# From Department of Clinical Science, Intervention and Technology (CLINTEC) Division of Orthopedics and Biotechnology Karolinska Institutet, Stockholm, Sweden

# FRACTURE HEALING, FUNCTIONAL OUTCOME AND HEALTH RELATED QUALITY OF LIFE IN YOUNGER PATIENTS WITH A FEMORAL NECK FRACTURE

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"Discipline is the bridge between goals and accomplishment."					
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### Fracture healing, functional outcome and health related quality of life in younger patients with a femoral neck fracture

### THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Katty, Isabel and Emelie

#### **ABSTRACT**

Few prospective studies have investigated the patient-reported outcome measures (PROM) in patients less than 70 years that sustained a femoral neck fracture (FNF) treated with closed reduction and internal fixation (CRIF). The health-related quality of life (HRQoL) using the self-administered questionnaires EuroQol 5 Dimension (EQ-5D) and Short Form-36 Health Survey (SF-36) and with a long term follow-up has not previously been examined in this group of patients.

Factors associated with healing complications leading to a major re-operation with a total hip replacement as well as mortality has not been investigated for this group. The ability of the questionnaires EQ-5D and SF-36 to reveal clinical important changes in health over time, the so called responsiveness, has not been studied for patients younger than 70 years with a FNF.

The comprehensive goal of this thesis was to investigate the HRQoL, functional outcome, factors associated with a major re-operation as well as mortality with a 4, 12, 24-month and 10-year follow-up in patients 20-69 years that sustained a FNF treated with CRIF. Another aim was to determine the responsiveness of EQ-5D and SF-36 in this specific group of patients.

#### Methods:

Study I: 182 patients with displaced and non-displaced FNF were included in a prospective multicenter study. At each follow-up, clinical and radiographic examinations were performed at 4, 12 and 24 months. Gathered data included HRQoL (EQ-5D and SF-36), hip function according to Harris Hip Score (HHS), fracture healing complications such as non-union (NU) and avascular necrosis (AVN), co-morbidities and major re-operations with a hip arthroplasty.

Study II: 128 patients from the same cohort as Study I with a displaced FNF were included. At inclusion, bone mineral density (BMD) was measured by DXA. A logistic regression was performed to find associated variables with a re-operation due to NU or AVN detected at 4, 12 and 24-months follow-up.

Study III: A 10-year follow-up of the cohort in Study I. The hip function was assessed using the Hip Disability Outcome Score (HOOS) and HRQoL was evaluated using the EQ-5D questionnaire. Deceased patients had the date of death recorded and associated factors with mortality were analyzed by regression logistic calculation of baseline data.

Study IV: The responsiveness of the HRQoL instruments SF-36 and EQ-5D was evaluated by estimating the standardized effect size (SES), standardized response mean (SRM), receiver operating characteristic curve (ROC) and area under the curve (AUC).

#### **Results:**

Study I: At 24 months, the hip function according to HHS in patients with a displaced fracture showed a good or excellent score in 73% and in those with a non-displaced fracture 85% (p = 0.15). EQ-5D and SF-36 were the lowest at 4 months and improved at 12 and 24 months but did not regain pre-fracture level (p<0.01) regardless of fracture type. Patients with a displaced FNF had a NU in 23% of the cases, AVN in 15% and a total of 28% had a major re-operation. No patients with a non-displaced FNF developed NU, 12% developed an AVN and a total of 8% had a major re-operation with a total hip replacement (THR). Study II: The rate of a major re-operation was 6%, 16% and 28% at 4, 12 and 24 months. Patients having a low BMD (OR 5.5, CI 1.1-27) and harmful alcohol consumption (OR 3.2, CI 1.2-8.8) were more likely to undergo a major re-operation due to NU or AVN. Study III: From initial 182 included patients, a total of 88 patients participated. The EQ-5D improved compared to 24-month follow-up (p=0.006). However, the EQ-5D did not

recover to the pre-fracture level (p<0.001). The score, however was equivalent to population data of Sweden. Factors associated with mortality at 10 years were higher age, co-morbidity, osteoporosis and smoking.

Study IV: SES at 4 months was large for EQ-5D and SF-36 and moderate at 12- and 24-month follow-up. The correlation between the changes in HHS (4–24 months) and HRQoL were moderate to weak but the correlation between total scores were strong. The ability to predict and follow the external standard as well as the effect sizes implies that the internal and external responsiveness of SF-36 and EQ-5D were good.

#### **Conclusion:**

The functional outcome was good or excellent in more than two thirds and the HRQoL continues to improve up to 10 years after sustaining a FNF in patients younger than 70 years treated with CRIF. However, the HRQoL did not reach the level before fracture, probably because all included subjects were 10 years older. The EQ-5D at 10-year follow-up were equivalent to sex- and age-matched reference population in Sweden. The majority of the patients with a displaced FNF healed and less than 10% of patients with a non-displaced FNF underwent a major re-operation. A low BMD and harmful alcohol consumption according to AUDIT increased the risk for undergoing a major re-operation with a total hip replacement. One third of the patients were deceased 10 years later and they were more compromised with illnesses and smoking comparing to surviving subjects. The HRQoL questionnaires EQ-5D and SF-36 were both responsive for changes in health over time. EQ-5D was easier to administer and can be used alone compared to the more complex and time-consuming SF-36.

#### LIST OF SCIENTIFIC PAPERS

I. Good functional outcome but not regained health related quality of life in the majority of 20-69 years old patients with femoral neck fracture treated with internal fixation- A prospective 2-year follow-up study of 182 patients

Pierre Campenfeldt, Margareta Hedström, Wilhelmina Ekström, Amer N. Al-Ani. Injury, Int. J. Care Injured, 48 (2017) 2744-2753.

- II. Low BMD and high alcohol consumption predict a major re-operation in patients younger than 70 years of age with a displaced femoral neck fracture- A two- year follow up study in 120 patients
  Pierre Campenfeldt, Amer N. Al-Ani, Margareta Hedström, Wilhelmina Ekström. Injury, Int. J. Care Injured, 49 (2018) 2042-2046.
- III. Health related quality of life and mortality 10 years after a femoral neck fracture in patients younger than 70 years Pierre Campenfeldt, Wilhelmina Ekström, Amer N. Al-Ani, Emanuel Weibust, Katarina Greve, Margareta Hedström. Injury, Int. J. Care Injured, in press.
- IV. Good responsiveness with EuroQol 5-Dimension questionnaire and Short Form (36) Health Survey in 20–69 years old patients with a femoral neck fracture: A 2-year prospective follow-up study in 182 patients Niklas Honkavaara, Amer N. Al-Ani, Pierre Campenfeldt, Wilhelmina Ekström, Margareta Hedström. Injury, Int. J. Care Injured 47 (2016) 1692–1697.

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#### LIST OF ABBREVIATIONS

ASA American Society of Anaesthesiologists

AUC Area under the curve

AUDIT Alcohol use disorder identification test

AVN Avascular necrosis

BMC Bone mineral content

BMI Body mass index

CRIF Closed reduction internal fixation

DXA Dual energy X-ray absorptiometry

EQ-5D The 5-dimensional scale of the EuroQol

FNF Femoral neck fracture

HHS Harris Hip Score

HRQoL Health-related quality of life

HOOS Hip disability and osteoarthritis outcome score

IF Internal fixation

MID Minimally important difference

NU Non-union

OR Odds ratio

PROM Patient-reported outcome measure

ROC Receiver operating characteristics

SD Standard deviation

SES Standardized effect size

SF-36 Short form 36

SRM Standardized response mean

THR Total hip replacement

#### 1 THESIS AT A GLANCE

## I. Good functional outcome but not regained health related quality of life in the majority of 20-69 years old patients with femoral neck fracture treated with internal fixation- A prospective 2-year follow-up study of 182 patients.

How was the HRQoL and hip function affected and to what extend did the fracture heal after a FNF in patients younger than 70 years treated with CRIF?

Patients: 182 patients with a FNF both displaced and non-displaced.

**Method:** Data of ASA, EQ-5D, SF-36, HHS and major re-operation were collected as well as radiological examinations at 4,12 and 24-month follow-up.

**Conclusion:** EQ-5D, SF-36 and HHS were at the lowest at 4-month follow-up and highest at 24-month follow-up, but the level of pre-fracture was not reached. Two thirds of the patients had good or excellent hip function according to HHS at 24-month follow-up. A third of the patients with displaced FNF underwent a major re-operation.

## II. Low BMD and high alcohol consumption predict a major re-operation in patients younger than 70 years of age with a displaced femoral neck fracture- A two- year follow up study in 120 patients.

Are there any predictors of failed fracture healing?

Patients: 120 patients with a displaced FNF.

**Method:** A DXA at inclusion, ASA and co-morbidities were collected and a logistic regression was performed to find variables associated with a major re-operation caused by a non-union or avascular necrosis at 24-months follow-up.

**Conclusion:** A low BMD and harmful alcohol drinking elevates the risk of a major reoperation.

### III. Health related quality of life and mortality 10 years after a femoral neck fracture in patients younger than 70 years.

How was the HRQoL and hip function affected and what factors were correlated with mortality 10 years after a FNF?

**Patients**: 88 patients with both displaced and non-displaced FNF participated through self-administered questionnaires. 170 patients participated in the mortality analysis.

**Method:** The EQ-5D was compared with previous results and hip function was assessed according to HOOS. Factors associated with mortality were analyzed by regression logistic calculation of baseline data of co-morbidities, DXA and life-style factors.

**Conclusion:** The functional outcome and HRQoL continues to improve up to 10 years after a FNF but the pre-fracture levels were not regained. One third of the patients were deceased and factors associated with mortality 10 years later were higher age, co-morbidity, osteoporosis and smoking.

# IV. Good responsiveness with EuroQol 5-Dimension questionnaire and Short Form (36) Health Survey in 20–69 years old patients with a femoral neck fracture: A 2-year prospective follow-up study in 182 patients.

Were EQ-5D and SF-36 responsive in measuring the change in HRQoL over time in patients less than 70 years that sustained a FNF treated with CRIF.

**Patients:** 182 patients with a FNF both displaced and non-displaced.

**Method:** Data of EQ-5D and SF-36 were collected at 4,12 and 24-month follow-up. The responsiveness was evaluated.

**Conclusion:** EQ-5D and SF-36 were both responsive in their capacity to detect subjective improvements or worsening in health after a FNF.

#### 2 INTRODUCTION

#### **Background**

The incidence of hip fractures in Sweden is around 16000 annually and the average age among these patients is 80 years [1]. Of all patients sustaining a hip fracture, less than 3% are younger than 50 years [2,3]. Hip fractures are classified according to X-ray findings whether the line of fracture goes through the cervical neck (Figure 1) or through the trochanteric area [4]. The femoral neck fractures (FNF) that constitutes about 50% of all hip fracture [1] are divided into non-displaced and displaced fracture according to the Garden classification (Figure 2) [5].



Figure 1. X-ray demonstrating a displaced femoral neck fracture.

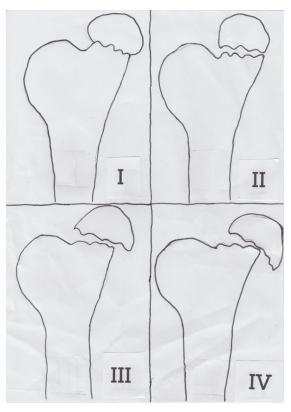


Figure 2. Garden classification I-IV.

#### **Diagnosis and treatment**

Diagnosis of a FNF, Garden classification, the postoperative surgical results as well as healing complications such as non-union (NU) or avascular necrosis (AVN) are assessed by an X-ray taken from two angles: anterior-posterior and a lateral projection [4,5].

The majority of patients with a FNF undergo surgery with either closed fracture reduction and internal fixation (CRIF) (Figure 3) or a hip replacement [1,2,6]. The choice of operating method depends on the patient's age, type of fracture and the patient's medical condition [7]. CRIF is the choice of surgical method in patients above 70 years of age if the FNF is non-displaced (Garden 1-2) [1] and in patients less than 65-70 years regardless of degree of displacement [2,6]. The desire to preserve the native hip joint is the rationale behind this recommendation which may facilitate the patients' future functional demand [8]. The life expectancy in these patients is longer and therefore the risk of surgical revision is increased if operated with hip a prosthesis [9].

During the last 10 years CRIF has gradually been replaced by hip replacement in patients above 70 years with a displaced FNF [1]. Only 2% of all displaced FNF were treated with a hip replacement in 1988 and 86% in 2017 [1].

However, in Sweden an increasing number of patients younger than 70 years suffering from a displaced FNF are treated with total hip replacement (THR) [1]. Another study showed

the same trend in the USA using the American Board of Orthopaedic Surgery database where 13% of patients younger than 65 years were treated with a THR compared to only 1%, twelve years earlier [10].



