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Osteoarthritis

Epidemiologic and genetic aspects

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To
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and Jóhann

Contents

List of papers

This thesis is based on the following papers:

I. Franklin J, Ingvarsson T, Englund M, Lohmander LS. Sex differences in the association between body mass index and total hip or knee joint replacement resulting from osteoarthritis. Ann Rheum Dis 2009;68:536–540.

II. Franklin J, Ingvarsson T, Englund M, Lohmander LS. Association between occupation and knee and hip replacement due to osteoarthritis: A case-control study. Submitted.

III. Franklin J, Ingvarsson T, Englund M, Ingimarsson O, Robertsson O, Lohmander LS. The natural history of radiographic hip osteoarthritis. A retrospective cohort study with 11-28 years follow-up. Submitted.

IV. Franklin J, Englund M, Ingvarsson T, Lohmander LS. The association between hip fracture and hip osteoarthritis. A case-control study. Submitted.

V. Franklin J, Ingimarsson O, Styrkarsdottir U, Jonsson GF, Ingvarsson T, Englund M, Lohmander LS. Relatives of patients with total hip replacement due to osteoarthritis do not have reduced risk of hip fracture: A study of the inheritance of hip osteoarthritis and hip fracture in Iceland. Manuscript.

Definitions and abbreviations

ACR American College of Rheumatology

AGES study Age, Gene, Environment, Susceptibility Study

AP Anteroposterior

BMI Body mass index

CI Confidence interval

Dichotome A binary variable

Extracapsular fracture Hip fracture that is outside the joint capsule (basocervical, pertrochanteric, and subtrochanteric fractures)

HR Hazard ratio

IBD Identical by descent

ILO International Labour Organization

Intracapsular fracture Hip fracture that is inside the joint capsule (fractures of the femoral neck)

K & L Kellgren and Lawrence

MJS Minimal joint space

MRI Magnetic resonance imaging

OA Osteoarthritis

OR Odds ratio

PIN Personal Identification Number

Qualitative measurement Measurement with an ordinal, subjective scale such as K&L grading of radiological OA

Quantitative measurement Measurement with a quantitative scale such as millimetres

ROC Receiver Operator Characteristic

RR Relative Risk

SD Standard Deviation

THR Total hip replacement

TJR Total joint replacement

TKR Total knee replacement

WHO World Health Organization

WOMAC Index Western Ontario and McMaster Universities Osteoarthritis Index

Thesis at a glance

Paper I: Sex differences in the association between body mass index and total hip or knee joint replacement resulting from osteoarthritis

Is body mass index associated with total joint replacement in the hip or knee?

Patients: 1473 patients (872 women) with THR and/or TKR and 1103 controls (599 women) that participated in the Icelandic OA Genealogy study. A randomly selected population sample was used as a secondary control group.

Methods: All cases and controls answered a standardised questionnaire containing 79 questions on the subject's height and weight, general health status, occupation, family history, physical activities, previous injuries and a detailed description of all musculoskeletal symptoms. The hospital records of all cases were reviewed to confirm that the diagnosis of OA.

Results: The OR, adjusted for age, occupation and presence of hand OA, for having a THR was 1.1 (95% CI 0.9 to 1.5) for overweight men and 1.7 (95% CI 1.0 to 2.9) for obese men. The OR for having a TKR was 1.7 (95% CI 1.1 to 2.6) for overweight men and 5.3 (95% CI 2.8 to 10.1) for obese men. The OR for having a THR was 1.0 (95% CI 0.8 to 1.3) for overweight women and 1.0 (95% CI 0.6 to 1.5) for obese women. The OR for having a TKR was 1.6 (95% CI 1.1 to 2.2) for overweight women and 4.0 (95% CI 2.6 to 6.1) for obese women.

Conclusion: The results of this study support a positive association between high BMI and TKR in both sexes, but for THR the association with BMI seems to be weaker, and possibly negligible for women.

Paper II: Association between occupation and knee and hip replacement due to osteoarthritis: A case-control study

Is occupation associated with total joint replacement in the hip or knee? Is the inheritance of occupation a possible confounder in this question?

Patients: 1408 patients (832 women) with THR and/or TKR and 1082 (592) controls that participated in the Icelandic OA Genealogy study.

Methods: Questionnaire data as outlined for Paper I above. Inheritance was calculated by comparing the cohort with the Icelandic Genealogy Database.

Results: The age adjusted odds ratio (OR) for male farmers getting a TKR due to OA was 5.1 (95% confidence interval (CI) 2.1-12.4) and for a male farmer getting a THR due to OA the OR was 3.6 (95% CI 2.1-6.2). The OR for a fisherman getting a TKR was 3.3 (95%CI 1.3-8.4). No other occupations showed increased risk for men. For women there was no increased risk for any occupation. Farming and fishing were also the occupations that showed the greatest degree of inheritance.

Conclusion: These results support an association in males between physically demanding work and both TKR and THR for OA, particularly farming. Farming is however also the occupation that has the greatest degree of inheritance and this might interact with the results.

Paper III: The natural history of radiographic hip osteoarthritis. A retrospective cohort study with 11-28 years follow-up

What is the future risk of THR and hip fracture in subjects with radiographic hip OA?

Patients: A cohort of subjects that had colon radiography in 1980-1997.

Methods: MJS was measured in each hip it and graded according to Kellgren & Lawrence. Subjects were followed until end of 2008. 1498 subjects supplied 2953 hips for analysis.

Results: The cumulative incidence of THR was 2.5% and the cumulative incidence of hip fracture was 2.6%. For hips with radiographic

hip OA (MJS 2.5 mm or less) the cumulative incidence of THR was 16.9%, and the hazard ratio (HR) for THR was 13.2 (95% CI 8.1-21). Using Kellgren and Lawrence grading, the HR for THR was 12.9 (95% CI 7.9-21) for hips with radiographic OA, compared to those without. The HR for all types of hip fracture for hips with radiographic OA (MJS 2.5 mm or less) was 0.47 (95% CI 0.15-1.5), for intracapsular fractures 0.29 (95% CI 0.04-2.1) and for extracapsular fractures 0.67 (95% CI 0.16-2.8).

Conclusions: The risk for THR due to OA is substantially increased in patients with radiographic hip OA, regardless of symptoms and increases with decreasing MJS. However, 11-28 years after having had radiographic hip OA, more than 4 out 5 of those having radiographic signs of hip OA had not had a THR for OA.

Paper IV: The association between hip fracture and hip osteoarthritis. A case-control study

What is the prevalence of hip OA in patients with hip fracture?

Patients: 562 patients with hip fracture at Akureyri University Hospital in 1990-2008 compared with 803 subjects from a colon radiography cohort.

Methods: Radiographies of cases and controls were examined for presence of hip OA. A nested study was done within the fracture cohort where comparison was made between the prevalence of possible risk factors of secondary osteoporosis in patients with hip fracture and hip OA on one hand, and patients with hip fracture, but without hip OA on the other.

Results: The age-adjusted odds ratio (OR) for subjects with hip fracture having radiographic hip OA was 0.30 (95% CI 0.12-0.74) for men and 0.33 (95% CI 0.19-0.58) for women, compared to controls. The probability for subjects with hip fracture and hip OA having a secondary cause of osteoporosis was three times higher than for subjects with hip fracture without hip OA.

Conclusions: The results of our study support the inverse relationship between osteoporosis and hip OA.

Paper V: Relatives of patients with total hip replacement due to osteoarthritis do not have reduced risk of hip fracture: A study of the inheritance of hip osteoarthritis and hip fracture in Iceland

Are patients with hip fracture and THR due to OA less related to each other, than can be expected in the Icelandic population?

Patients: 4228 patients with THR due to OA (THR-OA) and 8165 patients with hip fracture compared with controls from the Icelandic Genealogy Database.

Methods: The average pairwise kinship coefficient (KC) was calculated for patient lists and control lists and the relative risk (RR) was estimated for THR-OA and for hip fracture among relatives of patients with THR-OA. Ten thousand matched control lists, each the same size as the patient list, were created using the Genealogy Database.

Results: The RR for THR-OA among relatives of THR-OA patients was 2.80 for parents (95% CI 2.45-3.18), and 2.27 (95% CI 2.08-2.37) for siblings. The RR that parents of patients with hip fracture have had a hip fracture was 1.90 (95%CI 1.75-2.03). The RR that the parents of a patient with THR-OA would have an intracapsular hip fracture was 1.40 (95% CI 1.25-1.54). For extracapsular fractures the RR for parents was 1.17 (95% CI 1.00-1.34).

Conclusions: Relatives of patients with THR-OA do not have a decreased risk of hip fracture, and the risk for intracapsular hip fracture is even slightly increased, suggesting that the observed inverse relationship between OA and hip fracture is not explained by mutually exclusive genes.

Description of contributions

Paper I

Study design: Jonas Franklin, Thorvaldur Ingvarsson, Stefan Lohmander
Data collection: Jonas Franklin, Thorvaldur Ingvarsson
Data analysis: Jonas Franklin, Thorvaldur Ingvarsson, Martin Englund, Stefan Lohmander
Manuscript writing: Jonas Franklin
Manuscript revision: Jonas Franklin, Thorvaldur Ingvarsson, Martin Englund, Stefan Lohmander

Paper II

Study design: Jonas Franklin, Thorvaldur Ingvarsson, Stefan Lohmander
Data collection: Jonas Franklin, Thorvaldur Ingvarsson
Data analysis: Jonas Franklin, Thorvaldur Ingvarsson, Martin Englund, Stefan Lohmander
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Paper III

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Introduction

Osteoarthritis (OA) is an ancient disease. It has been found in the skeletal remains of dinosaurs[6] and Neanderthal as well as Cro-Magnon man[7]. The disease has also been found in Egyptian mummies[8] and was common among ancient Saxons in England[9]. Excavations have indicated that OA was common in Icelandic Vikings[10]. OA affects all races of man[11, 12] and is not confined to any particular geographic area[13].

Until the late 20th century OA was regarded as a mechanical disease, primarily affecting cartilage, the results of the inevitable wear and tear of the joints accumulated in life. The model of the 21st century, on the other hand, is that OA affects the whole joint as an organ, including cartilage, bone, synovium, muscles and ligaments and is influenced by age, mechanical stress and genetic traits to a varying extent[14]. Inflammation may contribute to symptoms and disease progression, at least in some patients and some disease stages[15].

OA is the most common joint disorder and the leading cause of disability in the elderly in the United States and Europe. Radiographic evidence of OA occurs in the majority of people by the age of 65 years, and in about 80% of those aged 75 years and older[16] and it is estimated that physician-diagnosed arthritis occurs in more than 50% of adults older than age 65 years and in more than 30% of adults aged 45–64 years[17]. Due to an ageing population, the prevalence of OA is expected to increase in the next decades. The prevalence of overweight and obesity is also increasing and this will increase demand for joint arthroplasties. In western countries, the increase in prevalence in the next 20 years is expected to be about 40%, making OA the fourth leading cause of disability[18]. Elderly subjects with chronic joint pain due to OA have a significantly lower quality of life[19]. The effects of OA in the lower limbs include reduced mobility and a resulting loss of independence as well as increased levels of healthcare utilization[20]. Although OA may affect any joint in the body, it most commonly affects the knee followed closely by the hip[21].

