Leisure time physical activity and smoking as potential risk factors for severe hip and knee osteoarthritis

The HUNT Study

by

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Abbreviations

BMI – Body mass index
CI – Confidence interval
CVD – Cardiovascular disease
HR – Hazard ratio
HUNT – The Nord-Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag)
LPA – Leisure time physical activity
NAR – Norwegian Arthroplasty Register
OA – Osteoarthritis
OR – Odds ratio
SNP – Single-nucleotide polymorphism
THR – Total hip replacement
TJR – Total joint replacement (hereafter TJR=hip and knee replacement combined)
TKR – Total knee replacement
List of papers


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Summary

Background
Together hip and knee osteoarthritis (OA) represent the highest proportion of the OA burden, and are the underlying cause for an increasing need for joint replacement. At present there is no curative treatment for OA, increasing the importance of identifying modifiable risk factors which may influence development and progression of the disease. Leisure time physical activity (LPA) and smoking represent modifiable lifestyle factors that may influence hip and knee OA and subsequently the need for total hip replacement (THR) and total knee replacement (TKR).

Objectives
The overall aim of this thesis was to investigate the association between LPA or smoking and the risk of subsequent THR or TKR.

Methods
We used information from the Nord-Trøndelag Health Study in combination with linkage to the Norwegian Arthroplasty Register for detection of THRs and TKRs. Methods used were I) a longitudinal study of LPA as a risk factor for THR or TKR, II) a mediation analysis of the total and indirect effects of smoking on the risk of THR or TKR, and III) a Mendelian randomisation study to investigate the causal effect of smoking on the risk of total joint replacement (TJR: THR and TKR combined).

Results and conclusions
I) A high level of LPA was associated with increased risk of THR and TKR among women, while for men, a high level of LPA was associated with increased risk of THR only, II) the total effect of smoking revealed a decreased risk of THR and TKR for men, while smoking was associated with increased risk of THR for women, and most of the effect remained unexplained by body mass index (indirect effect), III) we found support for a causal association between smoking and TJR. However the underlying mechanisms of this causal association may be twofold; smoking may protect against OA or smoking may reduce the probability of receiving TJR among people with OA.
Preface

This PhD thesis is part of a collaborative project between the Communication and research unit for musculoskeletal disorders (FORMI) at Oslo University Hospital (OUS), the HUNT Research Centre, and the Norwegian Arthroplasty Register (NAR). The HUNT OsteoArthritis Study (HOA) was created in March 2013. Two PhD candidates are included in the project: Alf Inge Hellevik and Marianne Bakke Johnsen.

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The goal of this PhD project was to investigate, in a large population-based cohort, the role of certain lifestyle factors that may contribute to reducing the increasing demand for hip and knee replacement surgery. It is our hope that the present project has contributed to existing OA literature and provided research questions to be elucidated in future studies.
1. Introduction and background

Osteoarthritis (OA) was ranked as one of the top causes (11th) of years lived with disability in the Global Burden of Disease study in 2010. Hip and knee OA are the main contributors to the OA burden, a burden that is anticipated to further increase due to an aging and more obese population. The total health service costs for treatment of musculoskeletal disorders in Norway were NOK 14.3 billion in 2009. The lifetime risk of symptomatic OA is high and has been estimated at 25% and 45% for hip and knee, respectively, in US population (Johnston County Osteoarthritis)4,5. The overall prevalence of OA in Norway was estimated to be 12.8%, in a population survey in 2004, where the site-specific prevalence was 5.5% for hip OA and 7.1% for knee OA6.

Hip and knee replacements as treatment for severe end-stage OA are two of the most frequently performed operations in Western countries7,8. However, the lifetime risk of undergoing total hip replacement (THR) or total knee replacement (TKR) is estimated to be substantially lower than the risk of developing symptomatic hip or knee OA. In the UK, data from the General Practice Research Database revealed that the lifetime risk of THR and TKR ranged from 8-11% for women and 5-8% for men, ages 50-709.

Arthroplasty surgery is reported to be a cost-effective procedure in terms of individual patient's improved pain and disability and reduced health care costs associated with OA10,11. In total, over 8400 THRs were performed in 2015 in Norway, which represented a 15% increase from 2010. Correspondingly, almost 6100 TKRs were performed in 2015, representing a 38% increase from 201012. The cost of primary THRs and TKRs in Norway was approximately NOK 1.8 billion in 2015. In addition, revisions cost over NOK 400 million within the same year13. With improvements in surgical techniques and modern anesthesia7, the future burden of primary and revision TJR surgery among younger patients (<65 years) is projected to increase substantially by 203014.

Given the large burden of OA and the associated burden of joint replacement surgery worldwide, it is important to understand the role of potentially modifiable factors for OA in order to prevent and reduce the burden of this disease.
1.1 Pathogenesis, clinical features and management of hip and knee OA

1.1.1 Pathogenesis

In the past, OA was considered to be a disease of purely mechanical cartilage degeneration; however it is now known to be a complex condition affecting the whole joint. In addition to systemic inflammation, cartilage, subchondral bone, and synovium probably all play a key role in the disease pathogenesis\textsuperscript{15}. However, the main characteristics of OA are loss of articular cartilage and changes in the subchondral bone, such as osteophyte formation, bone remodeling, and subchondral sclerosis\textsuperscript{16,17} (Figure 1).

\textbf{Figure 1.} Bilateral hip OA with decreased joint space, osteophyte formation, subchondral sclerosis and a cyst in the femoral head (left side).

The earliest pathologic changes in OA are commonly seen on the surface of the articular cartilage with fibrillation in the focal regions that experience maximal loading. In an attempt to repair, clusters of chondrocytes form in the damaged areas, likely in response to loss of matrix. This attempt subsequently fails and leads to degeneration\textsuperscript{16}. Synovitis is a common feature of OA, even in the early stages of the disease, which corresponds with clinical symptoms such as inflammatory pain and joint swelling. Synovitis might add to the vicious cycle of progressive joint degeneration by releasing inflammatory mediators and degradative enzymes that contribute to disease progression, including cartilage destruction\textsuperscript{15,16}. It has been debated whether OA is predominantly driven by abnormal mechanics which subsequently affect cartilage, subchondral bone and synovium\textsuperscript{18}, or if synovitis is the primary trigger of OA\textsuperscript{19}.
1.1.2 Clinical features

Clinically, hip and knee OA are characterized by pain, crepitus, stiffness and loss of movement. Pain is typically worst during and after weight-bearing activities, and stiffness is experienced after periods of inactivity. Loss of movement may limit daily activities like walking, stair climbing and squatting\textsuperscript{16}.

Plain radiography is the gold standard in imaging and diagnosis of OA joints, which includes features such as narrowing of joint space width, osteophyte formation, and the development of subchondral sclerosis and cysts\textsuperscript{15,16} (Figure 2). Kellgren and Lawrence classification has been widely used for grading OA in the hips and knees\textsuperscript{20}. Joints are scored to classify the severity of radiographic OA, with a focus on osteophyte formation, joint space narrowing, and bone sclerosis, rated on a scale from 0 to 4\textsuperscript{20}, where a grade\textsuperscript{2} is often the most widely used marker of definite radiographic OA\textsuperscript{21}. Kellgren-Lawrence grade 2 represents minimal radiographic changes (definite osteophytes, no joint space narrowing), whereas grade 3 refers to moderate changes (additional joint space narrowing) and grade 4 represents severe radiographic changes (additional bone sclerosis)\textsuperscript{22}.

![Figure 2. Standing radiographs with knees flexed 30 degrees, showing loss of joint space medially in the right knee, Kellgren-Lawrence grade 4.](image)

Other modalities to assess joint structures and synovium also exist, such as magnetic resonance imaging (MRI) and ultrasonography\textsuperscript{15}. Severity of OA is also dependent on clinical symptoms, like in the Global Burden of Disease study 2010\textsuperscript{2} where the severity of OA was
described by Kellgren-Lawrence grades 2-4, and additionally the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)\(^{23}\) pain subscale (score 0 to 20).

Radiological and clinical criteria for OA of the hip and knee have been proposed by the American College of Rheumatology (ACR)\(^{24,25}\). Their classification is dependent upon clinical symptoms of joint pain in addition to radiographic and/or laboratory findings criteria, and is particularly useful in differentiating OA from other joint diseases such as rheumatoid arthritis. An operational definition of OA proposed by the Osteoarthritis Research Society International (OARSI) Disease State working group suggests distinguishing between structural changes at joint level (the disease OA) and the effects on patient-reported symptoms (the illness OA) in future OA clinical trials\(^{26}\). Self-reported OA is found to have acceptable validity, in comparison to the ACR criteria, and is often the most feasible way to discover OA cases in epidemiological studies\(^{27,28}\). However, only modest agreement has been reported between radiographic, clinical and self-reported methods of diagnosing hip and knee OA\(^{29,30}\).

Development and progression of OA can take place over several years\(^{9,17}\). A retrospective cohort study from Iceland investigated the natural history of radiographic hip OA with regard to the association with subsequent THR\(^{31}\). In their cohort, 17% of those with radiographic hip OA at baseline had undergone a THR by the end of the study, 11-28 years later (mean time to THR 7.4 years)\(^{31}\). In a community sample of postmenopausal women in the US, 8 years follow-up resulted in 24% THR amongst those with hip pain and radiographic findings compared with 3% THR amongst those who had radiographic findings only\(^{32}\). The natural history of radiographic knee OA was documented in the Chingford Women’s Study, a community-based cohort that was followed for 14 years\(^{33}\). At baseline, 13.7% of the subjects had radiographic knee OA, and the prevalence had increased to 47.8% by the end of follow-up. Progression to TKR by year 15 was seen in 4.9%, 5.3% and 6.7% of the knees with K/L grades 1, 2 and 3 at baseline, respectively\(^{33}\).

### 1.1.3 Management

There is currently no cure for OA, although there are options for management and treatment of the disease. There are essentially three treatment modalities available for OA: non-pharmacological, pharmacological and surgical. Evidence-based guidelines for the treatment of OA have been published by ACR\(^{34}\), the European League Against Rheumatism (EULAR)\(^{35,36}\) and OARSI\(^{37-39}\). As there is no single modality which will relieve pain, improve
function and prevent structural progression of disease, management relies on combination of available therapies. The OARSI guidelines are used as a reference to describe the treatment options below; especially with regard to non-pharmacological treatments these guidelines are largely similar to the guidelines published by ACR and EULAR. In two recent Cochrane reviews, therapeutic exercise was shown to be a useful non-pharmacological intervention for reducing pain and functional disability in individuals with diagnosed hip or knee OA. Moreover, information and education about the objectives of treatment and the course of disease are important.

