OSTEOPOROSIS, BALANCE AND NUTRITION
IN ELDERLY WOMEN IN PRIMARY CARE

Hans Lundin

Stockholm 2016
OSTEOPOROSIS, BALANCE AND NUTRITION IN ELDERLY WOMEN IN PRIMARY HEALTH CARE

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Hans Lundin

Principal Supervisor:
Dr. Helena Salminen
Karolinska Institutet
Department of Neurobiology, Care sciences and Society
Division of Family medicine

Co-supervisor(s):
Dr. Maria Sääf
Karolinska Institutet
Department of Surgery and Molecular Medicine
Division of Growth and Metabolism

Opponent:
Prof. Kristina Åkesson
Lund University
Department of Clinical Sciences
Clinical and Molecular Osteoporosis Research Unit

Examination Board:
Prof. Per Kristiansson
Uppsala University
Department of Public Health and Caring Sciences
Division of Family Medicine and Preventive Medicine

Prof. Bo Abrahamsen
University of Southern Denmark
Institute of Clinical Research
Research Centre for Ageing and Osteoporosis

Prof. Lars Borgquist
Linköping University
Department of Medical and Health Sciences
Division of General practice
ABSTRACT

Objective: Some people get skeletal fractures as a result of a trauma which wouldn’t cause a fracture in a healthy individual. These fractures are sometimes referred to as “frailty fractures”. Common sites for fragility fractures are the spine, hip, upper arm, shoulder, distal forearm and pelvis. Great effort has been put into the construction of different fracture risk assessment tools. The clinical importance of a correct estimate of fracture risk comes from the effective treatments which are available to lower fracture risk. The aim of study I was to investigate whether participants classified by MNA at risk of malnutrition or malnourished had a higher mortality risk than participants with normal MNA. The aims of study II were to investigate whether one-leg standing time (OLST) could predict hip fracture risk and to compare the predictive accuracy of OLST to that of the fracture-risk assessment tool FRAX. The aims of study III were to investigate whether there was an association between high serum concentration of IGFBP-1 and high fracture risk, and to evaluate whether such an association could be mediated by either BMI or IGF-I. The aims of study IV were to investigate whether addition of either maximum gait speed or OLST could improve the predictive accuracy of FRAX, as measured by AUC, Harrell’s c and NRI.

Methods: Study population: All four studies were based on data from the same study population. Inclusion criteria were living in the Bagarmossen area south of Stockholm, Sweden, and being a woman born between 1920 and 1930. These criteria were met by 937 women in 1999. Two rounds of invitations were sent after which 351 women were included in the study. Bone mineral density measurements: Bone mineral density measurements were conducted in 1999-2001 using Hologic QDR 4500 DXA equipment (Hologic, Waltham, MD, USA). Calibration was performed daily with a phantom. Biochemical analyses: Serum IGFBP-1 was analyzed with radioimmunoassay (RIA). Total IGF-I was analyzed in serum by RIA after separation of IGF-I from IGF-binding proteins by acid ethanol extraction and cryoprecipitation. Functional tests: OLST was measured twice on each leg with eyes open. The longest time out of the four was used for analysis. Gait speed was measured at a walk as fast as possible 15 meters down a corridor with a flat floor, turn at a mark and then walk back again to the starting point. The average speed was calculated. Vitamin D was analyzed with Nichols Advantage® 25-Hydroxyvitamin D assay (Nichols Institute Diagnostics), a chemoluminescence analysis.

Results: In study I the age-adjusted HR for mortality was 2.36 (1.25–4.46) for the “risk of malnutrition” group with MNA ≤23.5 compared to the “normal nutritional status” group with MNA ≥23.5. In study II the age-adjusted HR of a hip fracture was 0.95 (0.92–0.98) for one second longer OLST. Participants with an OLST <10 s had an age-adjusted HR for a hip fracture of 2.60 (1.36–4.95). In study III IGFBP-I had a positive linear relation to both the risk of a hip fracture and the risk of any major osteoporotic fracture. This relation was partly mediated by 45% by femoral neck BMD (Figure 3). However, the relation between IGFBP-1 and hip fractures was not confounded by IGF-I. BMI or GFR as could be suspected. In study IV the age-adjusted HR for a hip fracture for gait speed <0.8 m/s compared to gait speed ≥0.8 m/s was 6.89 (2.87–16.51). Categorical NRI for addition of gait speed to FRAX was 0.24 (p=0.023) when highest quartile of FRAX-estimated fracture risk was denominated as the high-risk group.

Conclusions: A MNA score ≤23.5 was associated to an increased mortality but the relation could be explained by the use of loop-diuretics which indicated heart- or kidney failure as the cause of death. Both OLST and gait speed were FRAX-independent predictors of both hip fractures and major osteoporotic fractures. Although OLST and gait speed were moderately correlated, none of them was a confounder to the other’s relation to fracture risk. IGFBP-I had a positive linear relation to the risk of both hip fractures and major osteoporotic fractures. IGFBP-I was neither correlated to nor confounded by OLST or gait speed. However, FRAX-estimated fracture risk seemed to be a confounder.
LIST OF SCIENTIFIC PAPERS

I. Mini nutritional assessment and 10-year mortality in free-living elderly women: a prospective cohort study with 10-year follow-up

II. One-leg standing time and hip-fracture prediction

III. High serum insulin-like growth factor binding protein 1 (IGFBP-I) is associated with high fracture risk independent of insulin-like growth factor 1 (IGF-I)

IV. Gait speed and one-leg standing time each add to the predictive ability of FRAX

Contents

1. INTRODUCTION
   1.1 FRAGILITY FRACTURES AND THEIR CONSEQUENCES
   7
   1.2 ASSESSMENT OF FRACTURE RISK
   7
   1.3 THE STRUCTURE OF BONE
   7
   1.4 AREAL BONE MINERAL DENSITY AND DXA
   8
   1.5 DEFINITIONS OF OSTEOPOROSIS
   8
   1.6 THE DXA TECHNIQUE
   8
   1.7 SOURCES OF ERROR
   9
   1.8 PERIPHERAL MEASUREMENT OF BMD
   9
   1.9 OSTEOPOROSIS AND FRACTURE RISK
   10
      1.9.1 Osteoporosis with and without a high fracture risk
      10
      1.9.2 Risk factors for osteoporosis
      10
      1.9.3 Risk factors for fracture
      11
   1.10 FRAX
      11
      1.10.1 What is FRAX?
      11
      1.10.2 Shortcomings of FRAX
      11
   1.11 MALNUTRITION
      12
      1.11.1 Definitions of malnutrition
      12
      1.11.2 Screening for malnutrition
      13
   1.12 MNA
      13
   1.13 IGF-I AND IGFBP-I
      14
1.13.1 IGF-I and bone 14
1.13.2 IGFBP-I and bone 14

1.14 FALLS AND FRACTURES 15

1.15 ONE-LEG STANDING TIME 15
1.15.1 OLST and osteoporosis 15
1.15.2 OLST and fall risk 15
1.15.3 OLST and fractures 16

1.16 GAIT SPEED 16

2. AIMS 16

2.1 GENERAL AIMS OF THE PROJECT 16

2.2 STUDY-SPECIFIC AIMS 16
2.2.1 Study I 16
2.2.2 Study II 16
2.2.3 Study III 17
2.2.4 Study IV 17

3. MATERIAL AND METHODS 17

3.1.1 The study population 17
3.1.2 Follow-up data on fractures and mortality 17
3.1.3 Follow-up data on the use of medications 17
3.1.4 Statistical methods 18
3.1.5 Ethics 18
3.1.6 Study I 18
3.1.7 Study II 18
3.1.8 Study III 19
3.1.9 Study IV 19

4. RESULTS 20

4.1 NON-PARTICIPANTS 20
4.2 STUDY I 20
4.3 STUDY II 22
4.4 STUDY III 24
4.5 STUDY IV 26
4.6 CONFOUNDING BY MEDICAL TREATMENTS 29

5. DISCUSSION 30
5.1 MAIN FINDINGS 30
5.2 MNA AS A PREDICTOR OF MORTALITY 31
5.3 OLST AS A PREDICTOR OF FRACTURES 32
5.4 IGFBP-I, WHAT DOES IT MEASURE? 33
5.5 GAIT SPEED AS A FRACTURE PREDICTOR 33
5.6 STRENGTHS AND WEAKNESSES OF THE PROJECT 34

6. FUTURE PERSPECTIVES 34

7. SUMMARY IN SWEDISH 34

9. FINANCIAL SUPPORT 41

10. REFERENCES 41
LIST OF ABBREVIATIONS

AUC  Area under curve
BMD  Bone mineral density
BMI  Body mass index
CI   Confidence interval
CV   Coefficient of variation
DXA  Dual X-ray absorptiometry
FFMI Fat-free mass index
HR   Hazard Ratio
IGF-I Insulin-like growth factor 1
IGFBP-1 Insulin-like growth factor binding protein 1
ISCD International Society for Clinical Densitometry
MNA  Mini Nutritional Assessment
OR   Odds ratio
PEM  Protein-energy malnutrition
PRIMOS Primary health care and osteoporosis
ROC  Receiver Operating Characteristic
SD   Standard deviation
WHO  World Health Organization
1. INTRODUCTION

1.1 FRAGILITY FRACTURES AND THEIR CONSEQUENCES
Some people get skeletal fractures in situations where most people would stay intact. For example, most of us would not get a hip fracture if we fall on a flat surface or get a vertebral fracture when we lift our shopping bag. Fractures which occur as a result of a trauma which wouldn't cause a fracture in a healthy individual are sometimes referred to as “fragility fractures”. Common sites for fragility fractures are the spine, hip, upper arm, shoulder, distal forearm and pelvis. One example of the consequences of fragility fractures is a vertebral fracture of the spine. This may cause chronic pain, restrict the ability to perform activities of daily living such as washing, cleaning and cooking and result in a low quality of life (1,2). Another example is a hip fracture which for about 50% of the affected individuals means that they cannot return to their previous home but are dependent on daily external help for a longer period (3). Both vertebral and hip fractures are also associated with a shorter life expectancy (4,5). In Sweden, fragility fractures carry a cost for society of 13 billion Swedish crowns every year. To prevent fragility fractures is thus important both for the high-risk individual and for society.