Symptoms and signs of osteoarthritis

OA is a complex disease that may be triggered and driven by diverse environmental and constitutional factors. The clinical presentation of OA is variable in terms of onset of symptoms, joints involved, severity and rate of progress. The prognosis and outcome is equally variable. Disease manifestations include not only the classical features of cartilage loss, osteophyte formation, subchondral sclerosis and bone cysts, but also associated findings of ligamentous laxity, malalignment, low-grade synovitis and meniscal degeneration[22].

The primary symptom of OA is pain and it is the usual reason for patients seeking help within the healthcare system. Initially the pain is related to joint use and alleviated by rest. As the disease progresses the pain may become more persistent and may also occur at night. The mechanism behind the pain in OA is unclear, other than it does not arise in the worn away cartilage, as cartilage is aneural. It has been shown that bone marrow lesions, that can by demonstrated by MRI, are associated with pain in knee OA[23]. Other potential causes of the pain in OA include raised intraosseous pressure, inflammatory synovitis and periosteal elevation. Another symptom of OA is stiffness. Some patients may complain of early morning stiffness, more commonly associated with the classic inflammatory arthropathies, but most commonly the stiffness is related to inactivity. The third important symptom of OA is loss of function in the afflicted joint, which may lead to poor mobility and difficulties with the activities of daily living and loss of participation.

Signs that may be found by clinical examination include reduced range of movement, tenderness at the joint margins, crepitus, instability, and muscle weakness. Reduced range of motion is caused by osteophyte formation and

capsular thickening. Crepitus is caused by irregularities in the joint surface.

Natural history of osteoarthritis

Describing the natural history of OA is complicated by the fact that not many studies have been published on this matter and those that exist differ in their definition of disease progression. Progress of OA can be defined as radiographic or clinical. For radiographic definition of OA, several different grading systems exist and clinical outcome can be measured by different patient-reported outcomes and scoring systems, such as WOMAC or using the need for joint arthroplasty as a clinical end-point. Disease evolution in OA is usually slow, although a more rapid progress can be seen in some cases. Once established, OA can remain relatively stable, both radiographically and clinically, for several years. Several potential risk factors for progression of OA have been examined. For the knee there is strong evidence that malalignment increases the risk of progression and for the hip, superolateral migration of the femoral head and atrophic bone response have been shown to be associated with progression. For most other examined potential risk factors for progression, even those that have been established as risk factors for incident OA, the evidence is limited or conflicting[24]. It is important to note that studies on risk factors and incidence are greater in number than studies on progression. Also, due to the lack of a golden standard definition of OA[14], one has to regard the definitions of incidence and progression as somewhat arbitrary. If one is, for example, using the Kellgren and Lawrence scale, then a change from grade 1 to grade 2 constitutes a new case and is thus counted under incidence, but a change from grade 2 to grade 3 constitutes as progression in epidemiologic studies.

Radiographic features of osteoarthritis

The four main radiographic features of OA are joint space narrowing, osteophyte formation, subchondral sclerosis and subchondral cyst formation. Plain radiography has been the primary diagnostic modality for OA for many decades although recent magnetic resonance imaging (MRI) studies suggest that plain radiography has limited ability to detect osteoarthritic features at an early stage of disease[22].

Joint space narrowing is another cardinal feature of OA. Initially it is focal and begins at the point of maximal loading within the joint. At that stage the surrounding healthier cartilage may make the joint space width normal on radiographs[25] and this can reduce the validity of joint space width as a marker of OA disease.

Osteophyte formation is the most characteristic feature in OA and is thought to precede JSN. Osteophytes form by enchondral ossification at the junction where cartilage meets synovium or periosteum. It is not known what causes osteophyte formation, a commonly stated explanation is that they are formed in an attempt to repair and redistribute abnormal joint loading. Osteophyte formation might also be a response or side-effect to cytokines that are released in the OA process and thus not a reparative process. In some cases of OA osteophyte formation is minimal or absent and this is referred to as atrophic OA in contrast to hypertrophic OA, although the difference between these two forms is not clear cut and considerable overlap exists.

Subchondral sclerosis is also initiated before joint space narrowing becomes visible[26]. It occurs at sites of stress in the subchondral bone, resulting in deposition of new bone on pre-existing trabeculae and trabecular microfractures with callus formation[27]. Classically subchondral sclerosis has been seen as a secondary radiographic feature of the primarily cartilaginous disease that OA was believed to be. More recently the role that subchondral bone plays in the development and progression of OA has received increased attention and continues to be evaluated.

Subchondral cysts appear between thickened subchondral trabeculae. Microcontusions in bone are believed to lead to necrosis with subsequent extension of synovial fluid into the subchondral

bone or alternatively through the proliferation of myxomatous tissue within the bone marrow[27].

One of the difficulties with plain radiography relates to the assessment of a three dimensional structure using a two-dimensional image. Osteophytes that are overlapped by adjacent anterior and posterior bony features will remain undetected on plain radiography. MRI provides multiplanar tomographic imaging and therefore avoids the problem of superimposition of overlapping structures. MRI also provides soft tissue detail, including direct visualization of cartilage, and is thus well suited to assess the joint as a whole organ[28].

For epidemiological studies standard radiographs have many advantages and remain the most important source of information for classification of hip OA in community and population based studies[29]. Radiographs are practical in most study settings, the imaging technique and classification procedures can be standardized and reproduced and they are much cheaper and more readily available than MRI.

Definition of osteoarthritis

No universal definition of OA exists. Different studies have used different definitions and tools to define OA. Broadly, these can be categorized as self-query, radiological or clinical. There is considerable discordance between these definitions in any given cohort.

Self-query has been used in questionnaires and postal surveys to identify cases with OA. The subject is either asked specific questions on presence or absence of symptoms of OA or asked whether the subject has physician diagnosed OA.

Radiological definition of OA has frequently been used in epidemiologic studies. The most frequently used is the Empire Rheumatism Council system first described over five decades ago by Kellgren and Lawrence[30] and often referred to as the Kellgren and Lawrence grading system, which assigns one of five grades (0–4) to OA at various joint sites by comparison with a radiographic atlas. Another frequently used definition is minimal joint space (MJS), which is a measurement of the shortest distance between the two bones on either side of the joint.

Clinical definition of OA is either based on symptoms with radiographic changes, such as the American College of Rheumatology (ACR) criteria[31, 32] or total joint replacement.

Definition of hip fractures

Several different classification systems of hip fractures exist. In Scandinavia the most widely used in clinical work is similar to the AO group classification[33]. Hip fractures are classified as fractures of the collum femoris, basocervical (at the junction between the collum femoris and femur), pertrochanteric or subtrochanteric. The first mentioned can also be referred to as intracapsular and the latter three grouped together as extracapsular hip fractures.

Study methodology

Cohort and case-control studies are the main tools for analytical epidemiological research and epidemiological research is, to a large extent, of an observational character as opposed to experimental research. In experimental research, investigators can manipulate one factor while controlling others. Through repeated manipulation of one or more factors the research question can often be resolved. Observational epidemiological research has the disadvantage that extraneous factors cannot be manipulated by the investigators. By collecting and reviewing data from several studies, we approach this method of repeated manipulation and can gain knowledge of factors that might affect the results, subsequently adjusting for these in further studies. Nevertheless, findings from observational epidemiological studies are generally less conclusive than those from experimental studies because of the less strict control of extraneous factors.

Cohort studies start with healthy subjects that are divided into groups according to exposure to the risk factor being examined. These subjects

are then followed over time and the occurrence of disease is recorded. The measure of disease in cohort studies is the incidence rate and the measure of association between exposure and disease most often used is the relative risk. Cohort studies are either prospective (also known as current) or retrospective (also known as historical). In a prospective cohort study, the data concerning exposure are assembled prior to the occurrence of disease. In a retrospective cohort study, data on exposure and occurrence of disease are collected after the events have taken place. The cohorts of exposed and non-exposed subjects are often assembled from existing records or health care registries or by interviewing study participants and thus relying on their recall of the event being studied.

Case-control studies start with subjects that have the disease being studied (cases). The history of exposure to the risk factor being studied is acquired via interviews or by means of records or other sources. A comparison group (controls) is assembled typically consisting of individuals without the disease under study, and their past history is recorded in the same way as for the cases. The purpose of the control group is to provide an estimate of the frequency and amount of exposure in subjects in the population without the disease being studied. Whereas the cohort study is concerned with frequency of disease in exposed and non-exposed individuals, the case-control study is concerned with the frequency and amount of exposure in subjects with a specific disease (cases) and people without the disease (controls). In case-control studies, data are not available to calculate the incidence rate of the disease being studied, and the actual relative risk cannot be determined. When cases and controls are selected from among subjects in a cohort study the term „nested case-control study" is used. The measure of association between exposure and occurrence of disease most often reported in case-control studies is the odds ratio.

Confounding refers to the effect of external factors that may distort the findings of cohort and case-control studies. An external factor needs to meet two conditions to be considered a confounding factor. Firstly it needs to be a risk factor for the disease being studied. Secondly it needs to be associated with the exposure being studied, but may not be a consequence of that exposure.

Bias is defined as any systematic error in the design, conduct, or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease.

Relative risk is (RR) a measure relationship between typically two dichotomic (binary) variables and is a calculation of the ratio of the probabilities of the occurrence of the outcome of interest in group 1 to group 2. In cohort studies one often divides the cohort into groups according to exposure to the risk factor of interest. By first calculating the probability (Pr) of outcome (disease) in each group one can calculate the RR

$$RR = \frac{Pr_1}{Pr_2} = \frac{Pr_{exposed}}{Pr_{non-exposed}}$$

where $Pr_1$is the probability of the outcome in group 1 (exposed) and Pr_2 is the probability of the outcome in group 2 (non-exposed). An RR of 1 means there is no difference in risk between the two groups. An RR of < 1 means the event is less likely to occur in the exposed group than in the non-exposed group and similarly an RR > 1 means that the event is more likely to occur in the exposed group.

Odds ratio (OR) is the ratio of the *odds* of the occurrence of the event of interest in group 1 to group 2. The *odds* are the probability of occurrence divided by the probability of non-occurrence

$$Odds_1 = \frac{Pr_1}{1 - Pr_1}$$

the $Odds_2$ are defined in the same way using Pr_2. The odds ratio can therefore be mathematically expressed as

$$OR = \frac{Odds_1}{Odds_2} = \frac{\frac{Pr_1}{1 - Pr_1}}{\frac{Pr_2}{1 - Pr_2}}$$

when the probability of the disease is low in both groups, then the OR can be a good

approximation of RR. When Pr_x moves to zero, $1 - Pr_x$ moves towards 1, meaning that the odds approaches the risk and the OR approaches the RR. By example if the probability of the outcome is 60% in the exposed group and 20% in the non-exposed, then OR is 6, but RR equals 3 and in that case the OR is not a good approximation of the RR. Another important difference between OR and RR is that OR is symmetric, whereas RR is not.

$$OR_{OA} = \frac{1}{OR_{Not\ OA}} \qquad RR_{OA} \neq \frac{1}{RR_{Not\ OA}}$$

In most cases the outcome to choose is clear and this does not present a problem, but in some cases it might, e.g. choosing 'lived' or 'died' as outcome.