Paracetamol is the first choice of oral analgesic for mild-moderate OA pain for patients with symptomatic hip or knee OA. Non-steroidal anti-inflammatory drugs (NSAIDs) may be more appropriate for some sub-phenotypes of knee OA than others (e.g those without comorbidities) and should be taken at the lowest effective dose, their long-term use being avoided if possible. Patients with hip or knee OA who are not receiving adequate pain relief and functional improvement from a combination of non-pharmacological and pharmacological treatment might be considered for joint replacement surgery.

An international working group (OMERACT/OARSI) was created in 2004 to define the states of severity and indications for THR and TKR. Patients who were recommended for TJR had worse symptom levels of pain and functional impairments, than those who were not, and radiographic severity was a strong predictor for recommendation of TJR. However, there was considerable overlap in the symptom levels of the two groups, even after adjusting for radiographic joint status. Thus, there exists no definite cut-off or gold standard criterion concerning pain and disability leading to a TJR indication. Other important factors contributing to the decision for TJR surgery are willingness of the patient, the opinions of the referring physician or surgeon and the general health status of the patient.

1.2 Risk factors for hip and knee OA

The identification of risk factors is significant for the selection of targets for prevention and treatment. A number of risk factors for hip and knee OA have been identified and a selection which are especially relevant to this thesis are mentioned here (Figure 3).
1.2.1 Non-modifiable risk factors

Age
Increasing age is an important risk factor for the incidence of hip\textsuperscript{46} and knee OA\textsuperscript{47}. A non-linear relationship has been suggested, predominantly shown in European and US populations, with incidence increasing between the ages of 50 and 80, before levelling off around age 80\textsuperscript{46,48}. The same age-pattern is found in Norway, where the incidence of THR and TKR per 100 000 inhabitants’ is reported to increase from ages 50-59 up to ages 70-79, before it declines\textsuperscript{49,50}. The relationship between age and the risk of OA is most likely multifactorial; including articular cartilage’s reduced ability to withstand joint stress and injury due to tissue homeostasis declining with increasing age\textsuperscript{51}. Age may also be a proxy for the accumulation of risk factors and age-related changes over time\textsuperscript{52}.

Gender
A meta-analysis demonstrated sex differences in OA prevalence and incidence in the hand, hip and knee, with females generally at a higher risk\textsuperscript{53}. Sex differences were greater when OA was defined by means other than radiographic methods. Furthermore, females tended to have more severe knee OA than males, and sex differences in severity were most apparent among people aged ≥55 years\textsuperscript{53}. The prevalence of radiographic primary hip OA was found to be higher in men compared with women in another systematic review\textsuperscript{46}. However, when comparing prevalence within age groups, women had higher prevalence for radiographic primary hip OA in the majority of age groups, especially after age 50. A recent systematic
review and meta-analysis of 11 cohort studies assessing female gender as a risk factor, concluded that there was consistent evidence that females were at higher risk of knee OA. The increase in incidence of OA among women after menopause has created suggestions of hormonal influence on articular cartilage, e.g. through estrogen, however clinical and epidemiological studies have not universally corroborated this theory and the mechanisms remain unclear. In the Nordic countries, the incidence of THR and TKR due to primary OA are reported to be higher among women than men. The proportion of females undergoing THR and TKR in Norway is higher than in the other Nordic countries. Higher utilization rates of THRs and TKRs among women compared with men have also been reported in the UK and South Korea. Consequently, gender is an important factor to account for in studying the risk of both OA and later TJR.

**Genetics**

The development of OA is driven by a complex interplay of genetic and environmental factors. Heritability for radiographic OA of the knee, hip and hand are reported to be 39%, 60% and 59%, respectively. Despite the large genetic component of OA, to date only a small fraction of disease heritability (11%) has been explained by established loci. The growth/differentiation factor 5 (GDF-5), a protein involved in joint formation from the bone morphogenic protein family, was originally chosen by a Japanese group for examination as a potential OA susceptibility locus. It has consistently been associated with hip and knee OA in Asian and European cohorts, although the association between hip OA and the identified rs143383 single-nucleotide polymorphism (SNP) within the GDF5 gene has been more controversial than its link to knee OA.

The site- and gender-specific heterogeneity of OA is reflected in the associated genetic heterogeneity, and it is suggested that future assessment of the genetic contribution to OA should be done according to joint site and gender, and be performed using more homogeneous phenotypic definitions of OA, such as joint replacement. The genetic contribution to OA has important clinical implications. The identification of genes involved in the disease risk can help us to understand the mechanisms involved in the pathogenesis of OA. Also, by identifying sets of genetic variants associated with the risk of disease or with progression of OA, we can define phenotypic subsets of OA. Another possibility is to use genetic variants which are not directly associated with the risk of disease, but with an exposure of interest. Mendelian randomisation, a form of instrumental variable analysis, can thus be used to evaluate the causality of observed associations. A genetic variant in the
FTO gene associated with fat mass and obesity, rs804476 SNP, has been identified in a genome-wide association study (GWAS) on hip and/or knee OA in European populations\textsuperscript{63}. Rs804476 was strongly associated with OA; however whether the association was mediated by obesity could not be tested due to the study design\textsuperscript{63}. This was examined later in a Mendelian randomisation study where the association between rs804476 SNP and OA was exclusively mediated by its effect on BMI\textsuperscript{64}. In contrast, no association was found between rs804476 and OA or increased BMI in a Chinese population\textsuperscript{65}. However, the small sample size in the Chinese study may have prevented them from coming to any reliably conclusions\textsuperscript{65}. Further, genetic heterogeneity between ethnic groups (Asian vs. European) might be contributing to the inconclusive results compared to the former study of Panoutsopoulou and colleagues\textsuperscript{64}.

1.2.2 Modifiable risk factors

Joint injury
Joint injury is a powerful risk factor for the occurrence of OA, especially true for the knee. An injury to the anterior cruciate ligament, particularly with concomitant injury to the menisci, significantly increases the risk of radiographic knee OA\textsuperscript{66}. People who sustain a knee injury are 4 times more likely to develop knee OA compared to those without a knee injury\textsuperscript{67}. There is more limited epidemiological evidence for joint injury as a risk factor for hip OA\textsuperscript{68}, and, compared with knee OA, hip OA occurs more often without a history of previous associated injury\textsuperscript{69}. However, joint injury was a risk factor for hip OA in a systematic review with a combined odds ratio (OR) of 5.0 (95\% CI 1.4-18.2)\textsuperscript{70}; although it should be noted that this result was based on four studies only (with only one of them being prospective).

Obesity
Obesity is one of the strongest modifiable risk factors for OA. It can have both systemic and local effects. Obesity increases the mechanical load on weight-bearing joints, but might also increase susceptibility to OA through inflammatory mediators\textsuperscript{15}. The risk of knee OA is 2 to 3 times higher for obese or overweight persons than for those who are of normal weight, however it varies by joint\textsuperscript{47}.

A link to overweight/obesity has been consistently demonstrated for knee OA, while for hip OA the results have been inconsistent. A meta-analysis from 2011\textsuperscript{71} showed that BMI also
contributes to susceptibility to hip OA. They quantitatively assessed the association between increased BMI and the risk of hip OA. A 5 unit increase (5 kg/m²) in BMI was associated with an 11% increased risk of hip OA⁷¹. Correspondingly, in a meta-analysis of BMI and knee OA⁷², a 5 unit increase in BMI was associated with a 35% increased risk of knee OA, with the magnitude of association significantly stronger in women than in men, and stronger for OA defined by surgery (joint replacement) compared with OA defined by radiography and/or clinical symptoms⁷². This gender difference was also found in a Norwegian cohort study. When comparing the highest and the lowest quarters of BMI with the risk of TKR, the relative risk was 6.2 (95% CI 4.2-9.0) for men and 11.1 (95% CI 7.8-15.6) for women⁷³. Similarly, comparing the highest and the lowest quarters of BMI with the risk of THR gave a relative risk of 2.0 (95% CI 1.4-2.9) and HR 3.0 (95% CI 2.1-4.1) for men and women, respectively⁷⁴.

BMI is suggested to be a moderate determinant for the progression of radiographic knee OA, but not for hip OA⁷⁵. However, BMI has been strongly associated with the risk of THR and TKR, as markers of severe hip and knee OA, both in previous Norwegian cohort studies⁷⁶-⁷⁸, as well as in large cohort studies from Sweden⁷⁹ and Australia⁸⁰,⁸¹.

**Physical activity/exercise**

Physical activity and exercise are highly recommended clinical management interventions for people with hip or knee OA⁴⁰,⁴¹. However, little is known about the effect of physical activity, positive or negative, on the primary prevention or delay of onset of OA⁸².

In the Framingham Heart Study cohort, heavy physical activity was an important risk factor for developing radiographic and symptomatic (although the number of cases was small) knee OA, especially among obese individuals⁸³. They were, however, unable to specify which types of heavy physical activities that were responsible for the increased risk of knee OA. Later, in the Framingham Offspring cohort, no association was found between recreational walking, jogging or other self-reported activity and development of radiographic and symptomatic knee OA after 9 years of follow-up⁸⁴. In contrast, Cheng et al.⁸⁵ found that a high level of physical activity (running 20 or more miles per week) was positively associated with self-reported physician-diagnosed hip and knee OA among young men (age 20-49) at the Cooper Clinic, US. In a more recent study from the Norwegian HUNT cohort by Mork and colleagues⁸⁶, there was no association between physical exercise at baseline and self-reported hip or knee OA 11 years later. Although high BMI increased the risk of knee OA in
particular, there was no indication of a combined effect of BMI and physical exercise, and thus no interaction suggesting different effects of exercise across various BMI categories\textsuperscript{86}. Lastly, in the Johnstone County Osteoarthritis Project study\textsuperscript{87}, meeting the physical activity guidelines (≥150 min/week) was not associated with incident radiographic or symptomatic knee OA but it was associated with joint space narrowing (limited to those with K/L grade>2). To summarize, the results from previous studies are inconsistent with regard to the influence of physical activity/exercise on the risk of hip or knee OA. However, the definition of OA and physical activity also differs across the studies.

