

Diseases in the Hip

Exploring risk for fracture and
osteoarthritis

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UNIVERSITY OF GOTHENBURG

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Cover illustration: Hip fracture with pseudarthrosis, dated to the Medieval period. The bone comes from the Sigtuna Museum collection, Sweden. Photo Cecilie Hongslo Vala.

Diseases in the Hip- Exploring risk for fracture and osteoarthritis
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Til Tigergutt

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ABSTRACT

Objective: Hip fracture is the most serious condition linked to low bone mass or osteoporosis, and Sweden has one of the highest incidences in the world. The proportion of elderly is increasing in the Swedish population and in the world, and with increased age comes increased incidence for both fragility fracture and osteoarthritis. We therefore aimed to expand knowledge about risk factors for hip fracture and osteoarthritis.

Methods: All studies in this thesis were based on the entire Swedish population born between 1902 and 1952 (n=4,546,820). In Paper I we focused on married couples (n=904,451), in Paper II on farmers (n=97,136), in Paper III on women and men with total knee replacement (n=39,291), and in Paper IV we focused on widows and widowers (n=558,950). Statistics concerning risk factors were calculated with Poisson regression models.

Results: The risk of hip fracture was higher after hip fracture in a spouse, after total knee replacement, and after the death of a spouse, compared to non-exposed. Women and men combined had an increased risk for trochanteric fracture after total knee replacement. Farming seemed to decrease the risk for hip fracture in men only, but increased the risk of total hip replacement due to primary osteoarthritis in both female and male farmers.

Conclusion: A previous hip fracture in spouse increased the risk for hip fracture in women and men, most likely due to choosing a similar partner to oneself, along with shared lifestyle and environment. Farming seemed to protect against hip fracture in men but not in women, but increased the risk of total hip replacement. The reason for these results might be the high physical activity level and heavy loading, but why women did not have a lower risk for hip fracture is unknown. Both women and men had a higher risk for hip fracture after total knee replacement, which might be explained by reduced

mobility, pain, low bone mineral density, and changed kinematics. The risk for hip fracture also increased after the death of a spouse, which might be explained by the stress caused by grief and perhaps also from the stress caused by taking care of a dying spouse.

Keywords: Hip fracture, femur neck fracture, trochanteric fracture, osteoporosis, osteoarthritis, total hip replacement, total knee replacement, farmers, homogamy, assortative mating, bereavement

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Höftfraktur är den mest allvarliga konsekvensen av låg bentäthet och osteoporos. Sverige är ett av de länder i världen med högst risk för höftfraktur. Den åldrande befolkningen ökar och med stigande ålder ökar incidensen för både fraktur och artros. Målet med avhandlingen är att öka kunskapen om riskfaktorer för höftfraktur och artros.

Metod: Alla studier i avhandlingen är baserade på studier av hela svenska befolkningen födda mellan 1902 och 1952 (n=4,546,820). I den första studien fokuserade vi på gifta par (n=904,451), i den andra studien på bönder (n=97,136), i den tredje studien på alla kvinnor och män med total knäledsplastik (n=39,291), och i den sista studien låg fokus på änkor och änklingar (n=558,950). För statistisk analys av riskfaktorer användes Poisson regression i alla fyra studierna.

Resultat: Risken för höftfraktur ökade efter höftfraktur hos make, efter en total knäledsplastik, samt efter makes död. Män som var bönder hade däremot en minskad risk för höftfraktur, men både kvinnor och män inom bondeyrket hade en ökad relativrisk för total höftledsplastik. Både kvinnor och män hade en ökad risk för trokantär höftfraktur efter total knäledsplastik.

Slutsatser: Höftfraktur hos ens make ökade risken för höftfraktur, något som mest sannolikt beror på att man gifter sig med en som är lik sig själv och delar samma livsstil och miljö som sin partner. Bondeyrket hade för män, men inte för kvinnor, en skyddande effekt mot höftfraktur, men ökade i stället risken för total höftplastik hos både kvinnor och män. Den minskade risken för höftfraktur och den ökade risken för total höftplastik beror troligen på den ökade fysiska aktiviteten och tunga belastningen som ingår i bondeyrket. Varför kvinnor som var registrerade som bönder inte hade en minskad höftfrakturrisik vet vi inte. Kvinnor och män hade en ökad risk för höftfraktur efter total knäplastik. Det är svårt att veta direkt orsak, men troliga förklaringar innebär minskad rörlighet, smärta, låg bentäthet, samt förändrad biomekanik i knäet. Kvinnor och män hade en ökad risk för höftfraktur efter makes död, vilket kan ha orsakats direkt av stressen som sorgen innebär, men också stressen från att ha tagit hand om sin make innan döden.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. **Vala, CH**, Odén A, Lorentzon M, Sundh V, Johansson H, Karlsson M, Rosengren B, Ohlsson C, Johansson B, Kanis J, Mellström D.
Increased risk of hip fracture among spouses- evidence of a homogamy effect.
Osteoporosis International. 2017 Jan;28(1):95-102.
- II. Johansson H, **Vala CH**, Odén A, Lorentzon M, McCloskey E, Kanis J, Harvey NC, Lohmander S, Kärholm J, Mellström D.
Low risk for hip fracture and high risk for hip arthroplasty due to osteoarthritis among Swedish farmers.
Osteoporosis International. 2018 Mar;29(3):741-749.
- III. **Vala, CH**, Kärholm J, Kanis J, Johansson H, Sten S, Sundh V, Karlsson M, Lorentzon M, Mellström D.
Risk for hip fracture before and after total knee replacement in Sweden.
Submitted manuscript.
- IV. **Vala CH**, Lorentzon M, Sundh V, Johansson H, Lewerin C, Sten S, Karlsson M, Ohlsson C, Johansson B, Kanis J, Mellström D.
Increased risk for hip fracture after death of spouse- further support for bereavement frailty?
Submitted manuscript.

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ABBREVIATIONS

BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
DXA	Dual Energy X-ray Absorptiometry
FoB	Population and Housing Census
HR	Hazard Ratio
OR	Odds Ratio
RR	Relative Risk
SSRI	Selective Serotonin Re-uptake Inhibitors
SD	Standard Deviation
THR	Total Hip Replacement
TKR	Total Knee Replacement

1 INTRODUCTION

1.1 Hip fracture

Sweden has one of the highest incidences of hip fracture with approximately 18,000 events annually, but the prevalence of osteoporosis is similar compared to several other European countries ^[1]. Hip fractures are rare in individuals younger than 50 years, but after the age of 75 years hip fracture becomes the predominant fragility fracture ^[1]. In Sweden the mean age of hip fracture in men is 79 years and for women 82 years ^[2]. From 50 years and onwards, Swedish women have a 22.9% lifetime risk of hip fracture while Swedish men have a 10.7% risk ^[1]. Figure 1 shows the different hip fracture types.

