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IDENTIFYING INDIVIDUALS AT RISK OF FRAGILITY FRACTURES IN A DENTAL SETTING

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Cover illustration: The front-page photo is of the dried "skeleton" of a dead cactus that I found as a child in the Arizona desert in 1971. My father was a visiting professor at Arizona State University for a year and he often took my mom and us kids, age 4-12, on family trips to the desert. When we moved back to Sweden, we brought the cactus home with us. The trip, by car and airplane, took several weeks and we kids took turns carrying the carefully wrapped cactus. The others, alert to the risk of a fall and a fracture, cautioned the carrier "Mind the skeleton!".

Identifying individuals at risk of fragility fractures in a dental setting

Thesis for Doctoral Degree (Ph.D.)

By

Charlotta Elleby

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This thesis is dedicated to my late parents, Lars and Cristina Kihlborg. My father was a professor of inorganic chemistry. He inspired me, and gave me the genes, passion, and grit to pursue doctoral studies and research. My mother was enthusiastic and supportive without limit, regardless of what projects her children were drawn to. Her hip fracture late in life gave me new insight and motivation for my PhD project.

Popular science summary of the thesis

Fragility fractures are fractures caused by low trauma, such as falling from a standing height, a fall that normally would not cause a fracture. Vertebral fractures can even occur spontaneously. They are most common in older adults, and they can result in lowered quality of life and high cost for the society. Sweden has one of the highest incidences in the world, and about one-half of Swedish women and one-fourth of the men are expected to have at least one fragility fracture during their lifetime.

Contrary to visits in primary care, most adults in Sweden are scheduled for regular check-ups by their dentist. Regular dental check-ups offer a possibility to identify individuals with a high risk of having a disease or condition not only inside the oral cavity but also outside of the oral cavity. These check-ups often motivate radiographic examinations, and the resulting radiographs display features of the bone in the lower jaw that have been found to reflect the quality of the bone tissue in the rest of the body, the Bone Mineral Density (BMD). Low BMD is a risk factor for fragility fractures. Low physical performance is also a risk factor as a fall is often involved. The Fracture risk assessment tool (FRAX) is a web-based tool commonly used in primary care to assess the ten-year risk of having a fragility fracture. It takes several risk factors into account, such as age, sex, and previous fractures.

The aim of the thesis was to study different methods of identifying individuals with a high risk of fragility fracture, methods that could be used in a dental setting.

In the first three studies, we used data collected in 1969-1970, when 32,183 men and women living in Stockholm, 18-65 years old, received a questionnaire. Some of these were also asked to participate in a dental assessment including radiographs. From the National Patient Register we acquired data on hospitalizations due to fractures, etc. and date of death.

In the first study, we used two methods to assess if the appearance of the bone in the radiographs of the lower jaw could predict fractures. We assessed 837 men and women who were age 18-65 when the radiographs were exposed, and followed them for up to 47 years, but we found no fracture-predictive ability of either method.

In the second study, we studied the 16,766 participants 26-65 years old, who had answered five questions about their physical health and mobility. The men who had answered that they had problems with their physical health and mobility, had about three times as many hip fractures as those who did not have any problems. For women, this was only true for the younger age group, those who were 26-45 when they filled in the questionnaires. Problems with their physical health and mobility made no change in the fracture risk for the older women, 46-65 years old.

In the third study, we studied if the questions about alcohol consumption answered by 27,766 participants, 18-65 years old, could predict hip fractures during the 47 years that followed, but we found no such predictive ability. We also studied if a hospitalization with a diagnosis code indicating a high level of alcohol consumption could predict fractures. We found that those who were 18-25 at the start of the study and followed until they were 65-72 years old had about a three-fold increased risk. For those who were older, and therefore followed until they were older, there was no change in the fracture risk. Our interpretation of this is that persons with a high level of alcohol consumption have an increased risk of having hip fractures when they are relatively young.

In the fourth study, we interviewed patients at the Stockholm Public Dental Services about their thoughts about doing a FRAX assessment of ten-year fracture risk in a dental setting. Despite little knowledge or experience of osteoporosis or fragility fractures, the participants were positive towards doing a FRAX assessment, at a similar cost as in primary care. They were, however, doubtful if the dentists would have interest, time, or knowledge to do it. If found to have a high risk, they expected collaboration between the dental staff and primary care for further investigation, advice or treatment if needed.

Conclusively, we found that neither of the two methods to assess the pattern of the lower jawbone in intraoral radiographs could predict fractures in our study. Questions about physical health and mobility, and high alcohol consumption need to be further developed and studied. Using FRAX in a dental setting may be a feasible way to identify patients with a high risk for fractures, but further studies are needed.

Populärvetenskaplig sammanfattning

Benskörhetsfrakturer är frakturer som orsakas av lågenergi-trauma, som tex. att falla från stående - ett fall som normalt sett inte skulle orsaka en fraktur. Frakturer av ryggkotorna kan till och med uppstå spontant. De är vanligast hos äldre personer och kan orsaka stort lidande, sänkt livskvalitet och höga kostnader för samhället. Sverige är ett av de länder i världen där dessa frakturer är vanligast, och varannan svensk kvinna och var fjärde svensk man beräknas drabbas av minst en benskörhetsfraktur under livet.

Till skillnad mot besök i primärvården kallas de flesta vuxna till tandvården för regelbundna undersökningar av sin tandläkare. Dessa återkommande tandundersökningar erbjuder en möjlighet att identifiera personer med hög risk för sjukdom eller tillstånd i munhålan, men även i resten av kroppen. Vid en vanlig tandundersökning är det oftast motiverat att ta röntgenbilder. På dessa kan man se egenskaper hos käkbenet i underkäken som i tidigare studier har visat sig avspegla bentätheten i resten av kroppen. Låg bentäthet är en riskfaktor för benskörhetsfrakturer. Låg fysisk förmåga är också en riskfaktor eftersom ett fall ofta föregår en fraktur. Fracture risk assessment tool, FRAX, är ett web-baserat verktyg som främst primärvården använder för att bedöma risken för att få en benskörhetsfraktur inom tio år. Verktyget tar hänsyn till flera riskfaktorer såsom ålder, kön, tidigare frakturer mm.

Målet med denna avhandling var att studera olika metoder att identifiera personer med hög risk för benskörhetsfrakturer som skulle kunna användas inom tandvården.

I de första tre studierna använde vi data från den stora REBUS-undersökningen som gjordes 1970–71. En enkät med bland annat frågor om fysisk hälsa skickades då ut till 32 183 män o kvinnor, 18–65 år, i Storstockholm. Några av dessa erbjöds även att delta i en tandundersökning med röntgen. Från Socialstyrelsen erhöll vi data om sjukhusvistelser pga. frakturer med mera, samt dödsdag.

I den första studien använde vi två metoder för att undersöka om käkbenets utseende på röntgen kunde kopplas till framtida frakturer. Vi undersökte 837 män och kvinnor som var 18–65 år när röntgenbilderna togs och följde dem under 47 år, men vi kunde inte finna någon koppling till framtida frakturer med någon av metoderna.

I den andra studien hade vi 16 766 deltagare, 26–65 år, som hade svarat på REBUS enkätens fem frågor om sin fysiska hälsa och förmåga. De män som hade svarat att de hade problem med sin fysiska hälsa hade ca. tre gånger så många höftfrakturer som de som inte hade några problem. För kvinnorna gällde det endast den yngre åldersgruppen som var 26–45 år när de fyllde i enkäten. För de äldre kvinnorna, 46–65 år, var risken för höftfrakturer oförändrad, vare sig de hade problem med sin fysiska hälsa eller inte.

I den tredje studien använde vi frågorna om alkoholkonsumtion som besvarats av 27 766 personer för att studera om de kunde kopplas till inträffade höftfrakturer under den 47 år långa uppföljningsperioden, men fann inget samband. Vi undersökte även om sjukhusvistelser där sjukvården angivit en diagnoskod som tydde på hög alkoholkonsumtion kunde kopplas till senare inträffade höftfrakturer. Vi fann då att den yngsta gruppen, som var 18–25 år vid studiestart, och som följdes till 65–72 år, hade en ca tre gånger så hög risk att få en höftfraktur än de som inte hade en alkoholrelaterad sjukhusinläggning. För de som var äldre, och som vi alltså följde tills de var äldre, fanns ingen ökning. Vår tolkning av detta är att hög alkoholkonsumtion ökar risken för höftfrakturer som inträffar relativt tidigt i livet.

I den fjärde studien intervjuade vi patienter vid Folktandvården Stockholm AB om deras tankar om att göra FRAX-undersökning i samband med ett tandvårdsbesök. Trots ringa kunskap om osteoporos och benskörhetsfrakturer var deltagarna positiva till att göra en FRAX-undersökning om det skedde till samma kostnad som i primärvården. En del var dock tveksamma till om tandläkarna skulle ha intresse, tid eller kunskap att utföra testet. Om de befanns ha hög risk förväntade de sig samarbete mellan tandvård och primärvård så att de skulle kunna få fortsatt utredning och vid behov råd och vård.

Sammanfattningsvis fann vi att ingen av de två metoderna att undersöka underkäksbenets utseende på tandröntgen kunde kopplas till benskörhetsfrakturer. Frågor om fysisk hälsa och mobilitet samt alkoholkonsumtion måste utvecklas och studeras vidare. Att använda FRAX i tandvården skulle kunna vara ett sätt att identifiera personer med hög risk för benskörhetsfrakturer, men fler studier behövs.

Abstract

Introduction: The increasing life expectancy is only positive if the added years are healthy years. Fragility fractures are most common in older adults, and they can result in lowered quality of life and high costs for the society. About one-half of Swedish women and one-fourth of the men are expected to sustain at least one fragility fracture during their lifetime, so identifying the high-risk individuals would be favorable.

Regular dental check-ups offer a possibility to identify individuals with a high risk of having a disease or condition outside the oral cavity. Features of the mandibular bone shown on dental radiographs have been found to reflect the bone density of the skeleton. Low Bone Mineral Density (BMD) is a risk factor for fragility fractures. Low physical performance is also a risk factor as a fall often precedes a fracture. FRAX is a tool commonly used in primary care to assess the ten-year risk of sustaining a fragility fracture.

Aim: The aim of the thesis was to study different methods of identifying individuals with a high risk of fragility fracture, methods that could be used in a dental setting.

Material and methods: In the first three studies, we used the unique REBUS cohort, a stratified random sample of the Stockholm population, where 32,183 men and women between the ages of 18-65 received a postal questionnaire in 1969-70. A smaller sample of the cohort had a dental assessment including intraoral radiographs. We acquired data concerning fractures during 1970-2016 from the National Patient Register. In study I, we assessed the trabecular pattern of mandibular bone in intraoral radiographs with two methods, one visual, and one semi-automated. We followed 837 individuals 18-65 years old for 47 years. In study II, we studied the association between questions of physical health and mobility for 16,766 participants 26-65 years, and hip fractures during 20-35 years of follow-up. In study III, we studied the association between questions about alcohol consumption for 27,766 participants, 18-65 years old, and hip fractures during 47 years of follow-up. We also studied diagnoses indicating high alcohol consumption before a fracture and the relationship to hip fractures. In study IV, a qualitative study, we interviewed patients at the Stockholm Public Dental Services about their thoughts about doing a FRAX assessment of ten-year fracture risk in a dental setting.

Results: In study I, we found no fracture predictive value in the two methods of assessing the trabecular pattern of the mandibular bone. In study II, questions of physical health and mobility could predict a 2.69 (CI 1.85-3.90) – 3.30 (CI 1.51-7.23) increase in hip fractures. This was true for all men, 26-65 years old at the study start and followed for 20-35 years until they were 61-85 years old, but for women only for those who were 26-45 years old and followed for 35 years, until 61-80 years old. In study III, the questions about alcohol consumption had no fracture predictive value. A hospitalization event with a diagnosis indicating high levels of alcohol consumption resulted in a significantly elevated subhazard ratio (SHR) for hip fractures in men (3.29, CI 1.80-5.98) and women (2.73, CI 1.37-5.42), but only in the youngest age group who were age 18-25 at the start of the study and 65-72 years old at the end of the study. This was interpreted as an indication that high alcohol consumption has a predictive ability for hip fractures that occur at an early age, for both men and women. In study IV, the interviewed participants were mostly positive about doing a FRAX assessment of the ten-year fracture risk, but they expressed concerns that need to be considered before introducing FRAX in a dental setting.