With regard to severe hip and knee OA, defined as THR or TKR, an Australian cohort study found that the risk of TKR increased with increasing levels of PA (hazard ratio (HR) 1.04, 95% CI 1.01-1.07, p trend= 0.003) and with vigorous PA 1-2 times/week (HR 1.42, 95% CI 1.08-1.86) compared to none at all\textsuperscript{88}. They found no association with THR. The physical activity measure in this Australian study included intensity and frequency of activity during the last six months however they lacked detailed information on occupational activity which could have been used to rule out residual confounding from physical workload\textsuperscript{88}. In contrast to these results, other studies have suggested no overall association between physical activity and TKR or THR\textsuperscript{73,74,89}. However, in Norwegian cohort studies\textsuperscript{73,74}, physical activity was not the main exposure of interest and the definition was highly sports related, requiring participation in hard training or competition regularly and several times a week. In a Swedish cohort study, lower risk of THR was found among those women with the highest levels of physical activity compared to those with the lowest levels (HR 0.66, 95% CI 0.48-0.89) \textsuperscript{89}. However they specified that further studies are needed to confirm this possible difference among women. They found no significant association between physical activity and the risk of TKR.

Intensive exercise and sport participation have consistently been linked to an increased risk of severe hip and knee OA\textsuperscript{69,90}. One current systematic review concluded that participation in elite-level impact sports (soccer, hockey, handball, track and field) was associated with a 2- to 9-fold increase in the risk of hip OA (radiographic, arthroplasty)\textsuperscript{69}, while another review found that participants in soccer, elite long-distance running, weight lifting or wrestling were 3 to 7 times more likely to suffer from knee OA\textsuperscript{90}. However, the focus has been on male athletes and future research needs to study more female athletes. Another large cohort study, also predominantly focusing on males, of long-distance skiers in Sweden
found increased risk of THR and TKR associated with the number of successful Vasaloppet races and faster finishing times. The results were independent of previous joint injury. In summary, some prospective studies indicate that physical activity or exercise increases the risk of radiographic knee OA, self-reported knee OA or TKR. Other studies, however, have found no overall effect of physical activity on hip or knee OA, regardless of the definition of OA. One study showed that physical activity was protective of THR among women, while only sports-related studies found an increased risk of THR related to exercise. The body of evidence for a relationship (or not) between physical activity and OA is primarily based on studies of the knee. The inconsistent results might be related to differences in the source population (young vs. old), definition of physical activity (intensity, frequency, and duration), length of follow up or confounders available/selected for adjustments in the statistical analyses. As the abovementioned results are based on observational data, the relationship between physical activity and hip or knee OA is prone to confounding by design. However, in a long-term follow-up of a randomized controlled trial of patients with hip OA, exercise therapy (in combination with patient education) was found to reduce and delay the need for THR by 44% in comparison with patient education alone. Moreover, it is suggested that physical activity may play a different role regarding the risk of joint pain and stiffness (not OA-specific) depending on the age at which it is performed. Higher volumes of physical activity (> metabolic equivalent (MET) minutes/week) between the ages of 47 and 58 were associated with lower odds of joint pain/stiffness between the ages of 56-64, and self-reported PA at ages 52-58 seemed to be more important than at ages 47-52.

**Smoking**

There is conflicting evidence on the role of smoking in hip and knee OA, although the majority of studies have indicated a negative association between the two. Between 1989 and 1999, data from the Framingham Osteoarthritis Study showed a moderate protection against radiographic knee OA among heavy smokers compared with non-smokers, with a relative risk (RR) of 0.81 (95% CI 0.66-0.99). Similarly, a Swedish case-control study reported reduced risk of severe knee OA (TKR) among smokers compared with non-smokers for both men (RR 0.60, 95% CI 0.40-1.00) and women (RR 0.40, 95% CI 0.20-0.80).
Two meta-analyses based on literature up to 2010 (onset OA) and up to 2012 (progression of OA) have been published\textsuperscript{95,96}. The overall result from the meta-analysis on onset of OA (48 studies; 8 cohort) showed an inverse association between smoking and OA (OR 0.87, 95% CI 0.80-0.94)\textsuperscript{95}. However, due to heterogeneity and publication bias, a subgroup analysis was performed which demonstrated no association in cohort or cross-sectional studies, but only among case-control studies (OR 0.82, 95% CI 0.70-0.95). Further analysis within case-control studies showed that only hospital-based case-control studies accounted for the inverse association. Finally, a meta-regression was performed to adjust for covariates (study design, study population, exposure, definition of knee OA), which then ultimately attenuated the association in hospital-based studies and only studies with smoking as secondary exposure were marginally significant\textsuperscript{95}. The meta-analysis on progression of OA (16 studies; 11 cohort) from the same research group revealed no overall association between smoking and progression of OA\textsuperscript{96}. Some subgroup analyses were statistically significant: as for community-based studies, studies of radiographic OA or with joint replacement as an outcome, and studies adjusted for confounding factors (age, sex, BMI etc.). However, these results were not considered to be clinically important due to an upper limit of 95% CIs and odds ratios close to 1. More recent studies (after 2012) have found a protective effect of smoking on THR and TKR in large population-based cohorts\textsuperscript{73,97,98}, presenting HRs ranging from 0.49 (95% CI 0.40-0.60)\textsuperscript{97} to 0.66 (95% CI 0.56-0.78)\textsuperscript{73} for TKR, and 0.72 (95% CI 0.58-0.90) for THR\textsuperscript{98}.

Results from in vitro data have indicated that any protective effect of smoking may be related to the beneficial effect of nicotine on chondrocyte function\textsuperscript{99,100}, however studies which have assessed its effect on articular cartilage volume using MRI have been inconclusive\textsuperscript{101,102}. Moreover, smoking could act in an indirect manner through other lifestyle factors, e.g. BMI. Smokers are thinner than non-smokers, as corroborated in Mendelian randomisation studies investigating the association between smoking, cardiovascular risk factors and BMI\textsuperscript{103,104}. In this way, smoking may protection against OA by contributing to lower BMI and, thereby, a reduction in mechanical joint stress and a decrease in the influence of systemic factors on disease onset and/or progression. Further, smoking may have a protective effect on OA through nicotine sensitive acetylcholine receptors, where the net effect of stimulation of these receptors is anti-inflammatory\textsuperscript{105}. In contrast, daily smoking has been found to increase the risk of musculoskeletal complaints (pain and/or stiffness); in a former Norwegian HUNT study, 20% of smokers aged\textless50 years suffered from musculoskeletal complaints\textsuperscript{106}. Thus on the one hand, stimulation of the
nicotine acetylcholine may be beneficial reducing OA related inflammation, while, on the other hand, stimulation of the same receptors may induce musculoskeletal pain\textsuperscript{107}, potentially affecting the clinical course of OA.

In summary, the majority of studies have investigated the association between smoking and knee OA, especially radiographically defined OA. Studies with joint replacement as the outcome have investigated both THR and TKR. The majority of studies have found an inverse association between smoking and hip and knee OA, independent of the study design and definition of OA. However, as mentioned in the meta-analyses\textsuperscript{95,96}, we have to consider the validity of results in light of the inherent bias related to the different study designs. Few prospective cohort studies have investigated the effect of smoking on joint replacement\textsuperscript{73,97,98,108}. Thus, further well-designed prospective studies are needed to strengthen the evidence base.

\textit{Work/workload}

In the literature, occupational activities have been consistently associated with hip and knee OA\textsuperscript{109,110}. Heavy lifting and kneeling have been identified as occupational activities that increase the risk of OA. Male floor- and bricklayers and female healthcare assistants seem to have an especially higher risk of knee OA, while farmers have the highest risk of hip OA\textsuperscript{110-112}. Generally, the risk is found to increase with cumulative years of heavy workload in both men and women\textsuperscript{113}. Moreover, cumulative physical workload has shown to increase the risk of earlier THR surgery (up to 3.4 years)\textsuperscript{114}. However, the meta-analysis of occupational risk factors for knee OA\textsuperscript{109} showed a significant influence of publication bias and heterogeneity among the literature on occupational activities and knee OA. They found that the overall OR was 1.61 (95% CI 1.45-1.78) for knee OA, with cohort studies generating the lowest OR (1.38, 95% CI 1.10-1.74) and case-control studies the highest OR (1.80, 95% CI 1.48-2.19). In a systematic review by Sulsky et al.\textsuperscript{110}, it was not possible to develop pooled estimates for the risk of hip OA due to study designs being too heterogeneous. However, the included studies showed that heavy lifting and standing generally produced a 1.5-2.5 increase in odds for hip OA. Thus, the evidence base for work/workload as a risk factor for OA could be strengthened by more cohort or longitudinal/prospective studies\textsuperscript{109}. The combined effect of BMI and physical activity at work on the risk of THR was two and a half times higher for men in the upper BMI quarter (>27.4 kg/m\textsuperscript{2}) with intensive physical activity at work compared to men in the lowest BMI quarter (>23.4 kg/m\textsuperscript{2}) who had sedentary PA at work. The same comparison for women showed a relative risk which was more than four and a
half times as high\textsuperscript{74}. Similarly, persons with both high BMI and intensive physical activity at work were at greater risk of TKR surgery\textsuperscript{73}.

1.3 Epidemiological methods for assessing risk factors in observational studies

The ultimate goal of many observational studies is to estimate the causal effect of an exposure on an outcome. However in observational studies, association is generally not causation\textsuperscript{115}.

The randomized controlled trial (RCT) is the gold standard for establishing a causal association between an exposure and a disease; the random allocation of measured and unmeasured risk factors creates exchangeable groups and thus unbiased results. However, it is not always feasible to conduct a RCT due to financial, logistical or ethical issues. Thus, a cohort study is considered to be the next best design\textsuperscript{116}. In a prospective cohort study we follow a group of people forward in time and compare the occurrence of disease in groups of people with and without an exposure of interest. The participants must be free of the outcome at start of follow-up to ensure that the exposure precedes the outcome. This decreases the problem of reverse causation, as the measurement of exposure is not biased by knowledge of outcome status. However, the groups in a cohort study are no longer exchangeable in terms of measured and unmeasured factors, which limit the ability to make causal inferences\textsuperscript{115,116}. A cohort study can also be retrospective, or historical, when data on both the exposure and the outcome have been measured in the past, even if the outcome is measured after some follow-up period. The distinction between a prospective and a retrospective cohort study is dependent on whether the study was initiated before or after the occurrence of the outcome\textsuperscript{117}.