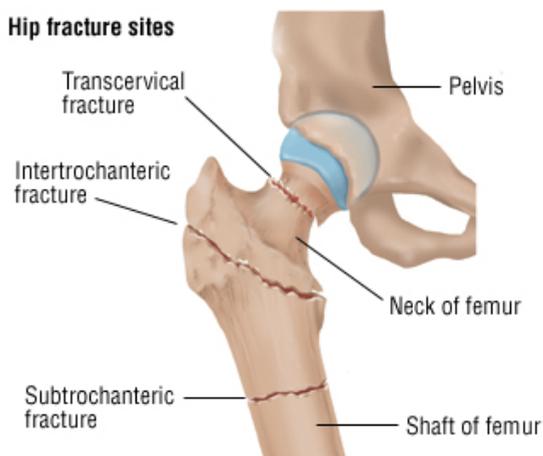


Figure 1. Different types of hip fracture. © <https://www.drugs.com/health-guide/leg-fracture.html>

Hip fracture is usually caused by falling from a standing position, but can also be caused by falling from a seated position or falling out of the bed, and may also happen spontaneously. Women have a higher risk than men ^[1]. The risk is also increased for individuals living in urban areas compared to those living in rural areas ^[3].

Risk factors for hip fracture include higher age, female sex, low bone mineral density (BMD), low body mass index (BMI), height, early menopause, low sunlight exposure, low calcium intake, smoking, high alcohol consumption, being unmarried, low physical activity, prior fragility fracture, genetic factors, parental history of hip fracture, glucocorticoid treatment, and diseases like rheumatoid arthritis and diabetes ^[1,4-12].

Hip fracture is the most serious osteoporotic fracture with a high risk for comorbidity, disability and mortality, and leads to surgical intervention ^[1]. Patients with hip fracture have an increased risk of mortality, especially in the first period after the fracture ^[1,13]. Up to 20% die within the first year, and the mortality rate increases with the number of other risk factors such as higher age, low weight, height, diet, mobility, falls, and previous fragility fracture ^[1,14]. Mortality is especially high in individuals with poorer health, daily smokers and in individuals with low BMI ^[15]. The relative mortality rate decreases with time, but remains higher compared to the general population ^[1]. During the first year after fracture, 30% of the excess mortality is directly caused by the fracture itself ^[1]. Patients with hip fracture often have comorbidities, which increases the risk of mortality ^[1,16]. A Swedish twin study showed that the mortality risk was increased for women and men independent of comorbidity, lifestyle and genes ^[17]. A Norwegian study of women and men above the age of 50 years with hip fracture (n=32,175), reported that men had greater comorbidity compared to women ^[16].

BMD from dual energy X-ray absorptiometry (DXA) is widely used to predict fracture. Hip fracture often occurs in individuals who do not have osteoporosis, but rather osteopenia (T-score between 1 and 2.5 standard deviation (SD) below the mean value for young adults). Therefore, more knowledge and other ways of predicting fracture is necessary ^[18]. FRAX, which calculates the ten-year risk for osteoporotic fracture, in combination with DXA gives a good prediction of the hip fracture risk ^[19].

1.2 Osteoarthritis

Osteoarthritis is a widespread disease, and is listed at place 11 on the Global Burden of Disease 2010 in terms of disability ^[20]. Osteoarthritis is characterised by loss of cartilage leading to narrowing of the joint space, bone change and new bone formation leading to subchondral sclerosis, cysts and osteophytes ^[21]. Osteoarthritis is also an inflammatory disease ^[22]. Risk factors include higher age, female sex, being overweight or obese, genetic

factors (which account for 60% of hip osteoarthritis and 40% of knee osteoarthritis), diet, certain diseases/disorders, trauma, and repetitive, intense and high-impact physical activity ^[21-23]. Knee osteoarthritis is more common in women^[21,24], but a systematic review showed no significant difference in prevalence in hip osteoarthritis between women and men ^[24].

Osteoarthritis can lead to pain, stiffness and inactivity ^[21,23]. Comorbidity is not uncommon for osteoarthritis patients; in a Swedish study almost 25% of the patients with hip or knee osteoarthritis had other diseases ^[25]. A systematic review revealed an increased mortality rate (hazard ratio (HR) 1.21; 95% confidence interval (CI) 1.10 to 1.34) due to cardiovascular disease among individuals with osteoarthritis ^[26]. The most effective treatment for severe hip or knee osteoarthritis is total hip replacement (THR) and total knee replacement (TKR), which can lead to pain relief, reduction in stiffness, improved physical function, and lower mortality ^[25,27-30].

The number of THRs and TKRs in Sweden has increased over the years, and will probably continue to increase due to the growing elderly population ^[31,32]. In the year 2010, almost 16,000 THRs were performed in Sweden ^[33,34]. In the year 2017 as many as 18,148 THRs were registered ^[35]. In the year 2000, 6063 TKRs due to primary osteoarthritis were performed in Sweden and in the year 2007 the number had increased to 10,380. In the year 2017 as many as 13,689 TKRs were registered in Sweden ^[25,36].

1.2.1 Osteoarthritis, loading and occupation

There is an association between osteoarthritis and occupations with heavy lifting, such as farming. Several studies have shown a higher risk for hip osteoarthritis in farmers ^[37]. An Icelandic study of women and men over the age of 60 years with THR or TKR, due to osteoarthritis, showed a higher probability for both THR (odds ratio (OR) 3.6; 95% CI 2.1 to 6.2) and TKR (OR 5.1; 95% CI 2.1 to 12.4) in male farmers ^[38]. For women there was no association between a higher risk for THR or TKR and occupation ^[38]. However, combined with being overweight or obese, both female and male farmers had a high risk for knee osteoarthritis; over threefold for men and over fourfold for women. Overweight is a known risk factor for knee osteoarthritis ^[39]. Men in the building and construction industry, who had worked there for 11-30 years, had a high risk for knee osteoarthritis ^[39].

Figure 2 shows the impact repeated occupation-dependent loading can have on bone. For the 85 year old farmer, bone strength and cortex thickness

seems to be more or less equal in both arms due to bilateral loading, while the 86 years old farrier has used his right hand more than his left, which has led to a stronger bone with thicker cortex in his right arm ^[40].

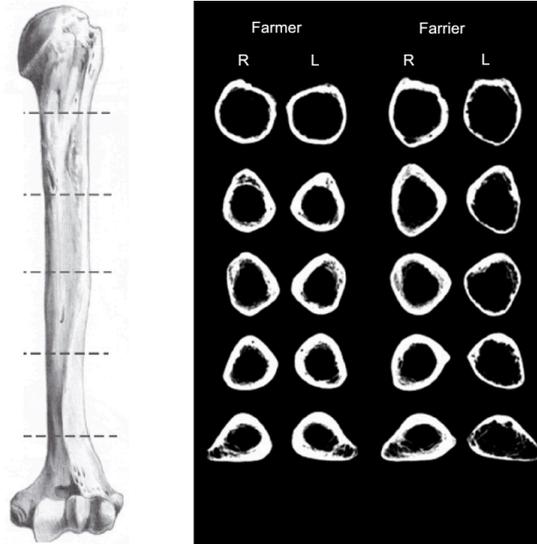


Figure 2. Cross sections from CT scans of left (L) and right (R) humerus of an 85 years old farmer and an 86 years old farrier. © Biver, E., Perréard Lopreno, G., Hars, M. et al. *Osteoporos Int* (2016) 27:1169. <https://doi.org/10.1007/s00198-015-3409-2>. Modified by Cecilie Hongslo Vala.