Conclusion: We found no evidence of fracture predictive ability using the semi-automated method. The visual method may not be suitable to use for all ages and both sexes. Questions about physical health and mobility, and high alcohol consumption need to be further developed and studied. Using FRAX may be a feasible way to identify high fracture risk, but further studies are needed.

List of scientific papers

I. Two methods of evaluating mandibular trabecular pattern in intraoral radiographs and the association to fragility fractures during a 47-year follow up. Elleby C, Skott P, Jonasson G, Theobald H, Nyrén S, Salminen H.
Eur J Oral Sci. 2021;129(5):e12801

II. Long term association of hip fractures by questions of physical health in a cohort of men and women. Elleby C, Skott P, Johansson SE, Nyrén S, Theobald H, Salminen H.
PLoS One. 2023 Mar 29;18(3):e0283564

III. The association between long term high alcohol consumption and hip fractures by sex. Elleby C, Skott P, Johansson SE, Nyrén S, Theobald H, Salminen H. (under review)

IV. Patients' thoughts about assessment of fracture risk in a dental setting using FRAX—a qualitative interview study. Elleby, C., Skott, P., Theobald, H., Nyrén, S., & Salminen, H.
Archives of osteoporosis, 18(1), 65

Contents

List of abbreviations

BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CIF	Cumulative incidence function
DXA	Dual-energy x-ray absorptiometry
FLS	Fracture liaison service
FRAX	Fracture Risk Assessment Tool
HR	Hazard ratio
HTA	Health technology assessment
ICD-8	The International Classification of Diseases, used in Sweden 1969-1986
ICD-9	The International Classification of Diseases, used in Sweden 1987-1996
ICD-10	The International Classification of Diseases, used in Sweden 1997- today (2023)
MRONJ	Medication-related osteonecrosis of the jaw
NPR	The Swedish National Patient Register
QCT	Quantitative computerized tomography
REBUS	"Rehabiliteringsbehovsundersökningen," a multidisciplinary study to assess the presence of disease, disability and need of care or rehabilitation of the population of Stockholm
ROI	Region of interest
SHR	Subhazard ratio
WHO	World Health Organization

1 Introduction

The increasing life expectancy of the general population brings us new challenges. The added years should preferably be relatively healthy years to be positive for the individuals, their families, and the community-at-large. An aging population could also mean rising healthcare expenditures, if the added years are not years of good health [1]. Therefore, it is important to identify individuals with a risk of having diseases or conditions that could cause decreased quality of life for the individual or higher healthcare costs, so this can be minimized.

Sweden has one of the highest incidences of fragility fractures (fractures because of low-energy-trauma) in the world. These are most common in older adults and can result in lowered quality of life and high cost for society. At the age of 50 years, 47.3% of Swedish women and 23.8% of Swedish men, are expected to sustain a fragility fracture during the rest of their lifetime [2], so identifying the high-risk individuals and treat them would be favorable. However, since there are no “pre-fracture-symptoms” urging the individuals to contact the primary care, many fractures occur in patients who were not aware that they were at risk.

Could interprofessional research and collaboration present solutions to some of these challenges? Could the regular dental check-ups be a way of identifying the high-risk individuals, not only for diseases in the oral cavity, but for conditions and diseases in the rest of the body? Could the dental staff help the primary care to identify patients with a high risk of sustaining fractures, so they could receive preventive treatment? These were the questions that initiated this doctoral research project.

2 Background

2.1 Frailty

Frailty is defined by WHO as “a clinically. recognizable state in which the ability of older people to cope with everyday or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems” [3]. Frailty is thought of as a geriatric syndrome as a result of diseases or medical conditions, rather than a natural consequence of aging or a single disease [4]. Frail older adults are characterized by weight loss, self-reported exhaustion, weakness (often measured as a decrease in grip strength), slow walking speed, and low physical activity [5]. Having three or more of these conditions is classified as frailty; one or two as pre-frailty. The transition from being a non-frail, robust, person to being dependent often goes via pre-frailty and frailty. This pathway is not only in one direction, although the transition to greater frailty is more common than the reverse [6]. Several studies from around the world find that about 10-20% of older adults are frail and about 40-50% pre-frail [7, 8]. There is an increasing prevalence of frailty with older age, female sex, and socioeconomic factors such as poverty and limited education [5, 8]. Falls and delirium are common results of frailty, but if the condition is identified, it is possible to decrease the symptoms by means of physical exercise, better nutrition (higher intake of proteins and energy, and vitamin D supplements), and reducing polypharmacy [4].

Evidently, musculoskeletal health is closely related to frailty [9] and sustaining a fracture often has large negative consequences for the older adult [10]. The fracture could either be a result of the older adult being frail, or it could lead to frailty. Identifying individuals who have an augmented risk of sustaining a fracture could therefore be a way to prevent events that lead to a lower quality of life and higher costs for society, and consequently add more healthy years to our lives.

2.2 Fragility fractures

Fractures that occur from a relatively low-energy trauma are called fragility fractures. The trauma could be caused by lifting a bag of groceries or from a fall from a standing height – a trauma that in a young and healthy person would ordinarily not cause a fracture. Vertebral fractures can even appear to occur spontaneously. These fractures are multifactorial, and despite the expression fragility fracture they are not only caused by “fragile” bone, i.e., bone with low mineral density, known as osteopenia or osteoporosis, although this is one of the factors [11]. The size and the micro-architecture of the bone also contribute to the resistance to fractures. Other factors are the tendency to fall, reaction time and muscular strength to parry a fall. Poor physical performance is associated with fragility fractures [12]. The tendency to fall, in turn, can be influenced by medication, balance problems, impaired vision, living in a cold climate with risk of ice, diseases like Parkinson's disease, etc. [13].

The number of fragility fractures is increasing globally due to the aging of the populations [14]. Scandinavia has the highest incidence of fragility fractures in the world. The mean age for radius fractures in Sweden is 61 years, and for hip fractures 81 years [15]. Fragility fractures increase mortality [16-19] and may decrease quality of life [10, 20]. There are huge costs for society associated with fragility fractures [14, 21]. In Sweden, this is estimated to be EUR 2.3 billion annually [22]. Although there are successful ways to prevent fragility fractures with medication, there is a large undertreatment [23]. The treatment gap in Sweden, i.e., the number of patients that do not receive medication compared to the proportion of the population that would benefit from medication, is 76% in women and 62% in men [24]. It may require large resources to find individuals at high risk, but it is still found effective [25].

In the bone tissue, there is a constant turnover where old, damaged bone tissue is degraded and new is formed. If the balance of this process is negative, the bone becomes weaker, resulting in osteoporosis. The strength of the bone is dependent on many factors ranging from the macroscale of bone morphology, through its microarchitecture and composition, down to the tissue properties on the nanoscale [26-28]. Morphology is, for example, the size and geometry of the bone, and its cortical thickness. The microarchitecture includes properties like the shape of the trabeculae or degree of cortical porosities, while the tissue properties is about the organic and inorganic components that constitute the bone. These variables depend on age, sex, genes, bone turnover, loading, physical activity, diseases, medication, etc., and frailty has implications on many levels of the macro- and micro-scale of the bone tissue.

2.3 Osteoporosis

The definition of osteoporosis is based on the measurement of bone mineral density (BMD). To establish if a patient has osteoporosis or not, BMD is measured using dual-energy X-ray absorptiometry (DXA) [29, 30]. It is noninvasive, and the radiation dose is low. It is usually performed, and best validated, on central locations of the skeleton: the femoral shaft, hip, or lumbar spine [31]. If the value is below -2.5 standard deviations (SD) of that of a young female reference population, it is classified as osteoporosis. Values between -1.0 and -2.5 SD are classified as osteopenia. Normally the BMD peaks around the age of 25-30 years to decrease slowly from then on. At menopause women have a sharp decline in BMD during about ten years, after which the BMD continues to decline but at a slower pace. In men, the decline starts after the peak at around 25-30 years and continues for the rest of their lives. Because women have smaller and less dense bones, an accelerated BMD-decline after menopause and longer life expectancy, 80% of the fragility fractures occur in women. Primary osteoporosis is a condition where the decrease in BMD is the main condition, due mainly to age without any underlying conditions, and if there has already been a fracture, it is referred to as "manifest osteoporosis". Secondary osteoporosis is a condition where low BMD is caused indirectly by another disease, condition, or medication as a side effect. Individuals with osteoporosis have the highest fracture risk, but since osteopenia is so much more common than osteoporosis, and there are other factors than BMD that influence fracture risk, most individuals who sustain a fragility fracture have osteopenia and not osteoporosis [32, 33].

2.4 Other risk factors for fragility fractures

The age-related decrease in BMD and muscular strength are not the only reasons why fragility fractures are more common late in life. To have a fracture there needs to be a trauma, and the cause is often a fall. Balance problems become more common with age and can result in falling. An extended reaction time or slow movements, for example due to stroke, dementia, or Parkinson's disease, can result in falling without having time to parry the fall. The result could be a fracture from a common fall such as stumbling over a carpet edge at home, a fall that would not lead to a fracture in a person with a normal reaction time.

Medications and diseases can negatively influence the BMD and thereby increase the fracture risk. Long-term cortisone medication is the most common example of this. Body weight, or rather the body mass index (BMI) can also influence the BMD and thereby the risk of fracture. A high BMI stimulates the bone and enhances the mineral content and structure, mitigating the risk of fracture. The opposite, low BMI, a condition associated with frailty, increases the risk of fragility fracture. Nutritional deficiencies such as Vitamin D deficiency, or deficiencies caused by, for instance, inflammatory bowel disease or bariatric surgery can lead to secondary osteoporosis. Hormonal imbalance or treatment caused by Type 1 diabetes, chronic kidney disease, Cushing's syndrome, thyrotoxicosis, hypogonadism, or hormonal medication can also imply secondary osteoporosis. Examples of lifestyle factors that are associated with a higher fracture risk are a sedentary life, smoking, and high alcohol consumption, although studies of the latter are not conclusive. Original studies and meta-analyses of previous studies have shown both significant positive associations and no significant associations between a high level of alcohol consumption and fracture risk. [34-37]. Even a protective effect of low alcohol-consumption compared with abstinence was found in two meta-analyses. In the first one including 23 studies, a J-shaped curve was found, where abstainers had more osteoporotic fractures and hip fractures than low consumers of alcohol [38]. The same was found for hip fractures (pooled RR=0.88 for light drinkers compared with non-drinkers) in another meta-analysis based on 18 prospective cohort studies including 3.7 million participants by Zhang et al. [39]. A reason for the varying results could be the different designs, cohorts and inclusion/exclusion criteria of included studies so other factors influenced the results, and that in all these studies, the assessment of alcohol consumption was subjective, i.e., based on questionnaires or interviews.

The most important risk factor for a fragility fracture is, however, having had a previous fracture. [40] and the more recent the previous fracture, the higher the risk for a new fracture [41].

2.5 Fracture risk assessment

2.5.1 Bone and mineral content

Methods to assess the bone, like radiographs, DXA and quantitative computed tomography (QCT) can be used to study the mineral content or the architecture of the bone tissue on a larger scale while different types of spectroscopies and electron microscopy are used for investigating the tissue properties on the smaller scale. For clinical purposes, there are other methods than DXA which can be used to assess the mineral content of the bone. These include peripheral DXA on the heel or wrist, ultrasound of the heel bone, and digital X-ray radiogrammetry of the hand. However, the recommended and most validated method of assessing the bone mineral density is DXA of central locations of the skeleton, such as the lumbar spine and hip.

2.5.2 Other risk factors to assess

Methods that assess the muscular dimension, such as gait speed, “one leg standing time” or grip strength, can add value to fracture prediction [42, 43]. Simple questions such as “Do you have impaired balance?” have also been found to be fracture predictive [44]. The use of clinical risk factors, e.g., prior fractures and medication with glucocorticoids, also add to the performance of BMD predicting fragility fractures in both men and women [45].

2.5.3 Risk assessment tools

It has been shown that the total number of risk factors is more important than BMD for predicting fragility fractures [46] and therefore, finding the individuals with augmented risk is difficult. To address this difficulty, several risk-assessment tools have been developed, for example, the FRAX® tool [47], the Garvan fracture risk calculator [48], and QFracture® [49]

The Fracture Risk Assessment Tool, FRAX [47], is a web-based questionnaire that calculates the ten-year probability of sustaining a fracture in hip, forearm, spine, or upper arm [50]. It includes questions about age, sex, weight, length, previous fractures and hip fractures of parents, current smoking, cortisone treatment, rheumatoid arthritis, alcohol consumption and diseases known to cause secondary osteoporosis. If available, BMD of the femoral neck can also be included. There are regional differences in the occurrence of fragility fractures, and as FRAX is based on metanalysis of studies in several different countries, it is the only tool that is specific for populations in different countries [51]. However, it contains a limited number of variables, and, for instance, questions concerning the type of fragility fracture in history, balance, previous falls, or physical activity are not included at all. Therefore, a new version, FRAXplus®, is being developed, where more factors are included, for instance the recency of a previous fracture, number of falls in the previous year, and duration of diabetes type 2. [52].