Recommendations for the design and how to conduct randomized clinical trials of primary prevention of OA, rehabilitation, and surgical interventions for OA have been published by OARSI\textsuperscript{118-120}, however, no recommendations have been published on how to conduct observational studies.

Two main errors that can occur in epidemiological studies are selection bias and misclassification. Selection bias occurs when there is a systematic difference, i.e. the relation between exposure and outcome is different among those who participate and those who do not\textsuperscript{116}. Furthermore, loss to follow-up is a common problem in cohort studies with longer follow-up times. Loss to follow-up may result in selection bias if it is associated with both
exposure and outcome\textsuperscript{117}. Misclassification may occur due to errors in the measurement of
the exposure or the outcome, e.g. due to recall bias or low accuracy of the instrument used
for obtaining the information\textsuperscript{116}. Misclassification is described as non-differential when the
amount and type of measurement error occurs equally for all groups, e.g. if misclassification
of the outcome is independent of the exposure in a cohort study. In most cases, this will bias
the effect towards the null. In contrast, misclassification is described as differential if
misclassification of the outcome is related to the exposure. Then, bias is harder to predict
and the result might be biased either towards or away from the null\textsuperscript{116,117}. Internal validity
refers to the degree to which results are free from bias (selection bias, misclassification and
confounding), while external validity refers to the extent to which results from a study can
be generalized outside of the study population\textsuperscript{116}. The external validity of a study is
dependent upon the internal validity. In epidemiological studies, external validity often
focuses on the representativeness of the study sample.

To make causal inferences from observational data, we need to adequately address
collusion. A common practice is to consider a covariate to be a confounder if it is
associated with the exposure and outcome, and is not on the causal pathway between the
exposure and the disease\textsuperscript{121}. Effect modification (or interaction) occurs when the association
between the exposure and the outcome differs across levels of a third variable, the effect
modifier\textsuperscript{117}. Where effect modification refers to for whom an effect occurs, mediation refers
to how an effect occurs in an attempt to explain the effect of the exposure on the outcome
through a mediator (or intermediate variable)\textsuperscript{122}.

New statistical methods for causal inferences in observational studies have been
developed, such as marginal structural models\textsuperscript{123,124}, including counterfactual variables and
inverse probability weighting and causal diagrams (direct acyclic graphs)\textsuperscript{121}. Additionally,
we can make distinctions between the total, direct, and indirect effects of an exposure on an
outcome through mediation analysis\textsuperscript{122}. A direct acyclic graph (DAG) is a way to portray the
conceptual framework of our statistical modelling. It can be used to facilitate and assist
discussions with fellow researchers. A DAG gives a visual representation of causal
relationships believed to exist between the variables of interest; the exposure, outcome, and
potential confounders and mediators. It can assist in the selection of which measured
variables to adjust for in the statistical analysis to minimize bias\textsuperscript{121,125}. In a DAG, an arrow
connecting two variables indicates causation, while variables with no direct causal
association (by knowledge or predefined assumptions) are left unconnected\textsuperscript{125}. 
Mendelian randomisation is another approach that allows us to assess causality in observational data\textsuperscript{126}. In Mendelian randomisation, the causality of epidemiological relationships is investigated by using a genetic variant (instrumental variable) as a proxy for the exposure of interest. The random assortment of genetic variants at conception makes them independent of the reverse causation and confounding that bias the associations in conventional observational studies\textsuperscript{62}. Similar to in a randomized trial, the genetic variant divides the population into groups (variant allele present or absent), which are exchangeable by design\textsuperscript{127} (Figure 4a).

**Figure 4.** a) Mendelian randomisation is a natural equivalent of the classical randomized controlled trial (RCT). Random allocation of alleles at conception ensures that the genotype is generally unrelated to later environmental exposure, thus reducing confounding. b) Mendelian randomisation model: the causal role of an exposure X on the outcome Y. A genetic variant, G, is associated with the exposure but not with confounders, U.

Assumptions of Mendelian randomisation studies include the genetic variant being reliably associated with the exposure. Further, the genetic variant should be independent of all measured or unmeasured factors affecting the outcome, i.e. the genetic variant affects the outcome only through the exposure and not through any other biological pathways\textsuperscript{128} (Figure 4b). Provided that these assumptions hold, we may suggest a causal association between the risk factor and the outcome\textsuperscript{127}. Previous studies that have investigated modifiable risk factors and OA have mainly been based on observational data with inherent bias according to the design. One exception is a recent Mendelian randomisation study which used a genetic variant in the FTO gene to investigate associations between BMI and OA\textsuperscript{64}, as mentioned in chapter 1.2.1 (genetics).

This thesis used the infrastructure available for epidemiological research in Norway, by linking observational data from a large population-based cohort with data from the national
arthroplasty register. The use of secondary data allowed us to study risk factors with a sufficient time frame for the development and progression of OA, however using a less time and resource demanding design. Our aim was to explore associations and potential causal inferences using different epidemiological methods.
2. Aims of the thesis

2.1 General aim

The aim of this thesis was to investigate the association between lifestyle factors, such as, physical activity and smoking, and severe OA, defined as THR or TKR surgery, using observational and register data.

2.2 Specific aims

I. To investigate the association between leisure time physical activity and the risk of THR or TKR due to primary OA (paper I).

II. To estimate the total and indirect effect of smoking on the risk of THR or TKR using a mediation analysis (paper II).

III. To investigate the causal role of smoking on total joint replacement (TJR) using a Mendelian randomisation analysis (paper III).
3. Material and methods

3.1 Study design and population

The studies included in the current thesis are based on exposure data from a population-based cohort study with prospective detection of the outcome (THR/TKR) in a nationwide register.

3.1.1 The Nord-Trøndelag Health Study

The Nord-Trøndelag Health Study (HUNT) is the most comprehensive health survey performed in Norway. It is a unique database of personal and familial medical histories, collected in three cross-sectional surveys over three decades: 1984-86 (HUNT1)\textsuperscript{129}, 1995-97 (HUNT2)\textsuperscript{130} and 2006-08 (HUNT3)\textsuperscript{131}. All residents in the county of Nord-Trøndelag, 20 years of age or older, were invited to participate in the surveys. The response rate was 89.4\% in HUNT1 and 69.5\% in HUNT2 but declined to 54.1\% in HUNT3\textsuperscript{131}. In addition to the main survey on adults, all adolescents aged 13-19 years were invited to participate in the Young-HUNT Study (YHUNT1: 1995-97, YHUNT2: 2001-03, YHUNT3: 2006-08)\textsuperscript{132}. The HUNT study is reinforced and supplemented by cross-referencing of regional and national registries\textsuperscript{131}. The population of Nord-Trøndelag is fairly representative of the Norwegian population, although the income and education levels are slightly below the national average. The county has little emigration, 0.3\% per year, a homogenous population with less than 3\% non-Caucasian, and is mostly rural and sparsely populated\textsuperscript{130}.

The main objective in HUNT1 was to study the prevalence and quality of health care related to hypertension, diabetes, and tuberculosis, whereas HUNT2 was aimed at large public health issues like cardiovascular disease, diabetes, obstructive lung disease, osteoporosis and mental health\textsuperscript{130}. The scope of the HUNT study has expanded over time, and HUNT3 also included topics like cultural participation and religious affiliation and the establishment of a new biobank\textsuperscript{131}.

3.1.2 The Norwegian Arthroplasty Register

The Norwegian Arthroplasty Register (NAR) was founded in 1987 by the Norwegian Orthopaedic Association with the aim of detecting inferior implants, cements and techniques as early as possible. Data on THR has been collected by NAR since September 1987\textsuperscript{133}. The
register was expanded to include all artificial joint replacements, including TKR, in 1994\textsuperscript{134}. NAR is a nationwide register with a registration completeness above 95\% for primary THRs and TKRs\textsuperscript{135,136}.

### 3.2 Data collection

**In HUNT**

In HUNT2 and HUNT3, data were collected by questionnaires, interviews, a physical examination and blood samples. An invitation letter was sent by post together with the first questionnaire (Q1) and an information pamphlet. Participants were asked to bring the Q1 and written consent when attending the physical examination. A second questionnaire (Q2) was handed out at the examination, which participants were asked to complete at home and post to HUNT Research Center in a pre-paid envelope. Relevant questions from the HUNT2 and HUNT3 questionnaires are presented in Appendix I. Full version of the questionnaires are available at https://www.ntnu.no/web/hunt/skjema. Clinical measurements including height, weight, waist and hip circumferences, blood pressure, resting heart rate, and a non-fasting blood sample were performed at the examination\textsuperscript{130,131}. DNA was extracted from the blood samples of all HUNT2 participants and stored at the HUNT biobank.

**In NAR**

In NAR, information is collected by having the orthopaedic surgeon fill in a form in conjunction with the surgical procedure. The form contains, amongst other things, information on the indication for arthroplasty, type of joint replacement (hip/knee) and the implant used\textsuperscript{134}. We had data on joint replacements available from September 15 1987 until December 31 2013. The registration forms for THR and TKR are depicted in Appendix II.

**In this thesis**

For the purpose of this thesis, observational data from HUNT2 and HUNT3 where linked with prospective ascertainment of THRs and TKRs in NAR to create a longitudinal design in all three papers (Figure 5).
**Figure 5.** Time-line showing the longitudinal design and possible events during the study period. THR=total hip replacement, TKR=total knee replacement. *Participants were censored at date of THR/TKR due to indications other than primary OA, at date of death/emigration or at end of follow-up, whichever occurred first.

HUNT1 data was not included as the survey was completed before the creation of NAR. Thus, we had no outcome-data from or prior to the baseline years in HUNT1 (1984-86). Paper I included data from HUNT2 and HUNT3, whereas papers II and III included only data from HUNT2. The reason for including HUNT2 only was to retain a more homogeneous cohort with regard to follow-up time and data available from the questionnaires. Date of inclusion in HUNT2 (or HUNT3) was considered as the start of follow-up (date of participation) in all three studies (Figure 5). The number of participants that were included and excluded in the different papers is described in Table 1.