1.2.2 Osteoarthritis, falls and fracture

Several studies have described an association between high BMD and osteoarthritis ^[41-44]. In individuals with hip osteoarthritis, BMD was increased in the hip, spine, distal radius and calcaneus ^[45-47]. High BMD is also associated with the prevalence of joint replacement surgery ^[48]. However, a small study of 27 men with hip osteoarthritis showed no association with increased BMD in the femoral neck, but instead a larger femoral neck size and higher bone mineral content ^[49].

Individuals with osteoarthritis have an increased risk of falls, which might be due to pain, stiffness, instability, muscle weakness and other factors associated with osteoarthritis ^[50-53]. Several osteoarthritis patients also have

osteopenia or osteoporosis ^[53,54]. One study showed that women with self-reported osteoarthritis had an increased risk (HR 1.9; 95% CI 1.05 to 1.13) for any clinical fracture. However, the risk for sustaining a hip fracture were not significantly different from the risk in the control group, consisting of women without arthritis ^[55]. Another study showed that individuals with prevalent radiographic knee osteoarthritis was associated with an increased risk of fracture, including hip fracture ^[56]. The unadjusted HR for hip fracture was 2.6 (95% CI 1.5 to 4.5), while adjusted for age, gender, height and weight the HR was 1.8 (95% CI 1.0 to 3.2). Adjusted for all available covariates, the risk of fracture was non-significant ^[56].

1.3 Homogamy

When searching for a partner, it is more likely for a person to choose a partner with a similar phenotype and cultural traits, such as height, weight, behaviour/personality, age, IQ, education, and religion, than expected by chance. This is called assortative mating ^[57,58]. Homogamy means, in our study, that married people have more in common with their spouse than is expected by chance. Married couples tend to share common environmental and lifestyle factors, such as smoking, drinking alcohol, diet, physical activity, and health ^[59-61]. A review found a concordance for physical and mental health between spouses ^[62]. Correlation in spouses have been found for having the same diseases and conditions, for example depression, cancer, metabolic disorders, major coronary risk factors such as blood pressure, and diabetes; conditions that to varying degree are thought to be caused or influenced by lifestyle and environment ^[59,62-65].

1.4 Bereavement

The loss of a spouse is a major life event, which can lead to severe grief and an increased risk for poorer mental health such as depression and anxiety. As many as about 28% of the women and men whose spouse has died experienced major depression, often in the first 6 months after the death of their spouse ^[66].

Bereaved women and men often experience sleep disturbances, which are especially prevalent in those who are depressed ^[66-68]. Sleep is extremely

important for both physical and mental well-being, and loss of sleep may lead to poorer health. Bereaved individuals have an increased risk for diseases and unhealthy conditions such as Takotsubo cardiomyopathy (broken heart syndrome), elevated blood pressure, higher heart rate, elevated cortisol levels, diabetes, and immune changes ^[67,69-74]. A genetic reaction to stress was found to lead to an increased systemic inflammation ^[75]. Hallucination is common among the bereaved, especially among older individuals ^[76].

Bereavement is associated with an increased risk of mortality, with the highest risk immediately after death of a spouse ^[77-79]. A meta-analysis showed a 22% increased mortality risk in widows and widowers compared to married people ^[80]. The mortality risk was also increased among elderly individuals whose spouse was hospitalized ^[81].

Caring for a sick or dying spouse can also lead to major stress and strain both mentally and physically, with symptoms such as fatigue, anxiety, and depression ^[82-84].

1.4.1 Mental stress can lead to falls, fractures and medication

Falls and fractures might be a result from poorer physical and mental health after bereavement ^[85]. Several studies have shown an increased risk of psychotropic medicine use among the bereaved ^[86,87]. An association between depression, falls and hip fracture have also been established ^[88,89]. Usage of selective serotonin re-uptake inhibitors (SSRI) has been associated with falls and fractures ^[90-94]. Polypharmacy (5 to more drugs) is common among the elderly in Sweden, affecting as many as 44% of women and men aged 65 years and older ^[95]. 74% of the individuals exposed to polypharmacy used the drugs continuously for 1 year or longer ^[96].

Compared to married women, widows have a worse health outcome with increased health damaging changes such as smoking and drinking, lowering the intake of vegetables, and losing their appetite ^[67,71]. Smoking and high consumption of alcohol, but also poorer diet are risk factors for hip fracture ^[1].

2 AIM

The general aim was to get a better understanding of risk factors for hip fracture and hip osteoarthritis.

Specific aims for each paper were:

- I. To determine the concordance for hip fracture in spouses.
- II. To determine the risk for hip fracture and total hip replacement in Swedish farmers.
- III. To determine the risk for hip fracture before and after total knee replacement.
- IV. To determine the risk for hip fracture after the death of a spouse.

3 MATERIALS AND METHODS

3.1 Subjects

All four studies have been based on the total population in Sweden, born between 1902 and 1952, during the period 1987 to 2002 (n=4,546,820). More information on the total population are described in Table 1 and Figure 3.

Table 1. Characteristics of the total population born 1902 to 1952, which all the studies are based on

	Women	Men
Total population	2,348,788	2,198,032
Married at baseline	1,389,542 (59.2%)	1,485,169 (67.6%)
Widowhood	449,767 (19.1%)	278,712 (12.7%)
Farmers	51,923 (2.2%)	123,054 (5.6%)
Hip fracture	150,628 (6.4%)	61,594 (2.8%)
Total hip replacement	48,335 (2.1%)	38,298 (1.7%)
Total knee replacement	29,918 (1.3%)	15,977 (0.7%)
Mean age at baseline 1987	56.57 ± 14.31	54.77 ± 13.71
Mean age at hip fracture	80.33 ± 8.62	77.48 ± 10.29
Mean age at total hip replacement	71.21 ± 8.87	69.58 ± 8.86
Mean age at total knee replacement	72.43 ± 7.67	71.45 ± 7.74