1.2 ASSESSMENT OF FRACTURE RISK
A tremendous amount of effort has been put into the construction of different fracture risk assessment tools (6). The clinical importance of a correct estimate of fracture risk comes from the effective treatments which are available to lower fracture risk. Patients who have a high risk of sustaining a fracture without treatment should be offered treatment while those with a low risk should have the opportunity to be reassured. Two of the most effective preventive treatment strategies are fall-preventive physical exercises (7,8) and bone-strengthening drugs (9).

1.3 THE STRUCTURE OF BONE

Bones are resilient and not stiff like dry twigs which are easily broken when bent.

Bone is a composite material with a protein (collagen) meshwork, like a carcass of a building but deflectable and elastic. This floppy meshwork is made stiff by the presence of mineral crystals. This combination of materials makes bone both hard and resistant to loading but still flexible enough not to break like the dry twig when suddenly exposed to bending or twisting forces (10). The major minerals in bone are calcium and phosphorous bound in the form of hydroxyapatite salt crystals. Bone also contains magnesium, sodium and potassium but these are predominantly conjugated to the hydroxyapatite crystals instead of forming crystals of their own (11).

Bones are not homogenous.

Imagine a long bone like the tibia as a long tube. It has a compact shell but its core is composed of a sponge-like bone structure at the ends (epiphyses) and of fat at the mid-shaft (diaphysis). A bone which is compact all through would be very heavy and not
considerably stronger than the in vivo tube-like construction described above. This can be illustrated by trying to tear a sheet of paper. The tear will start at one edge while the opposite edge is the part of the paper which is bent the most. The center of the paper is affected the least. Thus, to be resistant to bending or twisting forces, the outer parts of the bone are most important while you can save weight by making the center of the bone sponge-like or soft (12).

1.4 AREAL BONE MINERAL DENSITY AND DXA
Areal bone mineral density (aBMD) mostly abbreviated just ‘BMD’, means mineral content in grams per cm², a two-dimensional measure. Volumetric bone mineral density (vBMD) means mineral content per cm³, thus a three-dimensional measure. The clinical reason of measuring BMD is to assess bone strength as an estimate of a person’s susceptibility to skeletal fractures. Historically there have been several different techniques to measure bone mineral density but currently the standard method for clinical use is called dual X-ray absorptiometry (DXA) (13).

1.5 DEFINITIONS OF OSTEOPOROSIS
The original definition of osteoporosis is “a disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk” (14,15). However, that an individual person has microarchitectural deterioration of bone tissue and fragile bones has been hard to establish without non-invasive techniques. This has led to the WHO definition for women in 1994, based on BMD measured by DXA at the femoral neck, spine or midshaft radius (16). The measured BMD is compared to the mean BMD of a young (20-29 years) population and the difference from mean if measured in the number of standard deviations in the reference population. This measure is called T-score. A T-score $\leq -2.5$ SD is considered diagnostic for osteoporosis (16). To complicate things further, a third definition is used clinically, as recommended by the International Society for Clinical Densitometry (ISCD). The difference from WHO’s definition in that the T-score may be $\leq -2.5$ SD at either the femoral neck, total hip or lumbar spine L1-L4 (13).

1.6 THE DXA TECHNIQUE
The DXA technique is based on two different X-ray (photon beam) energies passing through the region of interest The exact energies differ between manufacturers of DXA-equipment but they are consistently close to 40 keV and 70 keV (17). The lower energy is set at the maximum attenuation of soft tissue. This means the part the X-ray energy spectrum which soft tissue absorbs the most. The other higher energy is set at the maximum attenuation of bone. The attenuation per gram of a specific type of tissue at a given photon energy is constant and called the mass attenuation coefficient. You know the energy of the photons you sent out and measure the energy of the photons you detect after they have passed through the body. With knowledge of the mass attenuation coefficient for a specific tissue type it is then possible to calculate the “mass per unit area” for a single tissue type (18). Unfortunately the body is composed of several types of tissues through which the photons of a known energy have to pass before they can be measured by the detector. This means, with just photons of one energy sent out
(emitted), you do not know what you are measuring. To solve this the DXA machine emits photons of two different energies, as mentioned above. You can then get specific patterns from each tissue type according to the ratio between the mass attenuation coefficient of the low energy and the mass attenuation coefficient of the high energy. This ratio is called the "R-value". The R-value enables us to distinguish between two components of a mixed tissue type portion of the body. The DXA machine needs to be able to distinguish between three different types of tissue; bone, fat and lean soft tissue. To be able to distinguish between these three types of tissue, the DXA machine applies three different two-component models of the body. 1) In portions of the body which contain bone, the DXA machine can separate soft tissue mass from bone mineral mass. 2) In portions of the body which do not contain bone, DXA can distinguish between fat mass and lean soft tissue mass. 3) In parts of the body where you have both bone and soft tissue, the soft tissue is supposed to have the same proportions of fat mass and lean soft tissue mass as adjacent soft tissue where bone is not present (19).

When a patient is examined with DXA he or she lies on a flat bed and a scanner head, either containing the radiation source or the detector, sits on a bow which can move above the bed to measure at different sites. The radiation dose is very low, comparable to the dose absorbed from background radiation during two days in life anywhere on the planet (20). The technique allows measurements of BMD at many different parts of the skeleton. However, the standard measuring sites are the lumbar spine, femoral neck and total hip (13).

1.7 SOURCES OF ERROR
Although DXA machines may show short-term coefficients of variation for BMD as low as 0.9% at the lumbar spine and 1.4 at the femoral neck (21), there are several sources of error. As mentioned, bones are not homogenous and they also contain fat in the bone marrow. The fat content of the bone marrow increases with age and this is a source of error. The amount of fat outside the measured bone may also influence measurements. Together these fat-related errors can cause miscalculation of BMD of ±20% (22,23). Another important determinant of the measured BMD is the positioning of the patient, especially for measurements of the femoral neck where an anteversion (internal rotation) of 30° of the femur can increase measured BMD by 8–45% (24). At the lumbar spine, facet joint sclerosis may have a profound effect on measured BMD so that in patients with advanced sclerosis, the BMD may be overestimated by up to 47% (25).

1.8 PERIPHERAL MEASUREMENT OF BMD
Measurements of BMD of the lumbar spine and hip are called “central DXA”. Since the equipment for such measurements is quite heavy and occupies considerable space, several different “peripheral DXA” methods have been developed. The fracture predictive ability is similar for DXL-measured BMD of many peripheral parts of the skeleton such as the finger phalanges, forearm and heel (26,27). However if a cut-off for osteoporosis of a T-score ≤-2.5 SD was used, the proportion of patients diagnosed with osteoporosis would differ largely depending which skeletal site was used. In one study T-scores from phalangeal DXA had a mere sensitivity of 35% for diagnosing osteoporosis as defined by
femoral neck T-scores. In another study T-scores from DXA of the calcaneus diagnosed 2% as osteoporotic when T-scores of the femoral neck diagnosed 21% of the same population as osteoporotic (28). Depending on the measurement site and measuring technique, the percentage classified as osteoporotic may vary between 19% and 66% (29). Another reason for these differences is the use of different reference populations for calculation of T-scores (30). These classification differences have led to the recommendation not to use peripheral sites for the diagnosis of osteoporosis (31). However this does not mean that peripheral measurements cannot be used for fracture risk assessments. Even though both T-scores and BMDs vary considerably in the same person, the global fracture-predictive ability of BMD measurements at the calcaneus has shown to be similar to central DXA measurements (32,33). However the highest accuracy for hip fractures is achieved from DXA of the hip, and for vertebral fractures, DXA of the spine (34).

1.9 OSTEOPOROSIS AND FRACTURE RISK

1.9.1 Osteoporosis with and without a high fracture risk
The clinical dilemma arising from definitions of osteoporosis based entirely on BMD is that you may have osteoporosis without a high fracture risk. Even though BMD is a strong predictor for future fractures, both bone fragility and absolute fracture risk are also determined by many other factors. Age, for example, has a very strong impact on fracture risk. If a 60 year old woman has osteoporosis (T-score $-2.5$ SD), she has a high relative risk compared to women of the same age with normal BMD. Because age is such a strong risk factor, her absolute fracture risk is still low. Conversely, a woman aged 90 has a high absolute fracture risk, even without osteoporosis, just because of her advanced age. This has implications for treatment recommendations, as on a population level it is much more rewarding to prevent many fractures in a group with a high absolute risk than a few fractures in a low-risk group. In other words, osteoporosis should sometimes be treated and sometimes not, depending on absolute fracture risk.

1.9.2 Risk factors for osteoporosis
The causes of osteoporosis can be divided into primary and secondary causes. Primary osteoporosis means that no specific disease can be found to explain the low bone mass. This type of osteoporosis comes with age, beginning at about 50 years of age. The activity of the bone cells declines, resulting in an imbalance between bone resorption and bone formation so that the net effect is loss of bone mass (35). The cause of this imbalance is multifactorial and involves genetic, epigenetic and lifestyle-related factors (35).
Secondary osteoporosis means that a disease, a medication or other "extraosseous" factor causes, or contributes to the loss of bone mass. There is a long list of secondary causes of osteoporosis, some examples are: diabetes mellitus type 1, hyperthyroidism, hyperparathyroidism, hypogonadism, excessive alcohol consumption, protein-energy malnutrition, vitamin-D deficiency, systemic corticosteroids, anti-androgen drugs, anti-estrogen drugs and cytostatic drugs.
1.9.3 Risk factors for fracture
From large cohort studies a number of independent risk factors for future fractures have been identified (36–40). Apart from low BMD/osteoporosis mentioned above, a long list of other clinical risk factors have been identified, for example, higher age, previous fracture, fracture in parent, systemic corticosteroid treatment (41), smoking, low BMI, impaired balance (42), high risk of falls (43) and impaired muscle strength (44). Some of these risk factors will be discussed further in this thesis.