Figure 3. A FNF treated with CRIF.

#### **Healing complications**

Different studies have shown fewer healing complications in elderly when displaced FNF are treated with hip replacement rather than CRIF resulting in less than 10% of surgical failure [11,12,13]. Displaced FNF treated with IF has a surgical complication frequency of 40-50% in elderly [8,11,14,15,16]. Most common complications are NU and AVN [8,11,14]. NU leads to a re-displacement of the fracture and displacement of the screws [11]. A re-operation is then usually done with a hip replacement [17]. About half of those patients developing AVN do not have any substantial effect on hip function and may not need a re-operation [18,19]. Patients with symptoms from AVN often undergo a re-operation with a THR [20].

Studies showing a high rate of healing complication have evaluated the results in patients with an average age of 80 years [11,12]. Patients 50-70 years of age have rarely been studied separately and are often added to the group of elderly patients [2]. Long time prospective studies in younger patients are lacking and The National Hip fracture registry in Sweden has a follow-up period of only four months and does not focus on re-operations [1].

#### Risk factors for healing complications

Studies analyzing variables connected to a re-operation due to healing complications are few in younger patients younger than 70 years with a FNF [21]. The blood supplying the

femoral head may be affected due to an altered anatomical structure such as fracture displacement and posterior comminution and may lead to AVN or NU [22].

A study by Lindequist et al showed that a screw position that is suboptimal is significantly related to the development of NU [23]. Other studies showed that patients younger than 70 years having a fair or poor fracture reduction have significantly higher frequency of reoperation [6,24]. A study by Parker et al including patients age 60-80 years reported an increased risk of re-operation in female patients with a FNF regardless of age [25].

Several studies have demonstrated an elevated risk for fracture-healing complications in patients having a low bone mineral density (BMD) [26,27,28], while another study did not find such relationship [29]. A low BMD has shown to impede fracture heeling which has been seen in several studies [30,31]. Osteoporosis appears to delay callus maturation and therefore affecting fracture healing [30] and the strength of fixation of an implant will be affected due to altered trabecular and cortical bone structure [31]. No study has investigated the effect of low BMD on the prevalence of healing complications in patients younger than 70 years having a FNF.

#### Bone mineral density measurements in the study

Dual energy X-ray absorptiometry (DXA) is an X-ray of low radiation with a capacity to detect small percentage of bone loss since absorption of radiation is sensitive to calcium content in the skeleton [32]. DXA is used to measure the bone density in the spine, hip and the whole skeleton [33]. Information of BMD provides a diagnostic criteria and can be followed for both treated and untreated patients and provide prognostic information on the probability of future fractures [32]. By densitometric techniques the BMD which is the amount of bone mass per unit area (areal density) or per unit volume (volumetric density), can be estimated in vivo [32]. The results are given in the two measures, T-score and Zscore [33]. The score indicates the amount the subject's BMD varies from the mean. A positive score indicates a higher BMD and a negative scores indicate a lower BMD [33]. The T-score is the relevant measure when screening for osteoporosis since the BMD at the site of the subject is compared to normal mean value of young reference group [33]. The Tscore compares the actual patient's BMD with healthy 30-year-old Caucasian female's BMD at the femoral neck and used in post-menopausal women and men above 50 years of age. The same diagnostic criteria using a female reference range is used in men [33]. The criteria as stated in World Health Organization (WHO) in the diagnosis of osteoporosis is a *T*-score value  $\leq$  −2.5 SD [34]. A *T*-score value  $\geq$  −1 SD is regarded as normal and *T*-score

between < -1 and > -2.5 SD is regarded as osteopenia [34]. The Z-score compares the subjects BMD with age-matched reference group and used in cases of severe osteoporosis, in men younger than 50 years, premenopausal women and in children [34]. The Z-score shows the difference of the standard deviation of the patient's BMD from the average BMD of their sex, age, and ethnicity [34]. A Z-score below -2 SD in young patients (20–49 years), is regarded as a low BMD stated in the International Society of Clinical Densitometry [35].

#### Alcohol use disorder identification test used in the study

Alcoholism has in one earlier study shown to be a significant predictor of surgical failure due to AVN and NU in patients younger than 60 years of age with a hip fracture [6]. High alcohol consumption affects bone metabolism and thereby BMD [36,37], contribute to malnutrition, increase the tendency to fall and causing comorbidities [38] that all may affect the risk for a re-operation.

Alcohol use disorder identification test (AUDIT) is an instrument validated to identify harmful alcohol consumption and dependence [39]. It has 10 questions in which each question has a score of 0-4 points. An indication of harmful drinking is a score of  $\geq 8$  in men and  $\geq 5$  in women [39].

#### **Health-Related Quality of Life**

The surgical outcome has by tradition been evaluated by general or surgical postoperative complications [2,7,19,26]. However, the patient's Health-related quality of life (HRQoL) and function postoperatively might be more relevant to evaluate in these younger patients with a hip fracture [21]. Elderly patients with a FNF often get a reduced HRQoL that persists for a long time [11]. There are several generic instruments for measuring the HRQoL by evaluating the patient-reported outcome measure (PROM) [40]. PROMs are divided into generic or disease-specific [40].

Two of the generic PROM questionnaires are EuroQol 5-Dimension (EQ-5D) and Short Form (36) Health Survey (SF-36) [41,42]. In elderly having a hip fracture, the EQ-5D and SF-36 have in several studies evaluated the outcome of HRQoL and has been found to be both valid and responsive [43,44,45,46,47,48]. The outcome of HRQoL and the responsiveness of SF-36 and EQ-5D have not previously been studied in patients younger than 70 years having a FNF.

#### **Short form 36**

SF-36 has eight different domain scales with 36 items. The first four domains are the SF-36 physical scale; role-physical (RP), physical functioning (PF), general health (GH) and bodily pain (BP). The score of these questions are added and then divided by four in order to get the SF-36 physical score which has a spectrum from 0-100. The last four questions are the SF-36 mental scale; vitality (VT), role-emotional (RE), social functioning (SF), and mental health (MH). By adding the scores and dividing by four the SF-36 mental score is calculated. The SF-36 total score is estimated by adding all scores from the eight questions and divide by eight [41].

#### The 5-dimensional scale of the EuroQol

EQ-5D has two parts; a visual analogue scale (VAS), and a questionnaire composed of five questions regarding five different dimensions; Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression. An index score from the response is calculated in which 1 corresponds to full health and 0 the worst possible health [41]. In order to determine values for 243 possible health states, the time trade off (TTO) method has been used in which the respondents were asked how many years in the current health they would trade off, in order to regain full health if they had 10 years left to live [49]. Dolan et al developed the frequently used UK description-based method [49] in which the responders were described which condition they had thus giving hypothetical values [49]. Burström et al developed a new set of values that is based on a Swedish population and instead of a description based method, an experience-based method was used in which the responders replied according to their own current health [50]. The description-based method is considered inferior to experience-based method since it's not affected by possible adaptation to changes in health [51]. The Swedish value set is more accurate in a Swedish population with a THR compared to the UK set [50]. A disadvantage of the Swedish value set is that it is harder to compare the results with older but similar studies that uses the UK method [51].

#### Responsiveness of EQ-5D and SF-36

The definition of responsiveness of an instrument is the capability to distinguish clinical changes over time in a specified condition and the responsiveness is an important part of validating an instrument [52]. The responsiveness may be divided into an internal and an external responsiveness [53]. The internal responsiveness represents the capability of an instrument to distinguish changes over a time frame and can be expressed in three ways:

change score, standardized effect size (SES) and standardized response mean (SRM) [53]. Change score is defined as the mean change in score between two measures or more in the same group of patients [53]. If the change score is of clinical significance the value is compared to minimally important difference (MID) [53]. The definition of MID is the mean change in score between two measures in which the patients reports a change (positive or negative) in their health [53]. The SES is calculated by dividing mean change score and SD of the baseline score [54]. The SRM is calculated by dividing mean change score and SD of the change score. Results are then evaluated by the Cohen's threshold: large (>0.8), moderate (0.8-0.5) and small (<0.5) [54].

External responsiveness reflects the degree in which a change in a measure corresponds to changes in a reference measure of health or a clinical status [53].

To analyze the external responsiveness an external criterion (EC) is necessary to produce for example using a self-related health (SRH) question [53], early complications [44] or fracture displacement [43]. A dichotomized ECs can then be created suitable for Receiver operating characteristics (ROC) analysis as well as Area under the curve (AUC) calculations [55]. This allows an illustration of the sensitivity and specificity of a measure to detect subjective changes in health [55]. The external responsiveness can also be analyzed by calculating correlations between different instruments.

#### Ceiling and floor effects on EQ-5D and SF-36

A ceiling effect happens when a high proportion of the patients receive the highest scores when performing a test. Therefore, discrimination between patients among the top end of that test is impossible. An acceptable ceiling effect should be less than 15% [56]. Since EQ-5D only can distinguish between 243 unique health states, the ceiling effect is between 26-72% [57,58,59,60]. Therefore, EQ-5D lacks the capacity to distinguishing between health states that are close to full health. [60]. The SF-36 has in several studies demonstrated a non-existing ceiling effect [57,58,60] and is therefore a better instrument for detecting differences between healthy subjects.

A floor effect happens when a high proportion of the patients receive the lowest scores when performing a test. Several studies have demonstrated that there are no floor effect for EQ-5D [57,60,61]. In the SF-36, the domains Role Physical and Role Emotional has in some studies demonstrated a marked floor effect [62,63].

#### Hip specific questionnaires in the studies

There are numerous different reliable and validated hip-specific questionnaires to estimate hip function in patients having a hip disorder such as Hip Osteoarthritis Outcome Score (HOOS) as well as Harris Hip Score (HHS) [64,65]. Both questionnaires have been used in studies with elderly patients with a FNF [66,67] but rarely on younger patients.

#### **Hip Disability and Osteoarthritis Outcome Score**

HOOS is a responsive and validated disease-specific questionnaire for the hip [64]. HOOS is an instrument for analyzing hip disability with or without osteoarthritis. It has five joint-specific subscales: pain, symptoms, ADL, function in sports and recreation and joint-related quality of life [68]. HOOS is used to measure pain and changes over time in patients having a hip disability [64]. Each subscale consists of questions that are graded 0-4 (0 means no problems and 4 extreme problems). Each subscale is scored from 0- 100 where 0 indicates worse outcome [68]. Each dimension of the HOOS is scored independently. When answering the questions, the patients are asked to take the last week into consideration. The test-retest reproducibility is high for HOOS (ICC >0.78) [68].

#### **Harris Hip Score**

HHS is an instrument that is validated and responsive and evaluates function, pain, deformity of the hip and range of motion [65,69]. It has a scale of 100 points in which no deformities of the femoral head gives 4 points and no loss of range of motions gives 5 points. Pain constitute 44 points in which no pain corresponds to a value of 44 and pain that is severe corresponds to a value of 0. Function includes evaluation of daily activities and walking ability and has a maximum level of 43 points. A total value of less than 70 points is categorized as poor, 70-80 good and a value above 80 is considered excellent [65].

#### Mental assessment in the study

The Short Portable Mental Status Questionnaire (SPMSQ) is a screening instrument for cognitive function which is easy to use by healthcare workers. It is composed of 10 questions and  $\geq 3$  errors indicates cognitive impairment [70].

#### **Mortality**

Few studies have investigated mortality among younger patients having a FNF and these were register studies, including several kinds of fractures involving the hip and investigating only a few mortality predictors [71,72]. A British cohort study of 300 women

younger than 65 years with a hip fracture showed a 46 times higher mortality in these patients compared to background mortality [73]. A population-based cohort study of 154000 hip fracture patients in Denmark showed an excess mortality in younger patients with diabetes mellitus [72]. Leu et al reported in a population-based cohort study of 4500 patients 20-40 years old with a hip fracture that factors associated with increased mortality were male gender, treatment with a hemiarthroplasty and a trochanteric fracture [71].

#### 3 RATIONALE

FNF are uncommon in patients younger than 70 years of age and few studies have investigated how the hip function, HRQoL and mortality are affected in these relatively young patients. Studies with a long-term follow-up are mainly retrospective, registry based, and mostly evaluating older patients with a hip fracture. The outcome in older population with a FNF fracture might not be applicable on younger patients despite having the same type of fracture.

Retrospective and registry-based studies are limited since there is a lack of ability to detect key variables missing from the collected data as well as being prone to selection bias. Further, the few studies on younger patients with a hip fracture have not focused on HRQoL and self-assessed function but on surgical failures. No study has looked into factors associated with surgical failure in younger patients with a FNF treated with CRIF. Few studies have investigated mortality in younger patients having a FNF. These studies are register-based, included all kind of hip fractures and examined few predictors of mortality.