2.5.4 Strategies for risk assessment

Screening the entire population or parts of the population for a certain disease, or a condition that can lead to disease, is an appealing idea. However, many aspects must be considered before implementing a screening program. A comprehensive cost-benefit analysis should be performed, including both monetary and quality-of-life dimensions. How common the condition is, how it affects the individual and society, if the method of screening is reliable, if there is a cure, and to the extent to which the quality-of-life is improved if found and treated, are some of the questions that need to be considered before implementing a screening program. Screening for the risk of fractures has its benefits but also its disadvantages. A benefit would be that many fractures could be avoided if the right measures, e.g., medication or physical training, were introduced. This would be an obvious benefit for both the individual and society. A disadvantage is that there is no method yet with good enough sensitivity and specificity, to find all individuals with a high risk, and to find only those with a high risk. Moreover, there is no cure for osteoporosis, although there is preventive treatment to reduce fracture risk, but only if done at the right time which means that the screening needs to be done at the right time or age for optimal benefit. So, screening for fracture risk could lead to unnecessary treatment, worrying patients, or giving false hope of not being at risk, and the screening would still be costly for society.

Sustaining one fracture is associated with a significantly increased risk of sustaining another fracture (RR = 1.86; 1.75-1.98 95% CI) [53]. The greatest risk of having a secondary fragility fracture occurs during the first year after a first fracture [54]. Secondary prevention would therefore be an effective way of reducing the number of fractures. It has been suggested, as a basic strategy, to start directly after a fracture offering further contact with the healthcare system for assessment and treatment [55, 56]. This fracture liaison service (FLS) has been found to be associated with a 40% decline of major bone fractures [57]. The FLS is operated by a coordinator in close liaison with the doctor. The Swedish National Board of Health and Welfare recommends FLS, but this has not yet been implemented in all regions of Sweden [58].

2.5.5 Risk assessment in a dental setting

The system of regular dental check-ups, common in the Scandinavian countries, has been proposed to be used for screening the population for conditions or diseases outside the oral cavity. Since about 80% of the adult population >64 years has contact with a dental clinic at least every other year [59], this could be a feasible way of reaching those individuals who do not have any regular contact with primary care. The possibility of using the dental visit for the identification of subjects with a high risk of experiencing a cardiovascular event was suggested in 2005 by Glick and Greenberg [60]. This hypothesis was confirmed by studies where dentists assessed the ten-year risk for a CVD event [61, 62] and soon the aim was to include other chronic conditions such as diabetes and hypertension

[63-66]. The cost-effectiveness of having oral health professionals screening for risk of systemic diseases has been investigated, discussed, and found to be a potentially feasible way of finding high-risk patients [67-71]. Other aspects to consider before implementing chair-side screening programs for medical conditions in a dental setting is how this is perceived by the patients, dental staff and physicians [72-79] as well as the views of the authorities [80]. It seems that all parties involved have a positive view of chair-side medical screening in a dental setting although some reservations were found.

2.6 Studies of the jaws

The quality of the bone is already of interest for dentists as a parameter to consider for example before placing an implant, both for the drilling protocol and for prognosis [81, 82]. In dogs, the lower jaw, the mandible, has been found to have a high bone turnover [83]. Human bone marrow stem cells of the orofacial bones differ from those of the iliac bone, and they proliferate more readily [84]. Subsequently, the bone of the mandible is thought to reflect the change in bone status faster than many other parts of the skeleton and many studies have investigated if there are early factors predicting fragility fractures to be detected in dental radiographs. These studies have used both extraoral (panoramic), and intraoral radiographs, as well as computed tomography (CT) and cone beam tomography (CBCT). Most studies were performed on the lower jaw (the mandible) but some on the upper jaw (the maxilla). Both the trabecular bone and the cortex were studied, using many different methods. Some methods have been manual and some more or less automated and computer based. Recent ones even use machine learning. Both the variables' relationship to BMD and their relationship to fractures have been studied, but the results are not consistent. The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) is commissioned by the Swedish Government to evaluate the scientific evidence supporting both new and established measures within health, medical, dental, and social services. It publishes scientific evidence gaps in their database accessible to everyone [85]. These knowledge gaps are identified through SBU Reports, National Guidelines, reports from the regional HTA organizations and published systematic overviews. On June 26, 2020, SBU published that a knowledge gap had been identified by the Regional HTA in Västra Götaland (Western Sweden) in a systematic review on the use of dental radiographs for the prediction of bone fracture risk, and their conclusion was that more primary studies were needed [86]. Although their literature search resulted in 2,377 articles, only three studies fulfilled their inclusion criteria, of which two, cohort studies, had fracture as outcome [87, 88], and a third, cross-sectional study, studied trabecular bone pattern as an indicator of BMD. [89]. The certainty of evidence according to the GRADE approach was low, to very low [90]. This research field, assessing the trabecular pattern in intraoral radiographs, was the start-off for this thesis. But how did it all begin? What happened then? And what studies have been made since this HTA was published?

The mandible consists mostly of cortical bone, in a relationship to the trabecular bone of 80:20 corresponding to that of the distal radius, but the trabecular bone structure can be well studied in both panoramic and intraoral radiographs. Henrikson et al. compared the relative density and calcium content of sections of the mandible and the radius and found that both the relative density (r=-0.634) and Calcium content (r= 0.664) correlated on a group level between the two bones [91, 92]. Some studies have found both jaws to contribute to the prediction of femoral and spinal BMD [93], but the mandible has been preferred in most studies. In the mandible, the premolar region seems to be the best location to assess bone mass [94], due to little individual variation in anatomy and the lack of major muscular fiber insertion in this region.

2.6.1 Studies of the cortical bone

Both the cortex and the trabecular bone can be studied using panoramic radiographs. The inferior cortex of the mandible becomes thinner and more eroded with osteoporosis and with aging. Taguchi et al. found a significant correlation of the width (Kendall's tau = -0.36) and morphology (Kendall's tau = -0.49) of the mandibular inferior cortex on panoramic radiographs to BMD of the 3rd lumbar vertebrae using DXA [95]. Lee K. et al. found that visual estimation of the inferior cortex could be used for identifying high-risk individuals in a cohort of postmenopausal women with DXA from the femoral neck and lumbar spine [96]. An index describing the degree of erosion [97] was found to be related to BMD, both in panoramic and cone beam computed tomography imaging, and has been used in several studies [98-100].

The width of the cortex measured in millimeters has also been used [101, 102], and a combination of both width and erosion [103], as well as a combination of the width, the erosion and/or mandibular indices on the panoramic radiographs [104, 105], and they have all been found to be associated with BMD of the standard sites for diagnosis of osteoporosis, the spine and femur. Combining clinical information with panoramic cortical width and shape has been tested and suggested to be useful in identifying subjects with low bone mass [98, 99, 106]. To avoid the hazard of the observer influencing the results, computer-aided assessments have been developed to obtain automated and semi-automated methods of assessing the inferior cortex of the mandible [107-110].

Low mean values of Fractal Dimension analysis (FD) of the mandibular cortical bone in panoramic radiographs was found to be more common in osteoporotic individuals than non-osteoporotic (AUC 0.820)[111]. Other methods to assess the inferior border on panoramic radiographs include measuring the antegonial angle and antegonial depth, which were found to add value in the process of identifying individuals with high risk for low BMD [112].

2.6.2 Studies of the trabecular bone - Visual method

The structure of the trabecular bone in the mandible, although only constituting 20%, can also be assessed as the trabecular bone is well displayed in both intraoral and panoramic radiographs. A visual method of assessment of the trabecular pattern of the mandibular bone was proposed by Lindh [81] to assess the bone before placing implants. This index was modified by Jonasson et al. using intraoral radiographs [113, 114]. The trabecular pattern of the mandibular bone in the premolar region was divided into three groups: sparse, dense, and mixed sparse and dense. In a study using the visual index on intraoral radiographs, including both men and women, the trabecular pattern was found to correlate significantly to BMD of the forearm in women ($r=0.55$, $p<0.001$) but not in men ($r=0.26$, $p>0.05$) [115]. In a large multicenter study, the OSTEODENT study, six hundred females 45-70 years old, had DXA analysis made at the hip and spine and intraoral radiographs of the premolar region of the upper and lower jaw. The visual method of assessing the trabecular pattern was found to have high specificity (91) but low sensitivity (28) in both jaws when identifying subjects with skeletal osteoporosis measured at the hip and lumbar spine [116]. Their conclusion was that this could be a "potential method to identify women at risk of having osteoporosis." In another study, also using intraoral radiographs, the visual index was found to correlate significantly ($r=0.57$, $p=0.001$) to forearm BMD, hip BMD ($r=0.36$, $p=0.02$) but not spine BMD ($r=0.20$; $p=0.19$) in post-menopausal women [117]. Crohn's disease is a disease known to be associated with a high risk of fractures. In a study with a cohort of subjects of both sexes and relatively young, aged 23-61 years, the trabecular pattern on intraoral radiographs, using the same visual index, was found to be significantly sparser compared to an age and sex matched control group: 31% of subject with Crohn's disease, and 12% of subjects without Crohn's disease, had a sparse trabecular pattern [118].

Visual assessment of the trabecular pattern can also be performed on panoramic radiographs. However, in a study by Pham et al. it was found to be more difficult to perform than when using intra-oral radiographs. To overcome this, they recommend training [119].

2.6.3 Studies of the trabecular bone - Other methods

In a five-year follow-up study of 131 women 22-75 years old, optical density (to obtain an indication of mandibular alveolar bone mass) and trabecular pattern, using analogous periapical radiographs, did not correlate to changes in skeletal BMD during the follow-up time [114]. In the same study, the radiographs were digitized, gray-level values were measured, and texture analysis was performed using specially developed software. Both the gray-level values and the texture analysis correlated moderately (r=0.33 and r=0.39 respectively) to the change of BMD in the distal forearm. In the earlier mentioned study by White et al., [99], analysis of the trabecular pattern in the mandibular ramus was also performed. They used custom software for strut analysis, a method where the average length of the struts constituting the trabeculae is analyzed in a set region of interest (ROI). They found the parameters included in this analysis to be less useful than the cortical width. Another attempt to study the trabecular pattern using a computerized method (previously developed by Geraets et al.) was made on the Osteodent cohort mentioned earlier. An automated method was used on four manually placed ROI in panoramic and intraoral radiographs. The software analyzed several features describing the trabecular pattern. Age accounted for 10-14% of skeletal BMD, but a combination of age with all the measurements on the dental radiographs increased it to 22-23% [120]. In a following study the researchers concluded that combining the mandible and the maxilla was best for BMD prediction in the hip and the spine, raising variance explained from 10-14% for just age, to 23-36% when including data of ROIs from both jaws in texture analysis, compared to 18%-27% for just one jaw. [93]. In another study of the same cohort, using the same computerized method to analyze the trabecular features, its value of predicting osteoporosis was found to be the same as age, one of the strongest risk factors for osteoporosis [89]. Combining the trabecular pattern with age significantly increased specificity, from 0.72 to 0.78, in finding individuals who have an elevated risk for osteoporosis defined by DXA at the lumbar spine and hip, but the change in sensitivity was not significant. Using the same semi-automated method and gray level values together with a visual assessment of the trabecular pattern, it was concluded that the visual assessment is based more on the gray level value than the actual geometric details in the ROI in the radiograph [121].

Fractal analysis (FD) of the trabecular structure in panoramic radiographs was found by two research groups not to correlate to BMD values [111, 122].

Cone Beam Computed Tomography (CBCT) of the jaws has also been used and in a study of 54 post-menopausal women, CBCT was compared with panoramic radiographs for the calculation of the mandibular cortical index (MCI) [100]. The sensitivity and specificity of both methods were lower than in previous studies of the MCI. This method has limited use in routine clinical practice so far but may in time become more common and more studied.