1.10 FRAX
1.10.1 What is FRAX?
Since so many risk factors may influence fracture risk, several multi-predictor risk assessment tools have been developed. A WHO working group has developed a risk assessment tool called FRAX (45). The fracture incidence may differ even within Europe so that Sweden has an age-standardized incidence of hip fractures which is twice that of Turkey (46). But since Sweden has such a large population of elderly, this translates into a lifetime risk for a hip fracture for a woman at the age of 50 of 28.5% in Sweden and 1% in Turkey (47). Unique for FRAX is that it has been adapted to 56 different countries’ mortality and fracture rates. FRAX calculates the country-specific absolute 10-year risk of both hip fractures and one of the so-called “major osteoporotic fractures”: fracture of the hip, clinical spine, shoulder and forearm (45) FRAX is based on 12 different risk factors and as a measure of accuracy the area under curve (AUC) for the receiver operation characteristic (ROC) has been calculated. For hip fractures the ROC area has been 0.7–0.73 (48–50) and for major osteoporotic fractures 0.64–0.83 (48–53).

1.10.2 Shortcomings of FRAX
FRAX takes twelve different risk factors into account, or eleven if BMD of the femoral neck is omitted. The results are given in two percentages, one for hip fractures and one for major osteoporotic fractures, as mentioned above. The outlines of the calculations are however hidden and even unpublished so that it is impossible to know how the country-specific mortality and fracture incidence is accounted for. This means that external validation of the statistical methods is not possible. The risk percentages are also given only as point estimates with no confidence intervals, which means that you cannot determine whether the difference between two persons’ fracture risk is statistically significant. Even more troublesome, you cannot see how wide the confidence interval is. As a physician, this means you can’t know the probability that your patient is low-risk, medium-risk or high-risk. If the actual confidence interval extends into more than one risk category, your patient could be classified as any of these. Since many national guidelines for treatment with bone-active drugs are based on FRAX-risk thresholds or categories, this uncertainty actually matters in clinical practice. In areas where central DXA is a limited resource, it would be useful to know how much better precision you get in that exact patient, by adding femoral neck T-score to FRAX. Is your risk assessment without DXA good enough or do you want to have better precision by sending your patient to a central DXA examination? ROC areas have been calculated for FRAX with and without inclusion of femoral neck BMD, but that only shows the mean accuracy on a population level, in that specific population.
High doses of corticosteroids are associated with a higher fracture risk than low doses (41). Perhaps the cumulative dose is also of importance. However, in FRAX you only have two risk categories regarding systemic corticosteroids. Either you have been treated with ≥ 5 mg Prednisolone (or equivalent dose) for at least three months in a row, or you haven’t. This of course means that the fracture risk of persons with repeated shorter treatments or higher doses than the mean dose in FRAX will have their fracture risk underestimated. However it is possible to manually adjust the FRAX risk, according to the dose of corticosteroids (54).

The risk of falling is a risk factor for fractures that is partly independent of BMD (55). Regarding the association between higher FRAX-risk and higher risk of falling, there are conflicting results (56,57). However there is still no uniform way to measure fall risk, which can be found in large studies with fracture as an outcome (58). The consequence of FRAX lacking fall risk is apparently that persons with a high risk of falling will have their fracture risk underestimated by FRAX. Different fracture locations carry different risks for new fractures (59). In FRAX all fractures are given the same weight. This means that for hip fractures and vertebral fractures, the fracture risk is underestimated by FRAX.

1.11 MALNUTRITION

1.11.1 Definitions of malnutrition

Malnutrition is used to describe several different conditions of nutritional deficit or even used directly translated to “inappropriate nutrition”, thus also including overnutrition as in obesity. It is sometimes used to describe suboptimal intake of specific nutrients such as vitamins and minerals. However, the most common use of the term is to describe a condition where the influx of protein and energy to the body is lower than the needs: a negative protein and energy balance. This negative balance can of course come from either increased needs or decreased intake or uptake. This condition is associated with an increased mortality and increased functional dependency (60). The prevalence of malnutrition in the elderly varies from 5% in the community-dwelling population to 50% in geriatric rehabilitation clinics (61). Protein-energy malnutrition (PEM), mostly just referred to as “malnutrition” also has some different definitions, none of which is accepted worldwide so far. The European Society of Clinical Nutrition and Metabolism (ESPEN) presented their latest consensus diagnostic criteria for adult malnutrition in 2015 (62). The Academy of Nutrition and Dietetics (Academy) and the American Society for Parenteral and Enteral Nutrition (ASPEN) presented their latest consensus diagnostic criteria for adult malnutrition in 2012 (63). The European criteria are based on establishing either of two different findings: either 1) a BMI < 18.5 kg/m² or 2) a combination of a low fat-free mass index (<15 kg/m² for women and <17 kg/m² for men) OR a low BMI (<20 kg/m² for persons < 70 years and <22 kg/m² for persons ≥70 years) AND unintentional weight loss (either >10% of habitual weight or <5% in 3 months). The American criteria are instead based on finding at least two of six hallmarks of malnutrition: insufficient energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation, and reduced grip strength.
1.11.2 Screening for malnutrition
Apart from BMI<18.5, to establish any of the criteria for malnutrition above might require both considerable effort or special training or equipment. To have less complicated ways of identifying persons “at risk”, which may need further evaluation, a number of different screening tools for malnutrition in adults have been developed (64–67).

1.12 MNA
Malnutrition in the elderly is associated with an increased mortality and increased functional dependency (60). The prevalence of malnutrition in the elderly varies from 5% in the community-dwelling population to 50% in geriatric rehabilitation clinics (61). MNA is the most commonly used screening tool for malnutrition in the elderly (68) and the prevalence of malnutrition according to MNA has been in different populations and in different care settings, from community-dwelling elderly to acute hospital care to nursing homes (68). The full 15-item MNA was constructed in 1991 from a population in Toulouse, France, of 165 hospitalized men and women. The mean age of the men was 78 years and of the women 79 years. The standard for nutritional status was nutritional status as rated by two physicians. As a basis for their assessment they had anthropometric measures, geriatric functional assessments, evaluation of dietary intake and biochemical analyses available for each participant (69). The participants were classified by the physicians into normal nutritional status (34%), malnourished (57%) and uncertain (8%). Step two was to validate the MNA in 1993 in another population in Toulouse where the same standard and classification procedure was used. This second population consisted of 120 participants with mean ages exactly as in the first Toulouse study. From these two studies, the cut-offs for the full MNA to classify patients as either normal, at risk of malnutrition or malnourished were set.

In 2001 six of the items were introduced to be used as a quick screening test called MNA short form (MNA-sf) (70). The maximum score on the first six items is 14 and the result is to be interpreted as follows: 12–14 points: Normal nutritional status; 8–11 points: At risk of malnutrition; 0–7 points: Malnourished. This six-item MNA has later been validated against the full MNA and found to have a sensitivity of 89.3% and a specificity of 94.3% for classification into the corresponding three full MNA categories. In 2009 this six-item set was introduced into the complete MNA and the name was changed from MNA-sf to just “MNA”. This may be confusing since the entire 15-item form was formerly called “MNA” and is still often referred to as such. The 15-item form, however, is currently called “full MNA” (71).

According to the user manual for MNA, called “Nutrition screening as easy as MNA” and found on the Nestlé nutrition institute web portal, the six-item MNA could be considered diagnostic for malnutrition (72). The result of the six-item MNA assessment is incorporated into an intervention algorithm in the manual. Oral energy supplementation is recommended for those with a score of <8/14 points or <12/14 points including weight loss. The recommended dose is 400–600 kcal/day which is equal to 200–300 ml oral energy supplement (73). Until recently, there have been no uniform European diagnostic criteria for malnutrition, to use as a standard to compare MNA to. The latest consensus criteria were presented only in 2015 (62). It could therefore be questioned whether there
is scientific evidence that a certain score on MNA can be considered diagnostic for malnutrition.

There seem to be no studies published on either six-item MNA or 15-item MNA compared to the current definitions of malnutrition mentioned above. Nor do there seem to be any studies published on MNA compared to measures of body composition, for example FFMI, which is included in the European definition of malnutrition (62).

1.13 IGF-I AND IGFBP-I

1.13.1 IGF-I and bone

The polypeptide insulin-like growth factor 1 (IGF-I) consists of 70 amino-acid residues. There is also an IGF-2 which has 67 amino acids. IGFs are produced by most cell types (74) but the major source of systemically circulating IGF-I is the liver where its production is stimulated by growth hormone (GH) (75). IGF-I activity is impaired in malnutrition (75). Bone tissue has a local production of IGFs, and locally produced IGF-I may have as important paracrine effects in bone beside the endocrine effects of the liver-derived IGF-I (76). IGFBPs are important for bone acquisition until early adulthood (77) as well as for the maintenance of bone mass and strength during adult life (78). With aging GH production decreases and as a result, so do the IGF-I levels (79). Bone remodeling seems to be stimulated by IGF-I by an increase in both bone formation and bone resorption (80). A low serum concentration of IGF-I is a risk factor for future fractures in both men (81) and women (82,83).

1.13.2 IGFBP-I and bone

IGFBP-I is one of six IGF-binding proteins and consists of 234 amino acids (84). As for IGF-I, the circulating IGFBP-I is mainly produced by the liver but also produced locally in a variety of cell types, for example in osteoblasts (85). As the name implies, the IGFBPs bind circulating IGFs and may thereby regulate the bioactivity of IGFs. However, the regulation is more complicated than just free or bound IGF-I because in bone, some IGFBPs (IGFBP-3 and -5) seem to have IGF-stimulatory effects and some (IGFBP-I, -2, -4 and -6) to have IGF-inhibitory effects (86). As for IGFBP-I, there is also evidence for IGF-independent effects in bone (87). The serum concentration has a diurnal variation with the highest levels in the morning (84). The production in the liver also reacts quickly to nutritional status so that in moments of negative energy balance, such as after an overnight fasting or physical exercise, the IGFBP-I levels are increased (88,89). Chronic kidney failure measured as a low GFR is also associated with high levels of IGFBP-I (90).