**Table 1. Overview of the study population in the three papers.**

<table>
<thead>
<tr>
<th></th>
<th>Included participants</th>
<th>Excluded participants</th>
<th>Study population (analysed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paper I</strong></td>
<td>n=64 978 from HUNT2 and n=9960 new participants from HUNT3, in total n=74 938</td>
<td>n=932 (THR/TKR before HUNT2 or HUNT3), n=176 (missing operation date), n=2 (emigrated/dead), n=6864 (missing LPA data)</td>
<td>n=66 964</td>
</tr>
<tr>
<td><strong>Paper II</strong></td>
<td>n=64 978 from HUNT2</td>
<td>n=833 (THR/TKR before HUNT2), n=172 (missing operation date), n=2579 (age≥80), n=5141 (self-reported OA), n=1063 (missing smoking status data), n=2 (emigrated)</td>
<td>n=55 188</td>
</tr>
<tr>
<td><strong>Paper III</strong></td>
<td>n=56 625 from HUNT2 (genotyped)</td>
<td>n=503 (THR/TKR before HUNT2), n=25 (missing operation date), n=3 (missing age at baseline), n=2 (emigrated/dead), n=347 (current smokers of pipes/cigars only)</td>
<td>n=55 745</td>
</tr>
</tbody>
</table>
3.3 Measurements

The different exposures and covariates from the three papers are shown in Table 2.

3.3.1 Main exposures

**Leisure time physical activity (paper I)**
Information about leisure time physical activity (LPA) was self-reported in the standard questionnaire (Q1 in HUNT2 and Q2 in HUNT3) as a response to the question: “How much of your leisure time have you been physically active in the last year?” Commute to and from work counted as leisure time. LPA during the last year was reported as light (no sweating or shortness of breath) and/or hard (sweating or short of breath) with four options of duration (0, <1, 1-2, ≥3 hours per week) in the questionnaires. LPA was further classified by us into inactive (no light or hard LPA), low (<3 hours of light, and no hard LPA), moderate (≥3 hours of light and/or <1 hour of hard LPA) and high LPA (≥1 hour of hard, regardless of any light LPA), as previously described[137]. Validation of the original LPA questions in HUNT showed that especially hard LPA correlated moderately with VO$_{2\text{max}}$ (Spearman r=0.46), metabolic equivalent (METs) values (r=0.31) and the International Physical Activity Questionnaire (IPAQ) (r=0.48). Hard LPA also showed moderate test-retest reliability (weighted κ=0.41)[138].

**Smoking behavior (papers II and III)**
Smoking status was categorised into never, former and current smokers based on answers to the question, “Do you smoke?”. Never smokers reported to have “Never smoked daily” and had no other smoking related information (papers II and III). Current and former smokers reported the number of cigarettes smoked daily (smoking quantity, paper III). Individuals, who reported being current smokers of pipes and cigars, but not cigarettes, were excluded from the analyses (paper III).

**Rs1051730 SNP (paper III)**
Genotyping of the C>T SNP rs1051730 in the CHRNA5-CHRNA3-CHRNB4 nicotinic acetylcholine receptor gene cluster on 15q25 was performed at the HUNT biobank using TaqMan genotyping assay (Applied Biosystems, Foster City, CA, USA). The rs1051730 SNP has demonstrated robust association with an increased smoking intensity among smokers[139,140]. The minor (T) allele of this genetic variant is associated with an average
increase in smoking quantity of one cigarette per day\textsuperscript{141}. Genotyping was performed on an Applied Biosystems 7900HT Fast real-Time PCR System using 10 ng of genomic DNA, as previously described\textsuperscript{103,142,143}. The call rate cut-off was set to 90\%. The genotyping success rate was 99.3\% and the quality score for each individual genotype was >90 (mean 99.6). The genotype was coded according to the number of minor T alleles (0=no T allele, 1=heterozygote for the T allele, 2=homozygote for the T allele). There was no evidence of departure from the Hardy-Weinberg equilibrium ($\chi^2$ test, $p=0.26$). The minor allele frequency (MAF) was in agreement with HapMap-CEU data (MAF=0.335 and 0.389, respectively).

Table 2. Overview of the included main exposures and covariates in the papers.

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
</tr>
</thead>
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<tr>
<td>Leisure time physical activity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td>No. of cigarettes smoked daily</td>
<td></td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Rs1051730 SNP</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Covariates</td>
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<td>Age</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sex</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
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<tr>
<td>Leisure time physical activity</td>
<td>(X)</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Workload</td>
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<tr>
<td>Education</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Alcohol consumption</td>
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<tr>
<td>Cardiovascular disease</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>(X)</td>
<td>(X)</td>
<td>(X)</td>
</tr>
</tbody>
</table>

(X)=not included in the final analysis.

3.3.2 Covariates

The potential risk factors described in sections 1.2.1 and 1.2.2, in addition to cardiovascular disease (CVD), diabetes and alcohol consumption, were considered to be covariates in the statistical analyses.

Age

Age refers to chronological age at the date of participation in HUNT2 or HUNT3. It was used as a continuous measure or for age groups (<45, 45-59, \geq60 years).
**BMI**

Height and weight were measured at the physical examination by trained personnel. BMI is weight in kilograms divided by height in meters squared (kg/m²).

**Education**

Participants were asked “What is the highest level of education you have achieved?” Education status was categorized according to the duration of education: <10 years (primary school), 10-12 years (high school/junior college) and ≥13 years (university/college)\(^\text{144}\). Education was included in the analysis as an indicator of socioeconomic status.

**Workload**

Participants were asked “How would you describe your work (including both paid and unpaid employment)?” with mutually exclusive response options, creating four categories: 1) mostly sedentary work (office or assembly work), 2) work that requires walking (teaching, shop assistant, light industrial work), 3) work that demands walking and lifting (postman, nurse, construction work) or 4) heavy physical work (heavy construction work, farming).

**Work status**

We used a binary measure to describe the current work status of the participants, which indicated whether they were employed (paid work, and/or, self-employed, full-time housework, student/military service) or unemployed (temporarily laid off, retired, receiving social benefits). Work status was included as a marker of socioeconomic status together with duration of education.

**CVD and diabetes**

Diabetes, myocardial infarction, angina pectoris and stroke/brain hemorrhage were defined by affirmative answers to the question “Do you have, or have you ever had any of the following diseases: diabetes and/or myocardial infarction and/or angina pectoris and/or stroke or brain hemorrhage?” CVD was defined as a composite of MI, angina or stroke\(^\text{145}\). It has been suggested that factors contributing to CVD play an important role in the outcome of severe hip or knee OA\(^\text{146}\), while diabetes mellitus has been associated with pain in persons
with erosive hand OA\textsuperscript{147}. Hip, hand and knee OA have also been associated with increased risk of mortality and CVD events\textsuperscript{148,149}.

**Alcohol consumption**

Alcohol consumption during the last two weeks was divided into four categories: 0, 1-4, 5-14 and >15 units\textsuperscript{106}. Alcohol consumption was included in the analysis, together with smoking, as a measure of lifestyle.

**3.3.3 Outcome**

The study end-point in all three papers was primary THR or TKR as marker of severe OA. The unique 11-digit identity numbers of Norwegian citizens enabled us to link individuals’ data in HUNT with the corresponding joint replacement data in the NAR. The registration completeness of primary THR and TKRs in NAR is high, >97\% (between 1999-2002)\textsuperscript{136} and >95\% (between 2008-2012)\textsuperscript{135}. The registration completeness is calculated by using the number of THRs or TKRs as the numerator and those reported to the Norwegian Patient Register as the denominator\textsuperscript{136}. We included only joint replacements due to primary OA, which is defined in NAR as a joint replacement caused by idiopathic OA. Participants with THR or TKR before baseline in HUNT2 (or HUNT3) were excluded. Similarly, we excluded participants whose primary operation dates were missing from NAR. Participants with THR or TKR as a result of previous injury (e.g. sequelae after ligament and menisci injuries) and joint replacements secondary to rheumatoid arthritis, sequelae after femoral neck fracture, congenital dysplasia, Perthes’ disease/epiphysiolsis, ankylosing spondylitis and osteonecrosis of the femoral head were censored. We counted persons and not joint replacements, thus participants with more than one joint replacement (hip/knee) were only counted once.

**3.4 Statistics**

The statistical analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL) (papers I and II), Stata version 13.0 and 14.1 (StataCorp LP, College Station, TX, USA) (papers I, II and III) and R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org) (paper II). Descriptive statistics were presented either as mean and standard deviation (SD) or frequency and percentage. P-values below 0.05
were considered statistically significant for all analyses. A summary of the study design, data source, outcome, and statistical methods is listed in Table 3.

**Table 3. Overview of the design, data source, outcome and statistical methods in the papers.**

<table>
<thead>
<tr>
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<th>Paper I</th>
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<td><strong>Design</strong></td>
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<td>Longitudinal</td>
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<td><strong>Data source</strong></td>
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<td>HUNT2</td>
<td>HUNT2</td>
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<td><strong>Outcome</strong></td>
<td>THR/TKR</td>
<td>THR/TKR</td>
<td>TJR</td>
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**Main analysis**

- Cox proportional hazards model
  - Time-scale: Years, Age
- Linear regression

**Additional analysis**

- Bootstrapping for 95% CIs
- Competing risk: X (CIF), X (SHR)

**Descriptive analysis**

- Chi square test: X, X
- ANOVA, analysis of variance: X
- Linear regression: X

*TJR=THR and TKR combined, CIF=cumulative incidence function, SHR=subhazard ratio.*

**Paper I**

The association between levels of LPA and THR or TKR was estimated using a Cox proportional hazards model with hazard ratios (HRs) and 95% confidence intervals (CIs). Additionally, crude incidence rates per 10 000 person-years were calculated according to age and sex. Follow-up was calculated from baseline in HUNT2 or HUNT3 until date of first THR or TKR due to primary OA, date of first joint replacement due to indications other than primary OA, date of death/emigration or end of follow-up (December 31, 2013), whichever came first. Potential confounders were selected a priori based on previous literature. For paper I, the potential confounders, as depicted in Table 2, were included in the initial multivariable regression analysis. However, as smoking, alcohol consumption, CVD and diabetes did not affect the magnitude or direction of the LPA estimate, nor were they statistically significant in the multivariable model, the final model included BMI, age (continuous) and workload in addition to LPA. The proportional hazards assumption was violated for the age variable. Thus, the analysis was stratified by age at baseline (<45, 45-59
and ≥60 years) in addition to sex. Test for trend across levels of LPA was calculated using the LPA variable as a pseudo-continuous variable in the regression model. We performed a sensitivity analysis to assess the robustness of our findings by excluding those with self-reported OA at baseline to address the possibility of reverse causation.