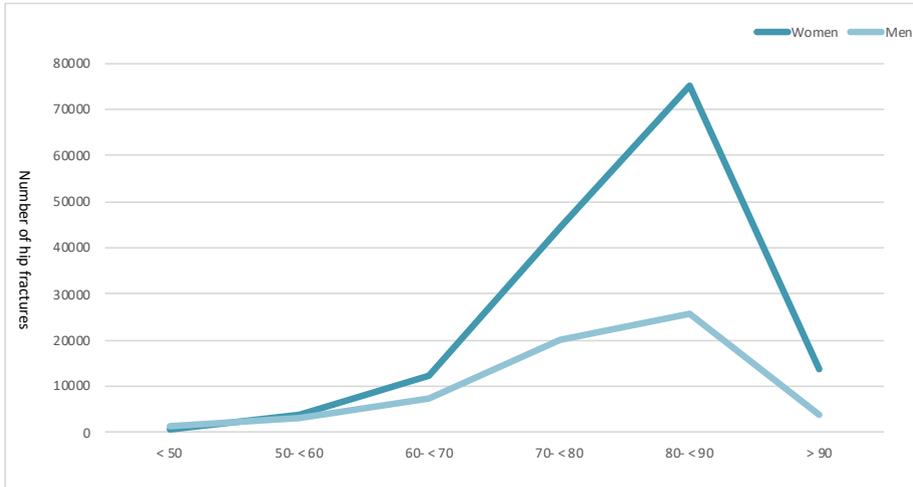


Figure 3. Number of hip fractures in each age-group from 1987 to 2002

3.1.1 Paper I

This study is based on married couples born between 1902 and 1942 (n=904,451) and married for at least 5 years at baseline. We excluded all those aged below 60 years and above 95 years. The control population comprised individuals whose spouse did not have a hip fracture. To compare the homogamy effect (previous hip fracture in spouse) with a sibling effect (previous hip fracture in sibling) on hip fracture, we performed a sub-analysis. This sub-study comprised married individuals born between 1932 and 1942 (n=280,754) with at least one sibling (n=600,814).

3.1.2 Paper II

This study comprised the total Swedish population from the age of 35 and up. The study populations consisted of registered farmers (n=97,136), while the control population consisted of individuals with registered occupations other than farming (n=3,463,360). As many as 75% of the farmers were men, while 53% of the control group were men. The mean age for farmers was 58.3 ± 12.2 years and for the control population 51.8 ± 12.1 SD years. Individuals with secondary osteoarthritis or unclear surgical codes were excluded from the studies.

3.1.3 Paper III

We studied the Swedish population aged 50-90 years (n=4,258,934). We excluded all individuals with a THR, individuals with diagnosis code for other than primary osteoarthritis of the knee in relation to TKR, and all with unclear surgical codes. The mean age for individuals with TKR were 72.1 ± 7.6 SD years. The control population consisted of age-matched women and men without TKR and THR. We also performed studies on risk of femoral neck fracture and trochanteric fracture (both intertrochanteric and subtrochanteric fractures). In the risk population, individuals with secondary osteoarthritis or unclear surgical codes were excluded from the studies. Women and men with THR were excluded from both the risk population and the control population.

3.1.4 Paper IV

We followed married women and men aged 60 to 100 years (n=1,783,170), who had been married for at least 5 years at baseline, between 1987 and 2002. Of these 891,274 were women and 891,896 were men. The risk population consisted of all who became widows (39.9%) or widowers (23.8%) during the follow-up period. The control population consisted of individuals who were still married during the follow-up period.

3.2 Registers

3.2.1 The Total Population Register

This register contains information on age, gender, marital status, immigration and emigration.

3.2.2 The Multi-generation Register

From this register we received information on family relations. This was used to identify siblings to married men and women in paper I.

3.2.3 The National Census Register

From this register we obtained information on occupation, income, education, geographical latitude, level of urbanisation of the place of residence.

Occupation was self-reported and obtained from Population and Housing Census (FoB) from the years 1975 and 1985. The code 401 was used for farmers, although the code is also used for foresters and market gardeners.

3.2.4 The National Inpatient Register

From this register we obtained information covering the years 1987 to 2002 on all hospital episodes with musculoskeletal diagnosis and related surgical procedure; hip fracture, THR and TKR due to primary osteoarthritis. This information was obtained from The Swedish National Board of Health and Welfare through Statistics Sweden. There was no information in the Swedish National Inpatient Register on which side had been fractured or operated. We also had no information on events of fracture and surgery before 1987 or after 2002.

3.3 Ethical considerations and approvals

The data from the registers were coded when we received them, we have no personal ID or names. We have an ethical approval from the ethical committee in Lund in Sweden (LU 630-99) and a later approval from the ethical committee in Gothenburg. No formal consent from the individuals was necessary according to the ethical committees.

3.4 Covariates

Available covariates were age, gender, calendar year of fracture, time since baseline, income, education, level of urbanization and graphical latitude, and previous hip fracture in spouse. We did not have any information on comorbidity, height, weight, BMD, habits or lifestyle.

Age, calendar year, time since baseline, and previous hip fracture in spouse were used as time-dependent covariates, which means that they were

recalculated at each period in risk time. Education was categorised according to the number of years in school on a 7-point scale; 1 was <9 years, 2 was 9 years, 3 was 10-11 years, 4 was 12 years, 5 was <3 years in university, 6 was >3 years in university, and 7 was post-graduate education. We had data of income from 1991, 1996 and 2002. The highest inflation-adjusted value of income was registered. We had some missing data on education and income, mainly in the oldest women and men in the birth cohorts 1902 to 1911. Urbanisation was categorised from a high to a low number of inhabitants per municipality on a six-point scale; 1 was >200,000, 2 was 100-200,000, 3 was 50-100,000, 4 was 25-50,000, 5 was 15-25,000, and 6 was <15,000. Latitude was categorised as following: south (55-57°N), middle-south (57-59°N), mid-north (59-61°N), and north (61-69°N).

3.5 Statistics

In all the papers we followed each individual in the Swedish Hospital Discharge Register from January 1st 1987 to December 31st 2002 and identified the first event of hip fracture, THR, TKR, or until death or emigration. To identify all patients with hip fracture, THR, and TKR we used the codes from the International Classification of Diseases 9 and 10. Patients had to have a diagnosis code for hip fracture and primary osteoarthritis, but also a surgery code for hip fracture, THR, and TKR (Table 2).

Table 2. International Classification of Diseases 9 and 10 used in our studies

	ICD 9	ICD 10
Diagnosis code hip fracture	820A-D, (paper I also 820W, 820X)	S720-S722, (paper I also S727-S729)
Diagnosis code primary hip OA	715B	M160-M161
Diagnosis code primary knee OA	715B	M17
Surgical code hip fracture	8200-8219, 8413,8414	NFB, NFJ
Surgical code THR	8414	NGB29,39,49
Surgical code TKR	8428	NGB29,39,49

OA=osteoarthritis, THR=total hip replacement, TKR=total knee replacement

A Poisson regression model is suitable for the study of time to a certain event in a given calendar time period. This method was therefore used for analysis of risk for hip fracture, and for paper II also risk for THR, in the time period 1987 to 2002. The calculation was performed in two steps. First the risk time for each individual was divided into short intervals; two months periods were used in paper I, III and IV, and one-month periods were used in paper II. This was gathered to a working file with many records per person, at most 96 for a follow-up of 16 years with six 2-months intervals per year. Then this data was put in to a regular Poisson regression model. The result from such a model is the same as obtained from a Cox regression model, but the Poisson model is more flexible when time varying covariates are included. We report results from the models as Hazard Ratios (HR) with a 95% Confidence Intervals (CI), and a p-value below 0.05 was considered statistically significant. HR is a measure commonly used in survival and time-to-event analysis, and estimates the effect that each risk factor in the model have on the relative risk of observing the studied outcome in any time interval. For example, a HR of 1.25 may be interpreted as showing a 25% increase of risk if a certain risk factor is present compared to the risk where the risk factor is absent. The time interval could be one day, one month, one year or anything else relevant.