Conversely, IGFBP-I is reduced directly after a meal (85). Insulin inhibits the production of IGFBP-I so that in states of hyperinsulinemia, as in pre- and early type-2 diabetes, the IGFBP-I levels are instead decreased (91). The production of IGFBP-I is also regulated by a number of other systemic hormones such as glucocorticoids, sex hormones, glucagon and thyroid hormones (85). The local effect of IGFBP-I is in turn regulated in several ways: by degradation of proteases, phosphorylation and binding to cell surface or extracellular matrix (87).
1.14 FALLS AND FRACTURES
The risk of falling is an important risk factor for fractures, especially for hip fractures (92). In the elderly, 87% of the fractures occur after a fall (93). The type of fracture sustained after a fall is age-dependent, at least in women (94). Women <60 years manage to stretch out their arms as a protective reflex so that they fall on their hands and sustain a forearm fracture. In women, from 60 years it becomes increasingly common, with increasing age, to fall directly on the hip, resulting instead in a hip fracture. An increased fall risk seems to partly overlap with a low BMD (55). Regarding overlap between FRAX-estimated fracture risk and incident falls, the results diverge (56,57). There are a considerable number of tools for fall risk predictions, from simple one-parameter tests like the “Timed-up-and-go test” (95,96) to multi-item screening protocols like the “Downton Fall Risk Index” (97) or “STRATIFY” (98).

1.15 ONE-LEG STANDING TIME
The one-leg standing time (OLST) test has been given many different names (99) and has been used for prediction of such disparate conditions as future need of care (100), forced vital capacity (spirometry lung function test) (101), mortality (102) and obesity (103). In this thesis, however, its relation to osteoporosis, fall risk and fractures will be the focus. OLST may also be measured in several different ways, e.g. eyes closed or open, arms crossed over the chest or along the sides. The studies referred to below have measured OLST with eyes open and, if described, the arms hanging down along the lateral sides of the trunk.

1.15.1 OLST and osteoporosis
A shorter OLST does not seem to be associated with osteoporosis according to the T-score based WHO definition in women (104). In men OLST has only been studied in relation to the definition of osteoporosis when the result from OLST was combined with two other balance tests (105). However, there was no significant difference in this combined balance performance between “osteoporotic” and “non-osteoporotic” men.

1.15.2 OLST and fall risk
The results from studies on the association between OLST and fall risk are inconsistent. Of prospective studies on incident falls there are two positive studies and two negative studies. A Japanese study on 865 community-dwelling men and women aged ≥65 years showed no association between short OLST and an increased risk of falls (106). An Australian study on 96 community-dwelling men and women ≥70 years old likewise found no association between shorter OLST and future falls (107). This study was described as positive in a review article on OLST by Michikawa and colleagues (99). A Japanese study on 658 community-dwelling men and women aged ≥65 years showed an association between shorter OLST and future falls (108). A study from the USA on 482 community-dwelling elderly men and women showed and increased risk of falls with shorter OLST for women. This study was described as negative in the review article on OLST by Michikawa and colleagues (99).
1.15.3 **OLST and fractures**
A one-leg standing time < 5s was associated with an OR of 2.13 (1.04–4.34) in an Australian study of 316 men and women with a mean age of 73 years. In a Finnish study of 2928 women aged 48–57 years and a mean follow-up time of 8.4 years, those who had an OLST <10 s had a HR of 9.11 (1.98–42.00) for a hip fracture. To exercise one-leg standing has been shown to decrease the risk of falling (109).

1.16 **Gait Speed**
Gait speed is usually measured at usual pace over a 3–6 meter long distance (110). A low gait speed may predict hip fractures independent of BMD (111,112). A slow gait speed is also associated with an increased risk of falling according to a systematic review from 2014 (113). However a more recent Dutch study showed no predictive ability of gait speed for falls (114). A slow maximum or usual gait speed measured over a short distance (3–6 meters), together with low muscle mass, is diagnostic of sarcopenia according to all current definitions of the condition (115). Gait speed at usual pace is also predictive of all-cause mortality (116). A low gait speed has also been associated to indicators of frailty such a unintentional weight loss, self-reported exhaustion, low physical activity, and low hand grip strength (117).

2. **AIMS**

2.1 **GENERAL AIMS OF THE PROJECT**
The general aim of the PhD project was to evaluate how MNA, one-leg standing time, IGFBP-I, gait speed were related to each other, to FRAX and to the risk of future fractures in our study population of community-dwelling elderly women. Since mortality is a substantial competing risk to fractures in the elderly, the relation of measures of postural balance and nutrition to mortality was also evaluated even when mortality was not the primary endpoint of the study. One purpose of these aims was to find fracture predictors which could be easily measured in primary care and contribute to the accuracy of FRAX. Another purpose was to see how these new fracture predictors affected each other’s associations with fracture risk.

2.2 **STUDY-SPECIFIC AIMS**

2.2.1 **Study I**
The aim of study I was to investigate whether participants classified by MNA at risk of malnutrition or malnourished had a higher mortality risk than participants with normal MNA.

2.2.2 **Study II**
The aims of study II were to investigate whether OLST could predict hip fracture risk and to compare the predictive accuracy of OLST to that of FRAX.
2.2.3 Study III
The aims of study III were to investigate whether there was an association between high serum concentration of IGFBP-I and high fracture risk, and to evaluate whether such an association could be mediated by either BMI or IGF-I.

2.2.4 Study IV
The aims of study IV were to investigate whether addition of either maximum gait speed or OLST could improve the predictive accuracy of FRAX, as measured by AUC, Harrell’s c and NRI.

3. MATERIAL AND METHODS

3.1.1 The study population
The same study population was analyzed in all four studies. Inclusion criteria were living in the Bagarmossen area south of Stockholm, Sweden, and being a woman born between 1920 and 1930. These criteria were met by 937 women in 1999. Invitations were sent in two batches after which 351 women were included in the study (Figure 1).

3.1.2 Follow-up data on fractures and mortality
The dates of death and all fracture diagnoses registered in both in- and outpatient care were obtained from the Swedish National Board of Health and Welfare. Diagnoses were identified according to the ICD-10 classification system during the period January 1, 1999 to December 31, 2009. A hip fracture was defined by the ICD-10 code S72.* where * means “any number”. A major osteoporotic fracture was defined as any of the codes S32.*, S42.*, S52.* or S72.*. All causes of fracture (any W-code) were included. The list of fracture diagnoses were carefully “deanned” for each patient so that diagnoses registered at appointments for checking fracture alignment or removal of osteosynthesis materials, were not classified as new fractures. The Swedish National Inpatient Register (IPR) has been externally validated and found to have a positive predictive value of 85–95%. I have found no external validation of the register for outpatient care (the OVR database). All hip fractures were registered in the IPR, and therefore the data regarding these fractures are the most reliable.

3.1.3 Follow-up data on the use of medications
All medications were registered at baseline. In 2011, all medical journals for the participants at Bagarmossen primary care center were read through. Prescriptions for the following medications were registered: calcium, vitamin D, statins, thiazides, loop-diuretics, systemic corticosteroids, inhaled corticosteroids, sedatives, hypnotics, systemic estrogens, local estrogens, SERMs and bisphosphonates. The treatment was considered to last from the first date of first prescription to the date of withdrawal noted in the journal, or if not noted, the date when the medication from the last prescription should be finished. The treatments yes or no and the time on each medication were each used for adjustments of results in all four studies. The results presented in the studies were however not significantly altered by any of these adjustments.
3.1.4 Statistical methods
Significance testing for differences in proportions were made with the chi-2 test. When there were five or less observation in any of the groups, Fisher’s exact test was used instead. Differences in mean for variables of normal distribution were analyzed with Student’s t-test. For skewed distributions, the Wilcoxon rank-sum test was used. Cox proportional hazards model was used for analysis of time to event data. For analyses of ROC areas, mediation and NRI, logistic regression was used instead. For analysis of subdistribution hazards in competing risks, Fine and Gray regression was used. Linear regression was used to analyze the relation between BMI and IGFBP-I.

The area under curve (AUC) for the receiver operating characteristic curves (ROC), is the traditional measure of predictive accuracy of a model. However, AUC often fails to show any significant improvement of an existing predictive model when a new predictor is added to the model, no matter how promising the new predictor has seemed to be (118). As stated in the article by Kanis and colleagues about pitfalls in externa validation of FRAX, the AUC will also become smaller with a narrower age range within the study population and with a longer follow-up time (119). New methods for predictive accuracy such as net reclassification index (NRI) have been developed to address these problems with AUC (120). However, with new methods come new pitfalls in the interpretation of the results. In the case of NRI and especially for category-free NRI, the gain from addition of a new marker to an existing predictive model may be misleadingly “inflated”, (121,122). Common recommendations to increase the clinical usefulness of NRI are to use no more than two categories, to show confidence intervals and the underlying reclassification tables (123). To account for the effect on sensitivity and specificity by the prevalence in the study population, weighted NRI may also be presented (124). Alpha was set to 0.05. The statistics software used was STATA 14.1 (StataCorp LP, Texas, USA).

3.1.5 Ethics
The study design and the procedure for obtaining informed consent were approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden. Verbal informed consent was obtained from all participants before inclusion. The fact that verbal and written information about the study had been given to each participant and that the participant had given verbal consent to participate was documented in the participant’s study protocol at the first study visit.

3.1.6 Study I
The MNA tool is described in detail above. All participants were assessed with the full MNA consisting of 18 items with a maximum score of 30 points. Cut-offs were chosen according to the official MNA manual where a score between 17 and 23.5 points is considered “at risk of malnutrition” while <17 points is considered as “malnourished”. All participants were examined by the same physician (H.S.).

3.1.7 Study II
The OLST test is described in the “introduction” section of the thesis. OLST was measured twice on each leg with eyes open. The longest time out of the four was used for analysis. Bone mineral density measurements were conducted in 1999–2001 using Hologic QDR
4500 DXA equipment (Hologic, Waltham, MD, USA). Calibration was performed daily with a phantom. The NHANES-III reference population was used for the calculation of T-scores. FRAX-assessments were obtained from the web interface calculator (45). Cox proportional hazards model was used for analysis. To compare predictive accuracy, both AUC (based on logistic regression) and Harrell’s c (based on Cox regression) were analyzed.

