someone being injured during the study must be considered low. DXA measurement has low radiation dose. The balance tests and physical tests that are done are closely monitored by a clinician and the risk of injury is very small. Overall, we believe that the benefits outweigh the benefits as preventive treatment/advice can be given that can prevent future suffering.

4 Results

In this section the main results of the studies are presented and summarised. More extensive information can be found in the original articles.

4.1 Results Study I

Participants in this study included 350 out of 351 women in study population 1 who had assessed SRH at baseline. The participants were divided in tertiles depending on how they had assessed SRH. Data on hip fractures and all-cause mortality were collected after 10 years. The women were aged between 69 and 79 years at inclusion, and median age was 72.4 years (IQR 71.1–73.8). The median value of SRH (range 0 mm to 100 mm) was 62 mm (IQR 50–81 mm). The three groups of SRH: low, intermediate and high (used as reference), did not statistically differ regarding age, BMD/T-score at femoral hip, self-reported fractures over age of 50, smoking or treatment with bisphosphonates/calcium and vitamin D3. There were differences between the tertiles of SRH at baseline regarding BMI (lower SRH-higher BMI), co-morbidity/having more than two diseases (more common in lower tertiles) and treatment with more than three drugs (more common in the lower tertiles). There were also differences regarding OLST, gait speed, chair rise test and time spent outdoor

During the 10-year follow-up, a total of 40 hip fractures occurred. We found a significant difference, with most of the fractures occurring among those who rated their health the worst ($p=0.020$). Using the Cox proportional hazard regression model, the age-adjusted hazard ratio (HR) of suffering a hip fracture also differed between the tertiles of SRH: 3.17 in the low tertile and 2.75 in the intermediate tertile compared with the highest tertile. When we adjusted for BMD at femoral neck (continuous variable), T-score at femoral neck (dichotomous variable below -2.5 or not) or FRAX% the difference in HR was larger (see Table 2). When an interaction term between SRH and BMD respectively T-score or FRAX was included in the regression models, it did not attain statistical significance. Adjusting for age, smoking and BMI did not affect the significance of the original model.

Table 2 Cox proportional hazards regression model testing the association between self-rated health (SRH) and hip fracture

Outcome: Hip fracture	n=	High SRH	Intermediate SRH	Low SRH
SRH	350	ref	2.86 (95% CI 1.12–7.31)	3.48 (95% CI 1.38–8.77)
SRH+ age	350	ref	2.75 (95% CI 1.08–7.04)	3.17 (95% CI 1.25–8.01)
SRH+ age + BMD ¹	339	ref	3.10 (95% CI 1.13–8.55)	4.08 (95% CI 1.50–11.16)
SRH+ age + T-score < -2.5 ²	339	ref	3.18 (95% CI 1.15–8.77)	4.04 (95% CI 1.48–11.02)
SRH + age + FRAX hip fracture risk ³	350	ref	2.94 (95% CI 1.14–7.60)	3.52 (95% CI 1.36–9.09)

¹BMD= bone mineral density at femoral neck, ²T-score (NHANESIII) at femoral neck, ²T-score (NHANESIII) at femoral neck ³10-year probability of hip fracture BMD included (%)

The probability of hip fracture illustrated in a Kaplan–Meier failure estimate graph differed between the three groups of SRH. The probability of hip fracture also increased earlier in the group with low SRH compared to the other tertiles (see Figure 1).

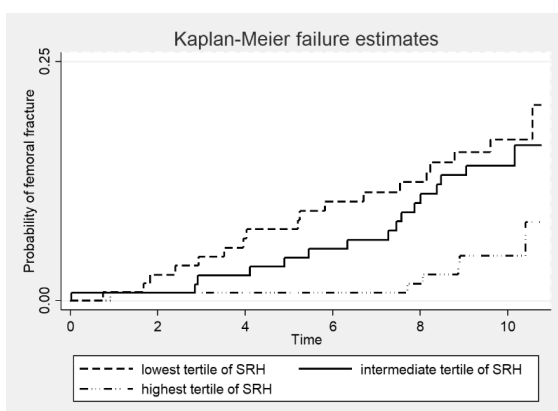


Fig 1. Kaplan Meier failure estimates for age 72.4 years (median age in the cohort)

During the 10-year follow-up 15 deaths occurred among those who also suffered from a hip fracture. The distribution did not differ significantly between the tertiles of SRH, nor did the all-cause mortality. See table 3.

Table 3 Deaths and survivals during the study in the tertiles of Self-rated health (SRH)

SRH	Low n=113	Intermediate n=118	High n=119	p-value
Hip fractures n (%)	18 (15.9)	16 (13.6)	6 (5.0)	0.020 ¹
Hip fracture and died, n (%)	8 (44.4)	6 (37.5)	1 (16.7)	0.557 ²
Died, total n (%)	27 (23.9)	26 (22.0)	19 (16.0)	0.292 ¹
Survived, no hip fracture, n (%)	76 (67.3)	82 (69.5)	95 (79.8)	0.072 ¹

¹ Chi²test ² Fisher's exact test

We also compared the SRH assessments between study population 1 and 2, SRH and EQ-VAS scores (see table 3). There was no significant difference in SRH even though study population 2 was slightly older. See table 4.

Table 4 Comparing self-rated health (SRH) and EQ-VAS score between study population 1 and 2

	Study population 1 SRH (0-100 mm)	Study population 2 EQ-VAS score (0-100 mm)	p-value
N=	350	109	0.020 ¹
SRH, median, (IQR)	62 (50-81)	67 (50-75)	0.919
Age, years, median (IQR)	72.5 (71.1-73.8)	76.4 (68.0-83.0)	0.005