2.6.4 Studies of the jaws and association with fractures

The previously mentioned studies are all about the relationship of radiographic indices of the jaws to BMD. There are fewer studies on the relationship to fractures. In the year 2000, Bollen et al. found that older individuals with self-reported fractures had an increased resorption and thinning of the mandibular inferior cortex using the Klemetti index on panorama radiographs than those without self-reported fractures (OR of osteoporotic fracture = 2.0 for moderately eroded cortex, and OR = 8.0 for severely eroded cortex) [123]. Yamada et al, on the other hand, did not find an eroded mandibular cortex to be associated with fractures in a Japanese cohort, even though it raised the OR for an osteoporosis diagnosis (from moderately eroded, OR = 1.4, to severely eroded, OR = 2.6) [124]. Studying the trabecular pattern on panoramic radiographs in a Swedish cohort of post-menopausal women with data on fractures from 26 years of follow-up, Jonasson et al. found the trabecular pattern to be a highly significant fracture risk predictor, with rising hazard ratios the sparser the trabecular pattern: dense (HR 0.21, 0.13-0.36 95% CI), mixed (HR 1.0), and sparse (HR 2.87, 2.17-3.80 95% CI) [125]. Still using panoramic radiographs, automated methods of texture analysis, as well the previously described visual assessment of the trabecular pattern, were included in a study of postmenopausal women during a follow-up of 26 years [126]. They found that a sparse trabecular pattern according to the visual method (AUC 0.800, 0.749-0.851 95% CI) correlated better to fractures that occurred during the follow-up time than the texture analysis did (AUC 0.603, 0.537-0.669 95% CI). Combining the two methods produced the best results (AUC 0.85, 0.808-0.894 95% CI). The same authors studied the trabecular pattern in panoramic radiographs of women with a 25-year follow-up, and found that the trabeculae in the mandible "lost detail and became more aligned in their main direction" with increasing age, i.e., they were accentuated in a 90-degree angle to the direction of the loading [127]. The change in the trabecular pattern was interpreted as "aging" and was accentuated in those who had sustained a fracture.

To evaluate the width and morphology of the inferior cortex in the mandible together with three clinical tools for assessment of fracture risk, a study was performed on panoramic radiographs in a 10-year longitudinal study [128]. The results showed that severely eroded cortex (RR 1.7, 1.1-2.8 95% CI), but not the width of the inferior cortex, was significantly predictive of fractures. Of the three clinical tools in the study, only FRAX-values over 15% (risk of sustaining a fracture in ten years) could significantly predict fractures (RR 4.1, 2.4-7.2 95% CI).

On periapical radiographs, White et al. used several computer-analyzed measurements of the trabecular pattern in the jaw on a cohort of elderly women [129]. They found that changes in trabecular pattern, measured as the average length of node to terminus struts to be predictive of hip fractures, and with each 1% decrease in average length per year hip fracture rate increased 1.3 times (HR 1.31 ranging from 1.05-1.61 with 95% CI) and slightly more if it was combined with clinical data (HR1.34 ranging from 1.04-1.72 with 95% CI). The visual method has also been used in studies with intraoral radiographs. In a retrospective study of men and women, 50-77 years old, with data of previous fractures, the risk of previous fractures was found to be increased when the trabecular pattern was sparse, where OR was 5.9 (3.0-11.6 95% CI) compared to those with a dense trabecular pattern (adjusted for age and BMI). In subjects 75 years or older OR was even higher, 7.1 (2.5-19.8 95% CI) [130]. In a study of women 38-54 years with a follow-up of 38 years, Jonasson et al found that the trabecular pattern was a highly significant predictor of future fractures, OR for having a fracture was 2.9 for sparse trabeculation, and 0.2 for dense trabeculation [125]. The older the individual, the better the fracture prediction.

Another study was performed to compare how three different methods of assessment of the trabecular structure on periapical radiographs, were associated with FRAX, and osteoporosis in women 35-94 years old [87]. The three methods were 1. The visual method described before, 2. The specially developed software described by Jonasson et al above [114], and 3. A program calculating the size and number of intertrabecular spaces, called Jaw-X. This is the original software with the same algorithm on which the Boneprox study version in our study I is based. Only the texture analysis had any predictive value for future fractures. Previous fracture and glucocorticoid medication could significantly predict future fractures (RR 6.3 (3.17-12.55 95% CI) and RR 5.01 (2.44-10.29 95% CI)) respectively, but not the diagnosis osteoporosis (defined as DXA value with t-score ≤ -2.5 SD), as would have been expected. In another cohort consisting of 277 men and women 79-81 years of age, the same three methods were used together with data for self-reported fractures [131]. They found that sparse trabeculation leads to an increased OR for having had a fracture, higher in men (OR 5.55) than in women (OR 3.35). For bone texture as an indicator of previous fracture, it was significant for women (OR 2.61) but not in men. The Jaw-X method showed no significant association with previous fractures.

To clarify if visual assessment of the trabecular pattern could add to the fracture predictive value of FRAX, a study was made on post-menopausal women of two age groups with a follow-up of ten years [88]. The relative risk of fracture was largest for the older group (62-78 years at baseline). In this group they found that RR for future fractures was 4.1 (2.4-7.2 95% CI) for subjects with FRAX values >15%, and for sparse trabecular pattern RR was 3.7 (2.2-6.4 95% CI), but for the subjects with both risk factors RR rose to 22.7 (5.62-92 95% CI). The predictive power measured as AUC for FRAX >15% as the sole predictor was 0.69 (0.63-0.74 95% CI), which rose to 0.75 (0.70-0.81 95% CI) when including sparse trabecular pattern.

In conclusion, many studies have been made during the last decades of the association between skeletal BMD, and fracture predicting ability of radiographic features in the jaws. The results are inconclusive in many cases, but severely eroded inferior cortex and sparse trabecular pattern have been associated with both low skeletal BMD and fractures in many studies. Sex, age, regional differences, and size of populations could explain the difference in results.

The aging of the population leads to an increase in fragility fractures that causes suffering to individuals and high costs for the society. Joint collaborations between the medical care providers and other care givers has been suggested as one way to face this problem. Could the dental care contribute to this? With an aim to reduce these fractures, this thesis explores possible methods to identify high-risk individuals that could be suitable in a dental setting.

3 Research aims

3.1 Overall aim

The overall aim of this thesis was to study different methods of identifying individuals at risk of fragility fractures that could be used by the dental staff in conjunction with a regular dental check-up. The methods studied include intraoral radiographs, questions about daily function and physical ability, alcohol consumption, and the FRAX risk assessment tool.

3.2 Specific aims

Study I
The aim was to explore the association between fractures and a visual and a semi-automated method of assessing the trabecular bone pattern in intraoral radiographs for both sexes including younger age groups during a long follow-up time of 47 years.

Study II
The aim was to study the hip fracture predictive ability of five questions about daily function and physical ability during a long follow-up time, and if there were age, sex, and follow-up time differences in a cohort with participants 26-65 years old at the start of the study.

Study III
The aim was to investigate whether there was an association between self-reported alcohol consumption and hip fractures during a long follow-up period. Another aim was to study whether hospitalizations due to high alcohol consumption, as a more objective indicator of high alcohol consumption, could be associated with hip fractures later in life.

Study IV
The aim was to explore the thoughts of dental patients about assessing the risk of fragility fractures using the FRAX tool in a dental setting, in conjunction with a regular check-up.

4 Materials and methods

4.1 Study Design

This thesis presents both quantitative and qualitative study design. Quantitative in the first three studies, and qualitative in the fourth study. The quantitative studies were observational cohort studies, with three different subgroups of the original cohort, described under 3.2, and different exposures to find an association with fragility fractures, especially hip fractures, during the follow-up time.

The qualitative, cross-sectional, study had an inductive approach to content analysis described by Graneheim and Lundman, with individual semi-structured interviews using an interview guide to freely explore the thoughts of the participants [132].

4.2 Participants

4.2.1 Studies I-III, the REBUS cohort

The first three studies are based on material from the REBUS study, which was a study of the population's health and disabilities, if they needed care or rehabilitation, and how their needs had been met [133]. In 1969-1970 a postal survey was sent to 32,183 inhabitants of the greater Stockholm area with 30 questions about their physical and mental health and their social situation (Table 1). Since impaired health and disabilities are uncommon at a younger age, they had to include more of the younger participants to obtain statistical significance, in a proportion of 3:2:1. Hence, the invitations were sent to 10% of the 485,000 inhabitants of the greater Stockholm urban area who were 18-25 years old (Age group 1), 5% to the inhabitants 26-45 years old (Age group 2), and 3% of the inhabitants 46-65 years old (age group 3). The response rate to the postal questionnaire was 88% – an impressive figure in today's environment. Study II includes those who answered the questions about daily function and physical ability in Age groups 2 and 3, in the paper named Age groups 1 and 2. Study III includes those who answered questions about alcohol consumption in all age groups. A smaller subset were invited to participate in more extensive examinations, including a physical examination and interviews. This population was used for validation of the alcohol index by Theobald et al. 1999, referred to in study III [134]. Half of this small cohort, 1,283 individuals, were invited to participate in a comprehensive dental examination. This included a full mouth intraoral radiographic examination and an extraoral panoramic radiograph. Those who fulfilled the inclusion criteria of having their own teeth and good enough quality radiographs of the area to be assessed were included in study I.

4.2.2 Study IV, Patients from the Public Dental Services in Stockholm

Study IV had, in addition to a different study design, a different study cohort. For the interviews we asked fellow dentists at the Public Dental Services in Stockholm to ask patients 65-75 years old of both sexes if they wanted to participate in an interview about using a fracture risk assessment tool in the dental clinic. To avoid bias, it was important that they were not patients at the clinic where CE works or had been treated by her. When they agreed to participate, their dentist sent their telephone number to CE, who did not have access to their dental journals or other medical data. We invited and interviewed participants until we reached saturation, which resulted in ten interviews.

Table 1. Description of the cohorts

			Total, n	Women	Men
Quantitative studies based on the REBUS cohort.	The original REBUS cohort	Were sent questionnaires	32,183		
		Filled in questionnaires	28,020		
	Study I The dental subcohort	Dental cohort invitations	1,283		
		Dental assessment w full mouth radiographic assessment	1,131		
		Fulfilled inclusion criteria	837	442	395
	Study II	Included only Age groups 2 and 3 (26-65 years) of the REBUS cohort	18,724		
		Answered 5 questions about physical activity and health	16,536	8,300	8,236
	Study III	Part 1: Answered 3 questions about alcohol consumption	27,766	14,364	13,402
		Part 2: Data on hospitalizations due to hip fractures and alcohol related events	27,766	14,364	13,402
Qualitative study, patients from Public Dental Services	Study IV	Invited to participate	11		
		Interviewed	10	7	3

4.3 Data

4.3.1 REBUS – Dental Radiographs

For study I, we went through the dental radiographs of all 1,131 participants that had a full mouth intraoral radiographic assessment, and we found 837 individuals, 442 women and 395 men, who fulfilled the inclusion criteria. The criteria included having teeth in at least one of the premolar regions of the mandible and a radiograph of the area with sufficient quality and enough bone depicted. The exclusion criteria were periapical lesions, severe periodontitis, artefacts, or disturbing structures in the area, e.g., exostoses. By default, we chose the right side, but used the left side in case the right side did not fulfil the requirements. We digitized the radiographs with a dental film digitizer (Medi-2200plus Type MMS-9600TFU2L; Microtek). The radiographic assessments were performed at the Department of Odontological Radiology, Karolinska Institutet in 1970–1971 using Kodak intraoral radiographic film and the parallel technique. This means that the radiographs were taken by specialists with an optimal placement of the film, positioning of the tube, and exposure. At the end of the analogous era of radiology, film for dental radiographs had been developed to enable as short exposure time as possible to minimize radiation exposure. This resulted in a coarse grain of the film. However, in 1970 the race for minimizing radiation exposure had not gone very far, and the film quality was good with a fine grain and suitable for digitalization. Instead, the insufficient quality of some radiographs was due to poor development/fixation of the film, difficulties in placing the film in the right position or anatomical variations. We used the 837 digitized intraoral radiographs from 1970-71 in study I with one visual and one semi-automated method of assessing the trabecular pattern as exposure variables.

4.3.2 REBUS - Postal Surveys

For studies II and III we used the participants' answers to the REBUS questionnaires from 1969-1970 as exposure variables. There were five questions pertaining to physical performance, balance, and daily function with three tick-box alternatives: "often," "sometimes," or "never" (Table 2). We formed a dichotomous index of these five questions for study II. If they had answered "often" to any of the questions, they were considered "at risk," otherwise not.