Hazard ratio (HR) is a measure of how often a particular event happens in one group compared to how often it happens in another group, over time. The HR is broadly equivalent to the RR. The HR is necessary when the follow-up times of subjects within a cohort are not the same. The *hazard rate* is the probability that if the event in question has not already occurred, it will occur in the next time interval, divided by the length of that interval. The HR is an estimate of the ratio of the hazard rate in the treated versus the control group. Thus the HR indicates the relative likelihood of the outcome being studied in the exposed versus the non-exposed group at any given point in time. If the outcome being used is OA, then a HR of 2 means that an exposed subject, that has not yet gotten OA, has twice the risk of getting OA at the next point in time compared to a non-exposed subject. On the other hand, the HR does not imply any information about the length of time to disease development. A HR of 2 does not mean that the exposed group will develop the disease in half the time that the non-exposed group will.

Epidemiology of osteoarthritis

The varied criteria used for case definition in studies of OA epidemiology make comparison of different studies difficult, as differences found between studies may arise due to different methodologies. A recent review of published literature on the prevalence of hip OA reported on 23 studies with 39 estimates of overall prevalence ranging from 0.9% to 27% with a mean of 8.0% and a standard deviation of 7.0%[34]. Overall, the prevalence of radiographic primary hip OA was higher in men with a mean of 8.5%, a standard deviation of 7.5%, and a median of 5.7% compared with a mean of 6.9%, a standard deviation of 5.9%, and a median of 4.6% for women. There was a clear trend toward an increased mean prevalence with advanced age groups. The mean prevalence was higher when using the Kellgren and Lawrence definition of OA (9.5%) than MJS (4.7%) and other methods (8.2%), which underlines the problem in epidemiological studies on OA. Population-based studies in the United States suggest knee OA prevalence rates comparable to those in Europe, rising from 1% for severe radiographic disease among people aged 25–34 to 30% in those aged 75 and above[35]. Knee OA appears to be more frequent among women than men, although the female-to-male ratio varies between 1.5 and 4.0 among studies.

The health care systems in Scandinavia are comparable and it can be assumed that indications for surgery and the standard of care are similar. Scandinavians also share a common descent. It has been shown that the prevalence of radiographic hip OA is greater in Iceland than Sweden[36] and that THR rates are higher in Iceland than the other Scandinavian countries[37]. Studies on knee OA in this context are lacking.

Epidemiology of hip fractures

Hip fractures occur mainly in the elderly. There is a geographic difference in hip fracture incidence in that the age- and sex-adjusted hip fracture rates are higher in northern Europe than in southern Europe. Another area with a high hip fracture incidence is North America. A study has estimated the 10-year risk of hip fractures all

over the world, where all incidence data were gathered, and the 10-year risk is highest in Scandinavia[38].

Risk factors for osteoarthritis

The most widely accepted model today for the pathogenesis of OA sees the joint as a biomechanical organ where cartilage, bone, muscles, ligaments and other joint tissues and structures maintain proper movement and prevent excessive loading. Risk of OA is determined by systemic factors, such as age, gender, sex hormones, bone density, ethnicity, nutritional factors and genetics, which may increase or decrease the susceptibility of the joint to OA. Risk is also determined by local biomechanical factors that impair the optimal functioning of the joint, such as obesity, mechanical loading associated with different activities and professions, joint injury, and joint deformity[35].

Age is probably the strongest risk factor for OA. Although increasing age does not cause OA per se, the prevalence and incidence of both radiographic and symptomatic OA rises sharply with age[39-41]. This increase is seen in all joints that are affected by OA, but is especially evident in the hip and knee. This effect of age might by mediated through excess joint loading from obesity over time, impaired muscle function and neurological responses that otherwise protect the joint[42-44] and increased joint instability due to ligamentous laxity[45]. Aging may also cause a change in the material properties of the tissues involved, e.g. the cartilage, making it more prone to failure. The repair capacity of the joint is also believed to diminish with increasing age.

Gender seems to be a joint specific risk factor. The prevalence of hip OA increases at about the same rate with age in both genders, but hip OA may progress more rapidly in women[4, 46]. In knee OA, women have a greater age-related increase of prevalence[47] but in contrast to the hip, studies have not shown a gender difference in progression of established disease[39, 48].

Sex hormones, particularly oestrogen in women, has been associated with OA risk. Most, but not all, studies on the effect of oestrogen replacement therapy (ERT) have shown a reduction in risk for hip and knee OA[49, 50]. There is risk for bias in these conclusions. Oestrogen users might see doctors more often and thus have their OA diagnosed. Oestrogen use is also associated with a more healthy lifestyle and oestrogen users are more likely to have osteoporosis, which is associated with a reduced risk for OA. The evidence for a protective effect of oestrogen use is more consistent in radiographically defined OA, than in OA defined clinically[51, 52].

Bone density is increased in patients with OA, both near to and distant from joints with OA[53-56]. High bone density is more strongly related to the presence of osteophytes than to the reduction of joint space[53, 56]. Patients with hip fracture have less OA than expected[57, 58], but the relationship between bone density and OA is complex and a simple protective effect of high bone density cannot be inferred. High bone density has been shown to increase the risk of incident knee OA, but paradoxically, patients with knee OA and high bone mineral density have a lower risk of disease progression[59, 60]. As with OA, much of the variation in susceptibility to osteoporosis in the population is believed to be greatly influenced by genetic causes[61].

Ethnicity as a risk factor for OA was studied by Kellgren and Lawrence more than 40 years ago and their basic findings mostly still stand. OA is generally more prevalent in Europe and America, than the rest of the world[62]. Caucasians and African-Americans in the United States appear to have similar overall rates of hip and knee OA[63, 64]. Comparative studies of the population of China and Caucasians in the United States have found that hip OA prevalence is one tenth in the Chinese population[65], but knee OA was equally prevalent in Chinese men and Caucasians in the United States and greater in Chinese women[66].

Nutritional factors may play a role in OA. It has been postulated that OA susceptibility is increased from oxidative damage from free radicals that are produced by chondrocytes in damaged cartilage[67]. Increased intake of dietary antioxidants, such as vitamins C and E might therefore, protect against OA[68]. Low vitamin C intake has been associated with accelerated progression, but not incidence of OA[68]. Similar results have been found with vitamin D[69]. Vitamin D is not believed to act as an antioxidant, but vitamin D is necessary for active bone turnover and chondrocytes in OA cartilage have an increased sensitivity to vitamin D[69]. The current evidence on the effects of nutrients on OA is weak.

Genetics of OA has been the subject of several studies. There is now good evidence indicating a genetic contribution to about half the population variability in susceptibility to hip and knee OA in women and hip OA in men[70-72]. A number of possible OA susceptibility loci have been identified but no single genetic variation has been found that has a strong association with OA[73]. Rather, the increased risks for carrying a given predisposing genetic variant appear to be fairly modest, which is typical of genetic risks for complex common diseases.

Obesity is among the strongest and best established risk factors for knee OA[74]. Obesity precedes knee OA[75, 76] and increases progression of the disease[48, 77]. Obesity seems also to be a risk factor for hip OA, although there are not as many studies on that as for the knee[78]. The effect of obesity might simply be the excess load it causes on the joint, but that does not explain the increased risk of hand OA caused by obesity[79], which suggests the presence of a systemic factor in obesity that affects cartilage breakdown.

Joint injury, including meniscal and ligament damage, fractures and dislocations has been shown to greatly increase the risk of subsequent OA[77, 80, 81]. In addition to the direct effects of the injury on cartilage, it may cause an alteration in the biomechanics of the joint, leading to cartilage degeneration. This is especially evident in the knee[82].

Mechanical loading has been studied both in the context of work and sporting activities. For hip OA, the strongest association has been with heavy lifting and the farming profession[83-85]. For knee OA the strongest association was shown for kneeling and heavy lifting[85, 86]. Moderate recreational sports participation does not appear to increase the risk of hip or knee OA independently of joint injuries that may be suffered in the course of these activities[87, 88]. Professional athletes, who submit their joints to much more load than recreational athletes, have been shown to have an increased risk for OA, even without major injury[87].

Joint deformity impairs normal biomechanical function, may cause focal overloading of joint surfaces, and leads to subsequent OA. Congenital hip dislocation, Legg–Calvé–Perthes disease and slipped femoral capital epiphysis, lead invariably to hip OA later in life[89]. Varus and valgus malalignment are found with much greater frequency in knees with evidence of OA involvement in the medial and lateral compartments respectively[90]. OA knees with a varus malalignment have a 3–4-fold increased risk of further joint space narrowing in the medial compartment, while OA knees with a valgus malalignment have a similar increased risk of further lateral compartment joint space narrowing[91]. Malalignment appears to be particularly important in individuals who are also overweight or obese[92].

Risk factors for hip fracture

The most important risk factor for hip fracture is age[93]. Age might exert its effect through reduced bone mass, increased co-morbidity, and increased risk of falls. Another important risk factor is gender. At the age of 50, the estimated lifetime risk of hip fracture is 23% in women and 11% in men in Sweden[94].

Aims

The general aim of this study was twofold. Firstly to evaluate the association between mechanical load on the joints and OA of the knee and hip, and secondly to evaluate the relationship between hip OA and hip fracture. In more detail the aims were:

- To assess the relationship between BMI and hip and knee OA leading to arthroplasty in Icelandic men and women.
- To assess the relationship between occupation and knee and hip OA leading to arthroplasty in Icelandic men and women.
- To explore the inheritance of profession as a possible confounder in the effect of occupation as a risk factor for OA.
- To evaluate the natural history of radiographic hip OA registered at colon radiography with regards to later THR due to OA, or later hip fracture.
- To assess if subjects with hip fracture are less likely to have radiographic hip OA than control subjects without hip fracture.
- To evaluate the inheritance of THR and hip fracture in Iceland and to determine if individuals with THR and hip fracture are more or less related to each other than can be expected in the general population.

Patients and methods

Overview of patient/subject allocation

Paper I

All patients in Iceland who had a THR or TKR resulting from OA before the end of 2002 were invited to participate in a study on the inheritance of OA (The Icelandic OA Genealogy Study). 927 patients with THR and 431 patients with TKR were selected from that study. 1103 first degree relatives of these cases served as controls. 2269 subjects from a population based study (the AGES study) served as secondary controls.

Paper II

From the Icelandic OA Genealogy Study mentioned above, 896 patients with THR and 400 patients with TKR were included after the exclusion process. 1082 first degree relatives of these cases served as controls.

Paper III

1498 patients, 35 years or older, who had undergone a colon radiography (double contrast, barium enema) during the years between 1980 and 1997 supplied 2953 hips for examination. These were followed until end of year 2008.

Paper IV

562 hip fracture patients admitted to Akureyri University Hospital during 1990-2008 served as cases. 803 subjects from the cohort in paper III served as controls.

Paper V

4228 patients with THR resulting from OA and 8165 patients with hip fracture served as cases. These were compared against the Icelandic Genealogy database that contains data on approximately 700,000 individuals.

Patient identification

All inhabitants in Iceland, as in the other Nordic countries, have a social security number, that contains their birthdate and an identification

		Paper				
		I	II	III	IV	V
The Icelandic OA Genealogy Study Cohort	Cases	1,473	1,408			
	Controls	1,103	1,082			
Data from the AGES study	Cases					
	Controls	2,269				
Cohort of colon radiographies	Cases			2,953 (hips)†		
	Controls				803	
Hip fractures at Akureyri University Hospital	Cases				562	
	Controls					
Icelandic THR registry	Cases					4,228
	Controls					
Icelandic hip fracture registry	Cases					8,165
	Controls					
The Icelandic Genealogy Database	Cases					
	Controls		Cases * 1,000			Cases * 10,000

Table 1 Cohorts used in Paper I-V. The numbers shown are cases/controls (individuals, except entry marked with †, which shows the number of hips) that remained after the exclusion process. When using controls from the Icelandic Genealogy Database, we create sets that are matched in numbers to the patient lists. In Paper II we used 1,000 such sets and in Paper V 10,000 sets.

number. Statistics Iceland, a government institution, keeps track of the name, social security number, domicile, marital status, and death of all Icelanders. Individuals use this social security number in contact with authorities and the health care system. All medical records, including radiographic examinations, are all registered with the social security number. This system permits the identification and life-long tracing of patients, including date of death. This is in contrast to the situation in most countries, where such tracing is an immense if not impossible task.