¹Mann-Whitney test

4.2 Results Study II

In this study, 338 women (out of 351 in study population 1) with baseline test results for levels of PTH and IGFBP1 were included. The participants were divided in four groups regarding levels of PTH and IGFBP-1(A): normal levels of PTH and low IGFBP-1; (B) normal levels of PTH and high IGFBP-1; (C) elevated levels of PTH and low IGFBP-1; and (D) elevated levels of PTH and high IGFBP-1. Follow-up data on hip fractures and all-cause mortality was collected after 10 years. The median age at baseline was 72.4 years (IQR: 71.1–73.8). There were no significant differences between the four groups at baseline regarding previous or present cancer diagnosis, diabetes, smoking, daily outdoor activities more than 30 minutes, prescription of bisphosphonates/calcium and/or vitamin D3 supplements and plasma levels of ionized calcium. The groups with elevated levels of PTH, especially if they also had low levels of IGFBP-1, had a larger proportion of persons with calcium over the upper reference

limit (1.29 mmol/L). Age was higher in the groups with elevated PTH. BMD at femoral neck was higher in the two groups with low levels of IGFBP-1, regardless of whether PTH levels were normal or high. The incidence of cardiovascular disease (ICD10 codes I00–I99) differed as well, where the groups with elevated PTH levels had a higher incidence and the group with elevated levels of PTH and high levels of IGFBP-1 had the highest incidence of cardiovascular disease. The group with elevated levels of PTH and high levels of IGFBP-1 had the highest creatinine levels. Regardless of PTH levels, the two groups with high levels of IGFBP-1 had a GFR of < 60 ml/min/1.73 m², (i.e. below the limit for normal renal function). Levels of 25-OH vitamin D were significantly lower in the groups with elevated PTH, regardless of IGFBP-1 levels. During the 10-year follow-up, 69 of the participants died (20%). The group with elevated levels of PTH and high levels IGFBP-1 were overrepresented (40%) among the 69 deaths (table 5).

Table 5 Number and percentage of deaths (all-cause mortality) within the groups during the ten-year follow-up period

	Normal PTH ¹		Elevated PTH ¹		p-value ³
	Low IGFBP-1 ²	High IGFBP-1 ²	Low IGFBP-1 ²	High IGFBP-1 ²	
Total n=	124	126	43	45	
Died n (%)	20 (16)	22 (17)	9 (21)	18 (40)	0.005

¹PTH= parathyroid hormone, ²Insulin-like growth factor binding protein 1, ³Chi²test, IGFBP-1= Insulin-like growth factor binding protein 1

Using the Cox proportional hazard regression model, the age-adjusted association with all-cause mortality was two to three times higher in the group with elevated levels of PTH and high levels of IGFBP-1 (table 6). The results were similar when we excluded the participants with diabetes at inclusion.

Table 6 Association with age-adjusted all-cause mortality by Cox proportional hazard regression comparing the group with elevated levels of PTH and high IGFBP-1 with the other groups

Outcome: all-cause mortality			HR (95% CI)	p-value
Elevated PTH High IGFBP-1	compared to	Normal PTH Low IGFBP-1	2.83 (1.48 – 5.41)	0.002
Elevated PTH High IGFBP-1	compared to	Normal PTH High IGFBP-1	2.64 (1.40 – 4.99)	0.003
Elevated PTH High IGFBP-1	compared to	Elevated PTH Low IGFBP-1	2.30 (1.03 – 5.14)	0.043

We also investigated the association with cardiovascular mortality using the Cox proportional hazard regression model. The association with age-adjusted cardiovascular mortality, comparing the group with elevated levels of PTH and high IGFBP-1 with the other groups, was HR 3.93, $p = 0.001$ (compared to normal PTH and low IGFBP-1); HR 2.85, $p = 0.004$ (compared to normal PTH and high IGFBP-1); and HR 2.48, $p = 0.049$ (compared to elevated PTH and low IGFBP-1).

We found no statistical difference between the groups regarding hip fractures, but the group with normal levels of PTH and low levels IGFBP-1 had the smallest percentage of hip fractures, see table 7.

Table 7 Number and proportion of hip fractures within the groups during the ten-year follow-up period

	Normal PTH ¹		Elevated PTH ¹		p-value ³
	Low IGFBP-1 ²	High IGFBP-1 ²	Low IGFBP-1 ²	High IGFBP-1 ²	
Total n=	124	126	43	45	
Hip fractures n (%)	10 (8)	16 (13)	6 (14)	6 (13)	0.565

¹PTH= parathyroid hormone, ²Insulin-like growth factor binding protein 1, ³Chi²test, IGFBP-1= Insulin-like growth factor binding protein 1

4.3 Results Study III

In this study 113 women were randomised in three arms: controls, exercise and treatment with an activating orthosis. 96 women completed the study. The median age of the women was 76 years (interquartile range: 68-82). There was no statistical difference between the three groups at baseline regarding age, height, weight, proportion treated with bone specific and/or calcium-vitamin D3 and/or vitamin D. There was neither difference between the groups in terms of proportion who reported that they had previously had an ankle, hip or vertebral fracture nor the proportion of X-ray verified vertebral fractures (X-rays revealed 13% more people with vertebral fractures compared to the self-reported number). There was a difference at baseline regarding the occasional use of pain medication in the three groups that was 35% in the control group, 21% in the spinal orthosis group and 10% in the training group. No woman used pain killers regularly. Pain (at the present and during last week) was measured by VAS and Borg CR-10. VAS at present and last week and Borg CR-10 last week did not differ between the groups at baseline. Present pain measured with Borg CR-10 was higher in the spinal orthosis group ($p < 0.05$) at baseline. The proportion of

kyphosis (kyphotic index ≥ 13) and back extensor strength did not differ between the groups at baseline. There was no significant difference between the groups in terms of change in pain (VAS/Borg CR-10) or change in back extensor strength during the intervention time analysed by a mixed model according to intention to treat as LS means and a contrast tests post hoc. Comparing how large the percentage increase in back extensor strength was in each group during the intervention (analysed by paired t-test per protocol), showed that the mean value of increase in back extensor strength was 26.9% ($p=0.053$) in the spinal orthosis group, 22.1% in the exercise group ($p=0.013$) and 9.9% (not significant) in the control group (see table 8).