There were three questions about alcohol consumption, of which we used two in study III (Table 2). The third one "Has the alcohol (consumption) become a problem for you?" was considered to render a false negative response too often, so it was not included. We formed two indices of these questions, the first one, Index 1, was the same as the index validated by Theobald et al. [134]. It included those who had answered "often" to the first question, regardless of their answer to the second question, and answered "sometimes" to the first question and "often" or "sometimes" to the second question. For Index 2 we omitted those who had answered "sometimes" to both questions.

Table 2. Questions from the REBUS survey composing indices in studies II and III

Questions from the REBUS Survey		Participants	Index "At risk", n	
Study II	Do you have difficulties in doing your daily activities because of poor physical health?*	16,536	1,237	
	Do you feel sick and unwell?*			
	Are you troubled by dizziness?*			
	Do you have difficulties climbing stairs?*			
	Do you have difficulties walking indoors?*			
			Index 1**	**Index 2*****
Study III	Do you drink alcohol?	27,766	5,125	2,937
	Do you drink at least half a bottle of hard liquor or at least a two bottles of wine per week?			

*Answering "often" to any of these five questions was considered to be "at risk" (Index =1).
**Answering "often" to the first question, regardless of the answer to the second question, and answering "sometimes" to the first question and "often" or "sometimes" to the second question were "at risk."
*** Answering "often" to at least one of the two questions.

4.3.3 Interviews

For study IV, the data is composed of face-to-face interviews of ten participants who were patients at the Stockholm Public Dental Services. All ten interviews were conducted by Interviewer 1 (CE), with an observer present at seven of them. The interviews were audiotaped and transcribed verbatim.

4.3.4 Data from the Swedish National Board of Health and Welfare

For studies I-III we acquired data concerning dates of death, and of hospital admissions, from registers kept by the Swedish National Board of Health and Welfare. We used data of hospital admissions due to fragility fractures as an outcome measurement for the first study. In studies II and III we concentrated on hip fractures. In study III, we also used data of hospital admissions with main and additional diagnoses related to high alcohol consumption. The registry of in-patient data started in 1969, and by 1972 all hospitals in the Stockholm region had joined, so the data on hospitalization events are incomplete only for a short period of our follow-up time.

We acquired data concerning diagnoses from hospital admissions during the whole time of the study, from 1970 to 2016, which meant that they were classified according to three ICD-systems, ICD-8 (1969-1986, ICD-9 (1987-1996), and ICD-10 (1997-2017). This made the request extensive. For example, the diagnoses for hip fractures requested were those coded 820, 821, 8200, 8201, 8210, 8211 according to ICD8 (if the fracture had occurred 1969-01-01 – 1986-12-31); coded 820, 820A, 820B, 820C, 820D, 820W, 820X, 821, 821A, 821B according to ICD9 (for fractures 1987-01-01 – 1996-12-31); and coded S720*, S721*, S722*, S723*, S72 according to ICD10 (for fractures 1997-01-01 and later). Specifying the diagnoses in three different ICD-code systems is difficult, as they do not always correspond. Sometimes the transition to a new ICD-system results in splitting codes, sometimes in merging. When there was any doubt about which diagnosis codes corresponded, we tried to include instead of omitting, not to miss any events. In study I, we presented results for the different locations of fragility fractures, but in studies II and III we only included hip fractures, as we only had data on hospitalization events, and other fractures may be undetected or handled without hospitalization. We lacked a record of the type of trauma, therefore, it is not certain that all fractures were caused by low-impact trauma.

In studies II and III the digitalized data of the participants, including personal identity numbers and the answers from the postal surveys, were sent to the Swedish National Board of Health and Welfare for the addition of the requested data (sex and dates of birth and death) and returned without any identification numbers. In contrast, in study I, the identity of the participants was kept so we could match the patient data with the radiographs in the participant's files.

4.3.5 Handling of data

We gained access to the complete physical files of the participants in the REBUS dental cohort at the start of the first study. They were moved from the Clinic of Public Dental Services in Stockholm where they had been previously stored, to the Academic Centre for Geriatric Dentistry. They were then sorted and stored in specially ordered, locked, document cupboards, to which only authors CE and PS had access.

All other data, which is in digital form, were stored in compliance with the rules of Karolinska Institutet for handling sensitive data if there is any possible link to the identity of the individual.

4.4 Methods of analysis

4.4.1 Dental radiographs - The visual method

We assessed and classified the trabecular pattern of the mandibular bone according to the index proposed by Lindh et al in 1996 [81], but we used the term “heterogeneous” instead of “alternating sparse and dense” as they renamed the category in 2008 [116] (Fig. 1-3). We mainly assessed the area between and around the roots of the premolars and first molar in the mandible, but we also took into consideration the pattern of the bone around the adjacent teeth. The visual assessment was performed in a darkened room using a 23" monitor (DELL P2314H, 1980x1080; Dell) by observer 1 (CE) after several sessions of training by observer 2 (GJ).

The kappa analysis of intra-observer agreement of 20 radiographs, containing all three categories of trabecular pattern, was very good (kappa = 0.91) when reassessing after 1.5 months. The inter-observer agreement was good (kappa = 0.79). All assessments in the study were performed blinded to the identity, sex, and age of the participants.

Fig. 1–3. Reference radiographs for the assessment of the trabecular pattern.

Fig. 1. “Sparse” trabecular pattern

Fig. 2. “Heterogeneous” trabecular pattern

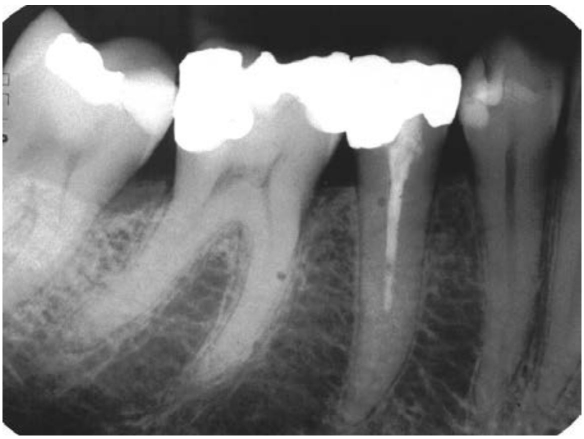


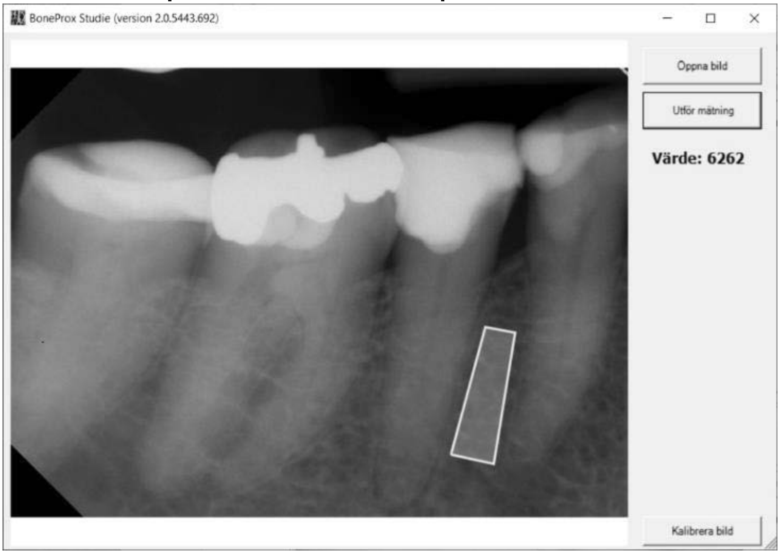
Fig. 3. “Dense” trabecular pattern

4.4.2 Dental radiographs - the semi-automated method

The semi-automated method, JawX by Boneprox, uses digital imaging algorithms to create a binary-filtered image to analyze the trabecular pattern in a region of interest by a probe placed by the observer. The software identifies the 20 largest intertrabecular spaces and computes a value according to the size and intensities of the intertrabecular spaces. The values are unitless and not further specified by Boneprox. Values range between approximately 3000 and 9000, where values ≥6500 are deemed to indicate "risk of osteoporosis" and values of ≥6300–<6500 indicate "risk of osteopenia" according to Boneprox. We used study version 2.0.5443.692 of the JawX software by Boneprox, and the digitized radiographs were imported into the program. Radiographs that were too dark or too light for optimal assessment were calibrated manually using a calibration tool within the software according to the manufacturer's instructions.

The probe was placed in the region of interest (Fig. 4). It was placed between the roots of the premolars, halfway between the crest and the apices of the roots, unless there was not enough room, then it was placed more apically or between the second premolar and the first molar. Observer 1 performed the calculation once in each radiograph and was kept blind to the origin of the radiograph in all assessments. The precision of the software was tested, and the intra-observer coefficient of variation was 5.0% for observer 1 (CE) and 4.3% for observer 2, and the inter-observer variation was 5.1% when using the method twice on 26 radiographs using the Advanced Precision Calculating Tool from the International Society for Clinical Densitometry [135]. Both the visual and the semi-automated method by Boneprox have been used in previous studies. We consider them sufficiently established to use only one observer at the assessments of the REBUS-radiographs, after completed training and inter- and intra-observer testing.

Fig. 4. The assessor's placement of the probe in the region of interest between the premolars in the Boneprox software



4.4.3 Statistical Analyses

Statistical analyses were performed using the software Stata/IC 14.2 for Windows (StataCorp) and the significance level was set to $p<0.05$.

To test the significance of sex differences of the occurrence of variables, we used the following comparative statistics methods in study I: The Chi2 test was used for variables with categorical data, but for low frequencies (≤5) we used the Fisher's exact test. The Wilcoxon rank sum test was used for variables with continuous data that were not normally distributed.

In studies I-III, survival analysis was done using different regression models to find an association between the variables of the studies and the fractures. In study I, we used a Cox proportional hazards model to analyze the proportional hazards ratio (HR). In study II, we started with a Cox proportional hazards model, but it was brought to our attention that the requirement for this model, proportionality over time, was not fulfilled. More suitable was then the Poisson model with time split at failures which led to time bands so small that we could assume proportionality within the time bands. This resulted in incidence rate ratios (IRR) with a 95% confidence interval (CI). When there was an interaction term between sex and index, we included a sex*index interaction term. Testing goodness of fit showed p-values ≥ 0.05, which is satisfactory. We also used a parametric model according to Lambert including competing risk [136]. Even though they were not suitable to use in this study, both the Cox and the Lambert models gave approximately the same results as the Poisson model. In study III, we used a regression model including competing risk according to Fine and Gray to estimate the subdistribution hazard ratio (SHR) [137].

4.4.4 The Qualitative Analysis

We used the method described by Graneheim and Lundman, with an inductive approach to identify the manifest and latent content of the interviews [132]

Four of the five authors of the study participated in the analysis group, and all analyses were performed blinded of the identity of the participants. Relevant meaning units were identified, condensed, and made into codes after discussions within the analysis group that led to a consensus. Similarly, the codes were grouped and regrouped, and classified into subcategories after discussions within the analysis group until a consensus was reached. We named three categories in which all subcategories would fit, and after discussions, we agreed on an overarching theme that would reflect the latent content of the categories. Quotes from the interviews were chosen to represent the manifest content of the interviews in each subcategory. These were translated by a Swedish dentist who has worked over a long period of time in both Sweden and Great Britain, who has exceptional knowledge of both countries' languages and dental care environments.

4.5 Ethical considerations

4.5.1 Study I-III

Studies I-III were approved by the Regional Ethical Review Board in Stockholm (Registration number 2016/902-31/2) and was, as well as the original REBUS study, performed according to the Declaration of Helsinki 1964 and its later amendments.

At the time of the original REBUS study there was no need for formal ethical approval for scientific studies including humans. The first, advisory, ethical committee at Karolinska Institutet was formed in 1966, as a result of the World Medical Association Declaration of Helsinki in 1964. The committee was informed about the study and had no objections. There have been several follow-up studies using the REBUS cohort and the collected material. When planning a follow-up study in 1996, the local ethical review board at Karolinska Institutet required that the participants were informed about the use of their data by advertisements in national newspapers. This was satisfactorily done, and by this, the committee considered that the participants had been informed and had consented to future use of their data unless they had contacted Karolinska Institutet for a retraction of their data from the database.