There is an increased usage of generic instruments for analyzing the HRQoL in the clinical settings but the instruments must be validated not only for the specific disease but also for the specific group of patients that are intended to be examined. EQ-5D and SF-36 has not been validated for younger patients with a FNF fracture nor the responsiveness to detect clinical important differences.

The aim of the thesis was to investigate how the hip function and HRQoL were affected in the long term after a FNF in patients younger than 70 years treated with CRIF. The thesis was also examining if there were factors associated with a major re-operation with a hip arthroplasty within two years and factors associated with mortality within 10 years after the fracture. Another aim was to determine the responsiveness of EQ-5D and SF 36.

#### 4 AIM OF THE THESIS

To evaluate fracture healing complications, re-operations, hip function and HRQoL two years after a FNF treated with CRIF in patients 20–69 years of age (*Study I*).

To identify which factors that are associated with a major re-operation caused by healing complications in patients younger than 70 years having a displaced FNF and were treated with CRIF (*Study II*).

To evaluate function of the hip, HRQoL and predictors of mortality 10 years after sustaining a FNF treated with CRIF in patients 20-69 years at the time of fracture (*Study III*).

To evaluate if EQ-5D and SF-36 are responsive in patients younger than 70 years having a FNF treated with CRIF (*Study IV*).

#### **5 PATIENTS**

#### **ETHICS**

The studies were conducted in accordance with the principles of the Helsinki Declaration [74]. All protocols used were approved by the local Ethics Committee (Dnr. 2001-427, Dnr. 2013-602-32). The study was reporting according to the STROBE checklist [75]. During the recruitment the patients were given verbal and written information regarding the study and the right to withdraw their consent at any time and for any reason. To protect the identity of the included patients, the collected data were linked to each patient through an unidentifiable code. The key for opening the patient identity was held separately and protected from the collected data. All results were presented on an aggregate-level. The follow-up included integrity questions regarding alcohol consumption as well as HRQoL but this was not an interventional study and the reply did not affect any treatment.

A low-dose radiation of an X-ray of the hip joint before and after surgery is regularly performed on all patients with a hip fracture. The included patients received an additional four X-rays of the hip in a period of 10 years in order to detect fracture healing complications. Early detection of healing complication such as NU lead to an early intervention and patients with a low BMD were referred to their family physician for follow-up and treatment. This may have been unethical toward the excluded patients in which the majority probably did not have any follow-up.

Patients that did not respond to a letter sent to them at 10-year follow-up were phoned by the authors included in paper III. This might have caused a sensation of forced participating in the 10-year follow-up as well as bringing up memories from the past that were not pleasant. However, the authors emphasized during the conversation that participation was voluntarily and explained how the study was being conducted and how handling of personal data was performed.

Previous research in this field is lacking and the total benefits for this group outweighs the risks participating in these studies.

#### **STUDY I**

#### Patients and inclusion criteria

A total of 182 patients having an age span of 20-69 years (median 59 years, 53% women) were consecutively recruited in a prospective multicenter study at four university hospitals in Stockholm, Sweden during a 3.5 year-period. All had a FNF either displaced or non-displaced fracture and all were treated with CRIF by two cannulated screws (Olmed<sup>®</sup>).

The inclusion criteria were independent living and able to walk before fracture. Those with reduced cognitive function according to Short Portable Mental Status Questionnaire (SPMSQ <3) [70] or with a mental disorder were not included. Patients having risk factors for a secondary osteoporosis such as chronic renal failure or hyperparathyroidism and a simultaneous fracture of a lower extremity were also excluded. Patients with a history of pathology in the fractured hip or fractures that were sustained longer than 48 hours before admission were also excluded.

#### Follow-up

The included patients had a follow-up at 4, 12 and 24 months. At 24-months follow-up a total of 170 patients were available, 5 missing and 7 patients were deceased (Figure 4).

#### **STUDY II**

#### Patients and inclusion criteria

A subgroup of 128 patients from Study I having a displaced FNF and with a median age of 58 years (range 20-69, 49% men) were included. The criteria of inclusion and exclusion were the same as for the Study I.

#### Follow-up

The included patients had a follow-up at 4, 12 and 24 months. At 24-months follow-up a total of 120 patients were available, 4 missing and 4 patients were deceased (Figure 4).

#### **STUDY III**

#### Patients and inclusion criteria

This was a 10-year follow-up of the same cohort as in Study I in which 88 patients participated having an age range of 34-80 years and a mean age of 66 years (44% men).

#### Follow-up

At 10-year follow-up, 55 patients were deceased, 35 patients declined participation and four patients were deregistered from public record. For mortality analysis, 178 patients were available (Figure 4).

#### **STUDY IV**

#### Patients and inclusion criteria

All 182 patients from Study I were included with the same inclusion and exclusion criteria as for the Study I.

#### Follow-up

The included patients had a follow-up at 4, 12 and 24 months. At 24-months follow-up a total of 170 patients were available, 5 missing and 7 patients were deceased (Figure 4).

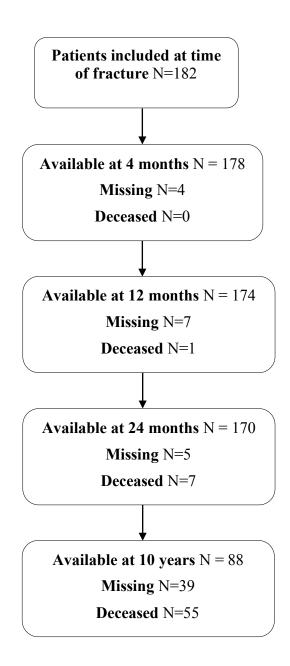


Figure 4. Flow chart of all included patients, missing and deceased at each follow-up.

# 6 METHODS

#### STUDY I

Closed fracture reduction was performed with the help of an image intensifier and the fracture was fixated with two parallel screws (Olmed®) and the operations were performed by both consultants and residents.

#### Recorded variables

At the time of inclusion, recorded variables were: gender, age, pre-fracture living condition, trauma mechanism, alcohol consumption assessed by Alcohol Use Disorder Identification Test (AUDIT) [39], and current smoking. The physical health of the patients was assessed by the American Society of Anesthesiologists (ASA) score and was done by an anesthesiologist [76]. The ASA score is a subjective assessment of the overall health of the patient and is based on six classes (ASA 1–6) [76].

All other assessments were done by research nurses except for the ASA score, fracture classifications and fracture healing complications.

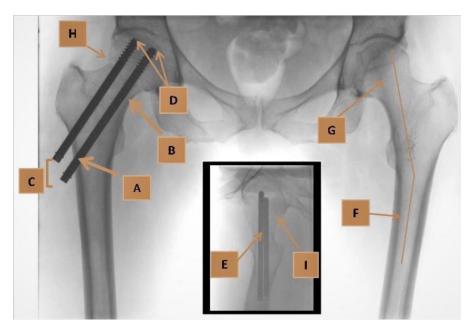
All patients underwent an X-ray before and after surgery and the FNF was classified according to Garden classification, [5]. All X-rays were assessed by three orthopedic surgeons in consensus. The fracture reduction according to the postoperative X-ray was assessed in regards to displacement, Garden angle and posterior angulation (Figure 5). A good reduction was a displacement  $\leq 2$  mm, Garden angle 160- $175^{\circ}$  and a dorsal angulation  $\leq 10^{\circ}$ . A fair reduction was a displacement 2-5 mm, Garden angle 160- $175^{\circ}$  and a dorsal angulation  $\leq 20^{\circ}$ . A poor reduction was a displacement  $\geq 5$  mm, Garden angle  $\leq 160^{\circ}$  or  $\geq 175^{\circ}$  and a dorsal angulation  $\geq 20^{\circ}$  [23]. The positioning of the screws was classified as good or not good (Figure 5). An X-ray of the operated hip was taken at each follow-up and signs of healing complication such as AVN or NU was recorded.

The hip function was examined by HHS [65]. The EQ-5D and SF-36 were used to rate the HRQoL [41,42]. Pre-fracture scores of EQ-5D and SF-36, were acquired by asking the patients to estimate their quality of life one week before the fracture. At 4,12 and 24-month follow-up HHS, SF-36 and EQ-5D were recorded. The change score of SF-36 (between pre-fracture level and 24-months follow-up) was compared to MID in order to estimate if

the changes were of any clinical importance. According to study IV, the MID for SF-36 was 8.2. Re-operations were recorded as minor if the screws were extracted and major if the patient had a THR. Deep wound infections that required a re-operation with screw-extraction and a Girdlestone procedure was recorded.

The living situation was registered as independent or institutionalized. The walking ability including using walking aids were registered as ability of walking outside, solely walking indoors or inability to walk.

Three types of mechanism of trauma were recorded. A fall at the same level was considered a low-energy trauma, a sport injury mainly by cycling and high-energy trauma from a road traffic injury or falling from a height.



**Figure 5**. A post-operative X-ray of the pelvis demonstrating a good position of the screws after treatment of a FNF with CRIF. The distal screw should be introduced at the same region as trochanter minor (A) and run just above the inferior calcar (B). The two screws should be 2 cm apart and run parallel (C). The tips of the screws must not get closer than 0,5 cm to subchondral bone. (D). Both screws must also run parallel on the lateral projection. Their position should be on the posterior third or central on the femoral neck and head (E). The Garden angle is the angle between the femoral shaft (F) and medial trabeculae in the femoral neck (G). A good reduction is a displacement less than 2mm (H), a Garden angle between 160-175° and posterior head angulation of less than 10°. (I).

#### STUDY II

#### **Recorded variables**

Gender, age, ASA score [76], Alcohol consumption according to AUDIT [39], BMD, smokers, mechanism of injury, fracture reduction and position of the screws. BMD of the contralateral hip was examined by DXA within three weeks after sustaining the fracture. The BMD from the lumbar spine was used when previous surgery had been performed in the contralateral hip. The time intervals for the follow-ups were 4, 12 and 24 months. An X-ray of the operated hip was taken at each follow-up and signs of AVN or NU were assessed by three orthopedic surgeons in consensus. Re-operations were recorded as minor re-operation if the screws were extracted and major re-operation if the patient had a THR.

### **STUDY III**

#### Recorded variables

The self-administered questionnaire EQ-5D and HOOS were sent to the patients and the results were recorded. All patients included in Study I and not participating in study III had their data extracted from the Swedish population registry that revealed any patients who were deceased and their date of death was then recorded. Baseline data used for regression analysis of predictors of mortality were gender, age, alcoholism, fracture type (displaced or non-displaced), co-morbidity, smoking, BMI and osteoporosis (T-score ≤ -2.5 SD in subjects >50 years or Z-score < -2 SD in subjects 20-49 years).

# **STUDY IV**

#### **Recorded variables**

Both internal and external responsiveness of SF-36, EQ-5D and HHS were evaluated at each follow-up. A self-related health (SRH) question was asked at each follow-up where the patients had to decide one out of five options describing their state of health; poor, fair, good, very good or excellent. The internal responsiveness of EQ-5D and SF-36 were estimated by calculating the change score, SES and SRM at each follow-up. The external responsiveness was assessed by producing an EC using the SRH question. Patients that changed their SRH between any follow-up were classified according to following: improved or not, deteriorated or not. A dichotomized ECs was created from these groups suitable for ROC analysis and AUC calculations. The external responsiveness was also analyzed by calculating correlations between HHS, EQ-5D and SF-36.

# 7 STATISTICS

When performing statistical calculations in study I, II and IV the SPSS version 22 and in Study III SPSS version 26 for Windows (IBM) were used. Statistically significance was considered when the p-value was less than 0.05 in all analyses. Mean, range, SD, median and percentage were used for descriptive statistics.

## Study I

When testing for normally distributed independent variables, the Student's t test was used. Differences in contingency tables were analyzed by Pearson's chi-square test.

### Study II

A logistic regression analysis was calculated when testing for variables associated with a major re-operation. The tested variables were; gender, age (20–49 or 50–69 years), AUDIT (low or high in women, and low or high in men), ASA (I-II or III-IV), mechanism of injury (low or high energy), fracture reduction (poor-fair or good), smokers or non- smokers, position of the screws (good or not good), fracture reduction (poor-fair or good), and BMD (normal or osteopenia-osteoporosis). A calculation of unadjusted and adjusted odds ratio were performed.

### **Study III**

Differences in contingency tables were analyzed by Pearson's chi-square test. When testing the differences in mean in normally distributed continuous variables the Student t-test and paired-sample t-test were used. Analysis of variance (ANOVA) test was calculated when analyzing the differences of EQ-5D between the groups according to age. In order to identify factors associated with a 10-year mortality, univariate and multiple regression calculations were performed. Patients still alive at 10-year follow-up were compared to deceased patients. The independent variables analyzed for mortality were: re-operation within two years after the fracture yes or no, gender, ASA 1-2 or 3-5, BMI normal (18.5-24.99) or not, age at time of fracture, non-displaced or displaced FNF, AUDIT low or high, diabetes mellitus yes or no, ongoing smoking, osteoporosis yes or no. The confidence interval and crude odds ratio were calculated. Cumulative survival was analyzed by a Kaplan-Meier curve

# Study IV

The change score was calculated by paired samples t-test. A ROC curve and AUC were calculated in order to illustrate the sensitivity and specificity of HHS, EQ-5D and SF-36 to predict the EC. A Spearman's rank correlation coefficient was used when analyzing the correlation between scores and changes in scores of HHS, EQ-5D and SF-36.