There were some limitations in data on education and income for the oldest individuals. In paper II we used Fisher's permutation test, a type of non-parametric T-test, when comparing baseline variables in farmer with other occupations.

4 RESULTS

4.1 Paper I

Increased risk of hip fracture among spouses- evidence of a homogamy effect

We followed all married couples (n=904,451) in Sweden, born between 1902 and 1942, from the years 1987 to 2002, in order to analyse the risk for hip fracture in women and men whose spouse have had a hip fracture.

4.1.1 Main results

- Women and men whose spouse had a hip fracture had a higher risk of hip fracture, 11% and 20% respectively, compared to married women and men whose spouse did not sustain a hip fracture during follow-up.
- Compared to age-matched controls, the highest risks for hip fracture after hip fracture in the spouse, were found in women aged 60-70 years and in men aged 70-80 years (Figure 4).
- There were no significant differences in results between being married longer than 25 years or married less than 25 years.
- The risk for hip fracture was increased by over twofold when having a sibling with hip fracture, compared to siblings without hip fracture.

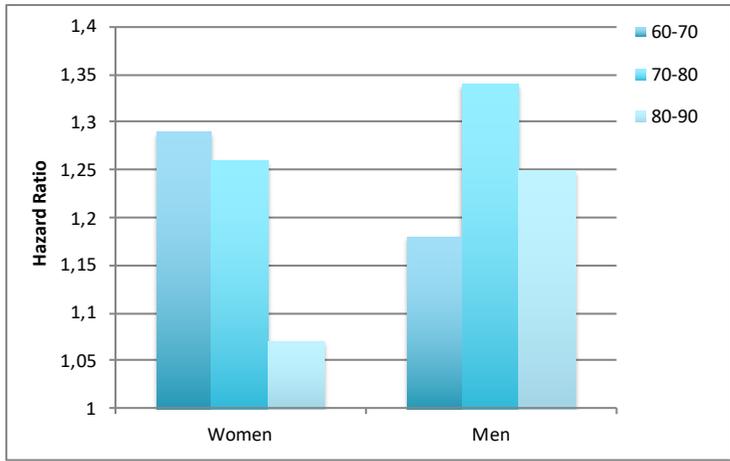


Figure 4. Hazard ratio for risk of hip fracture in different age intervals

4.1.2 Conclusion

Women and men whose spouse had a previous hip fracture had an increased risk for hip fracture, which reveals a possible homogamy effect. The hip fracture risk in siblings are higher than in spouses, but the spousal risk was independent of the genetic effect, shown in the model in the paper, including both hip fracture risk in spouses and siblings.

4.2 Paper II

Low risk for hip fracture and high risk for hip arthroplasty due to osteoarthritis among Swedish farmers

We followed all Swedish farmers (n=97,136) above the age of 35 years at baseline, in the period 1987 to 2002, to analyse the risk for hip fracture and THR due to primary osteoarthritis. We compared farmers to individuals with all other occupations that was registered in FoB 1975 or 1985.

4.2.1 Main results

- Both female and male farmers had an increased risk of THR due to primary osteoarthritis; the risk was 40% higher in women and twofold higher in men (Figure 5).
- Male farmers had a 40% lower risk for hip fracture compared to men with other occupations, when adjusted for all available covariates (Figure 5).
- The risk for hip fracture in female farmers was not significantly different from women with other occupations (Figure 5).

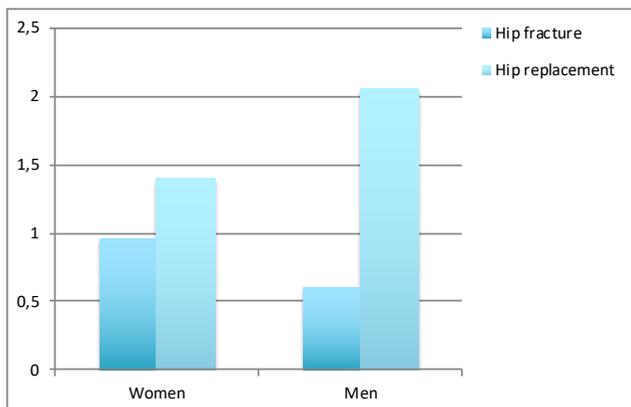


Figure 5. Risk of hip fracture and total hip replacement in female and male farmers

4.2.2 Conclusion

Our results showed that farmers had a high risk for THR due to primary osteoarthritis, compared to individuals with other occupations. Male farmers had a low risk for hip fracture, while female farmers risk for hip fracture was not significantly different from the risk for hip fracture in women with other occupations.

4.3 Paper III

Risk for hip fracture before and after total knee replacement in Sweden

We followed the entire Swedish population aged 50 to 90 years during the time period 1987 to 2002. We identified all patients who had a first event of hip fracture (n=195,860) and TKR due to primary osteoarthritis (n=39,291), to analyse the risk for hip fracture before and after TKR. We also analysed the risk of femoral neck and trochanteric fracture. The control population consisted of women and men without TKR in the time period 1987 to 2002. We mainly looked at the hip fracture risk in a ten-year period. However, for men and women combined we could study the risk one year before and one year after TKR, but not stratified in age, sex or fracture type because of too few hip fractures. More characteristics of the study population is presented in Table 2.

Table 3. Characteristics of women and men with total knee replacement (TKR) divided into hip fracture types

	Femoral neck fracture	Trochanteric fracture
Women	78.9%	77.3%
Mean age at baseline	78.3 ± 8.3 SD	79.4 ± 8.1 SD
Number before TKR	470	330
Number after TKR	1136	1109

4.3.1 Main results

- Women and men had a low risk for hip fracture before TKR, but the risk increased from the ten-year period before to the ten-year period after TKR.
- The risk for hip fracture the first year after TKR was increased, also when compared to the one-year period before TKR.
- Men had a higher risk for hip fracture in a ten-years period after TKR compared to men without TKR. For women the risk for hip fracture after TKR was not significantly different from the results for women without TKR.
- Compared to age matched controls, women and men in the age group 50-74 years had a higher risk for hip fracture in a ten-years period after TKR, while the risk in the age group 75-90 years was not significantly different from the control population.
- Women and men had a higher risk for trochanteric fracture in a ten-years period after TKR, while the risk for femoral neck fracture was not significantly different from the control population.

4.3.2 Conclusion

In conclusion, individuals with TKR had a low risk for hip fracture before surgery compared to the control population. The first year after TKR, women and men combined had an increased risk for hip fracture compared to the control population. Studying a five- years period after TKR, women and men combined had a higher risk for hip fracture in younger ages and for trochanteric fracture, compared to the control population.