4.5.2 Study IV

Study IV was approved by the Swedish Ethical Review Authority in November 2021 (2021 J. Ref. no. 2021–05,900-01). The study followed the ethical standards of the national research committee and the Declaration of Helsinki 1964 with its later amendments. Each participant was informed, orally and in writing, about the study, and the right to decline to participate without any negative effects, before giving a written informed consent.

5 Results

5.1 Study 1

We used a visual and a semi-automated method to assess the trabecular pattern of the mandible, methods that could be used in a dental setting. We investigated if the sparseness of the trabecular pattern could predict fragility fractures during a follow-up time of up to 47 years. Digitized intraoral radiographs from 837 male and female participants, 18-65 years old at the start of the study, were assessed.

5.1.1 Main results

In the visual assessment, the trabecular pattern was classified into "sparse," "heterogeneous", or "dense." There were very few participants with dense or sparse trabecular patterns using this method, 2% had sparse, and 5% dense (Table 3). The remaining 93% had a heterogeneous trabecular pattern. The semi-automated method had one cut-off level for "risk for osteoporosis" and one for "risk for osteopenia" There was a significant sex-related difference in results using the semi-automated method but not with the visual method.

Table 3. Results of assessments of trabecular pattern with the visual and the semi-automated method and number of fractures in the cohort.

Variable		Total population n, (%)	Women, n (%)	Men, n (%)	p-value sex difference
Visual method,	Sparse	20 (2)	11 (2)	9(2)	0.842*
Semi-automated method,	Risk for osteoporosis >6500	154 (18)	101 (23)	53 (13)	<0.001*
	Risk for osteopenia >6300	207 (25)	130 (29)	77 (19)	0.001*
First fracture	Hip fracture	75 (9)	52 (12)	23 (6)	0.001*
	Any fragility fracture	132 (16)	90 (20)	42 (11)	<0.001*

*= Chi2-test

When combining the data of sustained fractures and the assessments of the trabecular pattern, few fractures occurred in those with a sparse trabecular pattern (Table 4).

Table 4. Sustained hip fracture for individuals with a "sparse" or "not sparse" trabecular pattern using both methods.

Sex	Method of Assessment		Hip Fractures (n)	
			yes	no
Women n = 442	Visual	Sparse, n = 11	3	8
		Not sparse, n = 431	49	382
	Semi-automated	>6500, n = 101	6	95
		<6500, n = 341	46	295
Men n = 395	Visual	Sparse, n = 9	0	9
		Not sparse, n = 386	23	363
	Semi-automated	>6500, n = 53	2	51
		<6500, n = 342	21	321

A Cox proportional hazards analysis of the risk of sustaining a fracture gave no significant results for any method (Table 5).

Table 5. Cox proportional hazards model for risk of sustaining fractures

Hazard ratio (95% confidence interval)					
Event	Method of assessment	Women	Women, age adjusted	Men	Men, age adjusted
Any fragility fracture	Visual	1.62 (0.60–4.43)	1.05 (0.38–2.86)	x	x
	Semi-automated	0.58 (0.33–1.01)	0.86 (0.49–1.51)	1.07 (0.45–2.54)	1.37 (0.57–3.27)
Hip	Visual	2.04 (0.64–6.58)	1.40 (0.44–4.51)	x	x
	Semi-automated	0.37 (0.16–0.87)	0.56 (0.24–1.33)	0.60 (0.14–2.58)	0.88 (0.21–3.80)

X = Not enough individuals with a sparse trabecular pattern to perform the analysis.

5.1.2 Conclusion

The visual method is not suitable for fracture predictive assessment, at least not for all ages and sexes. As for the semi-automated method, there is still very limited evidence of using it to predict fractures.

5.2 Study II

We investigated if five simple questions about physical health and mobility, originating from the REBUS study in 1969, could predict hip fractures during a follow-up of 20-35 years.

5.2.1 Main Results

We omitted the youngest age group from the study, as we considered them too young to have any mobility problems. That resulted in two age groups, 26-45 years old and 46-65 years old at study start, which we followed for 35 and 20 years respectively, until they were about 60-85 years old. The five questions were each an exposure variable if they had answered "often," but we also composed an index which was positive if they had answered "often" to any of the questions. A Poisson regression analysis of hip fractures during the follow-up time was conducted, adjusted for sex and time-varying age, presented as inter rate ratio (IRR) in Table 6. If there was a significant sex*item (question or index) interaction term, men and women were analyzed separately. This was applied for Question 4 in Age group 1 and for the Index in Age group 2).

Table 6. Poisson regression of hip fractures, adjusted for sex and time-varying age, with risk according to the five questions.

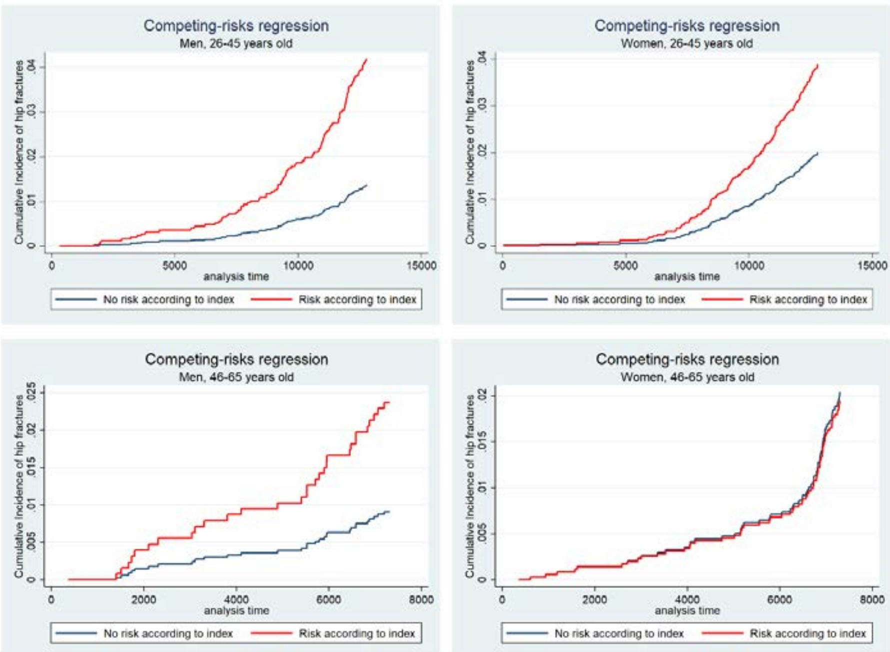
	Age group 1 26 - 45 years at baseline			Age group 2 46 - 65 years at baseline		
Questions	**IRR**	**95% CI**	**p**	**IRR**	**95% CI**	**p**
Q1. Do you have difficulties in doing your daily activities because of poor physical health?	1.55	1.17 - 2.06	0.002	1.63	1.09 - 2.43	0.017
Q2. Do you feel sick and unwell?	1.39	1.09 - 1.78	0.008	1.64	1.07 - 2.51	0.023
Q3. Are you troubled by dizziness?	1.37	1.04 - 1.81	0.025	1.43	0.95 - 2.14	0.088
Q4. Do you have difficulties climbing stairs?	3.78 (Men)	2.36 – 6.07	<0.001	1.48	0.98 - 2.24	0.062
	1.50 (Women)	1.00 - 2.25	0.049			
Q5. Do you have difficulties walking indoors?	2.21	1.42 – 3.42	<0.001	1.16	0.62 - 2.16	0.65
Index including all questions	2.69	1.85 - 3.90	<0.001	3.30 (Men)	1.51 – 7.23	0.003
				1.10 (Women)	0.59 - 2.05	0.77

Q1-Q5 risk (=1) is having answered "often" or "sometimes" to questions 1-5.
Index risk (=1) is having answered "often" to any of questions 1-5.
When there was a significant gender*item (question or index) interaction term, men and women were analyzed separately (applied for Q4 in Age group 1 and Index in Age group 2).

Analyzing the index's fracture predictive ability, we found significantly elevated IRR for both men and women in the younger age group, but only for the men in the older age group.

During the follow-up time, 16-28% of the study population died. We therefore used a competing risk model according to Lambert and calculated the cumulative incidence function of hip fractures [136]. Fig. 5 clearly shows how risk according to the index affects men in both age groups but only women in the younger age group.

Fig. 5. Competing risks regression according to Lambert et al. of hip fractures for men and women at risk according to index indicating poor physical health and mobility.



5.2.2 Conclusion

Our conclusion in this study is that the questions about physical health can have a predictive value for hip fractures for both men and women during a long follow-up time. However, for women, other factors dominate for the women in Age group 2 and wash out the predictive effect of the questions.

5.3 Study III

We studied if self-reported alcohol consumption, originating from the questionnaire in the REBUS study from 1969, could predict hip fractures later in life. We also studied if hospitalizations with diagnoses indicating high alcohol consumption during the 47-year follow-up could predict hip fractures.

5.3.1 Main results

Two indices indicating high alcohol consumption were formed according to the responses to the two questions about alcohol in the REBUS survey. The odds ratio (OR) for high alcohol consumption according to the indices for men versus women, was between 4 and 8.5. The third index was formed from hospitalization events during the follow-up time, with a diagnosis code indicating a high alcohol consumption. The OR for this index was 2.0-5.1 for men vs. women. We found that the two indices derived from the REBUS questionnaire lacked predictive value for hip fractures when analyzing the data with a regression model according to Fine & Gray [137]. We found that with the third index, based on hospitalization events, there was a significantly elevated subhazard ratio (SHR) for hip fractures for both men and women, but only for the youngest age group who were 18-25 at the start of the study and followed until they were 65-72 years old. (Table 7)

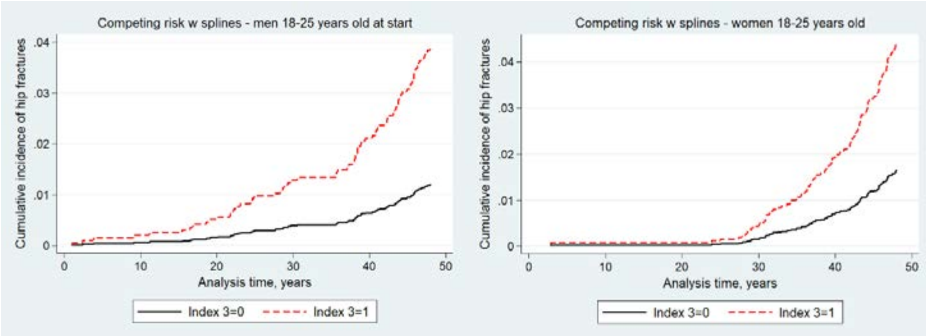
Table 7. Competing-risks regression with splines showing subhazard ratio (SHR) with a 95% confidence interval (95% CI) for hip fracture if hospitalized with a diagnosis related to high alcohol consumption before fracture.

	Age group 1, (age 18-25 at the start)			Age group 2, (age 26-45 at the start)			Age group 3, (age 46-65 at the start)		
	SHR	95% CI	p	SHR	95% CI	p	SHR	95% CI	p
Men	3.29	1.80–5.98	0.000	1.31	0.86–1.99	0.213	0.74*	0.32-1.70	0.477
Women	2.73	1.37-5.42	0.004	2.00*	1.24-3.20	0.004	0.86*	0.30-2.42	0.771

*= Assumption of proportionality over time violated

The cumulative incidence function (CIF) of hip fractures using splines for women and men in the youngest age group is shown in Fig. 6.

Fig. 6: Cumulative incidence function (CIF) of hip fractures.
CIF for men and women in Age group 1, after using the stcrreg command in Stata for competing-risks regression according to Fine & Gray using splines, with (=1) or without (=0) an alcohol-related diagnosis before a hip fracture (Index 3).



Index 3 = alcohol-related diagnosis at hospitalization that occurred before the hip fracture

5.3.2 Conclusion

The indices formed by questions about alcohol consumption in the questionnaires had no hip fracture predictive value. The third index, based on hospitalizations related to high alcohol consumption before a hip fracture, had a fracture predictive value, but only for the youngest age group, followed until the age of 65-72 years old. Our interpretation is that the fracture predictive value applies only to hip fractures that occur relatively early in life.

5.4 Study IV

We interviewed patients from the Stockholm Public Dental Services and made a content analysis with an inductive approach of their thoughts about doing FRAX in a dental setting. During the interview we also made a FRAX assessment of their ten-year risk of sustaining a fragility fracture.

5.4.1 Main Results

When analyzing the interviews, we found three categories with up to nine subcategories where their thoughts would fit (Table 8).