# 8 RESULTS

## Study I

Data of 170 patients were available at 24-month follow-up, five patients were not able to attend and seven patients were deceased. A total of 120 patients had a displaced FNF and 50 patients had a non-displaced FNF. Table 1 illustrates the baseline data of all included patients. Figure 6 illustrates the numbers of NU, AVN, deep wound infections, nearby fractures and re-operations. A total of 23% (n=27) of the patients with a displaced FNF developed NU and 15% (n=18) AVN. All patients with NU and less than half of patients with AVN (n=7) underwent a major re-operation. In patients who had a non-displaced FNF, no one developed NU but 12% (n=6) developed AVN in which later four patients had a major re-operation.

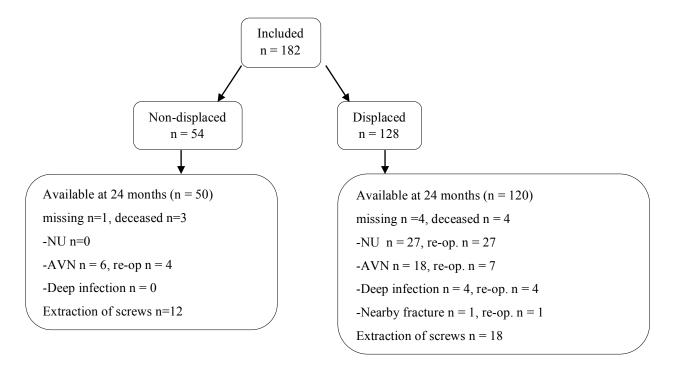
The overall re-operation rate was 41 % in which screw extraction (30%, n=30) and THR (23%, n=40) were the two most common surgical procedures. Four patients had a deep wound infection after the primary surgery and had a re-operation with a Girdlestone resection arthroplasty. A later re-operation with a THR was performed in two of these patients. A single patient had a re-operation with CRIF due to a nearby fracture.

The fracture reduction was considered good in 80% (n = 101) of the patients with a displaced FNF and fair or poor in 20% (n = 26). Positions of the screws in patients with displaced FNF were good in 76% (n = 97) and a position that was fair or poor in 24% (n = 30) compared to patients with a non-displaced FNF in which 85% (n = 46) were good and 15% fair/poor (n = 8).

**Table 1.** Baseline data for patients (n=182) according to type of fracture. Variables are expressed in N (%) besides age and BMI that are expressed in mean +/- SD.

	All patients N=182	Non-displaced N=54	Displaced N=128	p-value
Age mean ± SD Gender n (%)	57±8	57±8	58±9	0.39*
Women	97 (53)	35 (65)	62 (48)	0.043\$
Men	85 (47)	19 (35)	66 (52)	0.0.5
Alcohol AUDIT a n (9	%)			
Low	137 (77)	46 (87)	91 (73)	0.043§
High	41 (23)	7 (13)	34 (27)	
ASA score <sup>b</sup> n (%)				
1	67 (37)	22 (41)	45 (35)	$0.66^{\S}$
2	81 (44)	25 (46)	56 (44)	
3	30 (17)	6 (11)	24 (19)	
4	4(2)	1 (2)	3 (2)	
Smoking	72 (40)	20 (37)	52 (41)	0.651\$
Trauma mechanism				
Low-energy	137 (75)	39 (72)	98 (77)	$0.56^{\S}$
High-energy trauma	14 (8)	6 (11)	8 (6)	
Sport injury	31 (17)	9 (17)	22 (17)	
BMI mean ± SD	24±4	23±3	25±4	$0.008^{*}$

AUDIT: Alcohol Use Disorders Identification Test. ASA: American Society of Anesthesiologists classification. BMI: Body Mass Index, <sup>a</sup>Missing=4, <sup>b</sup>Missing=5, \*Student's t-test, \*Pearson's chi-square test.



**Figure 6.** All included patients (n=182) divided by fracture type with a summary of the numbers of NU, AVN, deep wound infection, nearby fracture and re-operations.

### **Functional outcome**

Patients with a non-displaced FNF had significant better hip function according to HHS at 4- and 12-month follow-ups compared to individuals with a displaced FNF; however, the differences levelled out at 24-month follow-up (Table 2).

**Table 2.** Harris Hip Score at 4, 12 and 24-month follow-up.

	All fractures	Non-displaced	Displaced	p-value
Harris Hip Score total score n (%)				
4 months <sup>a</sup>				
Poor function < 70	70 (41)	13 (25)	57 (48)	0.002
Good function 70-80	23 (14)	5 (10)	18 (15)	
Excellent function >80	77 (45)	34 (65)	43 (37)	
12 months <sup>b</sup>				
Poor function < 70	45 (27)	10 (21)	35 (30)	0.005
Good function 70-80	16 (10)	0	16 (14)	
Excellent function >80	103 (63)	38 (79)	65 (56)	
24 months <sup>c</sup>				
Poor function < 70	38 (24)	7 (15)	31 (27)	0.156
Good function 70-80	15 (9)	3 (6)	12 (10)	
Excellent function >80	109 (67)	37 (79)	72 (63)	

Patients having a displaced FNF and no re-operation had a good or excellent functional outcome in 80 % of the cases at 24-month follow-up compared to 57% in patients that underwent a major re-operation (p=0.001).

### Health-related quality of life

The score of EQ-5D was reduced from pre-fracture score and had the lowest value at 4-month follow-up (p<0.001) and did not fully recover at 24-month follow-up (p<0.001). Patients with a non-displaced FNF scored higher than patients with a displaced FNF at all follow-ups but there was no statistically significant difference at 24-month follow-up (Figure 7).

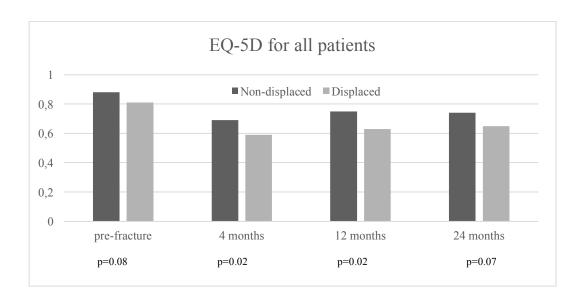


Figure 7. EQ-5D Index score at pre-fracture and at each follow-up.

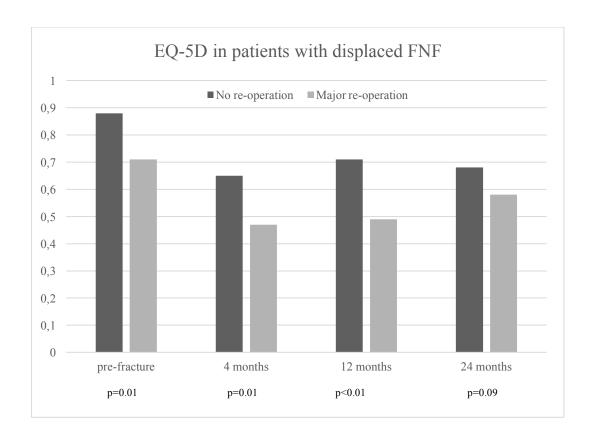
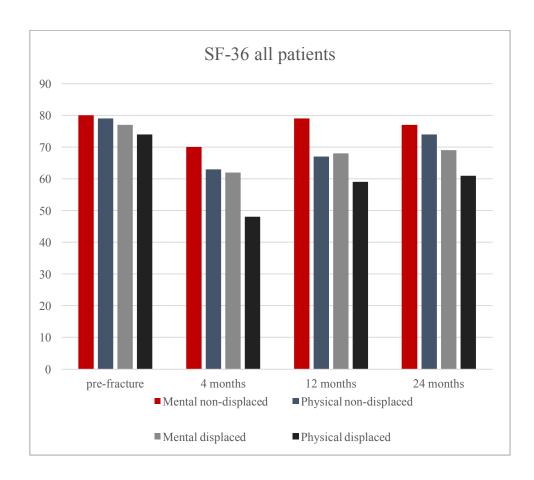


Figure 8. EQ-5D Index score for patients with a displaced FNF with or without a major re-operation.

Patients with a displaced FNF and a major re-operation with a THR scored significantly lower at each follow-up except at 24-month follow-up (Figure 8).

The mean SF-36 total score in all patients were at the lowest at 4-month follow-up. The recovery for the mental score was greater than physical score for all patients regardless of

the type of FNF (Figure 9). In patients with non-displaced FNF the changes from pre-fracture to 24-month follow-up was significant lower for PF, BP, GH, VT and MH. Patients with displaced FNF scored significant lower in each sub-scale between pre-fracture level and 24-months follow-up (Table 3). Patients with displaced FNF and a major re-operation had a significant lower values both before fracture and at 24-month follow-up at all sub-scales compared to patients with a displaced FNF and without a major re-operation.



**Figure 9**. SF-36 index score at pre-fracture and at each follow-up for non-displaced and displaced FNF. The index scores are divided into mental and physical subscales.

**Table 3.** The SF-36 subscales before fracture and at 24-month follow up and the change score. The values are presented as mean (SD). P-value for differences across the groups using the Pearson chi-square test.

	Non-displaced	Displaced	Displaced fractur major re-operation	re with or without a
			No major re- operation	Major re-operations
Numbers of patients	45	113	79	34
Physical functioning (PF)				
Before fracture	85 (23)	75 (29)	78 (29)	68 (31)
24-month	71 (31)	58 (31)	64 (30)	44 (29)
change score	14 (23)	17 (28)	14 (22)	24 (38)
p-value	<0.001	<0.001	<0.001	0.001
Role physical (RP)				
Before fracture	83 (34)	75 (37)	80 (34)	62 (43)
24-month	76 (37)	57 (44)	64 (42)	38 (43)
change score	8 (42)	18 (42)	16 (40)	24 (48)
p-value	0.2	< 0.001	< 0.001	0.008
-				
Bodily Pain (BP) Before fracture	87 (25)	80 (26)	84 (22)	72 (21)
24-month	87 (25)	80 (26)	84 (22)	72 (31) 56 (37)
	77 (27)	65 (32)	70 (29)	56 (37)
change score p-value	10 (27) 0.008	15 (30) <0.001	14 (24) <0.001	16 (41) 0.025
p-varue	0.008	<b>\0.001</b>	<b>\0.001</b>	0.023
General Health (GH)				
Before fracture	77 (20)	72 (23)	77 (20)	62 (27)
24-month	71 (24)	66 (24)	70 (23)	57 (24)
change score	6 (18)	6 (21)	7 (18)	5 (25)
p-value	0.04	0.001	0.002	0.2
Vitality (VT)				
Before fracture	76 (24)	71 (25)	76 (21)	60 (29)
24-month	68 (29)	62 (29)	67 (27)	50 (30)
change score	8 (23)	9 26)	9 (23)	10 (31)
p-value	0.03	< 0.001	0.002	0.09
Social functioning (SF)				
Before fracture	89 (24)	85 (23)	90 (18)	75 (28)
24-month	86 (23)	75 (30)	80 (28)	62 (32)
change score	3 (24)	11 (27)	10 (24)	13 (31)
p-value	0.4	<0.001	0.001	0.023
Role emotional (RE)				
Before fracture	83 (31)	80 (36)	87 (29)	64 (45)
24-month	74 (42)	65 (44)	74 (41)	44 (46)
change score	9 (43)	15 (46)	13 (41)	20 (57)
p-value	0.17	0.001	0.001	0.06
p - 1.11.10	V.17	0.001	0.001	0.00
Managella alda (MIII)				
Mental health (MH)	95 (20)	90 (20)	92 (10)	72 (22)
Before fracture	85 (20)	80 (20)	83 (19)	73 (23)
24-month	79 (24)	75 (27) 5 (24)	80 (24)	64 (30)
Change score	6 (18)	5 (24)	3 (23)	9 (28)
P-value	0.02	0.001	0.25	0.054

# **Study II**

A total of 120 patients were available at 24-month follow-up, four patients were not able to attend and four patients were deceased. Mean age was 58 years (20-69 years, 49 % men). Table 4 illustrates the baseline data of all included patients.