Populations examined

The Icelandic Genealogy study – In a study conducted 1998-2002 we invited all living patients that had received a THR or TKR in Iceland, from the beginning of joint replacement surgery in 1967 until end of 2002, to participate. Participating patients answered a questionnaire with 79 questions where we asked for the patient's height, weight, general health status, occupation, physical activities, family history, previous injuries and a detailed description of all musculoskeletal symptoms.

The AGES study – The Age, Gene, Environment Susceptibility-Reykjavik Study (AGES-Reykjavik) was initiated in 2002. It was designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. This cohort, consisting of randomly chosen population sample of elderly men and women, has been followed in Iceland since 1967 by the Icelandic Heart Association. The conductors of that study kindly granted us access to their material to use as secondary controls.

Patients undergoing colon radiography – Colon radiographies (double contrast, barium enema) from three different radiographic departments in Iceland during the years 1980-1997 had been previously examined in another study. The patients were referred for radiography at these radiographic departments from four different hospitals (community and academic), as well as from the primary health care system. Patients were from both rural and urban areas. Patients that were included in this cohort were 35 years or older at examination. The entire cohort was used for paper III. For paper IV, patients 60 years or older at examination were used as controls.

Hip fractures at Akureyri University Hospital – Through computer aided search of medical records and archives in the radiographic department we identified 806 consecutive cases of hip fracture that were admitted to Akureyri University Hospital during 1990-2008. This constitutes 24% of all hip fractures in Iceland during that time. We excluded all patients younger than 60 years, patients with previous hip fracture, pathological fracture and patients with rheumatoid arthritis. After the exclusion process, 636 remained for analysis. 74 radiographs were misplaced or missing in the archives, leaving 562 patients for analysis.

The Icelandic Arthroplasty Registry – This registry was first started in 1996 and included only THRs at first. It has been regularly updated since then and currently contains information on all THRs and TKRs done in Iceland until end of year 2008. The author of this thesis participates in maintaining this registry. Information on identity, sex, age at operation, and diagnosis and type of prosthesis is registered. Admission, operation and discharge dates are also registered.

The Icelandic Hip Fracture Registry – This registry has recently been established and contains information on all hospital treated hip fractures in Iceland since 1920. A computer-aided search of all medical records was done in all hospitals in Iceland that treat hip fractures. All available written documentation from orthopaedic and surgical departments and operating theatres was acquired. The registry currently contains information on hip fractures until end of year 2008. Information on identity, sex, age at operation, admission date, type of fracture, treatment given and date, and discharge date is registered.

The Icelandic Genealogy Database – Investigators at deCODE Genetics have entered all available Icelandic genealogy records from

the last 11 centuries into a computerized database. It is estimated that between 800,000 and 1,100,000 people have lived in Iceland since the original settlement. Approximately 700,000 of these individuals are now included in the genealogy database, including the entire current population of 320,000 and most of their ancestors back to the ninth century.

Radiographic techniques

Routine radiographic examination of the hip joint consists of two standard projections, taken with the patient supine. The hip is straight for the anteroposterior (AP) projection, and semiflexed and rotated for the "frog" or Lauenstein projection.

The double-contrast (barium enema) colon radiographs included at least two AP and several oblique exposures of the hip joint. The hip joints were assessed from an AP control colon radiograph, which is taken with the same tube-to-film distance of 100 cm that is used in a standard anteroposterior view of the pelvis. The measurements of hip joint space were done on the AP film. To be included in the investigation both hips had to be clearly visualized on an AP film. The oblique exposures were used to assess osteophytes, sclerosis, cysts and any signs of secondary OA.

Radiographic examination of a suspected hip fracture consists of three standard projections, taken with the patient supine. The first is a standard AP projection as described above and the second a lateral projection with the hip straight. The third is an AP projection of the pelvis and both hips.

Radiographic classification

Quantitative – Minimum hip joint space (MJS) was measured on the AP film with a ruler divided in mm[95] or an electronic calliper[96]. A minimum joint space of 2.5 mm or less was used as a definition of hip OA[95, 97].

Qualitative – Global joint assessment was done according to Kellgren and Lawrence as described in the Atlas of standard radiographs of arthritis[98]. Hips classified as grade 2 or higher were defined as having OA.

Statistical methods

Observer reliability – Interobserver and intraobserver reliability in assessing hip radiographs for OA was estimated by using the Kappa statistic for categorical variables and the intraclass correlation coefficient for continuous variables.

Odds ratio – Odds ratios (ORs) were calculated using logistic regression in a model adjusted for those covariates that were deemed relevant in each case.

Hazard ratio – Cox regression, adjusted for age and sex, was used to calculate hazard ratio (HR).

Frailty test – Frailty calculations were done to estimate the effect of bilaterality, when examining two hips from the same subject. Calculations were done using R (version 10.2, http://www.r-project.org/).

Kinship coefficient – The kinship coefficient (KC) is a measure of the relationship of two relatives. It is defined as the probability that a randomly selected allele from each of a pair of individuals is inherited from a common ancestor, i.e. that the alleles are identical by descent (IBD)[99]. For any pair of relatives the KC is approximately one half of the expected proportion of their genome shared due to common ancestry. In the case of no consanguinity the KC is 1/4 for first degree relatives, 1/8 for second degree relatives, 1/16 for third degree relatives, etc. In the study presented in paper V, patient lists were created consisting of subjects with either THR or hip fracture. The pairwise KC distribution for the patient list was calculated by calculating the KC of every possible pair of subjects (THR-THR, THR-fracture or fracture-fracture, depending on what was being calculated) and generating the average subject KC[100]. The result was compared to the distribution of the average pairwise KC for the 10,000 matched control lists.

Determination of relative risk in inheritance – The relative risk (RR) for a certain phenotype (THR-OA or hip fracture) among siblings of affected individuals is equal to the risk of a phenotype in siblings, divided by the risk of that phenotype in the general population. The RR can be calculated for different types of relatives, e.g., siblings, cousins, or mates.

Ethics

All studies were approved by the National Bioethics Committee of the Icelandic Ministry of Health and the Icelandic Data Protection Authority. All patients who participated in the Icelandic Genealogy study signed a written informed consent as requested of the National Bioethics Committee of the Icelandic Ministry of Health and the Icelandic Data Protection Commission.

Data encryption and protection of the individual

All patient lists used at deCODE Genetics were encrypted by the Icelandic Data Protection Authority, before arriving at the laboratory. Encrypted versions of the databases were used to examine the familial relationships in this study.

Summary of results of papers I-V

Paper I: Sex differences in the association between body mass index and total hip or knee joint replacement resulting from osteoarthritis

For men the mean BMI was 0.5 kg/m^2 higher (95% CI 0.1 to 0.9) in the THR group than in the control group and 1.3 kg/m^2 higher (95% CI 0.7 to 1.9) in the TKR group than in the control group. For those who had undergone both THR and TKR, the mean BMI was 1.6 kg/m^2 higher (95% CI 0.7 to 2.5) than in the control group. Subjects were divided into three groups according to the World Health Organization (WHO) classification of normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) and obese (BMI 30.0 kg/m^2 or above). The OR for having a THR for overweight men was 1.1, but this was not significant when 95% CI (0.9 to 1.5) was taken into account. The OR for obese men was 1.7 (95% CI 1.0 to 2.9) (Figure 1). The OR for having a TKR was significant for both overweight men (OR 1.7, 95% CI 1.1 to 2.6) and obese men (OR 5.3, 95% CI 2.8 to 10.1) (Figure 2).

For women the mean BMI of the THR group did not differ from that of the primary control group (mean difference 0.0 (95% CI 20.5 to 0.5)), whereas that of the TKR group was 1.7 kg/m^2 higher (95% CI 1.1 to 2.3) than that of the control group. In those who had both THR and TKR, the mean BMI was 0.8 kg/m^2 higher (95% CI 20.1 to 1.7) than that of the controls. Women with TKR had significantly higher BMI than women with THR, adjusted for age, occupation, and the presence of hand OA ($p<0.001$). We divided women according to the WHO classification found that the OR for having a THR was 1.0 (95% CI 0.8 to 1.3) for overweight women and 1.0 (95% CI 0.6 to 1.5) for obese women (Figure 1). Thus, neither overweight nor obesity in women was associated with THR. The OR for TKR was significant for both overweight (OR 1.6, 95% CI 1.1 to 2.2) and obese (OR 4.0, 95% CI 2.6 to 6.1) women (Figure 2).

Paper II: Association between occupation and knee and hip replacement due to osteoarthritis: A case-control study

For women, occupation classes were similarly distributed amongst cases and primary controls.

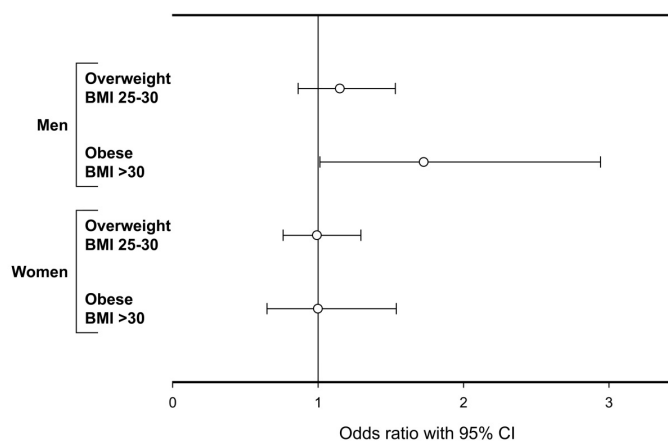

Figure 1 Odds ratio for having a total hip replacement (THR) according to gender and weight group (reproduced, with permission, from Ann Rheum Dis 2009;68:536–540)

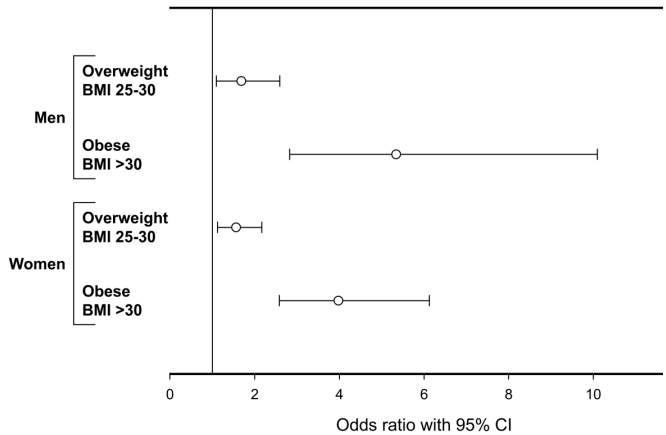

Figure 2 Odds ratio for having a total knee replacement (TKR) according to gender and weight group (reproduced, with permission, from Ann Rheum Dis 2009;68:536–540)

However, for men this distribution was not even, with TKR and THR patients being over-represented most notably among farmers.