**Paper II**
The effect of smoking on THR and TKR was estimated using a regression-based mediation approach (the product-method), where the total effect of smoking was decomposed into a direct and an indirect effect. Regression parameters for the different effects were obtained in two stages. Firstly, through a linear regression of BMI on smoking (mediator model), and secondly, through a Cox proportional hazards regression model of THR/TKR conditioned on smoking and BMI (outcome model). Finally, all effects were presented on the HR scale with 95% CIs. We used a DAG to depict the associations we believed existed between smoking, THR/TKR, potential confounders and the mediator (Figure 6). We adjusted for all selected confounders (age, sex, work, education and PA) in both models.

Follow-up was calculated from the date of participation in HUNT2 to the date of THR or TKR due to primary OA, date of first THR or TKR for indications other than primary OA, date of death/emigration or the end of follow-up on December 31, 2013, whichever came first. Bootstrapping with 5000 iterations was used to calculate the 95% CIs. The indirect effect of smoking through BMI was calculated on the ln(HR) scale and expressed as a percentage (100*proportion mediated). We restricted the study sample to those aged <80 years at start of follow-up, without prevalent OA and with data on smoking status. Age was used as the time-scale. All models were stratified by sex due to interaction with smoking status. We observed no violation of the proportional hazards assumption.

We performed a sensitivity analysis on the full cohort due to high numbers of missing values in one of the covariates (LPA). Additionally, we assessed the robustness of our findings by including individuals with prevalent OA at baseline to address the potential of selection bias. The cumulative incidences of THR and TKR were calculated and depicted using the Fine and Grey approach, including mortality as the competing event to joint replacement.
Figure 6. Model of the potential mediating effect of body mass index (BMI) on the relationship between smoking status and hip or knee replacement (THR/TKR) in paper II.

Paper III

To provide evidence for whether the association between smoking and hip and knee OA is likely to be causal, we used an instrumental variable (rs1051730) in a Mendelian randomisation analysis. The instrumental variable worked as a proxy for smoking intensity. A Cox proportional hazards model was used in both the observational and in the Mendelian randomisation analysis. Follow-up began on the day of inclusion in HUNT2 and ended at the date of TJR (THR and TKR combined due to low statistical power) due to primary OA, date of TJR for indications other than primary OA, date of death/emigration, or the end of follow-up (December 31, 2013), whichever came first. All analyses were adjusted for age (as the time-scale) and sex.

We estimated the observational age- and sex-adjusted associations between self-reported current smoking quantity (no. of cigarettes per day, expressed as restricted cubic spline) and the risk of TJR. A multinomial logistic regression and a linear regression were used to estimate the association between the rs1051730 T alleles and smoking status and between rs1051730 T alleles and smoking quantity, respectively. In the Mendelian randomisation analysis, the association between the rs1051730 SNP and TJR was examined as an overall association as well as in the strata of never, former, and current smokers. If smoking is causally associated with TJR, we would expect the association to be strongest for current smokers and absent among never smokers. Stratifying on an observed exposure might introduce spurious associations between the SNP and confounders of the exposure-outcome association. We therefore repeated the analysis between the SNP and TJR in strata of never
smokers vs. ever smokers (current and former smokers combined). We assumed an additive genetic model, so risk estimates represent HRs per additional copy of the T allele.

To assess whether the association between the SNP and TJR was modified by smoking, we included interaction terms between the rs1051730 T alleles and smoking status (examining interaction across strata of never, former or current smoking) and between current vs. never and former smokers combined (examining interaction with current smoking). Models with and without the interaction terms were compared.

In the sensitivity analyses, we adjusted for BMI (expressed as restricted cubic spline) and CVD (binary measure) at baseline. Further, we accounted for competing risk by calculating subhazard ratios (SHRs) according to the Fine and Grey method in a separate analysis\textsuperscript{152}. The proportional hazards assumption was tested by introducing interaction with time (\textit{tvc}) to the regression model.

3.5 Ethical aspects

The HUNT Study is approved by the Data Inspectorate of Norway and by the Regional Committee for Medical Research Ethics (REK). All information from HUNT is treated according to the guidelines of the Data Inspectorate. Participation in the HUNT study is voluntary, and each participant must give written consent regarding the screening, subsequent control and follow-up, and to the use of data and blood samples for research purposes\textsuperscript{130}. They also have consented to linking their data to other registers (subject to approval of the Data Inspectorate/REK). Genetic research was not included in the original consent form in HUNT2. Therefore, an information campaign about genomic research was performed in 2002 and a re-consent was obtained to include genetic research. In total, 1.9\%, of the original participants chose to withdraw their consent\textsuperscript{130}. Participants in the HUNT studies were informed that they could withdraw from the study at any time. All information and biological samples would then be destroyed. When the data files from HUNT are prepared for research purposes, all names and personal ID numbers are removed. Consequently, we only had access to the de-identified data.

Health examinations might contribute to dilemmas associated with screening, such as risk focusing, false positive/negative identification and medicalization. The collection of extensive genotypic information for each participant also raises the concern of how to handle potential incidental findings. However, REK agreed with the HUNT management
group that the benefits and opportunities in the HUNT study far exceeded the potential disadvantages for some individual participants. Directly after collection of data in HUNT, the participants received a written letter with some of the test results from the screening: blood pressure, cholesterol, glucose and hypo-/hyperthyroidism. Participants were asked to contact their general practitioner if they had any concerns. Individual feedback about risk of disease (genetic or non-genetic) based on later analyses of blood samples for research purposes is not given to the participants. However, regular information about HUNT is provided to the participants through a yearly newsletter and through the HUNT website (http://www.ntnu.no/hunt).

NAR has concession from the Data Inspectorate of Norway and REK, and is based on written consent from the participants. Participants consented to their information being linked with other registers (subject to approval of the Data Inspectorate/REK). NAR collects data on diagnosis, indication for surgery and information concerning the surgical procedure of arthroplasty. Participants may also be contacted by NAR at a later time point for follow-up information. NAR compares new and old prosthesis and procedures to improve the treatment and management of patients. Information from the register is also used to investigate the prevalence, cause and prevention of the diseases and injuries that create the need for arthroplasty. Participation in NAR does not disadvantage the individual patient, or affect their treatment. Data is stored for an indefinite period of time and can be used in future research projects, assuming they are in compliance with current laws and regulations. Participants can withdraw from the study at any time and demand that all collected personal data be deleted. Just as with the data from HUNT, the data from NAR was anonymous to us when we received them.

The present PhD-project was approved by the REK: 2013/151/REK sør-øst C. An additional approval was obtained for the Mendelian randomisation study (paper III), 2014/226/REK midt.
4. Summary of results

4.1 Paper I

*Leisure time physical activity and the risk of hip or knee replacement due to primary osteoarthritis: a population-based cohort study (the HUNT Study).*

A total of 66,964 participants (mean age 46.8 years, SD 16.3) were included in the analyses. We identified 1,636 THRs and 1,016 TKRs due to primary OA during a follow-up of 17.0 years (median). Participants with high LPA were somewhat younger at baseline and at a younger age when they received a THR/TKR than those who were less active. High LPA was significantly associated with THR for women <45 years (HR 1.78, 95% CI 1.08-2.94) and for men aged 45-59 years at baseline (HR 1.53, 95% CI 1.10-2.13). A trend between LPA and the risk of THR was only found for women <45 years old at baseline, p for trend=0.02.

LPA was significantly associated with TKR for women aged 45-59 years at baseline (HR 1.45, 95% CI 1.03-2.04), whereas no association was found between LPA and TKR for men.

At baseline, 5,244 (8%) out of the 66,964 participants self-reported having OA (physician diagnosed). The sensitivity analysis, excluding those with OA, revealed that the positive associations (increased risk of THR associated with high LPA) remained and were somewhat stronger among women <45 years and men 45-59 years old. The same was true for the association between high LPA and TKR for women 45-59 years of age. No association between LPA and TKR was found among men.

This study showed a positive association between a high level of LPA and the risk of THR for men and women. Increased risk of TKR was associated with a high level of LPA among women only. No associations were observed for less vigorous levels of LPA.

4.2 Paper II

*The mediating effect of body mass index on the relationship between smoking and hip or knee replacement due to primary osteoarthritis. A population-based cohort study (the HUNT Study).*

In total, 55,188 participants were included in the analysis. We identified 1,322 THRs and 754 TKRs during 17.2 years (median) of follow-up. Women accounted for 62% of the joint replacements. A greater proportion of women (never, former and current smokers) were of
normal weight, while in comparison a larger proportion of men were overweight. A larger proportion men than women (former and current smokers) had prevalent CVD and diabetes at baseline.

For men, the total effect of current vs. never smoking revealed a reduced risk of THR (HR 0.59, 95% CI 0.46-0.76) and of TKR (HR 0.47, 95% CI 0.32-0.66). For women, current smoking was associated with increased the risk of THR (HR 1.34, 95% CI 1.11-1.60). For men, 6% and 7% of the risk reduction for THR and TKR, respectively, was mediated by BMI. For women, the proportions mediated were not meaningful to interpret (due to opposite directions of direct and indirect effects) or could not be calculated due to numbers close to zero (ln(HR_{total~effect})).

The sensitivity analysis, excluding the LPA variable due to high numbers of missing values, revealed no change in the total effect of smoking for men. However, for women, the total effect of current smoking revealed a higher risk of THR. Furthermore, including those with prevalent OA at baseline in the full model did not influence the total effect of smoking. We found higher cumulative incidence of all-cause mortality among current smokers, compared to former and never smokers, especially for men. The cumulative incidences of THR and TKR, after accounting for mortality, were small in terms of absolute numbers. However, among men the incidences of both THR and TKR were highest among never smokers.

In summary, we found an inverse association between smoking and THR or TKR for men. In contrast, smoking increased risk of THR among women. For men, most of the effect of smoking on THR or TKR remained unexplained by BMI.

4.3 Paper III

The causal role of smoking on the risk of hip or knee replacement due to primary osteoarthritis: a Mendelian randomisation analysis of the HUNT Study.