**Table 4.** Baseline data for all patients (n=120) with a displaced femoral neck fracture.

Age, mean	58
	(SD=9)
	N %
Gender	
Male	59 (49)
Female	61 (51)
Age group	
20-49 years	19 (16)
50-69 years	101 (84)
Alcohol AUDIT a	
High	32 (27)
Low	86 (73)
ASA score b	
1-2	90 (78)
3-5	25 (22)
Mechanism of injury	
Low-energy trauma	91 (76)
High-energy/sports trauma	29 (24)
Smokers	45 (38)

AUDIT: Alcohol Use Disorders Identifications Test.

ASA: American Society of Anesthesiologists classification.

The development of AVN was seen in 15% (n=18) of the patients and NU in 23% (n=27). Screw extraction was performed in 15% (n=18) of the patients and 28% (n=33) had a major re-operation with a THR. The re-operation rate with a THR was 9% (n=2) in patients having a normal neck BMD comparing to 31% (n=25) in patients having a low neck BMD (p=0.05). Patients with a low risk of alcoholism according to AUDIT had a major re-operation rate of 22% (n=19) comparing to 44% (n=14) in those with a harmful alcohol consumption (p=0.02). Poor fracture reduction was seen in two patients and both had a major re-operation.

<sup>&</sup>lt;sup>a</sup> Missing n=2, <sup>b</sup> missing n=5

**Table 5.** Major re-operation due to NU or AVN and logistic regression analysis of all included variables.

	Re-operation Yes n=33			
	n (%)	No n=87	Unadjusted OR (95 % CI)	P-value
Age group 20-49 years	2 (11)	17 (89)	3.7 (0.80-17.05)	0.09
50-69 years	31 (31)	70 (69)	3.7 (0.00-17.03)	0.07
ASA score <sup>a</sup>	, ,			
1-2	23 (26)	67 (74)	1.7 (0.64-4.27)	0.29
3-5	9 (36)	16 (64)		
Alcohol AUDIT b				
Low	19 (22)	67 (78)	2.8 (1.17-6.60)	0.02
High	14 (44)	18 (56)		
Fracture reduction				
Good	23 (24)	71 (76)	2.0 (0.78-4.91)	0.15
Fair/ Poor	10 (38)	16 (62)		
Gender				
Male	15 (25)	44 (75)	1.2 (0.53-2.68)	0.66
Female	18 (30)	43 (70)		
Mechanism of injury				
Low energy	29 (32)	62 (68)	2.9 (0.91-9.03)	0.07
Sports or high energy	4 (14)	25 (86)		
BMD femoral neck c				
Normal	2 (9)	21 (91)	4.8 (1.03-21.9)	0.05
Osteopenia or osteoporosis	25 (31)	55 (69)		
Smoking				
No	17 (23)	58 (77)	1.9 (0.84-4.33)	0.12
Yes	16 (36)	29 (64)		
Position of the screws				
Good	23 (25)	69 (75)	1.7 (0.68-4-18)	0.26
Not good	10 (36)	18 (64)		

<sup>&</sup>lt;sup>a</sup> missing n = 5, <sup>b</sup> missing n = 2, <sup>c</sup> missing n = 17

The logistic regression analysis showed that a high AUDIT score and osteopenia or osteoporosis were significant factors for re-operation (Table 5) as well as in the multivariable logistic regression analysis (Table 6).

**Table 6.** A multivariable logistic regression analysis of high AUDIT and BMD of the contralateral hip and the association with a major re-operation.

	OR (95 % CI)	P-value
AUDIT <sup>a</sup> High versus low AUDIT	3.2 (1.16-8.76)	0.02
BMD b Normal versus osteopenia or osteoporosis	5.5 (1.15-26.8)	0.03

<sup>&</sup>lt;sup>a</sup> missing n = 2, <sup>b</sup> missing n = 17

# Study III

The participants were 88 patients with an average age of 66 years (34-80 years, 44% men). A total of 55 patients were dead, four patients deregistered from public records and 35 patients denied participation. For mortality estimate, data of 178 patients were available.

# Hip Disability and Osteoarthritis Outcome Score

Except for sport/recreation, women scored better than men in all domains but the differences were not significant in any domain (Table 7). No significant differences were detected comparing patients with displaced and non-displaced FNF (Table 7). Significant differences were seen between the younger age group compared to the older age in all domains except for symptoms (Table 7).

**Table 7.** Hip disability and Osteoarthritis Outcome Score (HOOS) 10 years after a FNF. All values are presented as mean and standard deviation (SD).

	Women	Men	p-value	Non- Displaced	Displaced	p- value	Age 30-69	Age ≥70	P-value
	N= 48	N=39		N=26	N=61		N=33	N=54	-
Pain	85 (19)	82 (23)	0.60	85 (20)	83 (22)	0.62	91(18)	79 (21)	0.01
Symptom	82 (17)	81 (23)	0.77	83 (21)	81 (19)	0.59	89 (18)	77 (20)	0.07
ADL	82 (21)	81 (24)	0.90	85 (20)	80 (24)	0.33	92 (17)	75 (23)	<0.01
Sport/ Recreation	65 (33)	68 (33)	0.68	73 (32)	64 (33)	0.26	84 (24)	56 (33)	<0.01
QoL	76 (23)	72 (30)	0.53	79 (24)	72 (27)	0.31	79 (24)	72 (27)	0.03

ADL= Activities of daily living

QoL= Quality of life

#### Health related quality of life

EQ-5D improved comparing to the 4 (p<0.001), 12 (p=0.001) and 24-month (p=0.006) scores (Figure 10). The pre-fracture level of EQ-5D however, was not reached (p<0.001) (Fig. 10). There was no statistically significant difference between gender (p=0.587), fracture displacement or not (p=0.942), (Figure 10), age groups (p=0.094), (Table 8), and mechanism of injury (p=0.385).

**Table 8.** EQ-5D in different age groups at 10-year follow-up. Values are given as Mean (SD), (p=0.094).

Age group	Mean (SD)
35–64 n=22	0.91 (0.22)
65–74 n=47	0.81 (0.18)
75+ n=19	0.79 (0.22)
Total n=88	0.83 (0.20)

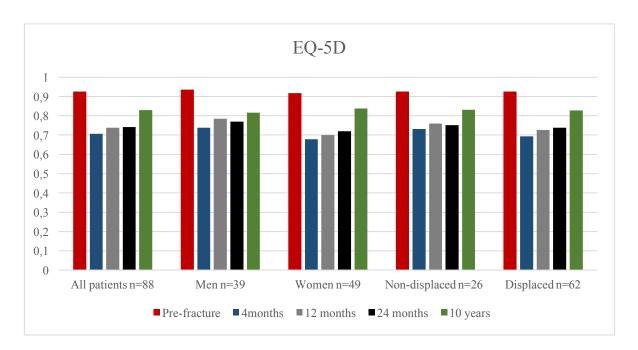


Figure 10. Mean EQ-5D for all patients, split into gender and type of fracture at each follow-up.

A non-response bias analysis of the patients (n=35) still alive and not participating in the study was performed. These patients had a mean age of 55 years when sustaining their fracture in comparison to 56 years for the patients included in the study. There was no statistically significant difference in the HRQoL at 24-month follow-up (p=0.122).

# **Mortality**

The mean age at death date was 70 and 68 years for women and men respectively. A Kaplan-Meier curve illustrates the cumulative survival according to gender and a gradual reduction of cumulative survival is seen. At 10-year follow-up 70% were still alive and 30% of the men and 32% of the women were dead (Figure 11).

Factors associated with mortality in the univariate regression analysis were ASA score 3-5, high age at time of fracture, diabetes mellitus, high AUDIT, osteoporosis and ongoing smoking (Table 9). Factors that were still significant in the multi-regression analysis were ASA 3-5, osteoporosis, age at time of fracture, and ongoing smoking (Table 10). Within the group of deceased patients, 49% had a high AUDIT, 22% diabetes mellitus, and 69% had an ongoing smoking at the time of fracture.

**Table 9.** Characteristics of all patients at inclusion, deceased and alive 10 years after the hip fracture. Data are presented as n (%).

	All patients	Deceased	Alive	<i>p</i> -value
	N=178	N=55	N=123	
Age at time of fracture mean (SD)	58 (9)	62 (5)	56 (9)	0.01
BMI mean (SD)	24 (4)	24 (3)	25 (5)	0.23
	n (%)	n (%)	n (%)	
Gender				
women	96 (54)	30 (31)	66 (69)	0.91
men	82 (46)	25 (30)	57 (70)	
Re-operation within two years <sup>a</sup>	37 (22)	13 (35)	24 (65)	0.25
ASA <sup>b</sup>				
1-2	139 (80)	30 (28)	109 (78)	< 0.01
3-5	34 (20)	24 (70)	10 (30)	
AUDIT <sup>c</sup>				
High	41 (24)	22 (54)	19 (46)	0.02
Non-displaced fracture	53 (30)	16 (30)	37 (70)	0.89
Displaced fracture	125 (70)	39 (31)	86 (39)	
Osteoporosis <sup>d</sup>	49 (32)	20 (41)	29 (59)	0.02
Diabetes mellitus	19 (11)	12 (63)	7 (37)	0.01
Smoking	72 (40)	38 (53)	34 (47)	< 0.01

<sup>&</sup>lt;sup>a</sup> Missing 12, <sup>b</sup> missing 5, <sup>c</sup> missing 4, <sup>d</sup> missing 25.

**Table 10.** Multiple regression analysis (n=144<sup>a</sup>) of factors at baseline associated with 10-year mortality. Data are illustrated as adjusted odds ratio (OR) and 95% confidence interval (CI).

Variable	Adjusted OR	CI (95%)
ASA 1-2 & 3-5	7.26	2.46-21.43
Age at time of fracture	1.15	1.05-1.26
Smoking	5.22	1.87-14.57
Osteoporosis	2.71	1.04-7.05

<sup>&</sup>lt;sup>a</sup> Missing 34.

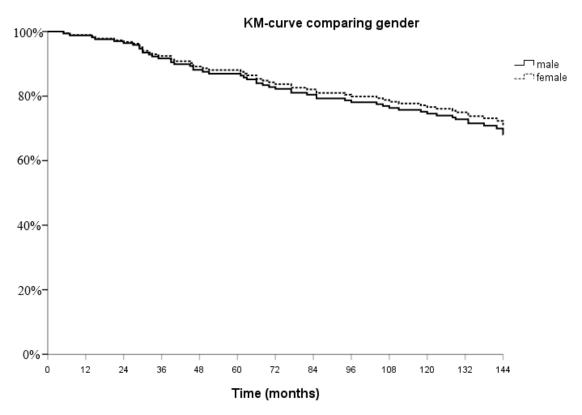


Figure 11. A Kaplan-Meier analysis of cumulative survival according to gender in patients with a FNF.

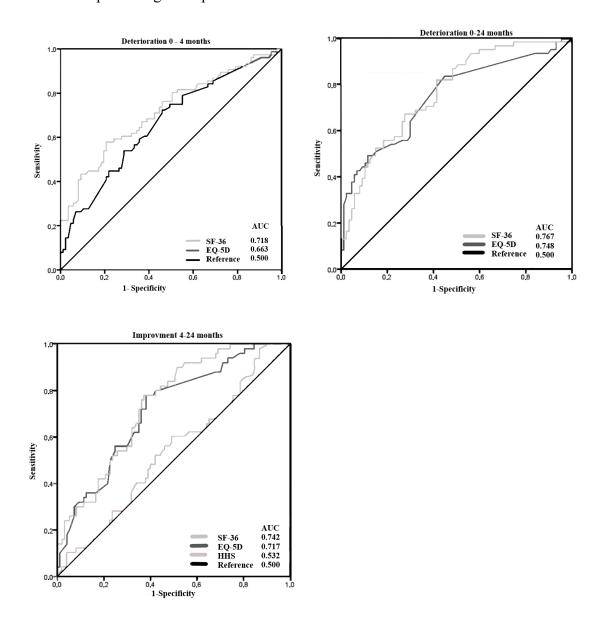
### Study IV

A total of 163 complete questionnaires of EQ-5D and 156 complete questionnaires of SF-36 from baseline, 4-months, 12 months and 24-months follow-up were available for analysis.

The ceiling effect of EQ-5D was 57% at baseline, 12% at 4 months, 20% at 12 months and 23% at 24-month follow-up. The ceiling effect of SF-36 were 3% at baseline and 0% at 4 months, 1% at 12 months and 3% at 24-month follow-up. Either EQ-5D nor SF-36 had any floor-effect. The MID was 8.2 for SF-36 and 0.05 for EQ-5D. At all follow-up the change scores of SF-36 and EQ-5D were significant larger than MID. Cohen's threshold [54] revealed that the SES for both SF-36 and EQ-5D were large at 4 months (Table 11). At 12 and 24 months the SES was moderate to large (Table 11). The change score between HHS and SF-36 (0.37, n=147), HHS and EQ-5D (0.44, n=156) and SF-36 and EQ-5D (0.64, n=152) had a correlation that was significant positive between 4 and 24 months. The correlation between SF-36 and EQ-5D was stronger comparing any of the generic HRQoL questionnaires to HHS (Table 12).