A sex-stratified multivariable logistic regression model was made with occupation as the exposure variable and case-control status as the dependent variable adjusted for age and BMI. For this model managers and professionals were used as the reference group.

For men a strong association for TKR was found in farmers with OR 5.1, (95% CI 2.1-12.4). Fishermen had an OR of 3.3, (95% CI 1.3-8.4), and craft workers OR 2.5, (95%CI 1.0-6.2). For THR in farmers an OR of 3.6 (95% CI 2.1-6.2) was found. For THR in service and shop workers the association was almost significant in this model with OR 2.1 (95% 1.0-4.1). Other occupation classes did not differ significantly from the reference group (Figure 3). For women there was no difference between the work classes for TKR or THR.

Cross referencing the data with the genealogy

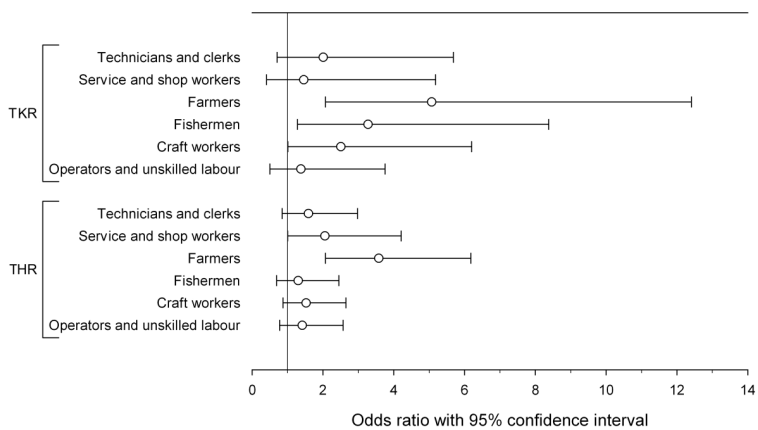

Figure 3 Odds ratios with 95% confidence intervals (error bars) for men in different work classes for having a joint replacement. Managers and professionals are used as reference group

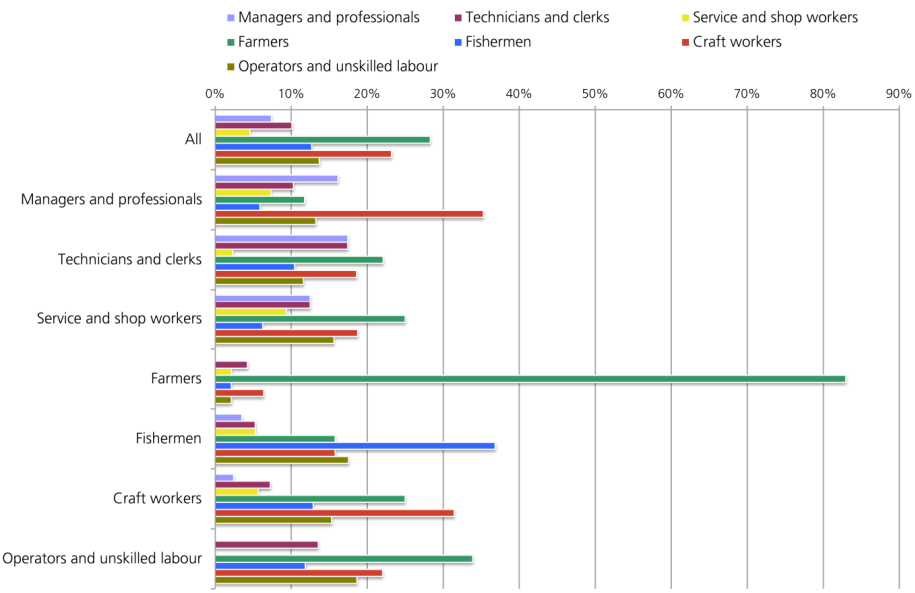

Figure 4 Father's occupation (%) as compared to son's occupation. Sons' profession in groups on the y axis. The bars show the percentage of fathers in each profession, e.g. more than 80% of farmers are sons of farmers.

database enabled the identification of 474 men and 576 women whose fathers were also in the database and 629 men and 887 women whose mothers were also in the database. Cross tabulating this enabled the determination of how occupation was "inherited" to the next generation. Several work classes had a significant inheritance, farmers by far the greatest (Figure 4).

Paper III: The natural history of radiographic hip osteoarthritis. A retrospective cohort study with 11-28 years follow-up

2953 hips were studied (57.0% female). The cumulative incidence of THR in the entire cohort was 2.5% and the cumulative incidence of hip fracture was 2.6%. For hips without radiographic OA the cumulative incidence of THR for OA was 1.6% (Figure 5) and for hips with radiographic hip OA (MJS 2.5 mm or less) the cumulative incidence of THR was 16.9% (Figure 5). For hips with OA the hazard ratio (HR) for THR was 13.2 (95% CI 8.1-21). Using the Kellgren and Lawrence grading, the HR for THR was 12.9 (95% CI 7.9-21) for hips with radiographic OA, compared to those without. Comparing subjects with OA to those without in figure 5 shows that the mortality in the OA group is higher. This was due to the higher mean age in the OA group. The HR for death, adjusted for age, was 1.1 (95% CI 0.88-1.4) when comparing those with radiographic OA to those without.

The more severe cases of hip OA had greater hazard ratios. Using MJS $\geq$ 3.5 mm as reference group and THR for OA as outcome we found that for MJS = 2.5 mm the HR was 3.7 (95% CI 1.1-12), for MJS = 1.5-2.0 mm the HR was 9.5 (95% CI 4.1-22) and for MJS $\leq$ 1.0 mm the HR was 51 (95% CI 28-93).

The HR for all types of hip fracture for hips with radiographic OA (MJS 2.5 mm or less) was 0.47 (95% CI 0.15-1.5), for intracapsular fractures 0.29 (95% CI 0.04-2.1) and for extracapsular fractures 0.67 (95% CI 0.16-2.8).

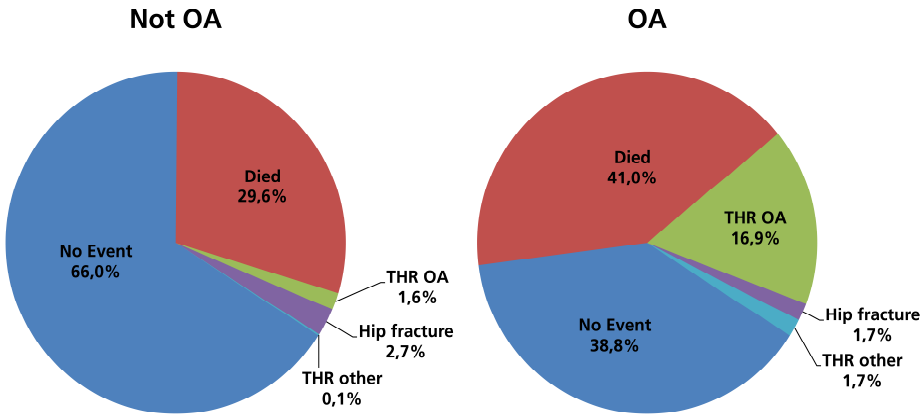

Figure 5 Cumulative incidence of registered events for subjects without and with radiographic OA (MJS ≤ 2.5mm)

Paper IV: The association between hip fracture and hip osteoarthritis. A case-control study

The standardized prevalence of hip OA in the control group was 11.5% in women and 11.4% in men. Similarly, for cases with hip fracture, the age standardized prevalence of hip OA was 5.1% in women and 4.1% in men. There was a difference between intra- and extracapsular fractures. For women the age standardized prevalence of hip OA in cases with intracapsular fractures was 2.7% and 9.4% for extracapsular fractures. There were only 7 men with hip OA and hip fracture and subdividing them was therefore not meaningful.

Using MJS ≤ 2.5 mm as definition of hip OA, the age-adjusted OR for subjects with hip fracture having radiographic hip OA was 0.30 (95% CI 0.12-0.74) for men and 0.33 (95% CI 0.19-0.58) for women, compared to controls. The ORs were similar when using Kellgren and Lawrence grade ≥ 2 as definition of OA. The

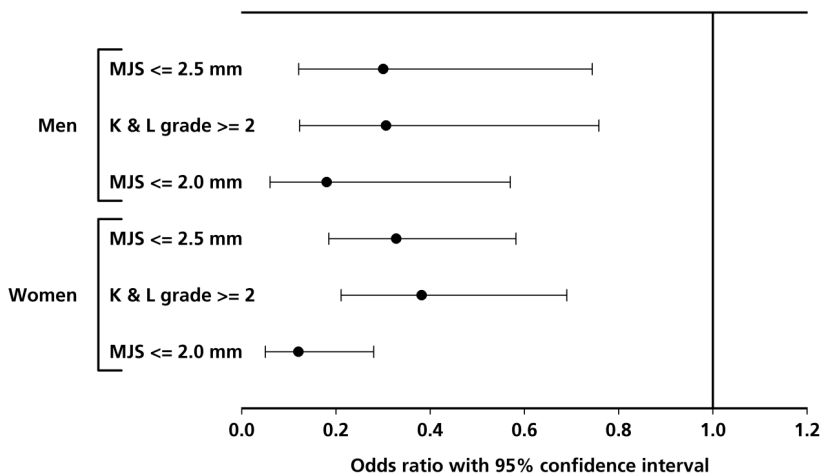

Figure 6 Odds ratio for hip OA in the fractured hip with 95% CI (error bars) for cases compared to controls using different definitions of radiographic hip OA. MJS = minimal joint space. K & L = Kellgren and Lawrence

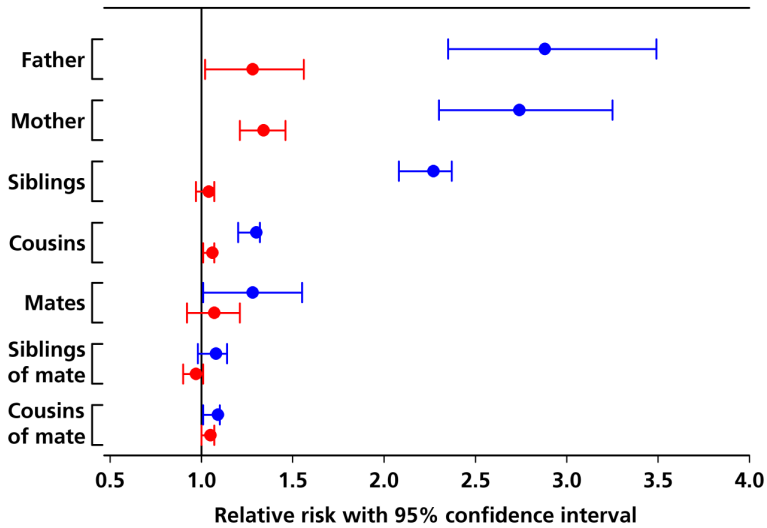

Figure 7 Relative risks for different relatives of a subject with THR due to OA to have THR due to OA (blue symbols) or hip fracture (red symbols)

ORs were lower when using MJS ≤ 2.0 mm as definition (Figure 6).

A nested study was done within the fracture cohort, comparing subjects with hip OA (and hip fracture) to subjects without hip OA (but with hip fracture) and a calculation made of the prevalence of possible risk factors for secondary osteoporosis. The probability for subjects with hip fracture and hip OA having a possible secondary cause of osteoporosis was three times higher than for subjects with hip fracture without hip OA.