In total, 54 898 participants were genotyped and had data on smoking status. This group included 16 705 (30.4%) current smokers, 15 350 (28.0%) former smokers and 22 843 (41.6%) never smokers. The number of T|Rs was 2601 (4.7%) during 17.2 years (median) of follow-up. By increasing number of rs1051730 T alleles, participants tended to be slightly younger and had lower BMIs. Among current smokers, the T allele was associated with a higher number of cigarettes smoked per day.
The observational analysis indicated an inverse association between self-reported number of cigarettes smoked daily and TJR (HR 0.97, 95% CI 0.97-0.98). The strong relationship between the rs1051730 SNP and smoking intensity (no. of cigarettes per day) that has been confirmed in previous GWA studies was substantiated in the current sample (0.66, 95% CI 0.54-0.79). In the Mendelian randomisation analysis, the rs1051730 T alleles were associated with reduced risk of TJR among current smokers (HR 0.84, 95% CI 0.76-0.98). There was no evidence of association among former or never smokers. The lack of association for non-smokers coincided with one of the key assumptions of the Mendelian randomisation: that the variant only operates on the outcome through its effect on smoking. There was an indication of a greater effect per T allele among current smokers when compared to never and former smokers combined (p=0.05). In the broader strata of ever vs. never smokers, rs1051730 T alleles were associated with reduced risk of TJR among ever smokers (HR 0.91, 95% CI 0.84-0.99). We performed additional analyses to assess the robustness of our findings. The results from these sensitivity analyses supported an inverse association between rs1051730 T alleles and TJR among current smokers, independent of BMI, cardiovascular comorbidity and competing risk of all-cause mortality.

Our findings suggest that smoking is causally associated with a reduced risk of TJR. However, additional studies are needed to further elucidate the underlying mechanisms of this causal association.
5. Discussion

5.1 Methodological considerations

The main strengths of the three studies included in this thesis are the large sample size of the population-based cohort, the length of follow-up, and the longitudinal study design. The HUNT study includes comprehensive health information, which was used to obtain the main exposures and covariates. We detected THRs and TKRs prospectively through linkage with the nationwide register, which ensured nearly complete data on joint replacements. The progression of study designs and statistical methods across the three papers introduce different levels of bias and assumptions that need to be addressed in the interpretation of the results.

5.1.1 Study design and statistical methods

In all three papers, the outcome-data available from NAR was from 1987 for THRs and from 1994 for TKRs. This may introduce bias, especially relevant for older participants who might have received a joint replacement before NAR was created. It could potentially create a problem of misclassification of outcome, resulting in TJR rates too low among the oldest age group, and reverse causation. In paper III, because of the Mendelian randomisation design, reversed causation is not a problem. An additional risk of reversed causation could be related to OA already present at baseline in HUNT, where the level of exposure might be affected by the disease state. The cohort study requires participants to be free from the outcome of interest at the start of the study. As the outcome of interest was TJR, one can argue that participants should also have been free from OA at baseline. This depends on whether we consider TJR predominately to be a proxy for the disease OA, or merely a proxy for the progression to severe OA. In paper I, we addressed this with a separate sensitivity analysis in which we excluded those with self-reported OA at baseline. For the same reason, in paper II we restricted the main analysis to those without self-reported OA and age < 80 years at baseline in HUNT. This also served to create a more homogeneous population-at-risk at the start of follow-up which we used to investigate both incident OA and TJR. In papers I and III, where those with OA at baseline were not excluded from the main analysis, we might have included both incident and prevalent OA cases. Still, only incident cases of TJR were included in all three papers.
The diagnosis of OA was self-reported in the questionnaire, and, although it was required to be physician-diagnosed, it was not joint-specific. Thus, one could also question the validity of the OA diagnosis and thereby the significance of excluding cases with OA at baseline or not, with regard to selection bias. Excluding those with OA at baseline would eliminate those who are potentially the most susceptible to the risk factors from the analysis. Whereas stratifying by presence or absence of OA in the analysis may induce bias by stratifying on a variable that is on the causal pathway between the risk factor and outcome (e.g. TJR)\textsuperscript{153}.

To make causal inferences from observational data, we need to adequately address confounding\textsuperscript{121}. Our approach for selecting confounders in papers I and II was based on a priori assumptions combined with a statistically-driven approach where we tested the effect of the potential confounders in the regression model to decide which confounders to include in the statistical analyses. **Paper I** had the design of a conventional observational cohort study with an inherent high risk of confounding. In paper I, we used a regular multivariable regression model with adjustments and stratification to control for confounding. There was a high proportion of missing LPA data due to non-response to the LPA questions in the questionnaire. We did not use multiple imputation techniques, thus our results are based on complete-case analyses potentially, introducing selection bias. Multiple testing might have given significant results that were actually due to chance and caused by stratification on both sex and age groups.

In **paper II**, we decomposed the total effect into direct and indirect effects in a regression-based mediation analysis\textsuperscript{150}, with the purpose of investigating a mechanism by which smoking may affect the risk of THR or TKR. We used a DAG to depict the potential causal relationship between smoking and THR or TKR, including BMI as a mediator. However, in order for effects to have a causal interpretation, fairly strong assumptions of no unmeasured confounding have to be made, sometimes referred to as exchangeability assumptions\textsuperscript{150,154}. The assumption of no unmeasured confounding also requires an assumption of temporal ordering for the associations to reflect causal effects\textsuperscript{155}. In observational studies, time sequence of exposure, mediators, and outcome may not be very clear\textsuperscript{156}. In paper II, smoking was measured prior to THR and TKR (outcome), whereas data on smoking and BMI (mediator) were collected at baseline in HUNT. We may assume a conceptual temporal ordering where smoking status reflects past and present exposure and BMI reflects present body weight and height. It is also plausible to assume the direction of the association from smoking to BMI, based on knowledge from previous Mendelian randomisation studies\textsuperscript{104,157}. 

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We can be more confident in a result if different methods lead to the same result, i.e. the understanding of causal effects is generally advanced by triangulation from multiple alternative sources\textsuperscript{128}. Therefore, in paper III, we used a Mendelian randomisation approach to further investigate the potential causal relationship between smoking and TJR, as this design overcomes many of the limitations of a conventional observational study. However, again this is only true if certain assumptions are made. First, the genetic variant (rs1051730) should be reliably associated with the exposure\textsuperscript{158}. The rs1051730 SNP has demonstrated robust association with smoking intensity among smokers with an additive effect per T allele\textsuperscript{139,140}. Second, the genetic variant should be independent of other factors which affect the outcome (i.e. no measured or unmeasured confounding)\textsuperscript{158}. There is good evidence that the rs1051730 SNP, unlike self-reported smoking intensity, does not associate with confounding factors like socioeconomic status and education level\textsuperscript{10,3,157}. In addition, genotype-phenotype associations are not biased by reversed causation, as the outcome cannot alter the genotype that an individual is born with\textsuperscript{141,157}. Third, the genetic variant should only be associated with the outcome through the exposure of interest, i.e. no pleiotropy (that the genetic variant affects more than one exposure)\textsuperscript{158}. As the rs1051730 phenotype is smoking intensity, we would not expect to find any association between the SNP and TJR among never smokers. This corresponded with our findings. Thus, the never smoking group can be used to test potential bias due to pleiotropy\textsuperscript{62}.

We primarily used Cox proportional hazards method to obtain estimates of the association between exposure and outcome, adjusting for potential confounders. In papers II and III, age was used as the time-scale in the Cox regression model, in which individuals enter the analysis at their baseline age and exit at their event or censoring age\textsuperscript{153}. This was done 1) because of the non-proportional hazards of age in paper I, and 2) because time since entry into the study might not be of direct biological relevance. By using age as the time-scale, we expect the hazards to change more as a function of age than of time in the study. For example, the hazards of two persons being 50 and 70 years who have both been in the study for 10 years are expected to differ more than the hazards of two persons of 55 years, with 5 and 15 years in the study\textsuperscript{153}.

An important assumption of Cox regression is to have non-informative censoring. In our study, this means that the mechanisms linked to the censoring of individuals should not be related to the probability of receiving a THR or TKR. In papers II and III, where smoking was the main exposure, all-cause mortality was considered to represent a competing risk due to
higher mortality among smokers than non-smokers. Consequently, competing risk was addressed in the statistical analysis.

5.1.2 Representativeness of the HUNT cohort

The HUNT surveys cover participants, with a wide range of ages, within a geographical area, and are thus, in many ways, representative of the general Norwegian population. The income and education levels were slightly lower than in Norway as a whole during the 1990s\textsuperscript{130}. The participation rate in HUNT2 was high (69.5\%), compared to other Norwegian cohort studies\textsuperscript{159-161}. The Tromsø Study reported an even higher response rate in their first surveys (>75\%), although it declined in the most recent survey in 2007-08 (66\%)\textsuperscript{162}. In general, the participation rate in epidemiological studies has been declining in recent years\textsuperscript{163}. There is a potential problem created by individuals “selecting” themselves to participate in the study. However, non-participation will not bias a prospective cohort study in which the outcome of interest has not yet occurred. Substantial non-participation could be a threat to the generalizability of findings (external validity), but not to the internal validity of the study\textsuperscript{116}. We did not select participants based on either exposure or outcome, although bias might have occurred as a result of our dependency on complete data of exposure (and covariates) in the regression analyses. Selection bias may also occur in prospective cohort studies due to loss to follow-up. Losses to follow-up can introduce bias if there are systematic differences between people who are lost to follow-up and those who have complete follow-up\textsuperscript{116}.

Participation in HUNT2 was age dependent, with the highest participation rate in both genders aged 60-69 and the lowest among men 20-29 years old\textsuperscript{130}. In the non-responder study after HUNT2 (n=685 subjects), the main reasons for not attending were lack of time or moving away (22-44 years), being busy at work or forgetting (45-69 years) or medical issues (>70 years)\textsuperscript{164}. Further, higher prevalence of smoking was found in the non-participating group. Consequently, our findings may have more limited generalizability among the young and those with a more complex health status.

In HUNT3, 54\% of the invited inhabitants responded to the survey. Non-participants had lower socio-economic status, higher mortality and higher prevalence of chronic diseases such as cardiovascular disease, diabetes mellitus, fibromyalgia and OA. The reasons for non-
participation were much the same as in HUNT\textsuperscript{2}\textsuperscript{165}. Only a small part of the total study sample in paper I (13\%) was included from HUNT3.

Through sensitivity analysis (paper I), and by restriction of the study sample (paper II), we excluded those with self-reported OA at baseline. No study has been performed to examine the validity of the self-reported definition of OA in HUNT. However, self-report of medically-diagnosed hip and knee OA correctly identified most of the cases with and without clinical OA (specificity >94\%) when compared to a gold-standard, the ACR-criteria\textsuperscript{28}. The self-reported OA diagnosis in HUNT was required to be physician diagnosed, however there was no option for reporting which joint was affected. Furthermore, it is possible that not all participants with OA reported having the disease. Thus, there is uncertainty regarding the validity of prevalent OA at baseline and conditioning on non-prevalent OA may thereby introduce selection bias. As a result, we did not exclude those with self-reported OA at baseline in paper III.