AUC calculations showed that both EQ-5D and SF-36 could predict improvement between

4 and 24 months better than the HHS and was significantly larger than 0.5 within 0–4 and 0–24-month follow-up (Figure 12.). The results indicated that a change in score in either SF-36 and EQ-5D that is positive had both a higher specificity and sensitivity compared to HHS when predicting an improvement in the EC.



**Figure 12.** ROC curve and AUC values of change in scores in EQ-5D, SF-36 and HHS. The lines represent connected dots of sensitivity and specificity of each individual value of change in score. The larger the area under the curve is, the better is the chance of predicting the actual state.

**Table 11.** SF-36 and EQ-5D median, mean, change scores and effect sizes at baseline, 4, 12 and 24-month follow-up.

	Baseline	4 months	12 Month	24 Months
SF 36				
Number of patients	175	170	160	156
Median (range)	87 (13-100)	59 (6-99)	73 (3-100)	76 (2-100)
Mean (SD)	77 (23)	59 (25)	67 (27)	68 (27)
Change score a	X	59 (25) 19 (20) *	67 (27) 13 (22) *	12 (22) *
(SD)				
SES	X	0.83	0.56	0.52
SRM	X	0.95	0.59	0.55
EQ-5D				
Number of patients	182	173	167	163
Median (range)	0.97 (0.44-0.97)	0.78 (0.40-0.97)	0.87 (0.40-0.97)	0.88 (0.40-0.97)
Mean (SD)	0.90 (0.11)	0.79 (0.13)	0.82 (0.14)	0.83 (0.15)
Change score a	X	0.12 (0.12) *	0.09 (0.13) *	0.08 (0.13)*
(SD)				
SES	X	1.09	0.82	0.72
SRM	X	1	0.69	0.62

SF-36= Short Form (36) health Survey, EQ-5D= EuroQol 5-Dimension questionnaire, SES=Standardized effect size, SRM= Standardized response mean, From baseline, p < 0.05.

**Table 12.** Correlation of SF-36 and EQ-5D index scores and HHS total score of all included patients (n=number of patients).

	Baseline	4 Months	12 Months	24 Months
Correlated Scores				
SF-36 EQ-5D	$0.80 (n=175)^*$	0.83 (n=169)*	0.87 (n=159)*	0.84 (n=155)*
SF-36 HHS		0.73 (n=167) *	0.75 (n=155)*	0.74 (n=154)*
EQ-5D HHS		0.75 (n=169) *	0.79 (n=162) *	0.76 (n=160) *

SF-36= Short Form (36) health Survey, EQ-5D= EuroQol 5-Dimension questionnaire, HHS= Harris Hip Score, p < 0.05.

# 9 DISCUSSIONS

# Study I

Healing complications, HRQoL and hip function were assessed in this paper with a followup of two years.

Two-thirds of patients having a displaced FNF healed and did not undergo any major reoperation and the functional outcome was good or excellent in three-quarters after two years.

Of all patients with a non-displaced FNF, none developed NU and 12% AVN. Only four patients had a major re-operation due to AVN. Regardless of fracture type, the pre-fracture HRQoL was not reached by the patients.

A trend today is to operate patients with a displaced FNF with a THR if the patient is in the age range of 60-69 years [1,10,77]. When comparing patients with displaced FNF, age groups 50-59 and 60-69 years in our study, the major re-operation rate was 34 and 31 % respectively. These results indicate that the chronological age should not determine treatment modality.

All patients with NU were re-operated but only 46% of the patients who developed AVN. Similarly, Haidukewych et al. showed that about 50% of patients developing AVN developed symptoms and were in need for a re-operation [19]. Jain et al showed that development of AVN did not lead to a significantly reduced functional outcome in younger patients with a FNF [18]. Our findings suggest that the development of AVN within two years after a FNF does not necessary lead to symptoms nor need for a re-operation.

The incidence of NU in younger patients with a FNF has been reported to vary between 0-59% [2,7,19,26,78,79]. However, the definition of NU varies in some studies defining NU as a re-displacement if it occurs within 4-6 month after the fracture [2,6]. In our paper, NU was defined as lack of healing regardless when that occurred and it affected 23% of all patients with a displaced FNF which is somewhat higher than other studies that looked into younger patients with a FNF [2,7,26]. The reason for our higher values could be that we included patients up to 69 years of age, had a long follow-up period and the definition of NU differed compared to other studies.

In our study, the functional outcome according to HHS was significantly better for patients with non-displaced FNF at 4 and 12-month follow-up compared to patients with a displaced

FNF. However, this difference had disappeared at 24-month follow-up. These findings probably reflect that patients who underwent a major re-operation with a THR had a longer time for recovery. Few studies have studied functional outcome in younger patients with a FNF treated with a CRIF. Haider et al showed in a retrospective study that the majority of younger patients with a FNF treated with internal fixation had an excellent function according to HHS at 5-year follow-up [80] which is in accordance with our results.

The EQ-5D in our study showed that regardless of fracture type, the pre-fracture level was not reached and the difference from 24-month follow-up was significantly. The MID of EQ-5D in our study material was 0.05 shown in study IV and was smaller than the change score between pre-fracture level and at 24-month follow-up for both patients with displaced and non-displaced FNF. A study by Tidermark et al showed that elderly patients with a non-displaced FNF without healing complications regained the pre-fracture level of EQ-5D which is in contrast to our study [81]. The reason might be that a slight functional impairment in younger patients with a higher functional demand may influence their HRQoL to a greater extent than in elderly.

The change scores of SF-36 had the same pattern as EQ-5D with the lowest values at 4 months and a recovery at 24 months but not to the pre-fracture level for any subscale. The mental scores recovered more than the physical scores for both patients with displaced and non-displaced FNF as well as those who had a major re-operation. Zidén et al. reported a profound psychological and social impact in elderly with a hip fracture [82]. As far as we know this has not been looked at in younger patients with a FNF and one could assume that rehabilitation should consider a reduction in mental health after a FNF.

### **Study II**

Predictors of fracture healing comlications after a FNF were assessed in this paper. The results showed that both osteopenia and osteoporosis as well as a harmful alcohol use according to AUDIT were factors associated with a major re-operation. The rate of reoperation in our study was 28% which is similar to other studies in younger patients with a FNF [7,83]. There are several studies reporting that the fracture healing is affected by a low BMD [30,31,84]. However, other studies did not find any association with a low BMD and increased re-operations in patients with a FNF but the mean age was above 80 years [29,85]. A DXA scan is the standard method of assessing the BMD but rarely performed

pre-operatively since the examination itself requires a thoroughly position of the patient on the investigation table which due to pain is not feasible [86]. Erhart et al showed that a CT scan with a calibration device performed pre-operatively on the non-fractured hip was easily obtained and estimated the BMD as well as a DXA [86]. However, if a CT scan could work as a tool for estimating the risk of a re-operation due to osteopenia or osteoporosis and thus being an aid to choose the best surgical method needs further research.

Our study showed that individuals with a high alcohol consumption according to AUDIT had a significantly higher rate of a major re-operation. A similar finding was seen in another study that showed a significant association between alcoholism and fixation failure in younger patients with a FNF [6]. The bone metabolism is affected by high alcohol consumption and therefore has an impact om the BMD [36,37]. The etiology of alcohol-associated bone disease is multifactorial [37]. Chronic alcohol abuse causes elevated serum parathyroid hormone (PTH) and low serum levels of vitamin D which cause malabsorption of calcium [37]. Alcohol also directly suppress the function of osteoblasts [37], increases the risk of falling, contributes to malnutrition and causes development of co-morbidities [37,38].

In the sub-analysis of major re-operations in different age-groups in our study, no statistically significance was seen and the reason for that could be a low number of patients less than 50 years of age or a type II error.

Female gender was not a risk for a re-operation in our study which is in contrast to another study that showed an increased risk in women regardless of age [8]. However, the average age in that study was 76 years and BMD was not measured [8] which may explain the difference.

The positions of the screws did not affect the re-operation rate in our study. A prospective study with a two-year follow-up by Lindquist et al, showed that a suboptimal position of the screws was significantly associated with NU [23]. The analysis of the screw position was slightly different, the BMD was not measured, included older patients [23] which all may have influenced the results compared to our findings.

Only two patients in our study had a fracture reduction that was poor and these patients underwent a major re-operation indicating that it is of clinical importance to achieve an optimal fracture reduction.

Smoking was not associated with a major re-operation in our study. However, there is overwhelming evidence that smoking has a negative impact on fracture healing [87,88,89,90]. Increased rate of non-union has been demonstrated among smokers with an open fracture [89]. We cannot tell why smoking did not influence the rate of major re-operation in our study but surgery with two cannulated screws were a relatively minor surgical procedure with little soft tissue trauma.

# **Study III**

The clinical outcome and HRQoL 10 years after a FNF and factors associated with mortality were assessed in this paper.

The results of HOOS at 10-year follow-up showed that the domain sport activities were most affected which has also been shown after THR in patients with osteoarthritis with a six-months follow-up [69].

Younger patients reported less hip-related complains compared to patients above 70 years in every subscale and the differences were statistically significant. Similar findings were demonstrated in a cohort study of normal population in Sweden that included 840 individuals that were randomly included and had an age-span between 18-84 years [91]. But in that study, men scored higher than women in every subscale of HOOS regardless of age which were in contrast to our findings [91]. The results in our study implies that a FNF affects men to a higher degree according to HOOS but the differences were not statistically significant.

The patients did not reach the pre-fracture score of the EQ-5D but continued to improve when comparing to the two-year follow-up. However, the results may have been affected that the patients were 10 years older [50]. Our results of EQ-5D were equivalent to an index population of Sweden that were age- and sex-matched [50] which implies that a FNF may have little or no effect on the HRQoL in the long term in patients less than 70 years with a FNF.

Studies that demonstrated a statistically significant reduction of EQ-5D due to a hip fracture included older patients, had a shorter follow-up than our study and included all types of different hip fractures [47,81]. Tidermark et al. demonstrated in elderly patients an inferior outcome of the HRQoL if the FNF was displaced compared to non-displaced FNF [81]

which was not seen at our study at 10-years follow-up. Our results were likely affected by the very long times span of 10 years.

The mechanism of injury did not affect the HRQoL at 10-year follow-up and the reason might be that mainly younger patients in our study had a high energy trauma and did not undergo a major re-operation within the two first years.

At 2-year follow-up 8% were dead which are quite low after a FNF fracture. At 10-year follow-up, two thirds of the patients were still alive. The deceased patients were more compromised with diabetes and unhealthy lifestyles with higher alcohol consumption and smoking compared to the patients still alive and to general population data of Sweden [92,93,94].

Osteoporosis was associated with a 10-year mortality in our study which has been demonstrated in another cohort study in patients with osteoporosis and younger than 70 years of age [95]. In contrast to other studies we could not reveal that men had increased mortality compared to women [96,97]. Several studies have shown that within a year there is a sharp reduction of survival in males with a mortality of up to 25% [98]. The average age was about 80 years in these studies which probably explains the difference from our findings [96,97,98].

#### Study IV

The responsiveness of the HRQoL questionnaires EQ-5D and SF-36 were assessed among patients 20-69 years of age with a FNF. Both instruments had large effect sizes at 4 months but were decreased at 12 and 24-month follow-ups. The EQ-5D and SF-36 questionnaires were more sensitive than the hip-specific instrument in their ability to detect subjective improvements of health.

#### **Internal responsiveness**

The internal responsiveness represented by the effect sizes were for both SF-36 and EQ-5D large at 4-month follow-up and decreased at 12 and 24-month follow-ups. The MID was significant lower than the mean change score at each follow-up indicating a good internal responsiveness for both SF-36 and EQ-5D. Other studies have also shown a good internal responsiveness of SF-36 and EQ-5D among relatively healthy elderly that sustained a hip

fracture [43,44,45,47,99]. However, Frihagen et al demonstrated in their study, small effect sizes of EQ-5D in patients sustaining a FNF with a 4 and 12-months follow-up [44]. The explanation for the lack of internal responsiveness according to the authors were that patients with cognitive impairment had a lower response rate [44].

### **Analysis of effect sizes**

There is a lack of consensus on which effect size to include as well as interpreting the results which makes comparison with other studies difficult [53,100,101]. The Cohen's threshold was used in our study when calculating and estimating the SRM and SES effect sizes, which is a method mostly used in orthopedic studies when estimating the internal responsiveness [102]. To measure recovery, the pre-fracture level is necessary to measure. This causes a concern of recall bias which is a systematic error caused by differences in completeness or accuracy of the recollections retrieved regarding the experiences from the past [103]. Previous studies that included pre-fracture scores of HRQoL in patients with a FNF showed equivalent values of Swedish reference population that were age and sexmatched and therefore recall bias appears to be low [43,45,104]. The internal responsiveness was also analyzed over multiple time frames. That allowed us to measure if it was possible to detect a change in EQ-5D and SF-36 up to two years after sustaining a FNF.