3.1.8 Study III
Serum IGFBP-I was analyzed with radioimmunoassay (RIA) according to the method of Povoa et al (125). The sensitivity of the RIA was 3 μg/l and the intra- and inter-assays CV were 3% and 10%, respectively. Total IGF-I was analyzed in serum by RIA after separation of IGF-I from IGF-binding proteins by acid ethanol extraction and cryoprecipitation. To minimize the interference of remaining IGFBPs, IGF-I was used as radioligand (126). The intra- and inter-assay CV were 4% and 11%, respectively. BMD was measured as in study II. Causal mediation was analyzed with the “medeff” command in the STATA package “mediation” (127,128) according to procedures described by Imai and colleagues (129).

3.1.9 Study IV
The participants were asked to walk as fast as possible 15 meters down a corridor with a flat floor, turn at a mark and then walk back again to the starting point. The average speed was calculated as 30 meters divided by the walking time in seconds. OLST was measured as in study II. Vitamin D was analyzed with Nichols Advantage® 25-Hydroxyvitamin D assay (Nichols Institute Diagnostics), a chemoluminescence analysis used for measurement of 25-hydroxy-vitamin-D in serum. At the time of the analysis of the samples from this study, the CV% was between 10.4 and 11.5 for 25-hydroxy-vitamin-D levels of 70–80 nmol/l. BMD was measured as in study II. FRAX assessments were obtained from the web interface (45).
4. RESULTS

4.1 NON-PARTICIPANTS
Out of all 937 eligible women, those who were not included in the study were older with a mean age of 74 compared to 73 years in the study population (p<0.001). There were no significant differences between these groups regarding self-graded health or the frequency of physical activity. The mortality rate during follow-up was however much higher among the non-participants, 35% compared to 21% in the study sample (p <0.001).

4.2 STUDY I
The median follow-up time was 10.1 years. Out of the 351 participants, 73 died during follow-up. Only one participant had an MNA score <17 points. Women with a MNA score ≤23.5 were older, had a lower body weight, a lower prevalence of asthma and a higher proportion had help with activities of daily living (Table 1). The age-adjusted HR for mortality was 2.36 (1.25–4.46) for the “risk of malnutrition” group with MNA ≤23.5
compared to the “normal nutritional status” group with MNA >23.5. The prevalence of asthma/COPD could have been a confounder in the relation between MNA and mortality (Table 2). The HR for a hip fracture was 2.14 (0.87–5.23) and for a major osteoporotic fracture 1.35 (0.61–2.99). These fracture data were not presented in the published article.

Table 1. Baseline characteristics for the two MNA groups

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>MNA (≤23.5) n=28</th>
<th>MNA (&gt;23.5) n=323</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD)</td>
<td>74 (2.5)</td>
<td>72 (2.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body weight mean (SD)</td>
<td>65 (13.8)</td>
<td>70 (11.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI mean (SD)</td>
<td>25.7 (5.6)</td>
<td>26.8 (4.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>4 (14%)</td>
<td>36 (11%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>4 (14%)</td>
<td>50 (15%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>5 (18%)</td>
<td>42 (13%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (11%)</td>
<td>26 (8%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (18%)</td>
<td>71 (22%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>7 (25%)</td>
<td>29 (9%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Living alone</td>
<td>10 (36%)</td>
<td>174 (54%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Help with ADL</td>
<td>3 (11%)</td>
<td>4 (1%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
Table 2. Adjustment for potential confounders in the relation between MNA and mortality. All results are adjusted for age.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio for MNA&lt;=23.5</th>
<th>Hazard Ratio for MNA&gt;23.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MNA &lt;=23.5</td>
<td>2.36 (1.25–4.46)</td>
<td></td>
</tr>
<tr>
<td>MNA &lt;=23.5 combined with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>1.96 (1.01–3.77)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.44 (1.29–4.60)</td>
<td></td>
</tr>
<tr>
<td>Malignant disease</td>
<td>2.26 (1.19–4.28)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2.28 (1.20–4.32)</td>
<td></td>
</tr>
<tr>
<td>Help with ADL</td>
<td>2.12 (1.11–4.03)</td>
<td></td>
</tr>
</tbody>
</table>

There was a significant difference between MNA ≤23.5 and MNA>23.5 regarding OLST (p= 0.0003), IGFBP-1 levels (p= 0.0286) and gait speed (p= 0.0009). When the age-adjusted HR for mortality for MNA ≤23.5 compared to MNA>23.5 was adjusted for the use of calcium and vitamin D during follow-up, it was lowered from 2.35 to 0.99 (0.93–4.28). Adjusted instead for the use of loop diuretics the HR was 1.60 (0.73–3.52).

4.3 STUDY II

The median follow-up time was 10.1 years. A participant was censored from the study (no longer regarded to be “at risk”) after first fracture or death. During follow-up 11.4% (n=40) of participants had at least one hip fracture and 20.8% (n=73) had at least one major osteoporotic fracture. OLST and FRAX risk were virtually not correlated at all with a Spearman’s rho of –0.002. There was a negative linear relation between OLST and hip fracture risk. In the entire interval from 0 to 30 s, the age-adjusted HR of a hip fracture was 0.95 (0.92–0.98) for one second longer OLST. Participants with an OLST <10 s had an unadjusted HR for a hip fracture of 2.83 (1.52–5.26) compared to ≥10 s. The HR adjusted for FRAX-estimated hip fracture risk was 2.96 (1.58–5.54). The age-adjusted HR was 2.60 (1.36–4.95). Adjustment for both age and BMD attenuated the HR to 2.15 (1.09–4.20) (Table 3). Both having an OLST <10 s and belonging to the highest quartile of FRAX-estimated hip fracture risks meant that the HR was about twice as high as having either an OLST <10 s or belong to the high-risk quartile of FRAX risks. The reference was having neither OLST <10 s nor belong to the high-risk quartile of FRAX (Table 3).

The HR for a hip fracture adjusted for just FRAX-estimated hip fracture risk, was significantly different from 1 at all values of OLST above 10 seconds, when 10 seconds was used as a reference (Figure 2, not published in article). The OR at baseline for having osteoporosis was 1.00 (0.97–1.02) for each second increase in OLST.
Table 3. Multivariate regression analysis of OLST <10 s compared to OLST ≥10 s, in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>HR for a hip fracture for OLST&lt;10s compared to OLST≥10 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>2.83 (1.52–5.26)</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>2.60 (1.36–4.95)</td>
</tr>
<tr>
<td>Adjusted for age and BMD a)</td>
<td>2.15 (1.09–4.20)</td>
</tr>
<tr>
<td>Adjusted for FRAX risk b)</td>
<td>2.96 (1.58–5.54)</td>
</tr>
</tbody>
</table>

a) Femoral neck BMD

b) FRAX-estimated risk of a hip fracture

Table 4. The multiplied hip fracture risk for the participants with both an OLST <10 s and a FRAX-estimated hip fracture risk within the highest quartile, compared to one of these.

<table>
<thead>
<tr>
<th></th>
<th>OLST ≥10 s</th>
<th>OLST &lt;10 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRAX risk quartiles 1–3, low risk</td>
<td>HR 1.00 (reference group)</td>
<td>HR 3.77 (1.59–8.95)</td>
</tr>
<tr>
<td>FRAX risk quartile 4, high risk</td>
<td>HR 3.56 (1.47–8.60)</td>
<td>HR 7.41 (2.85–19.25)</td>
</tr>
</tbody>
</table>
The unadjusted HR for a major osteoporotic fracture for one second longer OLST was 0.97 (0.95–0.99). Adjustment for the use of loop diuretics caused the HR to become non-significant (p=0.213). Adjustment for age or FRAX-estimated risk of a major osteoporotic fracture had no impact at all on this HR. After rounding they were identical: 0.97 (0.95–0.99). The age-adjusted HR for a major osteoporotic fracture for OLST <10 sec compared to OLST ≥10 sec was 1.82 (1.13–2.96). The HR for mortality for one second longer OLST was 0.93 (0.91–0.95). The results for mortality and for major osteoporotic fractures were not published in the article. Since the HR for mortality was even higher than the HR for a hip fracture, the HR for a hip fracture was also analyzed with Fine and Gray regression to be able to use hip fracture and mortality as competing risks. However, the results were very similar with a subdistribution HR for a hip fracture of 0.95 (0.92–0.98) for one second longer OLST. Spearman’s rho for the time-to-event for hip fracture and mortality was 0.84.

4.4 STUDY III
The median follow-up time was 10.1 years. IGFBP-I was weakly correlated to IGF-I and femoral neck BMD with Spearman’s correlation coefficients of -0.32 and -0.30. The correlation coefficient for IGFBP-I and BMI was moderate, -0.42. For every unit increase
in BMI, IGFBP-1 concentrations decreased by 5% (95% CI for β-coefficient: -0.06 to -0.04) (Figure 4). IGFBP-1 was not correlated to OLST, gait speed or 25-hydroxy vitamin D levels. IGFBP-1 had a positive linear relation to both the risk of a hip fracture and the risk of any major osteoporotic fracture. This relation was partly mediated by 45% by femoral neck BMD (Figure 3). However, the relation between IGFBP-1 and hip fractures was not confounded by IGF-I, BMI or GFR as could be suspected. The unadjusted HR for a hip fracture for one SD increase in IGFBP-1 was 1.43 (1.06–1.93). The age-adjusted HR was 1.46 (1.08–1.99). Adjustment for OLST or gait speed did not have a significant effect on the HR. Adjustment for FRAX-estimated hip fracture risk attenuated the HR from 1.43 to 1.37 and the HR was also non-significant (p= 0.054). The unadjusted and FRAX-adjusted HRs were not presented in the article. The age-adjusted HR for a major osteoporotic fracture for one SD increase in IGFBP-1 was 1.33 (1.05–1.69). This HR was attenuated to 1.19 and was non-significant (0.91–1.56) after adjustment for the use of calcium supplements, but not after adjustment for the combination of calcium and vitamin D3.

Figure 3. Mediated and direct effects by IGFBP-1 on hip fracture risk.