Table 8 Changes in back extensor strength within groups at baseline and after six months, analyzed per protocol

Baseline					Six months			p-value ¹	
Treatment group		n	mean \pm SD	95% CI	n	mean \pm SD	95% ci	Change %	
Muscle strength (N)	Spinal orthosis	35	64.4 \pm 32.8	53.2 – 75.7	27	81.7 \pm 41.3	65.4 – 98.0	26.9	0.053
	Training	38	59.6 \pm 30.8	49.5 – 69.8	30	72.8 \pm 37.3	58.9 – 86.8	22.1	0.013
	Control	36	62.3 \pm 25.2	53.7 – 70.8	32	68.4 \pm 27.0	58.7 – 78.1	9.9	0.153

¹ Paired t test

4.4 Results Study IV

As in Study III, 113 women were included, of whom 96 completed the study (Study population 2). They were randomised in three arms: control, exercise and treatment with an activating orthosis. Median age was 67 years old, and there was no significant difference in age between the groups at baseline. There was no statistical difference between the groups at baseline regarding BMI, smoking, proportion of X-ray verified vertebral fractures or previous hip fracture (self-reported), daily outdoor activities more than 30 minutes or need for home/community care. Assessments of pain during the last week at baseline with Borg CR-10 and VAS did not differ between the groups. There was a difference in the use of pain killers, where those in the exercise group used pain killers less often than the other groups (no one used pain killers regularly). There was no difference between back extensor strength (in Newton measured by Digi Max) nor hand grip strength between the groups (in kilograms measured by Jamar dynamometer). Evaluation of risk of falling by the Downtown

Fall Risk Index at baseline was 58% in the spinal orthosis group, with a high risk of falling (DFRI ≥ 3), compared to 35% in the controls and 32% in the exercise group. The need for walking aids was equal between the groups. There was no difference in previous breast cancer, asthma, chronic obstructive pulmonary disease (COPD) or type 2 diabetes between the groups at baseline. There was a difference in previous stroke between the groups, where no one in the exercise group had a stroke, 5.6% in the controls and 15.8% in the spinal orthosis group.

There was no significant difference (significant levels set at $p \leq 0.01$ for QoL) between the groups at baseline regarding quality of life assessed by SF-36. QoL assessed by QUALEFFO-41 showed a difference between the groups regarding the domains pain and jobs around the house at baseline.

We did not find any difference between baseline and six months between the groups in mean change (LS means) evaluated by SF-36. However, we did observe a tendency towards worsened vitality (SF-36) in LS means when comparing the spinal orthosis group to the control group ($P=0.02$), as well as worsened MCS index between the spinal orthosis group and control group ($P=0.04$) and exercise group and control group ($P=0.02$). There was also a tendency of worsened mental health in LS means comparing exercise group and controls ($p=0.03$) (see Table 9).

There were differences in change between the groups (baseline- six months) in QUALEFFO-41 when comparing LS means for the QUALEFFO-41 domain mobility in the spinal orthosis group ($P=0.01$) versus the control group, indicating a smaller effect on mobility in the spinal orthosis group than among the controls. There was also a tendency of worsened mobility in the exercise group compared with the control group ($P=0.05$). There was a tendency for worsened activities of daily living (QUALEFFO-41) in LS means when comparing the spinal orthosis group to the control group (see Table 9).

Table 9 Least squares mean (LS mean) changes measured by QUALEFFO-41 and SF-36 during the intervention, differences between the groups (QUALEFFO-41: zero indicates the best and 100 the worst possible QoL, SF-36: zero indicates the worst possible and 100 the best HRQoL)

	Spinal orthosis vs. controls	Exercise vs. controls	Spinal orthosis vs. exercise
QUALEFFO-41			
Pain	-1.9 (p = 0.065)	-0.3 (p = 0.95)	-1.6 (p=0.70)
ADL	6.3 (p = 0.02)	4.1 (p = 0.14)	2.2 (p=0.44)
Jobs	2.7 (p = 0.40)	-0.8 (p = 0.81)	3.5 (p=0.29)
Mobility	6.2 (p = 0.01)	4.7 (p = 0.05)	1.5 (p=0.54)
Social function	4.8 (p = 0.28)	-1.0 (p = 0.83)	5.8 (p=0.21)
General health	3.7 (p = 0.31)	3.5 (p = 0.32)	0.1 (p=0.97)
Mental function	3.0 (p = 0.25)	0.7 (p = 0.79)	2.3 (p=0.38)
Total score	3.5 (p = 0.08)	1.5 (p = 0.45)	2.0 (p=0.33)
SF-36			
Physical function	-4.59 (p = 0.20)	-1.92 (p = 0.59)	-2.67 (p = 0.46)
Role physical	-2.69 (p = 0.79)	-11.03 (p = 0.27)	8.35 (p = 0.41)
Bodily pain	0.42 (p = 0.94)	-2.85 (p = 0.59)	3.28 (p = 0.54)
General health	2.22 (p = 0.55)	5.32 (p = 0.15)	-3.10 (p = 0.40)
Vitality	-11.75 (p = 0.02)	-6.0 (p = 0.24)	-5.75 (p = 0.26)
Social function	-7.98 (p = 0.15)	-9.58(p = 0.09)	1.6 (p = 0.78)
Mental health	-18.47 (p = 0.08)	-22.73 (p = 0.03)	4.26 (p = 0.68)
Role emotional	-7.57 (p = 0.11)	-5.96 (p = 0.2)	-1.61 (p = 0.74)
PCS ¹	1.04 (p = 0.61)	1.07 (p = 0.60)	-0.03 (p = 0.99)
MCS ²	-5.93 (p = 0.04)	-6.53 (p = 0.02)	0.60 (p = 0.83)

¹ Physical component summary index (PCS) ² Mental component summary index (MCS) ³ Mixed model for repeated measures according to treat adjusted for age

Comparing changes within the groups, a significantly worse score was found in the role emotional domain of SF-36 in the exercise group at six months compared with baseline, but this was not seen at three months. There was also a significant change in the pain domain of the QUALEFFO-41 in the spinal orthosis group when comparing values at baseline and three months, though this was no longer present at 6 months (see Table 10).