#### **External responsiveness**

A weak positive correlation in change scores between HHS and HRQoL questionnaires were seen and a strong positive correlation for total scores. Similar findings have been shown in other studies in elderly [43,47,99]. The explanation for the moderate to weak positive correlation in change scores is that the scores are measuring outcomes that differs from each other and only partial address the same aspect of mobility and pain. HHS was inferior to both EQ-5D and SF-36 in predicting a subjective improvement in the time-frame of 4 to 24 months. EQ-5D had a somewhat smaller AUC than SF-36 in all time frames. HHS did not have a predictive value of changes in subjective health since the AUC was close to 0.5.

#### The choice of external criteria

Studies in elderly that sustained a hip fracture have illustrated an external responsiveness in both EQ-5D and SF-36 that was adequate, although the evaluation methods have varied [43,44,45,99]. In one of the studies, the external criterion used pain, range of motion and walking ability when calculating the correlation to the HRQoL [99]. A dichotomized ECs

was used in other studies that was based upon walking ability, displacement of the fracture, pain, complications or death [43,44,45,47]. In these studies, the EC was a measure of clinical outcome but the patient's subjective state of health was not necessarily address. Therefore, in our study we constructed an EC based upon the change in the subjective deterioration or improvement in health using the SRH-question. Using a change in SRH as the EC is not an obvious choice nor a "gold standard" but we believe it is superior since it can be used regardless of state of medical condition, being generic and there is no need for constructing an EC specifically for each medical condition.

### The Swedish experience-based value sets for EQ-5D

The value set developed by Burström et al and based on a Swedish population was used in this paper [50]. An argument favoring the Swedish experience-based value set is that subjects with their own experience from the health states are often considerably better informed about their condition compared with the value health states that is based merely on a description. The description method does not estimate adaptations to changes in health and therefore we believe it is inferior. However, using the Swedish value sets, it makes it more difficult to compare to older studies.

### **EQ-5D versus SF-36**

The ceiling effect of EQ-5D was larger than SF-36. A review study of EQ-5D showed that the ceiling effect was above 15% in half of the study groups but did not have any floor effect [105]. The ceiling effect at baseline of the EQ-5D were not an issue in this study and a fracture is expected to worsen the HRQoL. Incomplete SF-36 questionnaires were twice that of EQ-5D questionnaires probably because SF-36 takes more time to complete which has been demonstrated in other studies [42,50]. A SF-36 global score was constructed in our study in order to compare to EQ-5D, which has been done in a previous study evaluating responsiveness in orthopedic research [45]. A single score is preferred in our opinion when estimating HRQoL in a clinical setting. EQ-5D is easy to administer and calculate in comparison to the SF-36 which appears not adding additional information.

# 10 STRENGTH AND WEAKNESSES

The strengths of the papers were that high quality data collected by research nurses, low drop out, prospective multicenter design and a long follow-up which included radiological, clinical and functional outcome. Limitations were the wide age range of the included patients and the exclusion of patients that were compromised with renal failure, multiple fractures, hyperparathyroidism, inability to walk, staying in institution and having cognitive impairment. Therefore our findings may not be representative for all patients. Fracture healing complication may also have been affected by the nutritional state of the patients but no blood samples were analyzed for malnutrition in our study.

Another weakness is the wide CI in paper II due to a small sample size.

The included patients in paper III may not be representative for all patients initially included since 10 years had passed. However, a non-response bias analysis of non-included patients showed a similar age and EQ-5D score as the included patients at 24-months follow-up indicating that our results are representative. Another limitation in study III is the relatively few patients in each age- and sex subgroup and therefore a risk of type II error when comparing our results with large population-based cohort studies in Sweden.

# 11 IMPLICATIONS AND FUTURE DIRECTIONS

Our findings suggest that CRIF should be used in the majority of the patients younger than 70 years with a FNF regardless of fracture displacement since the functional outcome was good or excellent and a major re-operation rate was less than 30%. Only age as a guide for surgical method may not be rational and risk factors for a major re-operation should be taken into account.

The HRQoL and hip function in the surviving patients do recover over time and 10 years later the patients reach an equivalent value as the general population. A reduction in mental health was seen in these patients during the first two years and should be considered during rehabilitation.

A third of the patients died within 10 years after the fracture but these patients were compromised with co-morbidities and smoking. Male gender is not a risk factor for 10-year mortality, in contrast to what has been shown in elderly patients with a FNF.

Future studies should preferable have a control group without a hip fracture or hip disorder which would allow a more accurate analysis of the impact of a FNF on HRQoL and hip function. The debate on whether to operate a patient with a displaced FNF with CRIF or a THR are aimed at patients between 60-70 years of age. Future studies should specifically investigate patients in this range of age since comorbidities and mechanism of trauma differs in different age categories.

Osteoporosis increases the risk of a major re-operation within 2 years and mortality within 10 years. Studies analyzing the impact of osteoporosis on patients 60-70 years of age treated with either CRIF or THR after a displaced FNF would be of interest as well as prefracture modalities of accessing BMD.

Alcoholism is another risk factor for a major-re-operation in patients with a displaced FNF treated with CRIF. Alcohol consumption should always be a part of medical history and is relatively easy to obtain before surgery.

# 12 CONCLUSION

Two-third of the patients having a displaced FNF did heal after the CRIF and the functional outcome was good or excellent in three-quarters. The patients did not recover to the prefracture level.

HRQoL continued to improve between 4, 12 and 24 months as well as between 24 months and 10 years.

A low BMD and alcoholism were associated with a major re-operation within 2 years after the fracture.

10 years after a FNF, the hip function and HRQoL were in accordance to sex and agematched Swedish reference population.

A third of the patients had deceased within 10-year despite being relatively young and these patients were more compromised by co-morbidities and smoking.

Age, co-morbidity, smoking and osteoporosis were associated with 10-years mortality.

Both SF-36 and EQ-5D had a good internal and external responsiveness for patients less than 70 years with a FNF treated with CRIF.

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### 14 SUMMERING PÅ SVENSKA

Ett brott på lårbenshalsen kan ha långtgående konsekvenser på patientens livskvalitet, mortalitet och funktion speciellt hos patienter yngre än 70 år. Långsiktiga konsekvenser är okända då de flesta studier har en kort uppföljningstid. Denna avhandling består av fyra delarbeten som studerat en kohort av patienter 20-69 år gamla med ett brott på lårbenshalsen och behandlade med sluten reponering och internfixation med Olmed skruvar.

**Delarbete I:** Syftet med delarbete I var att undersöka hälsorelaterad livskvalitet, höftfunktion och kirurgiska komplikationer under de 2 första åren efter lårbenshalsfraktur. Patienterna var mellan 20-69 år och samtliga frakturer hade behandlats med sluten reposition och skruvfixation. Detta var en prospektiv multicenter studie med 4,12 och 24 månadersuppföljning. 182 patienter inkluderades och egenskattad livskvalitet (HRQoL) registrerades med utvärderingsinstrumenten EQ-5D och SF-36. Höftfunktionen mättes med Harris Hip Score (HHS). Röntgen av höften togs vid alla uppföljningar och uppkomst av pseudartros (ej läkt faktur) eller avaskulär nekros (AVN) av ledkulan registrerades samt om och typ av reoperation.

HRQoL skattades lägst vid 4 månader, ökade vid 12 och 24 månaders uppföljning men nådde inte prefraktur nivå. HHS var som lägst vid 4 månader och vid 24 månader var höftfunktionen god eller mycket god hos 73% av patienterna. Pseudartros utvecklades hos 23% och AVN registrerades hos 15%. Totalt genomgick 23% en reoperation med höftplastik inom de 24 månaderna.

HRQoL förbättras gradvis men når inte samma nivå som före frakturen. Majoriteten återfår en god eller mycket god höftfunktion och en fjärdedel reopereras med höftprotes.

**Delarbete II:** Syftet med delarbete II var att undersöka om det fanns faktorer vid frakturtillfället associerade med en senare reoperation med höftprotes p.g.a. läkningsstörning eller AVN efter en felställd lårbenshalsfraktur. Patienterna behandlades initialt med sluten reposition och skruvfixation och var mellan 20-69 år.

128 patienter inkluderades och under vårdtillfället registrerades ASA-grad (American Society of Anesthesiologists Physical Status), alkoholvanor (AUDIT), komorbiditet och rökning. Bentäthet (BMD) av höften mättes med DXA (dual-energy x-ray absortiometry) i nära anslutning i tid till frakturtillfället. Röntgenundersökning av frakturerade höften

utfördes postoperativt samt vid 4, 12 och 24 månader. Läkningsstörningar, tecken på AVN samt om reoperation utförts registrerades.

Samband mellan ovannämnda variabler och reoperation med en höftplastik under de första 2 åren efter höftfrakturen beräknades med en univariatanalys. En logistisk regression av de signifikanta variablerna beräknades och resultatet visade att ett lågt BMD i höften och hög alkoholkonsumtion hade en association med reoperation inom 24 månader.

**Delarbete III:** Syftet med delarbete III var att undersöka egenskattad livskvalitet (HRQoL) och höftfunktion 10 år efter lårbenshalsfraktur hos patienter mellan 20-69 år. Ett annat syfte var att identifiera faktorer associerade med 10 års mortalitet.

88 patienter kunde inkluderas i uppföljningen och HRQoL mättes med EQ-5D och höftfunktionen med Hip dysfunction and Osteoarthritis Outcome Score (HOOS).

En regressionsanalys av mortalitet utfördes med reoperation inom två år, kön, BMI, ASA klass, åldersgrupp 20-49 och 50-69 år, etylism, felställda och icke felställda frakturer, rökning, diabetes mellitus och bentäthet (BMD). Signifikanta vid univariatanalysen var ASA 3-5, hög ålder, etylism, diabetes, rökning och osteoporos. Dessa beräknades sedan i en logistisk regressionsanalys och resultatet visade att ASA 3-5, hög ålder, rökning och osteoporos hade ett signifikant samband med 10 års mortalitet. 55 av totalt 178 patienter hade avlidit under de första 10 åren efter höftfrakturen. Mortaliteten var 30% hos kvinnor och 32% hos männen.

HRQoL fortsatte förbättras men ej statistiskt signifikant jämfört med tidigare uppmätt 24-månaders nivå (delarbete I) men nådde ej prefraktur nivå. Ingen signifikant skillnad av HRQoL sågs mellan könen, åldersgrupperna, efter ett låg- eller högenergitrauma eller mellan felställda respektive icke felställda frakturer. Vid jämförelse av ålder- och könsmatchad EQ-5D värden i Sverige sågs ingen skillnad. HOOS visade ingen signifikant skillnad mellan kön eller typ av fraktur.

**Delarbete IV:** Målet med delarbete IV var att utröna responsivitet hos de hälsorelaterade livskvalitetsenkäterna och generiska instrumenten EQ-5D och SF-36 då de används hos patienter med lårbenshalsfraktur och en ålder < 70. 182 patienter inkluderades och följdes upp vid 4, 12 och 24 månader efter frakturtillfället. EQ-5D samt SF-36 mättes vid varje uppföljning. Smärta och höftfunktion skattades med Harris Hip Score (HHS) vid alla uppföljningar. Responsiviteten hos EQ-5D och SF-36 utvärderades genom beräkning av två effektmått; standardiserad effekt storlek och standardiserad skillnaden mellan medelvärden

av EQ-5D och SF-36 samt hur resultatet korrelerade med höftfunktion mätt med HHS och subjektivt hälsotillstånd.

EQ-5D och SF-36s sensitivitet/specificitet bedömdes med "receiver operating characteristic curve" (ROC-kurva) och area under ROC-kurvan och utfallen jämfördes med resultatet av HHS och subjektivt skattad hälsa. Studien visade att EQ-5D och SF-36 har en hög intern och extern responsivitet och är mer känsliga att påvisa förändringar i den subjektiva måendet än HHS för denna yngre grupp av patienter med lårbenshalsfraktur.

EQ-5D är enklare att administrera och besvara än SF-36 och slutsatsen är att frågeformuläret EQ-5D räcker för att undersöka hälsorelaterad livskvalitet hos yngre patienter med lårbenshalsfraktur.

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## **16 APPENDICES**

Appendix 1- Swedish version of the EQ-5D questionnaire



Hälsoenkät

**Svensk version** 

(Swedish version)

Markera,	genom	att kry	ssa i	en	ruta	i varje	nedanstående	grupp	(så	här	<b>1</b> ),	vilket
påstående	som bä	st beski	iver	Ditt	t hälse	otillståı	nd i dag.					