![Diagram of mediated and direct effects by IGFBP-1 on hip fracture risk](image)

This HR was not significantly altered by further adjustment for any of gait speed, OLST or FRAX-estimated risk of a major osteoporotic fracture.
4.5 STUDY IV

The median follow-up time was 10.1 years. The Spearman correlation between gait speed and OLST was 0.53, p<0.001. We used the cut-off of gait speed used in the European definition of sarcopenia, <0.8 m/s. The unadjusted HR for a hip fracture for gait speed <0.8 m/s compared to gait speed ≥0.8 m/s was 8.29 (3.62–18.97). The age-adjusted HR was 6.89 (2.87–16.51). After adjustment for FRAX-estimated hip fracture risk (but not for age) the HR was 8.23 (3.59–18.85). For one second shorter OLST adjusted for age, the HR was 1.06 (1.02–1.09). One SD decrease in gait speed resulted in an age-adjusted HR for a hip fracture of 2.16 (1.54–3.05). The unadjusted HR for a hip fracture was 2.26 (1.65–3.11). For major osteoporotic fractures, the HR was 1.33 (1.03–1.72) adjusted for age and 1.38 (1.08–1.75) unadjusted.

The ROC areas did not significantly between FRAX alone, FRAX + Gait speed and FRAX + OLST. Since there are no Swedish clinical cut-offs related to decision-making based on FRAX-estimated hip fracture risk, the highest quartile of fracture risks was chosen as high-risk category. This group had a FRAX-estimated absolute 10-year hip fracture risk of ≥15%. Categorical NRI for addition of gait speed to FRAX was 0.24 (p=0.023). For OLST categorical NRI was non-significant. Reclassification tables with calculations of NRI, sensitivity and specificity outlined are shown in tables 6 and 7 below. For major osteoporotic fractures, the HR for gait speed <0.8 m/s compared to ≥0.8 m/s was 3.71 (1.69–8.11) unadjusted, 3.43 (1.54–7.65) adjusted for age and 3.71 (1.69–8.12) adjusted.
for FRAX-estimated risk of a major osteoporotic fracture (but not for age). When 30% risk of a major osteoporotic fracture was used as cut-off, the categorical NRI for addition of gait speed to FRAX-estimated risk for a major osteoporotic fracture was 0.05, although non-significant (p=0.22).

We also investigated the 30% cut-off for major osteoporotic fracture, defined by the Osteoporosis Expert Group at the Swedish National Board of Health and Welfare. Yet that resulted in a nonsignificant categorical NRI of 0.087 (p=0.066).

When the age-adjusted HR for a hip fracture for gait speed <0.8 m/s compared to ≥0.8 m/s of 6.89 was adjusted for systemic estrogen treatment, the HR was 7.61 (2.98–19.46). Adjustment for local treatment with oestriol caused the HR to increase from 6.89 to 8.18 (3.22–20.76). Adjustment for the use of sedatives caused the HR to increase from 6.89 to 7.58 (3.00–19.18). Adjustment for loop diuretics caused the HR to decrease to 6.13 (2.36–15.91). The use of loop diuretics had an age-adjusted HR for a hip fracture of 2.53 (1.29–4.96).

For systemic estrogens the usage rate was 0% in the group with gait speed <0.8 m/s and 5% in the group with gait speed ≥0.8 m/s. For sedatives the rate was 42% for the group with gait speed <0.8 m/s and 45% for the group with gait speed ≥0.8 m/s. The association between sedatives and an increased mortality was nearly significant, HR 1.58 (p= 0.099), however there was no association to an increased fracture risk. Fine and Gray regression showed a non-significant HR for a hip fracture of 1.34 (p=0.380) when mortality was used as a competing risk.

The mean age of those who used systemic estrogens was 72 years and for non-users 73 years. The mean age of local oestriol users was 72 while the non-users were older with a mean age of 75. The mean ages of those sedative users and non-users were the same, 73 years. The HR for a hip fracture for one year increase in age was 1.18 (1.04–1.33). The relation between gait speed and major osteoporotic fractures was confounded by use of loop-diuretics but not by sedatives.
Table 6. Reclassification table. The effect of adding gait speed to FRAX regarding classification of the study population into a low-risk group with ≤15% risk for a hip fracture and a high-risk group with >15% risk.

<table>
<thead>
<tr>
<th>Participants with fracture during follow-up</th>
<th>( n ) before addition of gait speed to FRAX</th>
<th>Low risk after addition of gait speed to FRAX</th>
<th>High risk after addition of gait speed to FRAX</th>
<th>Addends to sum to NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk according to FRAX</td>
<td>33</td>
<td>19</td>
<td>14</td>
<td>+ 14/38</td>
</tr>
<tr>
<td>High risk according to FRAX</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>-1/38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants without fracture during follow-up</th>
<th>( n ) before addition of gait speed to FRAX</th>
<th>Low risk after addition of gait speed to FRAX</th>
<th>High risk after addition of gait speed to FRAX</th>
<th>Addends to sum to NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk according to FRAX</td>
<td>288</td>
<td>246</td>
<td>42</td>
<td>-42/309</td>
</tr>
<tr>
<td>High risk according to FRAX</td>
<td>21</td>
<td>10</td>
<td>11</td>
<td>+10/309</td>
</tr>
</tbody>
</table>

a) Gait speed was not tested at baseline for two of the participants who fractured, why the number of participants with a fracture in this table were 40-2=38.

**Results from table 6:**

NRI=14/38-1/38-42/309+10/309=0.24

**Sensitivity** changed from 288/309 to (246+10)/309=from 93% to 83%

**Specificity** changed from 5/38 to 18/38=from 13% to 47%
Table 7. Reclassification table. The effect of adding one-leg standing time (OLST) to FRAX regarding classification of the study population into a low risk group ≤15% for a hip fracture and a high-risk group with >15% risk.

<table>
<thead>
<tr>
<th>Participants with fracture during follow-up</th>
<th>n before addition of OLST to FRAX</th>
<th>Low risk after addition of OLST to FRAX</th>
<th>High risk after addition of OLST to FRAX</th>
<th>Addends to sum to NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk according to FRAX</td>
<td>34</td>
<td>21</td>
<td>13</td>
<td>+13/40</td>
</tr>
<tr>
<td>High risk according to FRAX</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>-2/40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants without fracture during follow-up</th>
<th>n before addition of OLST to FRAX</th>
<th>Low risk after addition of OLST to FRAX</th>
<th>High risk after addition of OLST to FRAX</th>
<th>Addends to sum to NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk according to FRAX</td>
<td>288</td>
<td>212</td>
<td>76</td>
<td>-76/309</td>
</tr>
<tr>
<td>High risk according to FRAX</td>
<td>21</td>
<td>10</td>
<td>11</td>
<td>+10/309</td>
</tr>
</tbody>
</table>

Results from table 7:

NRI = 13/40 - 2/40 - 76/309 + 10/309 = 0.061

Sensitivity changed from 6/40 to (13+4)/40 = from 15% to 43%

Specificity changed from 288/291 to (212+10)/291 = from 99% to 76%

4.6 CONFounding BY MEDICAL TREATMENTS

During follow up, the participants were treated with different medications according to table 7. All results in this thesis have been adjusted for the use of each of these medications. If not stated in the results section, the results were not significantly changed by adjustment for any of the medications in table 8. The possible reasons for the confounding in relations to hip fractures is mentioned in the discussion section and may be applied to major osteoporotic fractures as well. A significant change was defined as a
change in HR, OR, or beta coefficient after adjustment of more than 10% or a p-value >0.05.

Table 8. Proportions of the participants who used medications at any time during follow up.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D3</td>
<td>70%</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>30%</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>13%</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>15%</td>
</tr>
<tr>
<td>Calcium</td>
<td>66%</td>
</tr>
<tr>
<td>SERM</td>
<td>2%</td>
</tr>
<tr>
<td>Sedatives</td>
<td>46%</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>28%</td>
</tr>
<tr>
<td>Thiazides</td>
<td>33%</td>
</tr>
<tr>
<td>Local estradiol</td>
<td>12%</td>
</tr>
<tr>
<td>Local oestriol</td>
<td>3%</td>
</tr>
<tr>
<td>Systemic estrogens</td>
<td>5%</td>
</tr>
</tbody>
</table>

5. DISCUSSION

5.1 MAIN FINDINGS
The main overall findings were that both OLST and gait speed were FRAX-independent predictors of both hip fractures and major osteoporotic fractures. Although OLST and gait speed were moderately correlated, none of them was a confounder to the other’s relation to fracture risk. IGFBP-1 had a positive linear relation to the risk of both hip fractures and major osteoporotic fractures. IGFBP-1 was neither correlated to nor confounded by OLST or gait speed. However, FRAX-estimated fracture risk seemed to be a confounder. A MNA score ≤23.5 was associated to an increased mortality. A MNA score ≤23.5 was also associated to a shorter OLST, a higher IGFBP-1 and a slower gait speed.
The main finding of study I was that the group with "risk of malnutrition" according to MNA had a 2.37 times higher risk of dying at all points of time during follow-up, compared to the group which was characterized as "normal nutritional status". This finding was not confounded by differences in the baseline prevalence of smoking or cardiovascular disease or the presence of current or previous malignant disease. The main finding of study II was that for one second longer OLST the age-adjusted risk was 5% lower for a hip fracture and 3% lower for a major osteoporotic fracture. This association could partly be explained by BMD but not by FRAX risk. The predictive accuracy for a hip fracture of OLST was also similar to that of FRAX in our population. The age-adjusted HR for a hip fracture for OLST <10 s compared to OLST ≥10 s was 2.60 which is much lower than the HR of 9.1 found in Finnish women by Kärkkäinen and colleagues (130). This difference might be explained by the fact that the women in the Finnish study were much younger than in our study. The 95% CI was also very wide, 1.98–42.00 and overlaps our CI of 1.36–4.95 which means there is no significant difference in HRs between our studies. Other studies have evaluated the fracture risk for OLST <5s compared to OLST ≥5 s and found results similar to those in our study (42,131). The main finding in study III was that IGFBP-1 had a positive linear relation to the risk of both hip fractures and major osteoporotic fractures. To our knowledge, these relations have not been studied in any previous studies. The relation between IGFBP-1 and hip fracture risk was mediated by 45% by femoral neck BMD. However, the relations described in other studies between high IGFBP-1 and low BMI (132), high IGF-I (133) and chronic kidney failure with a low GFR (134) could not explain the relation between high IGFBP-1 and high hip fracture risk in our study. The main finding of study IV was that information about maximum gait speed seemed to have an incremental value to the predictive accuracy for hip fractures, when it was added to a FRAX assessment, compared to a FRAX assessment alone. OLST did not show an additive effect to FRAX according to NRL. In the study by Wihlborg and colleagues (42), gait speed was measured the same way as in our study. The results were also similar with an unadjusted HR of 1.42 (1.20–1.67) for a hip fracture for each SD decrease in gait speed compared to 2.26 (1.65–3.11) in our study.