Paper V: Relatives of patients with total hip replacement due to osteoarthritis do not have reduced risk of hip fracture: A study of the inheritance of hip osteoarthritis and hip fracture in Iceland

We calculated the RR for relatives of patients with THR for OA (THR-OA) to have either a THR or a hip fracture (Figure 7). Parents, siblings and cousins of a subject with THR-OA had a significantly increased RR for also having a THR-OA, while mates, or siblings and cousins of mates did not. For example the RR that a subject with THR-OA has a father with THR-OA was 2.8. This means that a subject with THR-OA is 2.8 times more likely to have a father with THR-OA than a matched subject, without THR-OA.

We also calculated the RR for relatives of subjects with THR-OA having a hip fracture. With the exception of mothers to subjects with THR-OA, all RRs calculated were not significant. If the hypothesis that subjects with THR-OA are less related to subjects with hip fracture compared to a matched subject in the population, it would have yielded RRs that are significantly lower than 1, thus this hypothesis is not true.

These calculations were repeated for intra- and extracapsular fractures separately and revealed that the RRs were in general higher for intracapsular hip fractures.

For relatives of patients with THR, the RR for these relatives having a hip fracture was significant for parents and borderline significant for cousins. Subdividing the hip fractures into intra- and extracapsular showed that it were intracapsular fractures that had an increased RR for hip fractures in relatives of patients with THR.

Discussion

Research methodology

Researching OA is not an easy task. There is no accepted gold standard definition of OA which leads to a variable definition of cases in the published literature. The question has also been raised whether OA can be seen as a single disease or a common end-stage of different, albeit related, diseases.

The first problem one encounters is the case definition. As no single definition of OA is accepted by all, we may interpret the different case definitions as different subsets of the disease. These different case definitions each have their strengths and weaknesses.

Self-report of symptoms for identification of OA has been shown to have poor sensitivity and specificity[101-103]. There is also poor correlation between radiographic changes and self-report of physician diagnosed OA[104]. The main strength is that it is a relatively cheap method and does not involve any radiation.

Radiographic definition of OA is common in epidemiologic studies. Of these the Kellgren and Lawrence grading scale has been the most commonly used. However, some confusion exists about the correct definition of this grading system. Discrepancies between the original atlas photos and legends, which place greater emphasis on joint space narrowing and subchondral bone changes, and later revisions which emphasised osteophytes have created confusion[29]. There is disagreement between major OA cohort studies on the definition and grading of disease according to the original K&L system[105]. This system has also been criticised in that it puts too much emphasis on the presence of osteophytes and that it assumes a sequential appearance of osteophytes, joint space loss, sclerosis and cysts. Using the Kellgren and Lawrence grading system usually yields high within-observer repeatability but poorer between-observer repeatability[106]. Despite these shortcomings, the Kellgren and Lawrence system, with the scoring of osteophytosis, is the radiographic grading system most closely associated with knee pain[107, 108].

MJS is the most reproducible measurement of OA in the hip joint and is the radiographic system that has the best correlation to clinical status in the hip[46, 95]. However, the use of MJS to define disease represents a challenge, since MJS is a continuous rather than dichotomous variable. The choice of cut-off for defining disease is arbitrary and is associated with a trade-off of sensitivity and specificity, resulting in different hip OA prevalence estimates[29]. MJS is reported in millimetres and cut-off points from 1.5mm to 3.0mm have been used. The cut-off point that is best supported is 2.5mm[95, 97] and was used throughout the work presented here. Several other grading systems exist. There is poor correlation between radiographic OA and clinical status, regardless of grading system used[5, 109].

Clinical definition of OA has been used in several studies, especially in hospital based cohorts. One such definition is presence of TJR for OA which is a dichotomous variable and thus simple and highly reproducible. One might assume that patients with joint replacement represent the most severe cases, but in a recent large international study it was shown that for the hip there is great variation in clinical disease severity at the time of THR[110]. This end-point may further be criticized because of the wide international variability in the frequency of TJRs, which may be a result of difference in health care systems or difference in prevalence in different countries and among different ethnicities. The clinical criteria from the American College of Rheumatology are derived from hospital data and their value in epidemiologic studies has been questioned[14].

The next problem a researcher is presented with is the study design. The advantages of cohort studies are that they usually give more

complete information on the exposure and the quality of the controls is higher. Cohort studies provide a clear temporal sequence of exposure and disease and thus causality can be assumed and risk (relative and absolute) can be calculated. Compared to case-control studies, cohort studies are more costly and take longer time to conduct and are therefore not as well suited to study diseases where the time between exposure and occurrence of disease is long, such as in OA. They do not allow for the simultaneous study of several possible causes of disease in the same manner that case-control studies do. The results of case-control studies can imply an association between the exposure and outcome, but causality can usually not be assumed. One challenge with case–control studies is the recruitment of appropriate controls. The controls should optimally be drawn from the same source population as the cases. Further, to avoid bias, it is also important that the data for cases and controls are gathered in the same way and at the same time. Due to this and the difference in the quality of controls, cohort studies are generally considered better and rank higher when systematic reviews of the literature are conducted.

When faced with a research question concerning the association between a possible etiologic factor and disease, the investigator has to choose an appropriate study design. A number of circumstances have to be considered, such as the incidence rate of disease, time elapsing between exposure and clinical manifestation of the disease, whether the exposure is associated with only one or more diseases, ethical issues, and funding available for the research. Some of these issues are especially pertinent for diseases of slow and gradual onset, such as OA.

Abnormal mechanical loading is a risk factor for OA

Previously OA was regarded to be the result of wear and tear of the joint, and like a machine that has a certain lifespan, the joint would eventually wear down. If you rub two surfaces together for a long time, the surfaces will eventually wear. In fact, the Icelandic name of the disease is “slitgigt”, “slit” meaning wear and “gigt” meaning arthritis, so “wear-arthritis” is the exact translation of the Icelandic name of OA. During the late 20th century more attention was given to the genetic aspects of OA and this “wear and tear” hypothesis was regarded less plausible. In recent years, interest has risen again in the consequences of mechanical loading on the joints.

The articular cartilage forms a biomechanical unit with the subchondral and cortical bone in order to attenuate forces through joints, particularly following impact loading. Changes in the articular cartilage impair the absorption of shocks that it should normally attenuate, impacting the subchondral bone and leading to secondary changes such as sclerosis and osteophyte formation. These subchondral bone changes have been subject to a classical “chicken and egg” debate. Recent research on bone biology has suggested that the structural changes in the subchondral bone begin early in OA and that the altered bone remodelling contributes to the breakdown of the articular cartilage at the joint.

Increasing evidence suggests that joint and bone homeostasis in both OA and osteoporosis are influenced by signalling pathways that are also involved in the development of cartilage and bone[111]. The Wnt/ β-catenin or “canonical” pathway is the most extensively studied and appears to be particularly important in bone and cartilage biology. This pathway involves the interaction of Wnt ligands with frizzled cell-membrane receptors coupled to co-receptors (low-density lipoprotein receptor-related protein 5 or 6). Mutations that increase the activity of this pathway lead to a higher bone mass[112, 113] and vice-versa, mutations that decrease the activity reduce bone mass[114, 115]. By measuring hydrostatic pressure, it has been shown that mechanical force increases the expression of Wnt agonists[116] and *in vitro* studies have shown that mechanical injury to cartilage causes release of proteins associated with mechanical cell disruption and

apoptosis[117]. The osteogenic potential of bone marrow cells from OA patients is increased, compared with that from normal, whereas both the chondrogenic and adipogenic potential of these cells is reduced[118]. The extracellular matrix becomes abnormal in OA and this can lead to an improper transmission within the bone microenvironment, thus the effect of mechanical loading could be different in different stages of the disease[119]. Therefore, biomechanical forces in OA may have an impact on the biological response of mesenchymal stem cells, chondrocytes and osteoblasts.

In **Paper I** we examined the association of BMI and OA. For knee OA, our results were in line with several previously published studies that have found a positive association between high BMI and TKR. This association was stronger for women than for men, but significant for both genders, and this is also in line with most previously published studies. The evidence for an association between BMI and THR was at the time of publication of Paper I considered to be moderate. Subsequent publications[78] have added to the accumulated evidence, which is now considered strong. However, the effect of BMI is not as strong for THR as it is for TKR[78]. In **Paper I** we found a stronger association between BMI and THR for men than for women. It has been proposed that the gender difference in the effect of BMI on the knee is due to anatomical difference between the genders. The reason for the gender difference that we found for THR might also be anatomical, or it might be hormonal. Taking into account that this is the only study that could be found that has found this sex difference in effect of BMI on THR, one has to consider that the result might be due to e.g. insufficient statistical power.

The simplest mechanism by which high BMI could affect OA is by the increased force acting across the joint in heavier individuals. This, however, does not explain the association between BMI and hand OA that has been described in other studies. Adipose tissue is a source of soluble mediators, producing a variety of proinflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukin 6 (IL6), and adipose tissue-specific cytokines called adipokines[120]. Of these adiponectin and leptin are the most abundantly produced. Leptin is a hormone that influences body weight homeostasis through effects on food intake and energy expenditure at the level of the hypothalamus. It was shown to be significantly increased in advanced OA cartilage compared with minimally damaged cartilage. Leptin levels are also significantly higher in synovial fluid than in serum samples. Leptin is known to have a detrimental effect on chondrocyte proliferation, and induces matrix metalloproteinase (MMP) protein expression[121], that trigger enzymes that lead to cartilage degradation[122]. This suggests that leptin is involved in OA development and affects cartilage metabolism directly as a proinflammatory cytokine with consequent catabolic effects on cartilage.