Table 8. Main categories and subcategories

Category	Subcategory
Experience and knowledge of osteoporosis and fragility fractures	
	The participants' own experiences
	Knowing others with experience of osteoporosis and fragility fractures
	Knowledge about osteoporosis and fragility fractures
Thoughts about the FRAX assessment	
	How the FRAX assessment was experienced
	Thoughts about the assessment result
	Perception of risk
	Actions after the result
Risk assessment in a dental context	
	Doing the FRAX assessment in the dental setting
	FRAX assessment as a screening method
	A preventive perspective on FRAX assessment
	Paying for the assessment
	Handling of the FRAX assessment result
	Structural problems
	The dental staff's engagement and competence
	Other contacts with healthcare
	Other health assessments in a dental setting

The overarching theme was that even though they were positive about doing FRAX in the dental clinic, they were doubtful if the dental staff would have the time, interest, or knowledge to do it.

The participants had never heard of FRAX and had little knowledge of osteoporosis and fragility fractures, *"My mother fell when she was 80 and broke her hip, but I don't think that was because of osteoporosis"* (female).

They found the FRAX assessment easy to do, and liked the fact that it was completely painless, which is not always the case in the dental clinic. They said that if they were found to have a low risk, they would be happy, but also glad to find out if they had a high risk, so they could do something about it. Some knew that physical activity could prevent osteoporosis and said they would probably do more physical training in that case.

Only one participant was negative towards doing FRAX in the dental setting. Paying for a FRAX assessment at the dental clinic was accepted by most, as long as the price did not exceed a visit to Primary Care, about EUR 25. Some expected the dentist to have collaboration with primary care so the patients would not be left alone with the results *"I would expect some kind of collaboration between dental care and primary care, so I would know how to go further. Maybe they could send an immediate referral or something like that… Don't leave me with the result, help me get on with it!"* (female). There were those who said they would only do the FRAX assessment if they trusted the dentist. Some were not sure there would be time at the dental appointment for this, or that the dental staff had enough knowledge to do the assessment or were even interested in doing it: *"Do they have the education to follow up and do this?… Do they have the interest? Well, I'm a bit doubtful"* (female). There were some participants who already had frequent contacts with the health care, and they were less positive towards health assessments in the dental care since they felt already taken care of elsewhere.

5.4.2 Conclusion

Despite little knowledge or experience of osteoporosis or fragility fractures, most of the participants were positive towards doing a FRAX assessment in a dental setting, at a similar cost as in the primary care. They were, however, doubtful if the dentists would have an interest, or the time or knowledge to do it. If found to have high risk, they expected collaboration between the dental staff and the primary care for further investigation, advice or treatment if needed.

6 Discussion

In the quantitative studies we found no association of fragility fractures to a sparse trabecular pattern using either of the two methods to assess the mandible in study I and a limited association of hip fractures to questions about physical health in study II. Of those “at risk” in study II, the men in both age groups had an increased risk of sustaining a hip fracture, but this was only true for the younger women, who were 26-45 years old at the study start. In study III we found no association of hip fractures to questions about alcohol consumption, but a limited association to previous hospitalization events related to high alcohol consumption. An elevated SHR for hip fractures was found only for the youngest men and women in this study who were 18-25 years old at study start, and followed until they were 65-72 years old. In the qualitative study IV, the interviewed participants were generally positive towards doing a FRAX assessment of the ten-year fracture risk, but revealed concerns that need to be considered before introducing FRAX in a dental setting.

In the first part of this section, different aspects of the results of all four studies will be discussed under five topics that can have influenced the results and our interpretation of them. They are sex, age and cohort size, bone mineral density, follow-up time and falls.

6.1 Sex

Using the visual method in study I there was no significant sex-difference of sparse trabeculation. In previous studies, women have been found to have a sparse trabecular pattern more often than men [115, 130]. Since only 2% of the cohort had a sparse trabecular pattern regardless of sex, it is possible that our cohort was too small and too young to show any significant sex-difference. Using the semi-automated method, we found that almost twice as many women (23%) than men (13%) were above the cut-off 6500, indicating “risk of osteoporosis.” The same applied to the cut-off 6300, “risk of osteopenia,” above which level 29% of the women were found, and 19% of the men. These results are similar to those of the only previous study with both sexes included [131].

In study II, we analyzed the index indicating poor physical health or mobility, and its fracture predictive ability. We found significantly elevated IRR for both men and women in the younger age group (26-45 years old) but only for the men in the older age group (46-65 years old). Our interpretation of this is that for women in the older age group, who we followed until an advanced age, other factors dominate, and wash out the predictive effect of the questions.

High alcohol consumption was much more common in men, regardless of which method we used in study III. It was about 3-5 times more frequent according to the REBUS questions and in-patient events were 2.4 times more common in men than in women. At the study start in 1969, it was more common for Swedish men to drink alcoholic beverages than for women, and men drank larger volumes. It was not socially accepted for women to drink large amounts of alcohol, and they may not have wanted to admit high alcohol consumption either to themselves or in the REBUS questionnaire. It is therefore not surprising that the men's answers more often indicated high alcohol consumption than the women's answers. Since then, a sex convergence of alcohol consumption, with women drinking more, and a switch from hard liquor to wine, has taken place in Sweden. Those who were young in the 1970's when wine became more popular were probably those who adopted these new habits to a higher degree. This could explain why the sex difference in occurrence of in-patient events due to high alcohol consumption during the whole follow-up time until 2017 is smaller than for the questions posed in 1969.

6.2 Age and cohort size

As for age-related findings in our studies, they were sometimes not as expected. In study I, the proportion of participants with a sparse trabecular pattern did not increase with age, not even in women. This contradicts the findings in a previous study where 1,003 women 38-54 years old were followed for 24 years with three assessments where the proportion of individuals with a sparse trabecular pattern in panoramic radiographs increased with time [138]. Their cohort also displayed a larger proportion of participants with a sparse trabecular pattern, although they followed their participants later in life. Again, our results may be due to few participants with a sparse trabecular pattern which made a statistically significant increase hard to detect. With the semi-automated method, where about 25% of the participants had a risk of osteoporosis or osteopenia, we found a smaller proportion to be "at risk" in the oldest age group than in those who were younger, contrary to expectations. However, although significant, this difference was small, 24% for the older age group and 26% for the younger age group. A tentative explanation could be that the peak bone mass, i.e., when the skeleton has the highest BMD, occurs around 25-30 years of age, and the youngest participants had not reached this age yet. However, considering the limited previous results in predicting BMD and fractures, we find it justified to doubt the function of this method.

In this same study, we found no significant predictive value of fracture risk of the trabecular pattern of the mandibular bone for all participants as a group, only divided by sex. This could have been because the participants were so young at the study start and it would take long before they had a hip fracture. Also, during the follow-up time, a large portion of them never reached the age where hip fractures are most common. So, we tried omitting participants who were <45 years old at the study start, but there were still no significant results with any of the two methods. However, this may have been because when restricting the studied cohort to only the oldest age group, there were too few participants with a sparse trabecular pattern to make any statistical significance possible. As for the semi-automated method, we could not see any development towards higher risk for osteoporosis or osteopenia with age.

In studies II and III we had the possibility to include the whole REBUS cohort, which meant that the statistical power was better. In study II, where we studied the questions about physical health, we omitted age group I, as we thought they were too young to have any physical disabilities, resulting in a remaining cohort of 16,536 participants. We also restricted the follow-up time until they reached an age of about 60-85 years. We then found that men who were 26-65 old at the start of the study had an increased risk of sustaining hip fractures during the follow-up time. In women, it was only the younger women, 26-45 years at the start, who had a significantly higher risk. Our interpretation is that other factors, e.g., BMD, dominate in middle aged and older women, washing out the predictive effect of the questions.

In study III, where we studied the predictive value of high alcohol consumption according to the REBUS questionnaire and in-patient events of high alcohol consumption, we included all age groups which resulted in 27,766 participants. The REBUS questions did not present any significant results in any age group. The more objectively measured high alcohol consumption, i.e.., in-patient events related to high alcohol consumption prior to a hip fracture, did have a fracture predictive value, but only for the youngest age group, who were followed up to 72 years. We found that the variable only had a risk predictive value for hip fractures that happen early in life. Those who had an in-patient event of high alcohol consumption were probably those who were the heaviest drinkers and who had their hip fracture at a young age. The older age groups reached a higher age during the follow-up period, but those with a high level of alcohol consumption may have had a shorter life than those without one, leading to that they never reached the age where hip fractures are most common. Theoretically, this could be the reason we did not see any fracture prediction in the older age groups but using the competing risk method according to Fine &Gray, should have compensated for this [137].

6.3 Bone mineral density

In study I, we found no association of a sparse trabecular pattern to fractures, and that a dense trabecular pattern was not significantly associated with absence of fracture. There are other factors that influence the trabecular pattern than age and sex, and these have not been considered in our study. Loading is known to stimulate the bone to become more mineralized, and thereby stronger. In the mandibular bone, loading could be chewing or bruxism. In the REBUS material there are no records of occlusal contacts in the region of interest. We could have checked the radiographs if there were corresponding teeth in the upper jaw, but that is not necessarily a sign of occlusal contacts. Whether the participants wore dentures or not was also not noted in our study, mainly because the loading effect of the individual denture on the occluding teeth could not be estimated. Records of bruxism are also lacking.

The questions in study II that we chose from the REBUS questionnaires, were those we thought would reflect the participants physical activity, which would have influenced the BMD (as well as balance and muscular force) and thereby a higher fracture risk. It is interesting that we see a higher risk in all men, who were 26-65 years old, but only for the younger women 26-45 years old at the study start. Since men sustain much fewer hip fractures, it is possible that low physical activity with the following low BMD has more impact on the fracture incidence than in women, whose BMD in any case will fall considerably after menopause.

Alcohol has both direct and indirect effects on bone tissue. It reduces bone formation and increases bone resorption, leading to secondary osteoporosis with decreased BMD and an increased fracture risk [139, 140]. However, as in our study III, high alcohol consumption is not always found to be fracture predictive [38]. This may be because it is hard to establish the true amount of alcohol consumption if relying on subjective answers.

6.4 Follow-up time

In both study I and study III, we used the whole study-time as follow-up time, 47 years. In study II we restricted the follow-up time to end earlier, so the participants were followed until they were about 60-85 years old. If we had restricted the follow-up time in study I, this would have meant fewer fractures, decreasing the possibility of significant results. In study II we found that the length of the follow-up time mattered and in study III we found that at what time in life the follow-up time took place mattered. We interpreted this as an argument for our variables being associated with certain kinds of hip fractures, i.e., the fractures that happen rather early in life. Later in life, the hip fracture risk is high for everyone that reaches a high age.

6.5 Falls

6.5.1 Risk of falling

The most important risk factors behind fragility fractures are sex, age, previous fractures, and previous falls. Falls often occur at an advanced age, but can also be a consequence of medications, frailty, and disease. In study II we tried to find an index composed of the questions about physical health and mobility in the REBUS questionnaires to reflect early signs of falls risk. Poor physical health could lead to less exercise, which in turn could affect both balance and muscular strength. Poor physical health could also lead to polypharmacy and frailty, which could both lead to a higher risk of falling. It is reasonable to assume that high alcohol consumption leads to higher risk of falling, directly as an effect of the alcohol, or indirectly as an effect of less physical activity.

6.5.2 High or low impact trauma

There was an incomplete record of type of trauma in the data from NPR, so it is not sure that all fractures were caused by low-impact trauma. We checked the hip fractures that occurred during 1997-2016 in the dental cohort, where we had some data of trauma type preceding the fracture. The cause was found to be low-energy trauma in 65%, high-energy trauma in 6%, and unspecified in 29% of the events. This is in line with previous studies where 81% of the hip fractures were found to be caused by low-energy trauma in a cohort of adults ≥20 years [141]. However, even though the definition of a fragility fracture is a fracture due to low-energy trauma, it is recommended not to make any distinction of trauma type when studying these fractures, since excluding high impact trauma may underestimate fragility fractures [142-145]. In the clinic, the advice is to include all non-vertebral traumas during post-fracture screening for osteoporosis [146].

6.6 Implementation

There are some obstacles in implementing the studied methods in this thesis. If visual assessments of radiographs of the jawbone were to be introduced in a dental setting, it would require the dental staff to learn and train using this method. Although we in our study had moderate interrater reliability, 0.79 according to Cohen's kappa, this still means that only 63% of the data are reliable [147]. Previous studies showed similar or lower interrater reliability [116, 119]. Pham et al also found that training was necessary to improve reproducibility. Maybe, as proposed for several other radiographic assessment methods, machine learning could be a way to solve this. The semi-automated method was a first step towards mitigating the difference in results when involving different assessors. However, even though Boneprox claim that they have developed a machine learning tool in assessing radiographs since our study version of the software, their product is not available on the market anymore.