4.4 Paper IV

Increased risk for hip fracture after death of spouse - further support for bereavement frailty?

In this paper we followed all married Swedish women and men (n=1,783,170), aged 60 to 100 years. They were followed during the years 1987 to 2002, to analyse the risk of hip fracture after the death of a spouse.

4.4.1 Main results

- Widows and widowers had an increased risk of hip fracture after the death of their spouse, compared to still married women and men.
- The risk of hip fracture was especially high during the first 6 months after the death of a spouse, the HR then decreased with time, but remained elevated.
- Divided into age groups and compared to an age-matched control population, the highest HR for hip fracture was seen for widows in the age group 70-79 years, and for widowers in the age group 60-69 years.

4.4.2 Conclusion

We conclude that women and men whose spouse died during the follow-up time had an increased risk of hip fracture. The highest risk was seen in the first 6 months after death of a spouse, and the highest HRs were seen in individuals below the age of 80 years.

5 DISCUSSION

Osteoporosis with fragility fractures is a major health concern, especially since the population is aging. Today there is a lot of knowledge in the area of osteoporosis and fragility fractures, but there is still a lot more to learn. With the growing ageing population follows an increased incidence and prevalence of several diseases such as osteoarthritis. Studies with large population cohorts and long follow-up periods are needed, and since the Swedish registers are of high quality ^[97], they are a good starting point for such studies. Our population studies come from these Swedish registers.

5.1 Paper I: Homogamy and hip fracture

In this study we found that women and men whose spouse had a previous hip fracture had an increased risk for hip fracture. This might be explained by assortative mating and homogamy, one choose a similar partner or become more similar, when it comes to appearance (eye-and hair colour, height and weight), IQ, age, mental and physical health, habits (smoking, alcohol consumption, physical activity), and socioeconomics (education) ^[57,58,98,99]. One study has also showed that there is a greater genetic similarity between spouses than between randomly chosen individuals ^[100]. The most important influence on health resemblance between spouses was education; individuals have a tendency towards marrying a partner with similar educational attainment ^[99]. The same study showed that the correlation between spouses did not change over the life course ^[99].

Sharing the same home and diet might also mean that spouses have the same or similar gut microbiota. Mouse studies have shown that gut microbiota regulates bone mass ^[101].

Diseases or conditions with spousal concordance such as diabetes have been associated with an increased risk of hip fracture, and cardiovascular disease has been associated with increased bone loss and fracture risk ^[102,103]. Individuals with type 1 diabetes had a greater risk for hip fracture than individuals with type 2 diabetes, with relative risks (RR) up to 7 and 1.3 respectively ^[102]. Type 2 diabetes can be hereditary and/or caused by diet and obesity ^[65,102]. BMI and daily intake of calories correlate amongst spouses

[104]. Diabetics with high BMI had a lower risk for hip fracture than diabetics with a normal BMI. However, diabetics have an increased risk of frailty, sarcopenia and falling, which increases the risk for fracture [102]. A Norwegian study showed that women with low physical activity and abdominal obesity had a 61% higher RR for hip fracture (95% CI 1.18 to 2.19) [105]. Other traits, habits and lifestyle shared by spouses have been shown to increase the risk for hip fracture, such as height, low BMI, abdominal obesity, smoking, high alcohol consumption, poor diet, low physical activity, reduced sunlight exposure, and lower socioeconomic status [1,106,107].

5.2 Paper II: Farmers risk for hip fracture and THR

In paper II we showed that both female and male farmers had a high risk for THR due to primary osteoarthritis, which for men, but not women, are supported by an Icelandic study [38]. The reason for the difference in risk for female farmers might be explained by the difference in number of female farmers, which in our study was 24,284 and in the Icelandic study 242 [38]. In our study male farmers also had a lower risk for hip fracture.

Farming is an occupation with a high level of physical activity including heavy lifting. Sunlight exposure is often high due to much outdoor work. It is well known that physical activity and heavy load and lifting have an impact on bone, both positive and negative [38,40,108]. Heavy loading and repeated occupational activity from young age, such as farming, are associated with higher bone strength through an increase in bone size [40]. However, occupations such as farming increases the risk for osteoarthritis, probably do to the high level of physical activity, repetitive movements and heavy lifting [38]. It has been common in Sweden, and other countries, that the farms remain within the family, traditionally the oldest son inherits the farm. Since hip osteoarthritis is hereditary [109,110], this might also explain at least some of the increased risk for THR in farmers.

It is also well known that osteoarthritis is associated with high bone mass [45,46,48]. Women and men with osteoarthritis tend to have a higher BMI and BMD, which protects against fractures in the hip and pelvis [53]. It might be that the high BMD gives the bone more strength to resist fractures, and in the cases with THR, they only have one or perhaps no hips to fracture. A study

of patients with hip fracture reported a lower probability for radiographic hip osteoarthritis (OR men: 0.30; 95% CI 0.12 to 0.74, women: 0.33; 95% CI 0.19 to 0.58) compared to the control population ^[111]. Yamamoto et.al. ^[52] found a low risk for hip fracture (standard fracture rate ratio women: 0.61; 95% CI 0.56-0.65, men: 0.77;95% CI 0.69-0.85) in 29,706 patients with hip osteoarthritis from Sweden. They also found a tendency for an increased risk for trochanteric fracture compared to femoral neck fracture in patients with hip osteoarthritis ^[52].

Mortality is a good measurement for health. A previous study showed that THR patients had a reduced mortality and a lesser degree of comorbidity such as diabetes, depression, and heart failure, compared to osteoarthritis patients without THR ^[112]. However, in a Swedish study of 1662 THRs almost 25% of the patients reported other diseases ^[25].

As described earlier, high physical activity, heavy load lifting and repetitive movements might lead to osteoarthritis, and individuals with osteoarthritis tend to have higher BMD and BMI. Higher physical activity and muscle mass, and higher BMD might lead to stronger bones and lower risk for fracture. This might explain the lower risk of hip fracture in male farmers. The reason why female farmers did not have a lower risk for hip fracture is probably complex. One problem is that we have no information on the work distribution on the farm. Traditionally the woman took care of the household, children, garden, and milking cows, and the man took care of most of the outdoor heavy work. If this was still the case for most of the farmers during the follow-up time 1987 to 2002 this might explain the differences in risk between women and men. Since we do not have this information it is difficult to explain the observed differences.

5.3 Paper III: TKR and hip fracture

Women and men with TKR had a low risk for hip fracture before surgery, with an increased risk for hip fracture the first year after surgery compared to the control population. The risk during the year before TKR increased significantly during the year after TKR. Compared to the control population, when stratifying gender and age, men and individuals in younger ages (50 to 74 years) had an increased risk for hip fracture in the ten-years period after TKR. The risk of trochanteric fracture, but not femoral neck fracture, was also increased in the ten-years period after TKR.