In **Paper II** the association between OA and physical workload was examined. The occupation title was used as the case definition. Very few prospective cohort studies exist, most studies on the effects of workload are case-control studies based either on work title or certain tasks, such as kneeling or sitting. Exposure to these tasks is usually evaluated by a questionnaire. In such cases the risk for recall bias is high. In using questionnaires there is a tendency to dichotomise the variables, which in most cases are continuous in nature. An example of this is asking whether the subject had squatted more than one hour each day. There is no basic science supporting such a definition. If squatting is detrimental for the knee, it seems reasonable that it is dose-dependent and the break-point at one hour is arbitrary. Nor do we know if squatting for five minutes 12 times a day differs in effect from squatting twice for 30 minutes. If squatting is detrimental for the knee, as some of the literature suggests, then it not surprising that Icelandic farmers have an increased risk. The majority of Icelandic farmers have sheep, cattle or both. Each cow is milked twice daily, for each milking the farmer needs to squat five times. Therefore, a farmer with 50 cows needs to squat 500 times daily or 3500 times per week. 35% of the THR cases and 32% of the TKR cases were

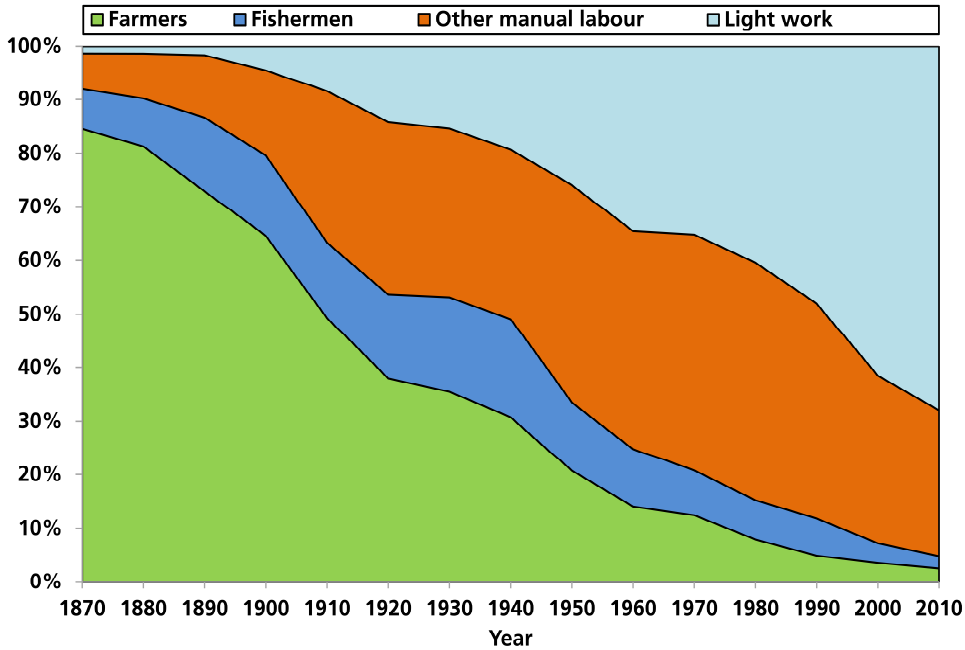

Figure 8 The evolution of the Icelandic workforce 1870 to 2010

farmers. Taking into account that farmers are now less than 4% of the Icelandic workforce, they seem greatly overrepresented amongst the cases. In this context one has to take into account the historical changes that have taken place in the Icelandic workforce (Figure 8). Nevertheless a significant association was found between farming and joint replacement for OA, both THR and TKR. This association was only found for male farmers. In the generation studied here the physical workload might not have been evenly distributed, the male farmer having a more physically demanding workload than the female. It was also found that farming was the profession with by far the strongest "inheritance", i.e. the profession being passed from father to son. In this case, inheritance does not explicitly imply a genetic factor; the farmer's son inherits both the environment and genes from his father. A more plausible explanation is that sons of farmers, being raised on a farm, were at a younger age than city-dwellers subjected to heavy physical workload. Studies have suggested that this is associated with OA.

Natural history of OA

There is no universally accepted definition of OA. The epidemiologist might be interested in the prevalence of radiographic OA, while the health care planner's interests lie in the incidence of total joint replacements. It has already been established in several studies that there is a poor correlation between joint pain and radiographic OA[123], i.e. the presence of radiographic changes in subjects with joint pain. There also a poor correlation between radiographic OA and pain[5], i.e. the presence of pain in subjects with radiographic changes. Concordance between self-reported and radiographic OA is low[104]. There is also a large variation in pre-operative clinical status of patients undergoing THR[110]. The different outcome measures used in OA studies are discussed in the introduction of this

Study	Year	No. of subjects/hips	Measure	Follow-up (years)	Reaching study endpoint %
Danielsson[1]	1964	121 hips	Clinical	10.0	19
			Radiographic	10.0	65
Seifert[2]	1969	83 hips	Clinical	5.0	83
van Saase[3]	1990	86 subjects	Radiographic	12.0	29
Ledingham[4]	1993	136 subjects	Clinical	2.3	66
			Radiographic	2.3	47
Lane[5]	2004	936 hips (all female)	Clinical	8.3	10
Franklin	2010	178 hips	Clinical	16.1	17

Table 2 Studies on the natural history of hip OA. (Modified from Dennison and Cooper (2003. Brandt K, Doherty M, Lohmander LS, editors. The Natural History and Progression of Osteoarthritis. Oxford: Oxford University Press, pp. 227–233) with permission).

thesis. Taking this into account one can say that different outcome measures represent different aspects of OA and that one definition is not necessarily better than another, but simply different.

In **Paper III** we examined the natural history of radiographic hip OA. There are not many studies published regarding this and some of the published studies were done before THR became widely available (Table 2). These studies are also heterogeneous in their definition of OA, case selection and outcome measure. One is on hospital referred cases of OA[4] and another included only elderly women[5]. Therefore one cannot expect the results to be comparable. Here the intention was to do a study that was population based. It is not ethically acceptable to subject healthy individuals to radiographic examination purely for research purposes. Therefore a cohort of individuals that had undergone colon radiography was followed. Only 17% of patients with radiographic OA had undergone a THR at the end of the study and in light of the long follow-up, one can state that there is poor correlation between radiographic OA and the risk for THR.

OA and hip fracture

It is a common observation amongst orthopaedic surgeons that patients with hip fracture rarely have OA. There are studies that claim that such a relationship exists[57, 58, 124] and others that refute it[104, 125]. In **Paper III**, which was a retrospective cohort study, 2.7% of patients without OA got a hip fracture compared to 1.7% of patients with OA. Even though this gives the impression that patients with OA have a reduced risk for hip fracture, one cannot draw that conclusion from the material in **Paper III** as there were only three patients with OA that got a hip fracture, i.e. there was insufficient statistical power to draw any conclusions. The aim of **Paper IV** was to establish the prevalence of OA in hip fracture patients. For this purpose, a cross-sectional case-control study is in fact better than a longitudinal cohort study. In longitudinal studies the exposure is determined at the beginning of the study and therefore not suited to determine the prevalence of OA at the time of fracture. In **Paper IV** it was found that the prevalence of radiographic OA was about one-third in hip fracture patients compared to controls (a colon radiography cohort). In comparison to other studies it is important to note that hip fracture and osteoporosis are not equivalent, not all subjects with osteoporosis get hip fracture and not all cases of hip fracture have pre-existing osteoporosis. If hip OA and hip fracture are mutually exclusive conditions, one has to explain the fact the subjects with both conditions exist. Women with hip fracture and OA were older than women with hip fracture, but not OA. The difference was not statistically significant for men, perhaps due to fewer men in the study. It was also found that patients with hip fracture and hip OA are three times more likely to have at least one risk factor for secondary osteoporosis than patients with hip fracture, but without hip OA. These subjects might therefore have OA and

would not have been subject to hip fracture if osteoporosis had not been induced by the use of corticosteroids or other causes of secondary osteoporosis. The weight of these results is reduced by limitations in the study design, but nevertheless indicates that secondary osteoporosis needs to be accounted for when studying the relationship between hip OA and hip fracture.

It has been established that patients with THR for OA in Iceland are significantly more related to each other than can be expected from the general population[72]. We wanted to see if the same applied to patients with hip fracture, and if that were the case, to determine if the inverse relationship between OA and hip fracture could be explained by inheritance. The hypothesis was that certain families would have OA and other families would have hip fractures. This relationship was not expected to be fully mutually exclusive, as that was not the case in **Paper IV**. In **Paper V** it was found that the inheritance of THR was stronger than that of hip fracture. The RR for a subject with THR for OA having a parent with the same condition was 2.8 in the study. In comparison, the RR for a subject with hip fracture having a parent with hip fracture was 1.9. When examining cross inheritance of THR for OA and hip fracture it was found that no mutually exclusive inheritance pattern existed between subjects with THR for OA and subjects with hip fracture. It might therefore seem that the conclusions of **Paper IV** and **Paper V** oppose each other. However, one has to take into account that the case definitions and outcome measures were not the same in these two studies. In **Paper IV** the radiographic prevalence of OA in hip fracture patients was examined, as opposed to **Paper V** where the inheritance of THR for OA and hip fracture was studied. As shown in **Paper III**, only a small proportion of radiographic OA cases get THR and to some extent **Paper IV** and **V** have to be regarded as apples and oranges, as different subsets of OA are being examined in these studies and therefore the conclusions of one of these papers do not necessarily contradict the other. In **Paper V** inheritance is being studied, not disease specific genes as such. It is therefore possible that inherited environmental factors, such as profession or other diseases, such as chronic obstructive lung disease and concomitant steroid use, confound the results.

Conclusions

- Increased body mass index is a strong risk factor for TKR due to OA, stronger for women but also significant for men
- Body mass index is also a risk factor for THR due to OA, albeit the strength of the effect is not as great as in the knees
- Male farmers have a greatly increased risk for both THR and TKR due to OA, and male fishermen may have an increased risk for TKR due to OA
- Radiographic OA of the hip is a weak predictor of future THR for OA
- The prevalence of radiographic OA in hip fracture patients is low
- Patients with THR for OA are not less related to patients with hip fracture than can be expected in the general population, i.e. a mutually exclusive inheritance pattern does not exist for these conditions

The overall conclusion of the studies presented in this thesis is that mechanical stress, exerted through increased body weight or heavy manual labour, is a risk factor for OA. We found support for the hypothesis that there is an inverse relationship between OA and osteoporosis, although this relationship does not seem to be explained by difference in inheritance.

Summary

The purpose of this study was to (I) assess the association between body mass index (BMI) and total hip replacement (THR) and total knee replacement (TKR) due to osteoarthritis (OA), (II) assess the association between the mechanical load of work and THR and TKR due to OA, (III) evaluate the natural history of radiographic hip OA with regards to THR and hip fracture, (IV) to determine the prevalence of radiographic OA in patients with hip fracture, and (V) to examine and compare the inheritance patterns of THR for OA and hip fracture.

OA was previously regarded as a consequence of the wear and tear the joint is subjected to during one's lifetime. At the turn of the century the genetics of OA were of high interest. In recent years there has been renewed interest in the effects of mechanical load on the joint. In **Paper I** it was found that there was a strong association between being overweight (BMI 25.0–29.9 kg/m^2) and the risk for TKR for both genders. This was even stronger for obese individuals (BMI 30.0 kg/m^2 or above). This association was weaker for THR and this is in agreement with another recently published study[78] that showed that the effect of BMI is less in THR than TKR. There are probably several factors that influence the effect of body weight on the risk for OA. For example malalignment has an additive effect of body weight on the development of knee OA. The effect may to an extent be purely mechanical, i.e. the increased weight putting more strain on the joint, but it has also been shown that cytokines originating from adipose tissue have an effect on cartilage metabolism. In **Paper II** the association between profession and total joint replacement in the knee and hip was explored. It was found that male farmers have greatly increased odds for total joint replacement, in both hip and knee, compared to other professions. It is not clear why farming has much greater odds for joint replacement due to OA than other physical labour professions. Farming was also the profession that showed the greatest degree of inheritance, so it is possible that it has a interacting effect. One possibility is that farmers, being raised on a farm, are exposed to heavy physical labour at a young age and it has been hypothesised that this can be detrimental for the joints.

In epidemiologic studies, definition of OA can be based on a set of questions, purely radiographic grading or a clinical definition, which may be presence of a TJR or a combination of radiographic changes and clinical symptoms and signs. Previous studies have shown discrepancies between these definitions. In **Paper III** a cohort of subjects that had undergone a colon radiography were followed for 11-28 years. Their radiographic hip status was registered at baseline. The most striking finding was that after 11-28 years, only 17% of those with radiographic OA at baseline had undergone THR. The individuals with radiographic hip OA that were subject to a hip fracture were so few, that no strong conclusions could be drawn based on that group.