Rörlighet Jag går utan svårigheter Jag kan gå men med viss svårighet Jag är sängliggande	
<b>Hygien</b> Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning Jag har vissa problem att tvätta eller klä mig själv	
Jag kan inte tvätta eller klä mig själv	
Huvudsakliga aktiviteter (t ex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter) Jag klarar av mina huvudsakliga aktiviteter Jag har vissa problem med att klara av mina huvudsakliga aktiviteter Jag klarar inte av mina huvudsakliga aktiviteter	
Smärtor/besvär  Jag har varken smärtor eller besvär  Jag har måttliga smärtor eller besvär  Jag har svåra smärtor eller besvär	
Oro/nedstämdhet  Jag är inte orolig eller nedstämd  Jag är orolig eller nedstämd i viss utsträckning  Jag är i högsta grad orolig eller nedstämd	

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Till hjälp för att avgöra hur bra eller dåligt ett hälsotillstånd är, finns den termometer-liknande skalan till höger. På denna har Ditt bästa tänkbara hälsotillstånd markerats med 100 och Ditt sämsta tänkbara hälsotillstånd med 0.

Vi vill att Du på denna skala markerar hur bra eller dåligt Ditt hälsotillstånd är, som Du själv bedömer det. Gör detta genom att dra en linje från nedanstående ruta till den punkt på skalan som markerar hur bra eller dåligt Ditt nuvarande hälsotillstånd är.

Ditt nuvarande hälsotillstånd

Bästa tänkbara tillstånd 100 Sämsta tänkbara

tillstånd

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## Hälsoenkät (SF-36)

1

**Instruktion:** Detta formulär innehåller frågor om hur Du ser på Din hälsa. Informationen skall hjälpa till att följa hur Du mår och fungerar i Ditt dagliga liv. Besvara frågorna genom att sätta ett kryss i den ruta Du tycker stämmer bäst in på Dig. Om Du är osäker, kryssa ändå i den ruta som känns riktigast.

1	I allmänhet, skulle Du vilja säga att Din hälsa är:	Utmärkt	Mycket god	God	Någor- lunda	Dålig
2	<u>Jämfört med för ett år sedan,</u> hur skulle Du vilja bedöma Ditt allmänna hälsotillstånd <u>nu</u> ?	Mycket bättre nu än för ett år sedan	Något bättre nu än för ett år sedan	Ungefär detsamma	Något sämre nu än för ett år sedan	Mycket sämre nu än för ett år sedan
3	De följande frågorna handlar om al Är Du på grund av Ditt hälsotillstå mycket ?					
	•			Ja, mycket	Ja, lite	Nej, inte alls
(a)	Ansträngande aktiviteter, som at saker, delta i ansträngande sporter	t springa, ly	fta tunga	begränsad	begränsad	begränsad
(b)	Måttligt ansträngande aktivitete bord, dammsuga, skogspromenade					
(c)	Lyfta eller bära matkassar					
(d)	Gå uppför <b>flera</b> trappor					
(e)	Gå uppför <b>en</b> trappa					
(f)	Böja Dig eller gå ned på knä					
(g)	Gå mer än två kilometer					
(h)	Gå några hundra meter					
(i)	Gå hundra meter					
(j)	Bada eller klä på Dig					

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4	Under de <u>senaste fyra veckorna</u> , har Du haft något av följande problem i ditt arbete eller med andra regelbundna dagliga aktiviteter <u>som en följd av <b>Ditt kroppsliga</b> hälsotillstånd</u> ?	
(a)	Skurit ned den <b>tid</b> Du normalt ägnat åt arbete eller andra aktiviteter	
(b)	Uträttat mindre än Du skulle önskat	
(c)	Varit hindrad att utföra <b>vissa</b> arbetsuppgifter eller andra aktiviteter	
(d)	Haft <b>svårigheter</b> att utföra Ditt arbete eller andra aktiviteter (t ex genom att det krävde extra ansträngning)	
5	Under De <u>senaste fyra veckorna</u> , har Du haft något av följande problem i ditt arbete eller med andra regelbundna dagliga aktiviteter <u>som en följd av <b>känslomässiga</b></u> <u>problem</u> (som t ex nedstämdhet eller ängslan)?  Ja Nej	
(a)	Skurit ned den tid Du normalt ägnat åt arbete eller andra aktiviteter	
(b)		
(c)	Inte utfört arbete eller andra aktiviteter så <b>noggrant</b> som vanligt	
6	Under de <u>senaste fyra veckorna</u> , i vilken utsträckning har Ditt kroppsliga hälsotillstånd eller Dina känslomässiga problem stört Ditt vanliga umgänge med anhöriga, vänner, grannar eller andra?	
7		ycket vår
8	Under de senaste fyra veckorna, hur mycket har värken eller smärtan stört Ditt normala arbete (innefattar både arbete utanför hemmet och hushållssysslor)?	

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9	Frågorna här handlar om hur Du känner Dig och hur Du haft det under de senaste fyra veckorna. Ange för varje fråga det svarsalternativ som bäst beskriver hur Du känt Dig.						
	stor del av tiden under de senaste veckorna har Du känt Dig riktigt pigg och stark?	Hela tiden	Största delen av tiden	En hel del av tiden	En del av tiden	Lite av tiden	Inget av tiden
(b)	har Du känt Dig mycket nervös?						
(c) (d)	har Du känt Dig så nedstämd att ingenting kunnat muntra upp Dig?har Du känt Dig lugn och						
(e)	harmonisk?har Du varit full av energi?						
(f)	har Du känt Dig dyster och ledsen?						
(g)	har Du känt Dig utsliten?						
(h)	har Du känt Dig glad och lycklig?						
(i)	har Du känt Dig trött?						
10	Under de <u>senaste fyra veckorna</u> , hur stor del av tiden har <u>Ditt kroppsliga</u> <u>hälsotillstånd eller Dina känslomässiga</u> <u>problem</u> stört dina möjligheter att umgås (t ex hälsa på släkt, vänner etc)?	Hela tiden	Största delen av tiden	En del av tiden	Lite av tiden	Inget av tiden	
11	Välj det svarsalternativ som bäst beskrive STÄMMER eller INTE STÄMMER in p						en
(a)	Jag verkar ha lite lättare att bli sjuk än		nmer ga	mmer nska ora (		Stämmer inte sär-skilt bra	Stämmer inte alls
(b)	andra människor Jag är lika frisk som vem som helst av de	m [	_	 			
(c)	jag känner Jag tror min hälsa kommer att bli sämre	Γ	_				
(d)	Min hälsa är utmärkt						
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Hip dysfunction and Osteoarthritis Outcome Score (HOOS), Swedish version LK 2.0

	<b>F .</b>	HOOS	C (	
	Fragetor	mulär för höft	patienter	
DATUM:		PERSONNUMM	ER:	
NAMN:				
INSTRUKTION höftled. Informati dagliga liv. Besvi stämmer bäst in ändå för det alte	onen skall hjälp ara frågorna ger på dig ( <u>ett</u> alterr	a till att följa hur nom att kryssa fö nativ för varje frå	du mår och fung ör det alternativ	gerar i ditt du tycker
<b>Symptom</b> Tänk på de <b>sym</b> <b>veckan</b> när du b			àn din höft den <b>s</b>	enaste
S1. Har du känt at Aldrig □	t det maler i höfte Sällan	n eller hör du klic Ibland □	kande eller andra Ofta	ljud från höften? Alltid □
S2. Svårighet att ta Ingen	a benen brett isär? Lätt	Måttlig □	Stor	Mycket stor
S3. Svårighet att ta Ingen	a ut steget när du j Lätt	går? Måttlig □	Stor	Mycket stor
Stelhet Följande frågor r ökat motstånd vi i din höft senas	d rörelser i höftle			
S4. Hur stel har di Inte alls	n höft varit när du Något □	ı just har vaknat p Måttligt	å morgonen? Mycket	Extremt
S5. Hur stel har di	n höft varit efter a	att du suttit eller l	egat och vilat <b>sen</b> :	are under
Inte alls	Något □	Måttligt □	Mycket	Extremt
Smärta P1. Hur ofta har de				
Aldrig	Varje månad	Varje vecka	Varje dag	Alltid

1

# Följande frågor rör den höftsmärta du eventuellt upplevt **den senaste veckan**. **Ange graden av smärta du har känt i följande situationer**.

P2.	Sträcka höften helt Ingen	Lätt	Måttlig	Svår	Mycket svår
P3.	Böja höften helt Ingen □	Lätt □	Måttlig	Svår	Mycket svår
P4.	Gå på jämnt underla Ingen	ıg Lätt □	Måttlig	Svår	Mycket svår
P5.	Gå upp eller ner för Ingen □	trappor Lätt	Måttlig	Svår	Mycket svår
P6.	Under natten i sängl Ingen □	äge (smärta som Lätt	stör sömnen) Måttlig	Svår	Mycket svår
P7.	Sittande eller liggan Ingen	de Lätt	Måttlig	Svår	Mycket svår
P8.	Stående Ingen	Lätt	Måttlig	Svår	Mycket svår
P9.	Gå på hårt underlag Ingen □	ex asfalt, betong Lätt	Måttlig	Svår	Mycket svår
P10	). Gå på ojämnt unde Ingen □	erlag Lätt	Måttlig	Svår	Mycket svår
Föl <b>up</b>	sisk funktion jande frågor rör dir plevt den senaste ftbesvär.				
A1.	Gå nerför trappor.  Ingen  □	Lätt	Måttlig	Stor	Mycket stor
A2.	Gå uppför trappor Ingen □	Lätt □	Måttlig	Stor	Mycket stor
A3.	Resa dig upp från s Ingen	ittande Lätt	Måttlig	Stor	Mycket stor

# Ange graden av **svårighet** du har upplevt den senaste veckan på grund av dina höftbesvär.

A4. Stå stilla Ingen	Lätt	Måttlig	Stor	Mycket stor
A5. Böja dig, t ex för a  Ingen	tt plocka upp ett Lätt	föremål från golvet Måttlig	Stor	Mycket stor
A6. Gå på jämnt under Ingen	ag Lätt	Måttlig	Stor	Mycket stor
A7. Stiga i och ur bil Ingen	Lätt	Måttlig	Stor	Mycket stor
A8. Handla/göra inköp Ingen	Lätt	Måttlig	Stor	Mycket stor
A9. Ta på strumpor Ingen	Lätt	Måttlig	Stor	Mycket stor
A10. Stiga ur sängen Ingen	Lätt	Måttlig	Stor	Mycket stor
A11. Ta av strumpor Ingen	Lätt	Måttlig	Stor	Mycket stor
A12. Ligga i sängen (v. Ingen	ända dig, hålla ho Lätt □	öften i samma läge Måttlig	under lång tid) Stor	Mycket stor
A13. Stiga i och ur bad Ingen	kar/dusch Lätt	Måttlig	Stor	Mycket stor
A14. Sitta Ingen	Lätt	Måttlig	Stor	Mycket stor
A15. Sätta dig och resa Ingen	dig från toaletts Lätt	tol Måttlig	Stor	Mycket stor
A16. Utföra tungt hush Ingen	ållsarbete (snösk Lätt	ottning, golvtvätt, o Måttlig	lammsugning et Stor	c) Mycket stor
A17. Utföra lätt hushål Ingen	lsarbete (matlagr Lätt	ning, damning etc)  Måttlig	Stor	Mycket stor

Funktion, fritid och idrott Följande frågor rör din fysiska förmåga. Ange graden av svårighet du upplevt den senaste veckan vid följande aktiviteter på grund av dina höftbesvär.

SP1. Sitta på huk				
Ingen	Lätt	Måttlig	Stor	Mycket stor
SP2. Springa				
Ingen	Lätt	Måttlig	Stor	Mycket stor
П	П	П		
_	_	_	_	_
SP3. Vrida/snurra	på belastat ben			
Ingen	Lätt	Måttlig	Stor	Mycket stor
П	П	П	П	П
_	_	_	_	_
SP4. Gå på ojämn	t underlag			
Ingen	Lätt	Måttlig	Stor	Mycket stor
П	П	П	П	П
_	_	_	_	_
Livskvalité				
Q1. Hur ofta gör s				
Aldrig	Varje månad	Varje vecka	Varje dag	Alltid
Q2. Har du föränd	rat ditt sätt att leva	för att undvika	a att påfresta höften?	
Inte alls	Något	Måttligt	I stor utsträckning	Totalt
Q3. I hur stor utstr	äckning kan du lit	a på din höft?		
Helt och hållet	I stor utsträckning	Måttligt	Till viss del	Inte alls
Q4. Hur stora prob	olem har du med h	öften generellt s	sett?	
Inga	Små	Måttliga	Stora	Mycket stora
ū				, L

Tack för att Du tagit Dig tid att besvara samtliga frågor!.