Table 10 Median (Md) values for the QUALEFFO-41 domains and the SF-36 domains in the study groups at baseline and at the six-month follow-up (QUALEFFO-41: zero indicates the best and 100 the worst possible HRQoL, SF-36: zero indicates the worst possible and 100 the best HRQoL)

	Median baseline/ Median six months/p-value ¹		
	Controls n = 37	Spinal orthosis n =38	Exercise n = 38
QUALEFFO-41			
Pain	60/ 53 p = 0.47 ²	60/ 55 p = 0.09 ³ (p =0.002)	43/ 35 p = 0.25 ²
ADL	13/ 9 p = 0.22 ²	19/ 19 p = 0.11 ²	13/ 6 p = 0.98 ²
Jobs	25/ 25 p = 0.22 ²	40/ 35 p = 0.81 ²	20/ 18 p = 0.17 ²
Mobility	28/ 20 p = 0.03 ²	28/ 31 p = 0.97 ²	19/ 19 p = 0.89 ²
Social function	33/ 38 p = 0.27 ² (p =0.02)	46/ 45 p = 0.11 ²	32/ 46 p = 0.90 ²
General health	58/ 50 p = 0.67 ²	58/58 p = 0.92 ²	50/ 46 p = 0.26 ²
Mental function	36/36 p = 0.28 ²	39/ 39 p = 0.58 ²	33/ 32 p = 0.75 ²
Total score	36/ 33 p = 0.23 ²	40/ 37 p = 0.86 ²	33/ 31 p = 0.97 ²
SF-36			
Physical function	60 /63 p = 0.22 ²	50/ 45 p = 0.52 ²	65/ 68 p = 0.25 ²
Role physical	25/ 38 p = 0.79 ²	12.5/ 0 p = 0.47 ²	50/ 50 p = 0.63 ²
Bodily pain	41/ 46 p = 0.95 ²	41/ 41 p = 0.29 ²	47/ 51 p = 0.76 ²
General health	52/ 54 p = 0.71 ²	50/ 52 p = 0.66 ²	55/ 62 p = 0.17 ²
Vitality	50/ 60 p = 0.14 ²	50/ 40 p = 0.14 ²	55/ 58 p = 0.94 ²
Social function	75/ 88 p = 0.41 ²	63/ 63 p = 0.19 ²	88/ 75 p = 0.06 ²
Role emotional	67/ 83 p = 0.86 ²	100/ 33 p = 0.03 ²	100/ 67 p = 0.001 ²
Mental health	72/ 80 p = 0.62 ²	68/ 76 p = 0.29 ²	80/ 80 p = 0.85 ²
PCS ¹	34/32 p = 0.54 ²	31/ 31 p = 0.23 ²	38/ 41 p = 0.05 ²
MCS ²	47/ 51 p = 0.91 ²	48/ 44 p = 0.04 ²	52/ 48 p = 0.05 ²

¹ Wilcoxon signed rank test, ² Not significant (p > 0.01) at three months, ³ Significant (p < 0.01) at three months,

⁴ Physical component summary index and ⁵ Mental component summary index.

There were no significant differences within the groups when comparing levels of CGRP and SP at baseline and six months. There was no difference between the groups regarding changes (baseline to six months) in levels of CGRP and SP. IL-6 was significantly lower at six months (p= 0.02) compared with baseline in the spinal orthosis group. The change was significant when comparing both the control group (p=0.04) and exercise group (p=0.01) (see Table 11).

Table 11 Median (Md) values for CGRP, IL-6, and SP levels at baseline and 6 months and p-values

	A Controls	B Spinal orthosis	C Exercise	Differences between groups. p-values ²		
	Median (IQR) / missing			A vs B	B vs C	A vs C
CGRP (ng/mL)	Median (IQR) / missing					
Baseline	50.5 (44.1-60.9)/ 7	55.6 (46.2-62.9)/8	53.3 (44.0-61.1)/8	0.52	0.41	0.96
6 months	54.9 (46.2-61.9)/ 5	50.8 (38.9-60.2)/16	55.6 (47.4-58.7)/10	0.41	0.54	0.88
Change in group ³	p= 0.38	p=0.65	p= 0.97	0.33 ⁴	0.88 ⁴	0.43 ⁴
IL-6¹ (pg/mL)	Median (IQR) / missing					
Baseline	3.5 (0.0-5.7)/ 5	4.0 (1.9-9.4)/8	0.0 (0.0-4.1)/8	0.20	0.002	0.07
6 months	3.5 (0.0-6.0)/ 7	1.2 (0.0-4.4)/16	3.0 (0.0-4.9)/10	0.26	0.44	0.69
Change in group ³	p= 0.81	p=0.02	p=0.25	0.04⁴	0.01⁴	0.54 ⁴
SP (pg/mL)	Median (IQR) / missing					
Baseline	107.1 (0.0-361.2)/ 3	134.8 (71.7-403.8)/8	143.0 (0.0-284.4)/8	0.70	0.81	0.99
6 months	135.4 (0.0-318.2)/ 5	107.1 (0.0-202.3)/16	323.0 (94.3-405.2)/10	0.45	0.02	0.14
Change in group ³	p=0.70	p=0.99	p=0.07	0.69 ⁴	0.22 ⁴	0.08 ⁴

¹ Two outliers with very high values in the control group are not shown ² Mann–Whitney test ³Signed rank test ⁴changes between baseline and six months compared between groups

The effect sizes for the differences across domains between the groups varied; however, none exceeded 0.8, and the majority remained below 0.5. This suggests that the observed differences were at most of moderate magnitude, with most being negligible.

5 Discussion

5.1 Summary of main findings

In Studies I and II, we investigated whether self-rated health or combined plasma levels of PTH and IGFBP-1 could predict the risk of suffering from a hip fracture or death in the next 10 years. In Study I, the results provide evidence supporting an association between SRH and hip fractures in older white women. SRH seems to contribute valuable information independent of BMD. Unexpectedly, we found no association between SRH and the risk of death within the next 10 years. In Study II, the results indicate that simultaneously elevated levels of PTH and IGFBP-1 were associated with a higher risk of all-cause mortality. The novel contribution in Study II is that, as far as we know, no previous study has investigated the combined effects of PTH and IGFBP-1. Unexpectedly, we found no association between combined PTH and IGFBP-1 levels and the 10-year risk of hip fractures.