The low risk for fracture before surgery can be attributed to osteoarthritis, BMD and BMI. Osteoarthritis is commonly associated with higher BMD and BMI ^[113]. The increased BMD seen in individuals with osteoarthritis might be due to osteophytes and subchondral sclerosis in the DXA measured site (e.g. femoral neck, lumbar spine) ^[48]. However, the role of the increased BMD in individuals with osteoarthritis might be overestimated, since several studies have suggested a poorer bone quality in individuals with osteoarthritis ^[113]. This might be one of the reasons for the increased risk of falls and fracture found in several studies ^[113,114]. In one study women with osteoarthritis had a 20% increased risk of fracture and reported 25% more falls than women without osteoarthritis, but these women were older and had more comorbidity (e.g. chronic obstructive pulmonary disease), which might influence the risk of fracture ^[50]. Our results showed a low risk for hip fracture before surgery, but the risk increased from the period before compared to the period after TKR. We had no information on activity level, BMD, BMI, or falls, which makes it difficult to interpret the results, but perhaps a tendency of osteoarthritis and most likely also high BMD and high BMI to be protective against hip fracture.

Bone loss after TKR is also well established in the literature ^[113]. The greatest loss has been seen during the first 3-6 months after TKR in both the area around the knee and in the hip. Fracture risk has been found to be increased after TKR in some studies ^[113]. A previous British study of 20,033 individuals with TKR, due to osteoarthritis, showed that compared to the control population, with no recorded knee pain, osteoarthritis, or knee arthroplasty, the TKR group had a 58% increased risk for hip fracture the first year after TKR, adjusted for age, BMI, smoking and alcohol intake ^[115]. In the years before surgery the risk for hip fracture was not significantly different from the risk in the control population, as were the same for the risk after one year after surgery ^[115]. A smaller Dutch study found a 54% increased OR for hip fracture after knee arthroplasty due to osteoarthritis, adjusted for several drugs and diseases/conditions/injuries ^[116]. As in our study, both the British and Dutch study also found a greater risk in younger individuals ^[115,116]. These studies support our result showing an increased risk of hip fracture after TKR. ^[115,116]

Lower physical performance, such as in grip strength, walking speed, and chair standing up, and low muscle strength increase risk of hip fracture ^[117]. Another study of quadriceps weakness showed an increased risk of several fracture types in men, including hip fracture, but only the risk for vertebral fracture increased in women ^[118]. A study of physical health problems following a TKR showed that the majority of the patients experienced leg

oedema and pain in the early postoperative period ^[119]. The majority also did not exercise or only partially completed the recommended exercises. Between 30 to 50% of these TKR patients had sleep disturbances, appetite problems and problems with their bowel function ^[119]. It appears that individuals with TKR are at risk of low physical activity. A systematic review revealed that patients had no improvement of physical activity 6 months after surgery, and after 1 year they still had a lower physical activity level than healthy controls ^[120]. The lower physical activity level, which might lead to muscle weakness and instability, but also obesity, which are risk factors for falls and fracture. The majority of women and men with knee osteoarthritis are overweight or obese. Obesity has been shown by most studies to be protective against hip fracture, but abdominal obesity increases the risk of hip fracture ^[105,107,121,122]. As many as up to 35.4% of individuals with TKR had a sarcopenic obesity phenotype ^[123]. Low muscle strength and physical performance, are risk factors for falls and hip fracture ^[117,123]. Obesity is a systemic inflammatory condition and increases the risk for type 2 diabetes and cardiovascular diseases, which are risk factors for hip fracture ^[103,121,122].

The reason for the increased risk of trochanteric fracture is hard to explain and needs to be further studied. However, one possible explanation might be the differences in aetiology and morphology between femoral neck fracture and trochanteric fracture. Women with trochanteric fracture are often older, shorter, have lighter weight, lower BMD, can be more influenced by hormonal and environmental factors, such as smoking, and differences in hip geometry ^[124-127]. Perhaps a combination of the morphology/aetiology of trochanteric fracture, type of fall and muscle weakness might be the explanation.

The reasons for the increased risk for hip fractures observed in individuals with TKR are complex, but can be attributed to a reduction of mobility due to pain and stiffness, changed knee kinematics, poorer balance, weaker muscles, bone loss, comorbidity, inflammation, and other factors yet to be established.

In our study, it is difficult to know if the increased hip fracture risk is due to the increased symptoms of the knee osteoarthritis before surgery or if it depends mostly on the surgery itself, but most likely the reason is due to both.

5.4 Paper IV: Bereavement and hip fracture

We have shown that recently bereaved widows and widowers, but also in later periods after bereavement, had an increased risk for hip fracture. Previous studies have shown that mental distress led to an increase in hip fracture risk ^[128], and that widows had an increased risk for hip fracture ^[129], which support our study results. Depression and sleep disturbance are common among the bereaved ^[130,131]. Depression has been associated with lower hip BMD, increased risk of falls and hip fracture, and decreased physical activity ^[132-134]. The reason is still unclear, but higher levels of cortisol and cytokines/inflammation have been found in depressed individuals, which can lead to bone loss and fracture ^[135-138]. Sleep disturbances, insomnia and poor sleep quality, which are especially common in sick and depressed individuals, have been associated with falls and fractures ^[139]. Both a too short or too long sleep duration increased the risk for falls, short sleep increased the risk of fracture but not hip fracture, and restless sleep increased the risk for falls and fracture ^[139]. A combination of antidepressant medication, such as SSRIs, and poor sleep quality/sleep disturbance might increase the risk of falls and fracture further. Studies have shown a connection between stressful life events and bone loss, and widowhood in men and reduced lumbar spine density ^[140,141]. However, the risk of bone loss in the hip after stressful events was small ^[140].

A previous study have shown no association between BMD in the proximal femur and marital status ^[141]. Furthermore, studies have shown that hip fracture patients have experienced more life events (for example bereavement, retirement, new family member, family problems, illness, changes in lifestyle and environment) ^[142], and that use of benzodiazepines and antidepressant medication were more common among hip fracture patients ^[143].

Diseases and conditions might also affect the risk of depression, sleep-disturbance, medication, falls, and fractures. A study of recently bereaved widows showed that as many as 86% already had up to several chronic conditions and 76% experienced a worsening of the already existing conditions or were diagnosed with new illnesses ^[144].

Possible explanations for our findings might be stress caused by bereavement, such as depression, anxiety, sleep disturbance, shared lifestyle and environmental factors, but also stress from the possibility of taking care of a sick spouse before death.

5.5 Strengths and weaknesses

All the information used in our four studies comes from Swedish registers with high quality and validity^[97]. We have originally based the studies on the entire Swedish population born between 1902 and 1952. As a result, each study has had both a large study group and a large control population, giving large numbers of hip fractures, THRs and TKRs. By including the entire Swedish population, we also avoided selection bias of healthy individuals and nonresponse. All individuals have been followed from the beginning of 1987 to the end of 2002, a follow-up period of 16 years. During this period, we registered the first event of hip fracture, THR or TKR. A limitation is that we had no information on women and men before 1987 and after 2002. The studies might also be considered as somewhat old since we have studied the population between the years 1987 to 2002. However, our population was born between 1902 and 1952, so many of them were still alive. Furthermore, we lack information on which side the fracture or surgery was, on comorbidity, BMD, BMI, diet and other risk factors of hip fracture and osteoarthritis. There are also missing data on education and income for the oldest individuals. However, we have a very large dataset with information on diagnoses and surgery, age, gender, marital status, place of residence with latitude and urbanisation level, income and education, and a long follow-up time. Specific limitations with comments are shown in Table 3.