Questions about mobility would probably be relatively easy to include in the health declaration that the dentist or hygienist fills in together with the patient at the check-up. The same would be true for the questions about alcohol consumption, but this could be perceived as a more sensitive issue. Including questions about alcohol consumption in a health declaration at the dentist is not common in Sweden. However, since high alcohol consumption is associated with oral cancer and coagulation disorder this could be something that the dental staff should pay attention to. The question remains though, if included in a health declaration, would the answers always be truthful?

The fourth study had a different approach to studying fracture risk assessment in a dental setting than the previous three studies. This qualitative study explored the participant's thoughts about doing FRAX assessment in connection with a regular dental check-up, something that needs to be investigated before it is possible to implement. Of course, the participating profession's thoughts also need to be explored, but this was a first step. We found that the participants were generally positive towards doing the FRAX assessment in a dental setting, but they doubted if the dentists would have an interest, or the time or knowledge to do it. These findings are in line with the results Gullberg et al. found in their study of attitudes regarding assessment of osteoporosis risk in a dental setting [148]. They interviewed both dentists, patients and medical specialists and their proposed assessment method was based on dental radiographs. Their patients were worried that the dentists did not have enough knowledge or time to do the assessment, thoughts that also the dentists had. General practicing dentists' medical knowledge is often not enough to estimate other risk factors' impact on the FRAX result. This was found in a study of Brazilian dentists by Ferreira et al that concluded that the dentists' knowledge of osteoporosis was insufficient according to a survey with basic questions about osteoporosis [149]. To evaluate risk factors for secondary osteoporosis, which is one of the questions in the FRAX assessment, even more extensive knowledge is needed. There are many conditions that could cause secondary osteoporosis. However, although included, this is not emphasized in the current curriculum of the dental education in Sweden. The situation could be different in countries where the dental education is a part of the medical education. If the dental hygienists were to do the FRAX assessment this would be a greater obstacle, as their curriculum is even less comprehensive. The suspected shortage of time that the participants expressed in our study was also found in Gullberg's study, where both patients and dentists worried that there would not be enough time to include the assessment in a regular check-up. The participants in our study also expressed a wish for collaboration between the dental clinic and the primary care to handle the result of the assessment if they were found to have an elevated fracture risk. This concern was shared by the participants in the study by Gullberg et al. A structure for handling the results must be developed and carefully planned before a more extensive introduction of the FRAX assessment in the dental setting. Another obstacle that would have to be addressed is the availability of dental staff, and dentist appointments. In Sweden, there is a shortage of dental staff, especially dentists, in rural areas, and until this situation is solved it would probably not be possible to implement FRAX assessment as a general screening method. The participants in our study expressed a willingness to pay for a fracture risk assessment if the sum was not greater than if performed in the primary care (about EUR 25). This was also a finding in a quantitative study where 129 of 144 post-menopausal women were willing to pay an average of EUR 35 in 2019 [150]. In the qualitative Gullberg study, the patients expected a lower additional cost to the fee for the check-up, about EUR 10-12, comparable to a mammography at the time of the study.

6.7 Strengths and limitations

6.7.1 Strengths

The main strength in studies I – III is the unique REBUS cohort with its stratified random sample of the population, the questionnaires with a very high response rate, 88%, and the possibility of a very long follow-up time, up to 47 years. In studies II and III we used a large part of the cohort, which resulted in 16,536-

27,766 participants. The Swedish system with civic registration numbers (personal identification numbers) makes it possible to acquire registered data of both death dates and in-patient data from the Swedish National Board of Health and Welfare. Focusing on hip fractures, we minimized the risk of missing data, as these fractures always require hospitalization. Another strength is that we used fractures, instead of BMD, as outcome measure, which is not always the case in other studies. The dental cohort in study I had intraoral radiographs taken at the Department of Oral Radiology at Karolinska Institutet which ensured good quality. In study II, our results were the same regardless of which of the three different statistical methods we used, which enhances the credibility. In study III, one of the indexes we used was validated in a previous study. Objective data of high alcohol consumption is hard to find, but in this study, we also used an objective variable, in-patient events related to high alcohol consumption during the follow-up time and before the fracture, and its association with fragility fractures. Strengths in the fourth, qualitative study, were that the participants were regular patients at the Stockholm Public Dental Services and that the interviewer was a dentist who is familiar with the dental setting and has a long experience in communicating with patients. Having two professions, both medical doctors and dentists, participating in the analysis process was also a strength.

6.7.2 Limitations

A limitation that has not been presented elsewhere in this thesis, is that the data on fractures were not complete. Vertebral fractures are not always detected, so they are often missing, and due to an error in our requisition of data, not all pelvis and vertebral fractures were registered. However, this only applies to study I, as we thereafter only included hip fractures. Another limitation is that in study IV we chose to only interview and assess participants with Swedish ethnicity, as FRAX is developed on a Swedish cohort. This may have limited the results of the interviews.

6.8 Methodological considerations

6.8.1 Study I-III

Internal validity: Systematic error could have been caused by using three different ICD-systems present during the long follow-up time because the inclusion of diagnoses in the ICD-codes sometimes changes in a new version. The high risk of confounding drop-out rates was in studies II and III adjusted by using statistical analysis with competing risk, which contributed to internal validity.

External validity: In studies II and III, the systematic error due to inclusion bias should have been minimized, as the REBUS cohort consisted of a randomized sample of the inhabitants of the greater Stockholm area, only selected by the proportions of participants by age, and the response rate was as high as 88%. The **generalizability** should therefore be high. In study I, a random sample of this population were invited to participate in a dental assessment at a dental school in the center of Stockholm. There is a risk of selection bias if all participants did not agree, or have the possibility, to participate in the assessment at this location. If the ROI was edentulous, it could not be assessed, and this could also have led to an inclusion bias of the participants. Since we found only 2% of sparse trabecular pattern with visual assessment in study I, the cohort size may have been too small for significant results. This could have contributed to the failure of the external validity.

The **reliability** was maintained in all three studies by adjusting the statistical methods after the conditions in the studies.

The observers not knowing any facts about the participants when assessing the radiographs contributed to the **objectivity** in study I.

6.8.2 Study IV

In the fourth, qualitative, study we explored the thoughts of patients using content analysis with an inductive, latent approach. The participants were fewer and selected by fellow dentists, probably by their willingness to communicate and it is possible that they do not represent all patients, but this is not the aim in this kind of study. To achieve **trustworthiness** in this study we considered the following:

The invited participants were regular patients at the Stockholm Public Dental Services which contributed to **credibility**. The researchers who participated in the analysis process were of different professions, which enabled investigator triangulation and contributed to the credibility. The interviewer's background as a dentist could have influenced the responses and the interpretation and analysis of the interviews, which may have been a limitation. On the other hand, being familiar with the dental setting could have facilitated the research and added credibility.

To increase the **dependability** and **confirmability** of study IV, all steps of the analysis process were carefully documented and discussed by the researchers, and a comprehensive description of the analysis process was included in the paper. In seven of the ten interviews there was an observer present who took field notes and these were discussed after the interview.

Checking the data for saturation in the last interviews and stopping when saturation seemed to be reached was a way to ensure **transferability**.

7 Conclusions

We found no fracture predictive value in the two methods of assessing the trabecular pattern of the mandibular bone. Few participants with a sparse trabecular pattern were found, and no significant results were found. The semi-automated method did not perform as expected, and there is still poor evidence of its validity.

The questions of physical activity and mobility could predict an increase in hip fractures in men 26-65 years old at the study start and followed for 20-35 years until they were 61-85 years old, but for women only for those 26-45 years old and followed for 35 years, until 61-80 years old. Our interpretation of this is that for women in the older age group, other factors dominate, and wash out the predictive effect of the questions.

The questions about alcohol had no fracture predictive value, while a hospitalization event with a diagnosis indicating high alcohol consumption resulted in a higher SHR for both men and women in the youngest age group who were age 18-25 at the start of the study and 53-60 years old at the end of the study. This was interpreted as an indication that an objective measure of high alcohol consumption can predict hip fractures at an early age for both men and women.

In the qualitative study the interviewed participants were mostly positive about doing a FRAX assessment of the ten-year fracture risk, but they expressed concerns that need to be considered before introducing FRAX in a dental setting.

Dental radiographs are the most common radiographs to be exposed. They are relatively inexpensive and accessible. This is a huge resource for research and potentially a resource for screening. Therefore, at the start of the studies in this thesis, we hoped that the intraoral radiographs regularly taken at the dentist could be of use to also identify individuals with a high risk of sustaining fragility fractures. Previous studies indicated that assessment of the trabecular pattern in intraoral radiographs could be a possible way. Our results in the first study showed that this is not an easy task, and it may not be possible in all age groups or in men. Our hopes for the semi-automated method were not fulfilled, and the service is not available anymore. However, if there is a way to analyze features in oral radiographs that can predict fragility fractures, be it panoramic or intraoral radiographs, our hopes are set on the new era of machine learning.

Both questions about physical health and mobility and in-patient data of hospitalizations can predict hip fractures sustained relatively early in life. However, the questions in our study had an outdated formulation and need to be modernized if used for this purpose. Introducing questions about alcohol in the health declaration at the dentist could be motivated for other reasons than fracture prediction, maybe using already existing and validated instruments such as Audit (Alcohol Use Disorders Identification Test, originally developed by WHO). The use of in-patient data indicating high alcohol consumption for fracture prediction may be more useful for primary care.

FRAX, the most validated and used method for fracture prediction in post-menopausal women or older men in primary care, could also be used in a dental setting. Our qualitative study was the first step to investigate the patients' thoughts about this, and it needs to be followed by more studies of what the different professions in the dental practice and in primary care think about this.

8 Points of perspective

This thesis discusses the possibilities of identifying individuals with a high risk of sustaining fragility fractures in a dental setting. Of course, many new ideas were born during this journey.

When studying the mandibular trabecular pattern, the idea to test the fracture predictive ability of other features of the mandible, naturally occurred. The REBUS dental cohort also contains panoramic radiographs, which would make such a study possible. If we wanted to focus on older participants, the Stockholm Public Dental Services has a large databank of digital radiographs, including panoramic, after the introduction of digital radiography in the clinics at the beginning of the century, thereby enabling a long follow-up time.

Studies of other methods to assess the physical function of patients and their fracture predictive value could be done in a dental setting. However, this would require several years of follow-up time after the assessment to obtain fracture data. Simple tests such as OLST would not need the time of a dentist, which would make these methods more feasible and less costly. Qualitative studies of such methods would also be appropriate before considering use in a dental setting.

Since previous studies have shown different results for the fracture predictive value of high alcohol consumption, a validated method, such as Audit, would be interesting to use in a study of its association with fragility fractures. Such a study could be made on a cohort that had already answered these questions. It could also be used in a dental setting with a new cohort but would then need several years of follow-up.

The FRAX-study naturally inspired further research. First, other qualitative studies investigating the thoughts of the dental staff that would participate in the assessment, and then the thoughts of the staff in the primary care who would be responsible for further investigation of patients found to have a high ten-year risk of fragility fractures. Second, investigating the dentists' knowledge and capability of using the FRAX tool, with a combined qualitative and quantitative approach, possibly a mixed-methods study, could also be in place.

One of the main benefits of assessing fracture risk in a dental setting is more knowledge and communication about osteoporosis and fragility fractures. Since many patients avoid medication for osteoporosis because of the risk for medication-related osteonecrosis of the jaw, MRONJ, many go untreated. If dentists, physicians, and patients were more informed about how small the risk for MRONJ is when treating osteoporosis compared with how large the fracture preventive effect is, compliance would increase, and fractures would diminish. Knowledge of how oral health can be maintained despite medication for osteoporosis is also important to spread among dentists, physicians, and patients to optimize compliance. Assessing fracture risk in a dental setting would require more medical knowledge among dentists about fragility fractures and osteoporosis. Hopefully, they would also acquire more knowledge about how to prevent MRONJ and diminish their often unfounded skepticism towards the treatment of patients on medication against osteoporosis. Ideally, they would also share this with both the primary care and the patients, which would raise compliance, diminish fractures and lead to added healthy years to their lives and diminished medical expenditures for society.

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