5.2 MNA AS A PREDICTOR OF MORTALITY

The relation between MNA and mortality was confounded by each of calcium/vitamin D3 treatment and treatment with loop diuretics. The participants who were treated with calcium/vitamin D did not have a lower vitamin D at baseline but a significantly lower T-score at the femoral neck. A low T-score is a strong predictor for mortality why the lower T-scores in the calcium/vitamin D3 treated group was probably the reason for this treatment being a confounder. Treatment with loop diuretics is associated with chronic heart failure which shortens life considerably which I probably why this treatment was a confounder.

Even though our study confirmed other studies' findings that a lower MNA score is associated with a higher mortality, this does not say whether the increased mortality is due to malnutrition. We have some doubts as to whether it is correct to use merely an MNA score to establish the diagnosis of malnutrition and from that, to make
recommendations that oral supplements are of benefit for that patient. This is what the algorithm on page 8 in the MNA manual from the official MNA site implies (72). It is important to offer oral supplements to elderly who actually are malnourished (135) but the diagnosis may need more support than just an MNA score. Our reasons for this view follow.

The initial construction and validation of MNA in the early nineties, described below, was thorough. Both the full MNA and the six-item MNA have shown to be predictive for mortality in various populations (68) and compared to screening tools for adjacent conditions such as frailty (136). However, we have not been able to find that, since the first two studies, MNA has ever been validated against a gold standard for the diagnosis of malnutrition in any other populations. Nor have we found any validations of the six-item MNA against other malnutrition standards than the full MNA. MNA has been correlated to FFMI in COPD patients (137) but failed to identify individuals with a low FFMI in rheumatoid patients (138).

5.3 OLST AS A PREDICTOR OF FRACTURES

In our study, age-adjusted OLST had a predictive accuracy for hip fractures comparable to that of FRAX. Since OLST and FRAX were not correlated, but had similar ROC areas, they probably both identified only some of the high-risk individuals, but the high-risk individuals they identified were not the same persons. This theory is supported by the fact that there is a statistical interaction between OLST and FRAX risk. As a result, those with both a short OLST and a high FRAX-risk had a much higher risk of a hip fracture than persons who had only one of short OLST or high FRAX-risk (Table 3). Although they were not correlated and were both strong risk factors with fairly good predictive accuracy, the addition of OLST to FRAX did not show any clinical value in our population according to any of our measures of predictive accuracy AUC, Harrell’s c and NRI. Yet, to gain sensitivity you must often sacrifice specificity and if you look at the reclassification tables and calculate the changes in sensitivity and specificity, you get a much more detailed view. The sensitivity, which was very low at a mere 15% with FRAX as an only predictor, increased to 43% with the addition of gait speed while the specificity decreased from 99% to 76%. Perhaps the situation with a better balance between sensitivity and specificity, 43% and 76%, is preferable to 15% and 99% even though NRI shows no benefit. The effects on NRI are also much dependent on the risk cut-offs used for categorization. In this case there was no predefined clinical cut-off available why the highest quartile of FRAX risks was the designated high-risk group. Another cut-off would have resulted in a different NRI. The 30% cut-off used for major osteoporotic fractures resulted in a nonsignificant NRI. This is probably because OLST is not as strong a risk factor for major osteoporotic fractures, as it is for hip fractures. This can be demonstrated by the fact that the age-adjusted HR for OLST <10 sec compared to OLST ≥10 sec was 2.60 for a hip fracture but only 1.82 for a major osteoporotic fracture. The analysis of mortality as a competing risk did not significantly change the HR for a hip fracture. This may be explained by the fact that the times-to-event were strongly correlated.
5.4 **IGFBP-I, WHAT DOES IT MEASURE?**

The relation between IGFBP-I and fracture risk has never been studied before. The most interesting thing is not that a high IGFBP-I may be associated with an increased hip fracture risk, but that the relation between high IGFBP-I and hip fractures is not explained by differences in either BMI or IGF-I. Also, BMD only explains 45% of the effect of IGFBP-I on hip fracture risk so there are probably other fracture risk factors associated with IGFBP-I. The hip fracture risk factors gait speed and OLST do not seem to be confounders to the relation between IGFBP-I and hip fractures. Since there is evidence that both a slow gait speed and a short OLST could be associated with an increased risk of falling, perhaps the association between high IGFBP-I and a high hip fracture risk may not be explained by an increased fall risk. What apart from low BMD could then be the reason for the increased hip fracture risk?

Unfortunately we have no data on muscle strength or bone quality which might be able to explain some of the association. Low muscle strength may impair the protective responses in a fall so that it leads to fracture when the patient falls directly on the hip (139). BMD does only measure some aspects of bone strength so that a bone with the same BMD may have different resistance to trauma (140).

5.5 **GAIT SPEED AS A FRACTURE PREDICTOR**

Gait speed <0.8 m/s was a very strong risk factor for both hip fractures and major osteoporotic fractures in our study. Added to FRAX, gait speed also seemed to have an incremental value to FRAX alone in the accuracy for hip fracture prediction according to categorical NRI. The FRAX-estimated hip fracture risk was a negative confounder to the age-adjusted HR for gait speed <0.8 m/s compared to ≥0.8 m/s. This may be explained by the fact that gait speed was moderately correlated to BMI, which is included in FRAX. The unadjusted HR for a hip fracture was 8.29 which is close to the FRAX-adjusted HR of 8.23. For major osteoporotic fractures the situation was similar with an HR of gait speed <0.8 m/s compared to ≥0.8 m/s of 3.71 both unadjusted and adjusted for FRAX-estimated risk for major osteoporotic fractures.

Thus gait speed was a FRAX-independent risk factor for both hip fractures and major osteoporotic fractures in our study population. However, there was no interaction between gait speed and FRAX-risk, as for OLST.

The hip fracture risk was not higher for participants who used sedatives. The negative confounding by the use of sedatives could be due to the higher usage rate in the group with gait speed ≥0.8 m/s and that the use of sedatives had a close to significant HR for an increased mortality. This could cause the risk of a hip fracture to be underestimated by Cox regression, because they died before they had a chance to fracture. This theory could unfortunately not be supported by analyzing the effect of sedative use on fracture risk with mortality as a competing risk. The HR for a hip fracture was still non-significant. The use of loop diuretics was a confounder to the relation between gait speed and hip fracture risk which can be explained by that the use of loop diuretics was a risk factor for hip fractures. The mechanism for this can however not be explained by the results in our
study.
The use of systemic and local estrogens were negative confounders to the relation between gait speed and hip fracture risk which could be explained by the fact that the participants who used systemic or local estrogens were younger and that higher age was associated with a higher hip fracture risk.

Gait speed is usually measured at “habitual pace” and over a shorter distance than 30 meters and without turning halfway as was the case in our study (110). Our gait speed measurement shows similarities to the “Timed up-and-go test” (TUG test). In a TUG test the test person is timed as he or she rises from a chair, walks three meters, turns and walks back to sit down again on the chair. The TUG test has been thoroughly studied as a risk factor for falls (95, 96) and found to be a good predictor of previous falls, but to have a limited ability to predict future falls. Unfortunately, we have no follow-up data on incident falls, only fractures.

5.6 STRENGTHS AND WEAKNESSES OF THE PROJECT
A strength of the project is that it is population-based why the results may more easily be generalized to any population of elderly Swedish women. Other strengths are the long follow up of ten years and that no one was lost to follow up. A weakness is that the population is quite small which means that less strong associations may pass undetected. Another weakness is that the study population was quite healthy compared to the general elderly population. One consequence of this “healthy participant bias” is that we had very few participants with signs of malnutrition. This means for example that we cannot be sure that the relation we found between IGFBP-I and fracture risk is BMI-independent also in less well-nourished individuals.

6. FUTURE PERSPECTIVES
It would be valuable to validate the MNA against newer definitions of malnutrition, including measures of body composition by either DXA or Bioimpedance (BIA). This should be done to ensure that MNA may diagnose malnutrition in settings different from the original e.g. in community-dwelling individuals. Since many of the risk factors for hip fractures either make the bone more fragile or increase the risk of falling (37) it would be interesting to look at the association between IGFBP-I and fall risk. Since high IGFBP-I also has been associated with increased mortality (141), it would be interesting to investigate the relations between high IGFBP-I and both sarcopenia and the “frailty phenotype”. This is a syndrome which is associated with increased mortality in the elderly, characterized by weight loss, weakness, exhaustion, slowness and a low degree of activity (142). The clinical value of adding either OLST or gait speed to FRAX should be evaluated in larger study populations.

7. SUMMARY IN SWEDISH
Bakgrund
Fragilitetsfrakturer kallas de frakturer som uppstår till följd av en belastning som är så liten att den inte borde orsaka fraktur hos en frisk person. Vanliga fragilitetsfrakturer är höftfraktur, kotfraktur, överarmsfraktur, underarmsfraktur och bäckenfraktur.