In Studies III and IV, we compared the impact of wearing an activating spinal orthosis compared to training with physiotherapy equipment and no intervention (control group). In Study III, we found that both treatment with exercise and an activation orthosis increased the back-extensor strength compared to controls. There was no difference in the intervention effect between the intervention groups regarding pain, back extensor strength or kyphotic index. In Study IV, we surprisingly found no difference in change between the treatment groups regarding HRQoL measured by SF-36 or QUALEFFO-41. We also did not find any differences in plasma levels of SP and CGRP between the groups. However, we saw that IL-6 levels decreased in the spinal orthosis group but not the other groups.

5.2 Discussion of the results

5.2.1 SRH or Concurrently Elevated PTH and IGFBP-1 Levels as Predictors of Fracture and All-Cause Mortality Risk.

In Study I, we found an association between SRH and the risk of future hip fractures, and the findings align with several earlier studies that identified SRH as a predictor of hip fractures, especially among older white women [98–100]. However, not all studies have found an association between SRH and hip fractures [98, 101–104]. The variability in the results may suggest that SRH is not a robust or universally reliable predictor of hip fractures. This may lay in the nature of SRH, which assesses QoL in a non-disease-specific way and does not concentrate on osteoporosis specific aspects of QoL. Also, SRH is subjective and influenced

by demographic factors, such as ethnicity, gender, and age, reducing its reliability as a universal measure [30, 43, 67–69, 105]. Our results and the results from previous studies indicate that there may be an association between SRH and hip fractures in older white women, who are a group known to have a high risk. When we added BMD, T-score and FRAX in our model the risk remained, suggesting that SRH may contribute with valuable information independent of BMD/T-score and potentially FRAX. Since fractures are known to occur even in individuals without osteoporosis according to BMD, the different combinations could help identify individuals with varying risk profiles [34, 106]. Current evidence suggests combining clinical risk factors and bone mineral density (BMD) for optimal hip fracture prediction. SRH may be a potential measure that can be used in that context.

When we adjusted the association between SRH and hip fractures by adding physical performance tests (OLST, gait speed and ability to rise from a chair) one at a time, the association became weaker and inconsistent. This may indicate a possible collinearity between SRH and the physical performance tests. Similar reflections were made by Wolinsky et al., who found an association between subsequent hip fractures and both SRH and dizziness in crude rate ratio analysis, but in the final multivariate model, no individual significant effect was shown. The authors suggested that this could be due to collinearity between SRH and dizziness [100]. It is well accepted that minor falls cause most of the fragility fractures of the hip in people with osteoporosis [46, 107]. Difficulties in balance/physical performance that lead to falls and thereby the risk of fracture may be part of the process that leads to a decline in SRH, and may partially explain the SRH-fracture link in our study. This explanation is also in line with the literature describing sarcopenia as an independent risk factor for hip fractures [108]. Sarcopenia means loss of muscle mass and strength and may lead to adverse events, such as falls and hip fracture, especially in combination with osteoporosis [109, 110]. Gait speed and chair rise are physical performance tests included in the diagnosis of sarcopenia [108]. When we combined gait speed and ability to rise from a chair in a combination variable and added the variable to the age adjusted model, the association between SRH remains. Sarcopenia itself is also associated with poor quality of life and death [108].

Contrary to our expectations, no significant association was found between SRH and mortality in Study I. SRH is widely recognised as a predictor of mortality across various

populations and contexts. Numerous studies have demonstrated strong associations between poorer SRH and increased mortality risk, suggesting that SRH effectively captures an individual's overall health status, encompassing both physical and psychological dimensions [63, 111]. The utility of SRH as a mortality predictor has been established, even after controlling for clinical and demographic factors, including chronic diseases, physical functionality and socioeconomic status [63, 65]. Despite its strong predictive validity, the relationship between SRH and mortality may vary by age, gender and ethnicity [63, 66], which may have influenced our results.

Given that we have two study populations that are quite similar to each other, we thought it would be interesting to examine whether SRH is at approximately the same level in both, despite differences in measurement methods. SRH was assessed at baseline in both study populations. In study population 1 the participants were asked to answer the question "How would you rate your health right now" (0-100 mm) ranging from "worst imaginable" to "best imaginable". In study population 2 the participants responded to the EQ-5D VAS score questionnaire (see table 3). The two populations' results agreed.

In Study II, we investigated whether combined plasma levels PTH and IGFBP-1 could predict the risk of suffering from a hip fracture or death in the next 10 years. In this study, the results were the opposite of what were observed for SRH: we found an association between simultaneously elevated PTH and IGFBP-1 and mortality but not hip fractures. Individuals with both elevated PTH (≥ 65 ng/L) and high IGFBP-1 levels had significantly higher mortality rates compared to those with either normal PTH levels or high PTH paired with low IGFBP-1 levels.

Elevated PTH levels have long been associated with adverse health outcomes, but may differ between populations [112, 113]. In a meta-analysis, it was confirmed that elevated PTH is an independent predictor of all-cause mortality [114]. Elevated PTH levels have also been associated with cardiovascular mortality, even within the upper normal range [115, 116]. Elevated IGFBP-1 has earlier been associated with higher all-cause mortality in older persons [117, 118]. An association between low IGFBP-1 and cardiovascular mortality/negative cardiovascular risk profile has been described in older women and men [119, 120]. An earlier publication from the same cohort showed that both high and low IGFBP-1 levels (compared to moderate levels) were associated with an increased risk of all-cause mortality

[121]. In Study II, we also found a significant association when comparing the group with elevated IGFBP-1 and high PTH to the other groups regarding cardiovascular mortality, this may indicate that CVD explains a large part of the mortality in this study. Previous research supports this connection, with elevated PTH linked to vascular calcification, endothelial dysfunction and CVD mortality [115]. Moreover, IGFBP-1 has been associated with insulin resistance and metabolic syndrome, which predisposes individuals to cardiovascular complications [122]. The findings suggest that the combined elevation of PTH and IGFBP-1 exacerbates higher “overall mortality” from cardiovascular diseases in this population.