Table 4. Specific limitations for each paper

Paper I: Increased risk of hip fracture among spouses- evidence of a homogamy effect
Limitation: Some married couples do not live together.
Comment: The number of these couples are probably too few to have an effect on the result.
Limitation: Some married couples have divorced, but are still a part of the study or control population registered as married.
Comment: The number of these couples are too few to have an effect on the result, and the homogamy effect may persist after divorce.

Limitation: The sibling study was limited to individuals below the age of 66 years.

Comment: The results for older individuals might differ somewhat.

Paper II: Low risk for hip fracture and high risk for hip arthroplasty due to osteoarthritis among Swedish farmers

Limitation: Occupation was self-reported.

Comment: We could not distinguish between being a female farmer or a farmer's wife which could have affected the results.

Limitation: Due to differences in gender roles these results are only applicable for Sweden or countries with similar culture.

Comment: The results for the men are probably applicable to other countries and cultures since traditionally the man has had the role as farmer with most responsibilities outdoors including heavy lifting.

Limitation: THR is optional.

Comment: Might be partly influenced by occupation if you operate or not.

Limitation: No information of THR or hip fracture before 1987.

Comment: This might affect the risk. If a person had THR before 1987, there would only be one or no hip left to fracture.

Limitation: Included in the category farmers were also professional gardeners and foresters.

Comment: This probably only applies to a relatively small number and their exposure to physical activity and heavy loading are most likely similar.

Limitation: Lower physical activity and increased obesity among farmers due to new farming technologies during the last perhaps 60 years.

Comment: Changes in BMI cannot alone explain the results we found.

Paper III: Risk for hip fracture before and after total knee replacement in Sweden

Limitation: We had no information of BMD or BMI, so we were therefore not able to adjust for this.

Comment: Low BMD and BMI are two major risk factors for hip fracture. However, most individuals with knee osteoarthritis are overweight or obese and several have high BMD, which can be protective against hip fracture ^[121]. On the contrary, abdominal obesity seem to increase the risk of hip fracture ^[107].

Limitation: We had no information on surgery (hip fracture, THR, TKR) before 1987.

Comment: This could affect the results, e.g. THR decreases the risk for hip fracture since there is only one or no hips left to fracture. A previous hip fracture would increase the risk for a new hip fracture. In what way bilateral TKR would affect the results we do not know, but probably increases the risk as shown in a similar Dutch study ^[116].

Limitation: Selection bias towards healthier individuals.

Comment: Very sick individuals are probably not operated if not absolutely necessary. Most likely would this lead to a lower risk of hip fracture.

Limitation: The rehabilitation after surgery is most likely different today compared to 20 years ago.

Comment: Rehabilitation might to some extent affect the risk of hip fracture, and different level and type of rehabilitation might affect applying our results to todays` risk of hip fracture after TKR.

Paper IV: Increased risk for hip fracture after death of spouse-further support for bereavement frailty?

Limitation: We had no data on comorbidity so we could not adjust our data for this.

Comment: Comorbidity might to some degree affect our results. However, the variation over time of relative risk is not likely to be affected in any important way.

BMD= bone mineral density, BMI=body mass index, THR= total hip replacement, TKR= total knee replacement

6 CONCLUSION

We have conducted large studies with a long follow-up period on potential risk factors for hip fracture (previous hip fracture in spouse, TKR, the death of a spouse) and the relationship between hip fracture and osteoarthritis (farming and TKR). We have shown that the risk of hip fracture increased after hip fracture in a spouse, but also after the death of a spouse. The risk of hip fracture was low before TKR, which can possibly be explained by often occurring increased BMD and BMI in individuals with osteoarthritis. After TKR the hip fracture risk was increased compared to the control population consisting of individuals without TKR. Divided into sex and hip fracture types, men had a higher risk, and both women and men combined had a higher risk for trochanteric fracture in a ten-year period after TKR, but the risk for femoral neck fracture was not significantly different from that of the control population in the same period. The highest relative risk was observed in the youngest individuals, when comparing to aged matched individuals. We have also shown that farming might protect against hip fracture, but increases the risk of joint replacement surgery. The increased risk for hip fracture after a hip fracture have occurred in one's spouse is likely to be explained by homogamy and assortative mating, involving similar appearance, habits, environmental and health factors such as smoking, weight, and physical activity level. The high risk of THR and low risk of hip fracture in farmers can be explained by physical activity, heavy load and high sunlight exposure, but also heredity for hip osteoarthritis. The changes in risk for hip fracture after TKR is very complex, mostly because we do not have any information on important covariates. However, we do believe that the increased risk of hip fracture after TKR can be attributed to both the pre- and the post-surgery period. Possible explanations might involve bone loss, changed knee kinetics, lower physical activity level, BMI, and increased fall risk. The high risk of hip fracture in bereaved spouses can be contributed to the direct loss of a life partner, but can also involve taking care of a sick or dying spouse before death. Contributing risk factors might involve depression, sleep disturbance, and medication usage.

7 FUTURE PERSPECTIVES

In contrast to osteoarthritis, hip fracture is a more or less new phenomenon, at least to the extent we see today. Hip fracture has historically been a rare condition, which is confirmed by archaeological excavations and analysis of old skeletons ^[145]. This might mostly be explained by people living to older ages today, but some studies indicate changes in the hip geometry over time ^[146,147].

The life expectancy is increasing and with older ages comes increased risk for hip fracture, but also for other diseases. More studies of epidemiology, risk factors, hip geometry, and of the understanding of the whole body as a unit are therefore needed. The increased risk for hip fracture confirms the importance of fracture prevention in individuals whose spouse has sustained a hip fracture, whose spouse have died, or in those who have had a TKR. The incidence and prevalence of knee osteoarthritis, and as a consequence also TKR, will increase due to the increasing population and the increasing ages and overweight/obesity ^[148]. It is therefore important to understand more about the relationship between hip fracture and osteoarthritis. The high incidence of hip fracture in Sweden is a complex question with a compelling need for further studies. Several studies on risk factors for hip fracture have been conducted, but mostly about clinical factors. Several of these clinical factors have been incorporated in the FRAX-model used to calculate the ten-year risk for fragility fractures ^[19]. We have mostly studied social and psychological risk factors, except from in paper III, which is not incorporated in any existing diagnostic instrument. Hip fracture in a spouse and the death of a spouse could potentially be incorporated into the FRAX model. However, our results do not answer the question of why we have so many hip fractures in Sweden today. More knowledge is needed to be able to understand the complexity of hip fracture. With our studies we have provided a platform for further studies of social and psychological risk factors for hip fracture, but also of hip fracture in relation to osteoarthritis.

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