Fragilitetsfrakturer är ett folkhälsoproblem som medför stora negative hälsoeffekter och stora kostnader för samhället. Sverige är tillsammans med de övriga nordiska länderna särskilt drabbat då vi har världens högsta antal höftfrakturer per invånare med cirka 18000 höftfrakturer per år. En höftfraktur medför i snitt kostnader för samhället på 125 000 kr första året. Kostnaden för frakturer hos äldre är cirka 12.5 miljarder per år i Sverige. Det positiva i sammanhanget är att det finns effektiva metoder att förebygga fragilitetsfrakturer hos de som har en hög risk för detta. Metoderna innefattar både fallförebyggande åtgärder som fysisk träning och skelettstarkande läkemedel. Bekymret har varit att med någon större säkerhet veta vem som kommer drabbas av en fraktur om hon eller han inte får någon förebyggande behandling. Vi vet att kvinnor har en dubbelt så hög ris som män för att drabbas av en fragilitetsfraktur och att risken också ökar med ökande ålder från cirka 50 års ålder och uppåt. De som redan haft en fragilitetsfraktur har också en kraftigt ökad risk för att få ytterligare frakturer. För att bedöma skelettets styrka gör man ofta en mätning av bentätheten i gram/cm² med hjälp av en rögtenteknik förkortat kallad DXA (Dual X-ray absorptiometry). De som ha ett bentäthetvärde under en viss gräns sägs ha benskörhet eller "ostoporos" vilket i sig alltså inte är en sjukdom utan en riskfaktor. Att ha en låg bentäthet mått med DXA innebär dock en starkt ökad risk för fragilitetsfrakturer. En del har bara oturen att drabbas av osteoporos utan att det går att finna någon viss orsak till tillståndet. En del sjukdomar och tillstånd kan dock medföra osteoporos och den kallas då för "sekundär osteoporos". Exempel på sådana sjukdomar och tillstånd är hyperthyreos (överskott av sköldkörtelhormon), hyperparathyreos (överskott av bisköldkörtelhormon), hypogonadism (brist på könshormoner), överkonsumtion av alkohol, ökad fallrisk, undernäring och diabetes typ 1. Om någon av ens föräldrar haft en fragilitetsfraktur medför det också en ökad risk för att själ drabbas av en fraktur. Det finns en hel rad av kända riskfaktorer för fragilitetsfraktur och för att underlätta sammanvägningen av sådana faktorer finns ett flertal bedömningsinstrument eller "riskkalkylatorer" varav FRAX är den mest använda i Sverige. FRAX innefattar elva olika riskfaktorer och man kan lägga till en tolle i form av bentäthet i lårbenshalsen, om ett sådant värde finns tillgängligt. FRAX ger ett resultat i form av två 10-års risker för fraktur. En risk för höftfraktur och en risk för en "major osteoporotic fracture" vilket innefattar höftfraktur, symtomgivande kotfraktur, fraktur av överarm/axel och fraktur av underarm.

FRAX har visat sig fungera medelbra till bra men inte så väl som man skulle önska. Det finns fortfarande ett stort antal patienter som felaktigt bedöms ha en så låg frakturrisk att de inte behöver någon frukturövervakande behandling och ett stort antal patienter som rekommenderas behandling i onödan. Av detta skälet är det av intresse att försöka hitta nya sätt att bedöma risken för fragilitetsfrakturer att använda antingen som enklare och snabbare alternativ till FRAX eller som komplettering till FRAX. Syftet med detta doktorandprojekt är att undersöka hur väl ett antal nya faktorer kan bedöma risken för framtida fraktur, och relationen mellan dessa faktorer. De faktorer som undersöks är ett test för undernäring kallat "Mini Nutritional Assessment" (MNA), ett balanstest kallat one-leg standing time (OLST), ett protein i blodet kallat "insulin-like growth factor binding
protein 1° IGFBP-I och ett mätt på maximal gånghastighet för enkelhetens skull kallat "gait speed".

**Delstudie 1** är en studie av om låga poäng på det screening-instrument för undernäring, MNA, som ofta används inom svensk vård är associerat med en kortare överlevnad. Anledningen till att undersöka detta i vår studiepopulation är att MNA bara i enstaka fall värderats för hemmaboende äldre, och inte heller med en så lång uppföljningstid.

**Delstudie 2** undersöker om den maximala tiden som studiedeltagarna kunde stå på ett ben med öppna ögon (OLST), har ett samband med risken för att drabbas av höftfraktur under de kommande tio åren. Studien undersöker också hur exakt en skattnings av frakturrisk med hjälp av OLST är jämfört med FRAX i vår studiepopulation.

**Delstudie 3** utvärderar sambanden mellan serumkonzentrationen av IGFBP-I, insulin-like growth factor 1 (IGF-I), BMI, bentätighet och risken för en höftfraktur. Anledningen till att studera detta är att IGFBP-I vanligtvis ses som ett protein som liksom namnet säger, inte har egna effekter i kroppen utan enbart verkar via att binda upp IGF-I. Låga koncentrationer av IGF-I har kända negativa effekter på skelettomsättning och är associerat till en ökad frakturrisk. IGFBP-I stiger vid negativ energibalans varför det finns en förhoppning om att det ska kunna vara en markör för undernäring.

**Delstudie 4** undersöker sambandet mellan maximal gånghastighet på 15 meter x 2 med en 180 graders vändning emellan och risken för en höftfraktur. Den undersöker också om gånghastigheten eller OLST skulle kunna förbättra exaktheten i riskbedömningar gjorda med FRAX.

**Material och metoder**

**Studiepopulationen**


**Mini Nutritional Assessment (MNA)**


**Bentäthetsmätningar**

Bentäthetsmätningarna utfördes på Karolinska universitetssjukhuset i Solna med mätutrustningen Hologic QRD 4500. Dagliga mätningar med en fantom med känd bentäthet utfördes för att säkerställa exaktheten i mätningarna.

**Mätning av one-leg standing time**


**Analyser av IGFBP-I, IGF-I och D-vitamin**

Alla blodprover togs fastande mellan klockan 8 och 10 på förmiddagen. Provrören sparades i frys så att alla analyser av vardera IGFBP-I, IGF-I och D-vitamin kunde analyseras vid ett tillfälle. Analyserna utfördes på det molekylärmedicinska laboratoriet på Karolinska Universitetssjukhuset i Solna. IGFBP-I analyserades med metoden “radioimmunoassay” (RIA) vilket har betydelse för jämförelser med studier som använder andra metoder vilka ger helt andra vården på IGFBP-I.

**Mätning av maximal gånghastighet**

Gånghastigheten mättes då studiedeltagaren uppmanades att så fort som möjligt gå från ett streck på golvet till ett annat streck 15 meter bort, vända och återvända till starten. Hastigheten mättes som 30 meter dividerat med antalet sekunder, alltså medelhastigheten.

**Etikprövning**

Projektet godkändes av Humanetiska kommittén vid Huddinge sjukhus och av Strälskyddskommittén vid Karolinska Sjukhuset.

**Resultat**
**Delstudie 1** visade att ha en MNA-poäng <24 poäng innebar en 2,4 gånger ökad risk att dö jämfört med att ha en MNA-poäng ≥24 poäng. Detta samband kunde dock delvis förklaras av att fler i gruppen med MNA <24 poängs behandlades med vattendrivande läkemedel av typen loop-diuretika någon gång under uppföljningstiden. Loop diuretika används framförallt vid hjärt- eller njursvikt vilket i sig medför en ökad risk att dö oavsett om man är undernärd eller inte.

**Delstudie 2** visade att ju längre tid som deltagarna kunde stå på ett ben (OLST), desto lägre risk hade de att drabbas av någon typ av fragilitetsfraktur (någon av höftfraktur, symtomgivande kotfraktur, överarmsfraktur, underarmsfraktur eller bäckenfraktur). Detta samband var oberoende av vilken frakturrisken som FRAX bedömt deltagarna ha när studien startade. Exaktheten i riskbedömningarna var jämförbara när risken bedömdes med tiden de kunde stå på ett ben och om man bedömde den med FRAX. En hög FRAX-risk och en samtidigt kort OLST förduubblade risken för fraktur jämfört med om man hade bara en hög FRAX-risk eller bara en kort OLST.


**Delstudie 4** visade att den maximala gånghastigheten var en stark riskfaktor för alla typer av fragilitetsfrakturer. De som inte kunde gå minst 0,8 m/s hade 6,9 gånger högre risk att drabbas av en höftfraktur när man tog hänsyn till skillnader i deltagarnas ålder. Risken var oberoende av vilken FRAX-beräknad frakturrisk deltagarna hade vid studiestart. Tillägg av gånghastighet till FRAX förbättrade exaktheten i bedömningen av vilka som hade en tioårs höftfrakturisk på <15% respektive ≥15%, med 24%.

**Slutsatser och betydelse**


Vad gäller gånghastighet så verkar det kunna tillföra något till FRAX riskskattningar. Det vore mycket intressant att få studera detta i större studier. Att både ha hög FRAX-risk och långsamt gånghastighet ökar dock inte risken för fraktur jämfört med om man har en av dessa riskfaktorer.
8. ACKNOWLEDGEMENTS

I would like to thank the following persons for supporting me in my PhD project:

Helena Salminen, my main supervisor for always being available, knowledgeable, supportive and an excellent travel companion.

Maria Sääf, my co-supervisor for patiently listening to my incomplete reasoning and giving well-founded advice.

Lars-Erik Strender, my co-supervisor for being supportive and taking worries out of parts of the academic process which could seem frightening to a newbie.

Sven-Erik Johansson, professor in epidemiological statistics, for enthusiastic help with statistical dilemmas.

Sven Nyrén, Radiologist and head of the bone mineral section at Karolinska Universitetssjukhuset in Solna for ambitious review of the articles, an always friendly response and a thrilling series of Facebook updates.

Bo Freyschuss, my mentor, for taking the time to meet me although having a terribly congested calendar, and for careful listening and well-reasoned advice.

Faramarz Torabi, for patient work with medical journals and for being a first-class roommate.

My family, Maria, Saga, Vera and Arvid—always on my mind, reviving my occasionally sinking spirits in times of cognitive meltdown during the writing of this thesis. Love you all and always!
9. FINANCIAL SUPPORT
The project has received grants from Stockholm County Council.

10. REFERENCES


125. Povoa G, Roovete A, Hall K. Cross-reaction of serum somatomedin-binding protein in a radioimmunoassay developed for somatomedin-binding protein