Regarding hip fractures, we found no relationship between elevated PTH and IGFBP-1. Previous studies have reported conflicting findings as well. Elevated PTH levels in hyperparathyroidism are associated with an increased risk of fracture due to enhanced bone resorption [123]. Elevated PTH levels and low serum 25-hydroxyvitamin D, even in the absence of secondary hyperparathyroidism, have also been linked to increased bone turnover [113, 124]. In a study of patients diagnosed with osteoporosis and non-osteoporotic controls, higher levels of IGFBP-1 were observed in the osteoporosis group [125]. In another study, no association was found between levels of IGFBP-1 and BMD at the hip or spine after adjusting for age and BMI [126]. Previously, a study in the same cohort, showed a linear association between IGFBP-1 and hip fractures [127]. This could be because in this study, we compared IGFBP-1 levels at a group level in contrast to the linear association we found earlier, or it could reflect a weakening of IGFBP-1's direct relationship with fractures when analysed in conjunction with PTH (contradicting our hypothesis). In our study, elevated levels of PTH and IGFBP-1 were not effective in identifying individuals at risk of fractures but seem to highlight a population with increased vulnerability.

5.2.2 RCT Evaluating Non-Pharmacological approaches to Osteoporosis: Exercise and use of an Activating Spinal Orthosis

Providing optimal healthcare for individuals with osteoporosis is challenging due to treatment gaps, limited therapeutic effectiveness and unmet needs for treatment addressing health-related quality of life, particularly chronic pain and functional impairments [82, 91]. In Studies III and IV, we focused on the non-pharmacological management of osteoporosis. Exercise is a well-established treatment method, but the use of an activating orthosis remains debated and is not yet recommended in Sweden's

osteoporosis care guidelines [53]. Exercise is a cornerstone in managing osteoporosis, with or without vertebral fractures, due to its multifaceted benefits. Previous research shows that structured, targeted exercise programmes improve bone mineral density (BMD), enhance muscle strength, reduce falls, support physical function, alleviate chronic back pain and promote quality of life. Strengthened back extensors by specific exercise can reduce kyphosis and improve spinal alignment, reducing the risk of fractures in osteoporotic individuals [21, 22, 24, 128, 129]. There is far less research on back orthoses and the semi-acute effects in patients with osteoporosis and vertebral fractures. However, studies have demonstrated effects such as increased back muscle strength, improved posture, and enhanced HRQoL, as well as reduced chronic pain after 3–6 months of use [29, 130, 131].

In Study III, we found that back extensor strength increased **in the intervention groups**: 22.1% in the exercise group and 26.9% in the spinal orthosis group after six months. However, we found no **difference in change between the intervention groups** regarding back extensor strength, back pain (Study III) and HRQoL (Study IV). The majority of studies assessing training effects have used straightforward statistical approaches with within-group comparisons. More participants to ensure sufficient power are demanded, especially with small effects or heterogeneity. In Study III, we found no significant difference in back pain reduction between the groups, and in Study IV, we found no significant difference in the change of HRQoL between the groups during the six-month study period. This is surprising, as we had anticipated improvements in both HRQoL and pain. The results of HRQoL may be considered inconclusive to some extent as the different instruments, at the domain level, did not point in the same direction and in some domains, we even found a decline [worsened mobility (QUALEFFO-41) in the spinal orthosis group compared to the control group and worsened emotional role functioning (SF-36) in the exercise group]. The total score/summary scores for both instruments showed that there was no significant effect on HRQoL. It is also important to note that QUALEFFO-41 is a disease-specific assessment tool designed for patients with vertebral compression fractures, and only 44% of our participants had such fractures. SF-36 is a generic assessment instrument, making the results not entirely comparable.

Other studies evaluating the effect of exercise on HRQoL also show varying results, underscoring the complexity of evaluating HRQoL outcomes in this population. Stanghelle et al. (RCT: 12-week supervised exercise programme twice a week in older women with

osteoporosis and vertebral fractures) also failed to demonstrate significant improvements in HRQoL measured by the generic SF-36 and the disease-specific QUALEFFO-41. They suggested that high baseline HRQoL among the participants may have limited the potential for measurable gains [26]. In our study, baseline differences were observed between the groups in the QUALEFFO-41 domains of 'jobs around the house' and 'pain'. This may have influenced the results in the pain domain of QUALEFFO-41, which showed significant improvement in the spinal orthosis group at 3 months but not at 6 months. Also, the mean values in the domain role emotional in QUALEFFO-41 in the spinal orthosis and exercise group were already the highest possible at baseline. Other studies have documented benefits in HRQoL; for example, Bergland et al. (RCT: combined programme with supervised exercise twice weekly and a three-hour educational session in older women with osteoporosis and vertebral fractures) demonstrated significantly better results in mean value from baseline registration to the 12-month registration in QUALEFFO-41 total score and three out of five domains (including pain) [132]. Grahn Kronhed et al. (RCT: four-month supervised exercise twice weekly in older women with established osteoporosis) found significant improvements in six out of eight SF-36 domains (including bodily pain) and also in the mental summary score, though no changes were detected using QUALEFFO-41 [25]. Evstigneeva et al. (RCT: 12-month supervised exercise programme twice weekly in older women with osteoporotic vertebral fractures) also found a significantly improved physical function and pain, total QUALEFFO-41 score, four out of five domains (including pain)) [133].

A recent systematic review evaluated QUALEFFO-41 among patients with osteoporotic vertebral fractures. The authors concluded that QUALEFFO-41 may be a valid and reliable questionnaire for evaluating HRQoL in osteoporosis and vertebral fractures, but due to limitations in methodological consistency across included research, they recommended more research using standardised guidelines regarding patient-reported outcome measures to ensure validity and reliability [134].

We did not find any significant differences between the groups in terms of change in pain (VAS/Borg CR-10) during the intervention time analysed by a mixed model according to intention to treat as LS means. Grahn Kronhed et al. found a significant decrease in worst pain measured by VAS evaluating an exercise programme [25]. Evstigneeva et al. and Bergland et al. also found a significant improvement in QUALEFFO-41 domains of pain when evaluating exercise programmes [132, 133]. Other studies have also demonstrated

the effect of exercise on pain, but the results are heterogenous and the data is sparse [21, 24, 26, 135–137].