In a publication four decades ago it was claimed that there was an inverse relationship between hip OA and hip fracture. Since then there have been publications both supporting and refuting this claim. In **Paper IV** the prevalence of radiographic hip OA in a cohort of patients with hip fracture was examined. The odds for having radiographic hip OA were one third in patients with hip fracture, compared to controls. The prevalence of risk factors for secondary osteoporosis was further examined and revealed that patients with hip OA and hip fracture were three times more likely to have a risk factor for secondary osteoporosis than patients with hip fracture, but without hip OA. This suggests that secondary osteoporosis needs to be accounted for and adjusted for when studying the relationship between OA and osteoporosis.

Based on these findings we hypothesised that this inverse relationship between hip OA and hip fracture might be explained by inheritance. The theory was that both THR and hip fracture run in

the family, but in distinctly separate families. Previous publications have shown that patients with THR are more related to each other than the population in general. **Paper V** therefore examined if patients with THR were less related to patients with hip fracture than can be expected in the population. This hypothesis was found to be false. It was revealed that patients with hip fracture were more related to other patients with hip fracture, as expected, but the apparent inverse relationship between hip OA and hip fracture could not be explained by inheritance.

Populärvetenskaplig sammanfattning på svenska

Syftet med denna studie var att (I) utvärdera sambandet mellan övervikt mätt med det s.k. body mass index (BMI) och operation med höftleds- eller knäledsprotes (konstgjord led) på grund av artros, (II) utvärdera sambandet mellan mekanisk belastning på grund av yrke och operation med höftleds- eller knäledsprotes på grund av artros, (III) utvärdera naturalförloppet för en person med artros i sin höft påvisad vid röntgenundersökning med hänsyn till risken för senare operation med höftledsprotes eller risken för höftfraktur, (IV) undersöka förekomsten av höftartros påvisad vid röntgenundersökning hos patienter med höftfraktur och (V) utforska och jämföra ärftlighet för operation med höftledsprotes och höftfraktur.

Man har tidigare ansett att artros främst är orsakad av mekanisk förslitning av lederna. Vid millenniumskiftet var det dock ärftligheten av artros som fångade störst intresse i forskningsvärlden. De senaste åren har emellertid betydelsen av fysisk belastning på lederna åter uppmärksammats som orsak till artros.

I **Delarbete I** fann vi ett starkt samband mellan övervikt (BMI 25.0–29.9 kg/m^2) och risken för operation med knäledsprotes hos både män och kvinnor. Detta samband var ännu starkare för kraftigt överviktiga (BMI 30.0 kg/m^2 eller mer). Sambandet var svagare för operation med höftledsprotes och detta stämmer med en nylig stor svensk studie[78] som visade att effekten av BMI är mindre för operation med höftledsprotes än för knäledsprotes. Det finns sannolikt flera faktorer som samverkar med effekten av kroppsvikt för risk för artros. Till exempel har vinkelfelställning i knäleden en kumulativ effekt tillsammans med kroppsvikt för att öka risken för artros i knäna. Effekten kan till viss del vara mekanisk, dvs. ökad vikt ger ökad belastning på lederna, men det har också visats att vissa molekyler (cytokiner) som har sitt ursprung i fettvävnad påverkar omsättning i broskvävnad.

I **Delarbete II** utforskade vi sambandet mellan yrke och operation med höft- eller knäledsprotes. Vi fann ett starkt samband mellan att vara manlig lantbrukare och konstgjord led i både höft och knä. Lantbrukare var också det yrket som visade sig ha mest ärftlighet. Detta kan påverka den risk för artros som yrket i sig medför. En möjlighet är att lantbrukare, som är uppväxta på en gård, i ung ålder blir utsatta för tungt fysiskt arbete och det kan möjligen vara skadligt för lederna.

I **Delarbete III** följde vi en grupp individer, som hade varit på röntgenundersökning av tjocktarmen mellan 11 och 28 år tillbaka i tiden. Vi studerade röntgenbilderna av deras höfter med avseende på förekomst av artros (eftersom dessa leder är synliga på översiktsbilden av nedre delen av magen). Mest slående var att endast 17% av de som hade artros påvisad på röntgenbilderna redan vid detta undersökningstillfälle hade fått konstgjord höftled under observationstiden på upp till 28 år.

I en artikel som publicerades för fyra decennier sedan hävdades att där finns ett omvänt samband mellan artros och höftfraktur. Sedan dess har det publicerats flera artiklar som stödjer denna hypotes och andra som vederlägger den. I **Delarbete IV** undersökte vi förekomsten av artros påvisad vid röntgenundersökning hos patienter med höftfraktur. Risken att ha artros hos patienter med höftfraktur var en tredjedel av den som vi fann hos kontrollgruppen. Vi undersökte även förekomsten av riskfaktorer för sekundär benskörhet (orsakat av t.ex vissa läkemedel). Vi fann att hos patienter med både artros i höftleden och höftfraktur var det tre gånger mer sannolikt att hitta riskfaktor för sekundär benskörhet än hos patienter med höftfraktur, men utan höftledsartros.

Baserat på dessa fynd antog vi att det omvända sambandet mellan artros i höftleden och höftfraktur eventuellt kunde förklaras av ärftlighet. Tidigare artiklar har visat att patienter med konstgjord höftled på grund av artros är mer

i släkt med varandra än befolkningen på Island i allmänhet. Hypotesen var att både operation med höftledsprotes och höftfrakturer gick i släkt, men i olika släkter. I **Delarbete V** utforskade vi om patienter med konstgjord höftled är mindre släkt med patienter med höftfraktur än man kan förvänta sig i bakgrundsbefolkningen. Vad vi fann var dock att patienter med höftfraktur var mer besläktade med varandra, liksom att patienter med höftprotes på grund av artros var mer släkt med varandra än befolkningen i allmänhet. Vår studie kunde dock inte bekräfta att dessa familjetyper var mindre släkt med varandra än förväntat. Vi tolkar detta resultat som att det omvända sambandet mellan höftledsartros och höftfraktur inte kan förklaras av ärftlighet.

Ágrip á íslensku

Markmiðið með þessari rannsókn var að:

(I) Kanna tengsl milli líkamsþyngdar mældri með s.k. „body mass index“ (BMI) og gerviliðaaðgerða í mjöðm og hné vegna slitgigtar.

(II) Athuga hvort tengsl eru á milli starfsgreina og gerviliðaaðgerða í mjöðm og hné vegna slitgigtar.

(III) Kanna hvernig einstaklingum með slitgigt í mjöðm samkvæmt röntgenrannsókn vegnaði með tilliti til áhættu á gerviliðaaðgerð síðar meir eða áhættu á mjaðmarbroti.

(IV) Kanna tíðni slitgigtar við röntgenrannsókn hjá einstaklingum með mjaðmarbrot.

(V) Bera saman erfðir slitgigtar í mjöðm sem leitt hefur til gerviliðaaðgerðar annars vegar og mjaðmarbrots hins vegar.

Áður var talið að slitgigt væri fyrst og fremst afleiðing álags á liðina eins og nafnið gefur til kynna. Um aldamótin var mestur áhugi á erfðum slitgigtar og talið að þær lægju til grundvallar í flestum tilvikum, en hin síðari ár hefur hins vegar vægi álags á liðina aftur lent í sviðsljósinu.

Í **grein I** fundum við sterk tengsl á milli ofþyngdar (BMI 25.0–29.9 kg/m^2) og hættu á að þurfa gervilið í hné, bæði hjá körlum og konum. Þessi tengsl voru enn sterkari hjá þeim sem voru mjög þungir (BMI 30.0 kg/m^2 eða hærra), en tengslin voru ekki eins sterk við hættu á að þurfa gervilið í mjöðm. Líklegt má telja að það séu margir þættir, sem samhliða líkamsþyngd, geta haft áhrif á hvort einstaklingar fái slitgigt. Til dæmis hefur verið sýnt fram á að öxulskekkja í hnélið (kiðfættir og hjólbeinóttir) eykur áhrif líkamsþyngdar á slitgigt í hné. Þessi áhrif eru að hluta bein áhrif þyngdarinnar sem eykur álagið á liðinn, en einnig hefur verið sýnt fram á að efni sem upprunnin eru í fituvef hafa áhrif á niðurbrot brjósks við slitgigt.

Í **grein II** könnuðum við tengslin milli starfsgreinar og gerviliðaaðgerða í mjöðm og hné. Þar kom í ljós að karlkyns bændur eru í langmestri hættu á að þurfa gervilið í mjöðm eða hné. Bóndastarfið var einnig sú starfsgrein sem gekk mest í arf. Þetta getur haft áhrif á þá hættu sem bóndastarfið felur í sér. Ein hugsanleg skýring er að bændur, sem sjálfir alast upp í sveit, byrji á unga aldri í þungri líkamlegri vinnu og það geti mögulega verið skaðlegt fyrir liðina.

Í **grein III** fylgdum við hópi einstaklinga, sem höfðu farið í röntgenrannsókn á ristlinum, 11-28 árum áður en rannsókn okkar var gerð. Röntgenmyndir frá ristilrannsókninni voru skoðaðar en þær má nota til að meta slit í mjöðm. Það sem kom mest á óvart í þeirri rannsókn var að einungis 17% þeirra sem voru með slit í mjöðm í ristilrannsókninni fengu gervilið í mjöðmina á þessu tímabili sem einstaklingunum var fylgt eftir.

Fyrir um fjórum áratugum var birt grein þar sem því var haldið fram að einstaklingar með slit í mjöðm fengju sjaldan mjaðmarbrot og öfugt, þ.e. einstaklingar með mjaðmarbrot væru sjaldan með slit í mjöðminni. Síðan þá hefur birst fjöldi greina sem hafa ýmist stutt þetta eða andmælt þessu. Í **grein IV** könnuðum við tíðni slitgigtar hjá einstaklingum með mjaðmarbrot. Hættan á slitgigt var einn þriðji hjá einstaklingum með mjaðmarbrot miðað við samanburðarhópinn. Einnig var könnuð tíðni áhættuþátta á lágri beinþéttni hjá einstaklingum með mjaðmarbrot. Það kom í ljós að einstaklingar með mjaðmarbrot og slitgigt í mjöðm voru þrisvar sinnum líklegri til að hafa slíka áhættuþætti en einstaklingar með mjaðmarbrot en ekki með slit í mjöðm.

Með tilliti til lágrar tíðni slitgigtar hjá einstaklingum með mjaðmarbrot töldum við að þetta gæti hugsanlega skýrst af erfðum. Áður hefur verið sýnt fram á að einstaklingar með gervilið í mjöðm vegna slitgigtar eru náskyldari en Íslendingar almennt, m.ö.o. slitgigt sem leiðir til gerviliðaaðgerðar gengur í arf. Við vildum því athuga hvort eins væri farið með mjaðmarbrot og hvort mjaðmarbrot og slitgigt lægju í mismunandi ættum.

Í **grein V** könnuðum við því hvort einstaklingar með gervilið í mjöðm vegna slitgigtar væru fjarskyldari einstaklingum með mjaðmarbrot en öðrum Íslendingum almennt. Niðurstaðan var sú að einstaklingar með mjaðmarbrot voru náskyldari en Íslendingar almennt og sama gilti um

einstaklinga með gervilið í mjöðm vegna slitgigtar. Það var þó ekki hægt að sýna fram á að einstaklingar með mjaðmarbrot væru fjarskyldari einstaklingum með gervilið í mjöðm en öðrum Íslendingum almennt. Þetta táknar að þessi lága tíðni slitgigtar hjá einstaklingum með mjaðmarbrot skýrist ekki af erfðum.

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