The evidence in the literature regarding the effect of spinal orthoses on QoL, postural stability and pain is not entirely consistent, as highlighted by several reviews. The quality of the studies included in the reviews has also varied, and while effects have been observed in some studies, the evidence is insufficient to conclude that treatment with orthoses is superior to treatment without [27, 138–142]. However, Pfeifer et al. reported significant improvements in daily activity limitations, back extensor strength and pain compared to controls when using Spinomed for 6 months, but not after 12 months [29]. Similarly, Valentin et al. observed that Spinomed III orthoses improved back muscle strength significantly and pain and physical functioning with borderline significance [130]. Kim et al. (2014) reported no significant difference to controls for general health status with regard to SF-36 PCS, however SF-36 MCF declined compared to baseline in the two spinal orthosis groups, but not in the controls. Also, Dionyssiotis et al. found that Spinomed decreased pain and increased trunk muscle strength over 6 months [131]. Li et al. similarly found that subacute use of both SpinoMed® and soft lumbar orthosis improved pain and limitations of daily life after ten weeks, but both groups improved equally [143]. It remains uncertain, due to the inconsistent results and low-quality evidence, whether spinal orthoses provide significantly better outcomes than those achieved without bracing. Further international multi-centre randomised trials are needed to clarify this and strengthen the evidence [140–142]. To our knowledge, no other study has compared the use of a spinal orthosis with exercise.

One factor that may have influenced the lack of significant results regarding differences between groups in pain is that we included women presenting with mild to severe back pain. The median self-reported pain scores during the past week were 3 on the Borg CR-10 scale and 42 mm on the visual analogue scale (VAS), indicating moderate pain. Also, the fact that we included participants with self-reported osteoporosis and varying fracture status (44% had vertebral fractures) may have introduced heterogeneity, which could have diluted treatment effects. Additionally, the intervention dosage may have influenced our results, as guidelines recommend exercise for individuals with osteoporosis, with or without vertebral fractures, at a frequency of 2–3 sessions per week [21]. That may not have been achieved in our study because we offered supervised exercise once a week, but

encouraged the participants to participate in a home exercise programme at least 4 times a week.

The effectiveness of exercise is well-documented, however, adherence to exercise recommendations is poor. Studies indicate that up to 50% of individuals enrolled in exercise programmes drop out within the first six months [144]. Compliance with soft or semi-rigid orthoses ranges from 30% to 90%, influenced by comfort, design and usability [29, 131, 143]. Although our study did not demonstrate a difference in treatment effects between exercise and spinal orthosis, the finding of improved back muscle strength in both groups is noteworthy. Since compliance with exercise can sometimes be a challenge, especially in older individuals who may not be able to engage in exercise, a spinal orthosis could serve as an alternative. This requires additional examination in future studies. In a follow-up qualitative study by Alin et al., 18 women from the study's treatment arm involving spinal orthosis were asked about their experiences. Participants perceived the activating spinal orthosis as beneficial, enhancing posture, alleviating pain and improving strength and daily activity. Many described it as a supportive "close friend", while others reported challenges with fit, comfort and usability. Proper customisation and follow-up were identified as critical for maximise the effect and user acceptance [58]. Also, in a postintervention follow-up study of the RCT, 57 participants from the spinal orthosis and exercise groups were included. They were instructed to continue either wearing the spinal orthosis or performing their exercise regimen voluntarily, without supervision or scheduled follow-ups, for an additional six months. At the end of this period, back extensor strength and back pain were reassessed. Findings indicated that improvements in back extensor strength were preserved, while pain levels remained unchanged, suggesting sustained adherence to the respective interventions and supporting their long-term feasibility [151].

5.2.3 RCT Findings on Pain-Related Markers: interleukin-6 (IL-6), calcitonin gene-related peptide (CGRP), and substance P (SP)

A secondary aim of Study IV was to examine the effects of the RCT interventions on plasma levels of potential markers of pain in osteoporosis, including the sensory neuropeptides SP and CGRP, as well as the inflammatory cytokine IL-6. We found no change in plasma levels of CGRP or SP within the groups or between the groups. However, we saw that IL-6 levels decreased in the Spinal orthosis group but not the other groups.

There are no other similar studies to our knowledge. IL-6 is a pro-inflammatory cytokine that is elevated in osteoporosis. It promotes osteoclast activity, bone resorption and inflammation-associated pain [83, 84, 145]. In an osteoporotic mouse model, anti-IL-6 improved mechanical hyperalgesia in the hind limbs but showed no effect on bone loss, indicating that IL-6 is involved in postmenopausal osteoporotic pain [146]. Anti-IL-6 treatment in rheumatoid arthritis (RA) patients resulted in improvement of the disease with rapid symptom relief by decreasing inflammation and other symptoms associated with RA, but there are few studies that specifically focus on evaluating pain [147]. Our results may indicate that the use of a spinal orthosis influenced the inflammatory signalling pathway, but we did not see any effect in assessments of pain, which is contradictory. Biomarkers of inflammation may be of interest for clinicians as an additional tool for identifying patients at risk for fracture and for selecting future treatment options, though further studies are needed [145].

5.3 Strengths and limitations

One of the strengths with Studies I and II is its longitudinal design, with a follow-up period of nearly 10 years, facilitated by Swedish national registers that ensured no loss to follow-up. In Studies III and IV, the 6-month intervention duration is notable, as many comparable studies use shorter timeframes. The randomised design, which included two intervention groups and a control group, further strengthens the Study III and IV's validity.

However, there are also several limitations. The use of a single-item self-rated health (SRH) measure in Study I complicates comparisons with studies utilising different scales. Our SRH variable was categorised into tertiles for analysis. Most studies employ a five-point scale, often aggregated into two or three categories. Published research earlier addressed that comparison between different scales may need rescaling to some extent for comparability. Furthermore, the SRH measure was generic rather than osteoporosis-specific, which may have influenced the findings in Study I. The cohort in Study I however included both osteoporotic and non-osteoporotic individuals. One single question also has the positive aspect that it is not so demanding for the participants.

The study cohort size in Studies I and II presents another limitation, particularly given the wide confidence intervals for hip fractures, leading to uncertainty regarding the effect sizes despite statistical significance. The relatively low number of events—40 hip fractures

and 72 deaths—further contributes to this uncertainty. Limited generalisability is another concern, as the findings apply primarily to older, predominantly white women in Sweden and may not be representative of other populations. Additionally, a healthier sample bias may exist, as non-participants were slightly older, reported more previous hip fractures, and had lower self-perceived health status compared to participants.

Methodological constraints for Studies III and IV include the lack of power calculations for endpoints related to quality of life and pain markers, which may have resulted in insufficient statistical power for these analyses. Despite prior power calculations, the sample size in Study III may have been insufficient. Advanced statistical methods, such as mixed models and intention-to-treat (ITT) analysis, typically require larger sample sizes to ensure adequate statistical power, particularly when dealing with small effects and heterogeneity. Also, recruitment bias may have influenced outcomes. The limited research team size precluded blinding of investigators, potentially introducing bias. The self-reported osteoporosis diagnosis and inclusion of participants with and without vertebral fractures may have added heterogeneity to the study population.

Another limitation concerns the reliability of pain markers due to a high number of missing values and large standard deviations, which may have affected result consistency. Similarly, back extensor strength assessments exhibited significant variance. Lastly, the analysis focused solely on bone mineral density (BMD) values and T-scores at the femoral neck, without considering BMD at other skeletal sites or the microstructural properties of bone, which may have limited the comprehensiveness of the findings.

6 Conclusions

Hip fractures are a severe complication of osteoporosis, highlighting the need for early identification of at-risk individuals, preferably before they experience their first fracture. Self-rated health (SRH) shows potential as a predictor of fracture risk, that may contribute with valuable information to BMD and FRAX, though more studies are needed. While simultaneously elevated parathyroid hormone (PTH) and insulin-like growth factor-binding protein-1 (IGFBP-1) levels were not linked to hip fractures, their association with the 10-year all-cause mortality risk may assist in identifying individuals at risk for mortality rather than hip fractures. This could be valuable for planning and tailoring care in the near term. The activating spinal orthosis demonstrated no significant differences in change in back pain, extensor strength and quality of life compared to control and equipment training groups. However, a within-group analysis revealed a 27% increase in back extensor strength in the orthosis group. These findings suggest a spinal orthosis could serve as an alternative to exercise, particularly among individuals with poor adherence to exercise.

We found no differences concerning change in pain, back extensor strength or HRQoL between the intervention groups. Existing evidence suggests that exercise benefits bone mineral density, pain, muscle strength and balance performance in older women with osteoporosis. Conflicting results regarding HRQoL may indicate that the impact on HRQoL may be less pronounced. The modest effect sizes and varying outcomes, as well as the heterogeneity in our study population, warrant cautious interpretation. The observed reduction in Interleukin 6 (IL-6) levels, without changes in Substance P (SP) or Calcitonin-gene related peptide (CGRP) levels, underscores the need for further investigation into the inflammatory and neuropeptide mechanisms in osteoporosis-related pain.

These findings emphasize the importance of tailored strategies for early risk identification, improved management of osteoporosis-related complications and exploration of novel therapeutic approaches targeting inflammation and pain.

7 Points of perspective

Osteoporosis is a common condition, and its prevalence is expected to increase further. The consequences of the disease, fractures, can be prevented, preferably before the first fracture occurs. Osteoporosis is an underdiagnosed and undertreated condition, and even those who have already suffered a fracture do not receive the treatment they are entitled to, and which could help prevent additional fractures.

Improving osteoporosis care in Sweden requires increased awareness and knowledge among healthcare professionals and in society.

Since osteoporosis is asymptomatic prior to the occurrence of fractures, it is inherently challenging to diagnose and treat at an early stage. Fractures, on the other hand, typically necessitate medical attention, which provides an opportunity to diagnose and treat. This is important because an osteoporosis-related fracture significantly increases the risk of subsequent fractures. Unfortunately, this opportunity is often missed. It is well-established that post-fracture care programmes, such as Fracture Liaison Services (FLS) and Orthogeriatric Services (OGS), enhance the diagnosis and treatment of osteoporosis and reduce morbidity and mortality rates [18]. However, these programmes are not consistently available across all regions, and the referral and reporting of fractures for further investigation and treatment vary widely.

To identify individuals with osteoporosis before their first fracture, further research is needed within primary care, where the majority of at-risk individuals are likely to be encountered. In our study, SRH emerged as a potential risk factor that could aid in identifying individuals at risk of future fractures. It is particularly interesting that SRH appeared to provide additional information beyond BMD and FRAX, which are currently used for diagnosing and estimating the risk of future fractures. Considering the multifaceted aetiology of osteoporosis, it is likely that unexplored variables or factors exist that could enhance the identification of individuals at risk for fractures. SRH requires further investigation, and the study needs to be replicated. It would be valuable to assess SRH at multiple time points and in larger studies to determine if the association varies across age groups.

Quality of life (QoL) in patients with osteoporosis, particularly those with vertebral fractures, encompasses multiple dimensions, including pain, functional impairment and the broader social and physical context. Improving QoL requires a comprehensive approach that integrates both medical and non-medical interventions, as well as the development of novel therapeutic options in both domains. Our study did not show that participants in the spinal orthosis group had superior effects on back strength, QoL or pain compared to the exercise group or control group. However, back strength improved during the treatment period. A qualitative study (not included in this thesis) suggested that orthoses were perceived as supportive within a broader context. Spinal orthoses need to be explored further in large randomised trials to clarify their effect. Interestingly, we observed a reduction in IL-6 levels in the spinal orthosis group, despite no observed effect on pain. The mechanisms underlying pain in manifest osteoporosis remain insufficiently understood. IL-6 needs to be further investigated especially regarding long-term trends, intervention effects and its precise role in osteoporosis. Exploring treatments targeting the effects of inflammatory cytokines and neuropeptides could provide valuable insights into pain alleviation.

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9 Declaration about the use of generative AI

The following AI assisted tools, Chat GPT40, was used in writing the comprehensive summary of the thesis for language support.

I take full responsibility for the content of the comprehensive summary of the thesis.

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