The exposures in HUNT were measured prior to the outcome detected in NAR, thus recall bias should not be a problem in our papers. However, both LPA and smoking behavior are measurements that are prone to misclassification/misreporting.

5.1.3 Measurements

We included both self-reported and clinical exposure data, along with register-based outcome data in this thesis.

Main exposures

LPA was the main exposure in paper I. The LPA questions in HUNT have been validated in young men (n=108)\textsuperscript{138}. Hard LPA, referring to vigorous activity (being out of breath or sweating) showed moderate correlation with objective measures like VO\textsubscript{2max} and the metabolic equivalent (METs) values. Thus, hard LPA seems to be a valid measure of vigorous LPA, whereas the light LPA question correlated poorly with these objective measures of physical activity\textsuperscript{138}. In our study, those who performed hard LPA were included in either the moderate (<1 hour of hard LPA) or the high LPA group (≥1 hour of hard LPA).

Self-reported LPA is prone to misclassification; in comparison with more objective measures of physical activity, participants may categorize themselves into a more desirable/higher LPA level than is accurate\textsuperscript{166}. However, due to the design, any misclassification would most
likely be non-differential as the LPA question was asked in HUNT prior to, and unrelated to, the detection of the outcome. Thus, estimates of the association between LPA and THR/TKR will generally underestimate the true effect\textsuperscript{116}.

We had no repeated measure of LPA during follow-up. Data on changes in LPA could have both strengthened and attenuated the observed associations. In a sub-sample of the HUNT cohort (n=1843), self-reported LPA at HUNT1 was positively associated with VO2 peak at follow-up 23 years later in HUNT3. Thus, men and women who reported a high level of LPA at baseline had higher VO2 peak at follow-up, compared with men and women who were inactive at baseline\textsuperscript{167}. However, as we had no follow-up data, we can only speculate to what degree the participants in HUNT2 maintained their LPA habits. Moreover, the questions regarding LPA did not comprise the type of activity that had been performed (aerobic/strength). Thus, we were unable to attribute the related risk to any specific activity. This limits the comprehensiveness of a possible mechanistic explanation that we were able to draw from the results in paper I.

**Self-reported smoking status was the main exposure in paper II.** Because of the complexity of the mediation analysis we included only smoking status as exposure in the analysis. Smoking status assessed via self-report can lead to imprecision and bias. It is possible that smoking intensity was underreported as it is seen as socially undesirable and the associated health hazards are well known. Further, the categories of smoking status may include quite heterogeneous groups in terms of smoking quantity, years smoked or years since cessation. All of which might weakened the association between smoking and THR/TKR. We had no interval information on smoking exposure between baseline and follow-up, which means that some of the results could have occurred by chance and the full mechanisms of THR/TKR cannot be delineated.

The self-reported data on smoking behavior becomes less of a problem once a genetic variant has been identified, as the variant itself is then a proxy for smoking exposure\textsuperscript{168}.

**Allele T on the SNP rs1051730 was the main exposure in paper III.** Rs1051730 is the strongest genetic contributor to smoking behavior identified in genome-wide association studies to date\textsuperscript{139,140,169}. The effect of the rs1051730 variant has been shown to be similar for both genders and be robust to population-wide changes in smoking habits over time\textsuperscript{140}. Carriers of the variant smoke more than non-carriers and are less likely to quit smoking (i.e. have higher rates of nicotine dependence), however the variant does not seem to influence
smoking initiation\textsuperscript{140}, although suggested\textsuperscript{142}. It is, thus, not currently clear to what extent the genotype influences smoking initiation\textsuperscript{170}.

Rs1051730 is an instrument for lifetime cumulated tobacco exposure\textsuperscript{171} and, thus, a better measure of smoking quantity than a one-time measure of cigarettes smoked. This instrument has been shown to explain more of the variance (4\%) in serum cotinine, a biomarker of tobacco exposure, than self-reported numbers of cigarettes per day (1\%)\textsuperscript{172}. Although, rs1051730 is currently the best proxy of smoking quantity it only explains a small portion of the estimated 50\% of total variance in smoking behavior that is due to genetic factors\textsuperscript{141}. Other signals for smoking behavior have been identified\textsuperscript{169} and may be included in future Mendelian randomisation studies to help explain the genetic contribution more thoroughly.

\textit{Covariates} \\
Age and sex were included as potential confounders in all three papers. BMI was measured at the physical examination at baseline in HUNT2 or HUNT3, thus avoiding bias associated with self-reported BMI\textsuperscript{173}. Education, workload, work status, CVD and diabetes were all self-reported in the HUNT questionnaire. We lacked educational status for the HUNT3 participants (not asked for in the HUNT3 questionnaire). Therefore, we did not include education as a potential confounder in the analysis in paper I. We tested the effect of education (on the HUNT2 cohort) in a sub-analysis; however it did not change the results.

Diabetes and CVD were crude indicators (yes/no) of prevalent disease at baseline. It was not possible to make a distinction between type 1 and type 2 diabetes (not asked for in the questionnaire). Both CVD and diabetes represent a degree of comorbidity which could confound or mediate the indication for TJR surgery. Alcohol consumption was included together with smoking in paper I to represent potential confounding by lifestyle.

The question about workload included four response alternatives of physical activities at work, representing increasingly mechanical joint-stress. We used the workload variable in paper I to estimate the effect of LPA, independent of physical activity at work. However, a large number of participants had missing workload data. Thus, in paper II we included work status (employed/unemployed) as an indicator of socioeconomic status instead, despite lacking the adjustment for occupational physical activity in the analysis.
Unfortunately, we had no information about previous injury at baseline. This is a major limitation, particularly in paper I and for knee OA, and may have biased the association between LPA and TKR. We had information about previous injuries at the time of arthroplasty in the register. Accordingly, THR or TKRs secondary to injury were censored (not counted as an event).

**Outcome**

We used THR or TKR as the outcome in all three papers, although they were combined as TJR in paper III due to low statistical power. We were interested in THRs and TKRs due to primary OA. In the register (NAR), the information about the indication for joint replacement is dependent on the operating surgeon who fills in a form in conjunction with the surgical procedure. Data from NAR showed that from 1995 to 2011, 73% of the THRs in Norway were due to primary hip OA\(^1\)\(^7\)\(^4\), while 87% of the TKRs between 2001 and 2009 were due to primary knee OA\(^1\)\(^7\)\(^5\). There has been no validation study of the diagnosis of primary OA in NAR. However, the primary OA diagnosis was confirmed in 66 of 78 cases with THR in the Danish Hip Arthroplasty Registry, giving a positive predictive value of 85%\(^1\)\(^7\)\(^6\). These results are probably comparable to what we can expect to find in NAR. There are no results available for the validation of the diagnosis of primary OA in those who received TKRs.

As the majority of previous studies on LPA and smoking have been performed with knee OA as the main outcome, we decided to investigate THR and TKR separately in papers I and II. Additionally, we wanted to be able to compare our results with those of studies that have investigated both THR and TKR in the same cohort\(^\text{88,89,98}\). If the aetiology and indications for THR and TKR differ, the most suitable solution is to investigate hips and knees in the same cohort to minimize bias due to heterogeneity of the study samples. Additionally, the incidence of THR is reported to be higher for women than for men in all the Nordic countries, with the highest gender-specific incidence rate in Norway\(^5\)\(^4\).

Joint replacement is a well-known marker of severe OA; it is performed at a stage in the disease when it has considerable impact on the quality of life for the individual patient. However, there exist no gold standard criteria for when to perform THR or TKR\(^4\)\(^3\). Indications for joint replacement depend on factors related not only to the disease severity itself, but also willingness and eligibility of the patient, the orthopedic surgeon's preferences, and the capacity of health care\(^4\)\(^4\),\(^4\)\(^5\). Consequently, there are confounders
associated with joint replacement that is not, at least in the same sense, associated with the development and progression of OA. Therefore, the associations we have found may represent both an increased/decreased risk of development and progression of OA as well as an increased/decreased likelihood of receiving THR or TKR among those with OA. The entire HUNT cohort is from the same geographical region, with theoretically similar access to health care services and similarities in demographics, and prevalence of disease, which may decrease potential confounding from these non-disease related factors. However, by using TJR as an outcome, we might have introduced a selection bias with those without comorbidities and with a good or acceptable general health status being the ones considered for surgery\textsuperscript{177}. Thus, the incidence of joint replacements may underrepresent the total burden of OA in our cohort. Although, the detection of TJRs was nearly complete in the register and, thus, in that sense, a trustworthy end-point.

5.2 Main results

5.2.1 Leisure time physical activity and the risk of hip or knee replacement

We found that a high level of LPA was associated with increased risk of THR due to primary OA (paper I). However, for TKR, high LPA was associated with increased risk among women only. Our results agree with the findings of an Australian population-based study where increased risk of TKR was associated with a high/vigorous level of LPA\textsuperscript{88}, but contrast with the inverse association found between high LPA and THR in a Swedish population-based study\textsuperscript{89}. Our findings were evident for those under 60 years of age at baseline. Similar results have been reported regarding BMI: that weight gain at a younger age (age <40 years) increases the risk of THR and TKR more than weight gain at an older age\textsuperscript{76-78}. The cumulative effect of excess bodyweight over several decades may offer a possible explanation for the increased risk of OA linked to high BMI at a young age. This may also act as a potential explanation for high LPA as a risk factor for those middle-aged or younger, but not for those at an older age. In line with this, Cheng et al.\textsuperscript{85} found that high LPA was positively associated with self-reported physician-diagnosed hip and knee OA among younger men (age <50 at baseline). Further, the risk of hip and knee OA is found to increase with cumulative years of heavy workload in both men and women\textsuperscript{113}, which may lend support to the “wear-and-tear” theory of a mechanical load effect in the process of developing OA.
We had information about the weekly average intensity and duration of LPA for the participants in HUNT, but unfortunately not about the frequency or type of activity. Likewise, previous studies have offered limited descriptions of risk related to type of activity when discussing LPA. Our data included a combination of duration and intensity of LPA. If we compare the distribution of the level of LPA in our study with the national recommendations for physical activity\textsuperscript{178}, it would only be possible for those engaging in high LPA (30%) to meet the current recommendations of 150 minutes of moderate (defined as increased breathing frequency, e.g. fast walking), or 75 minutes of vigorous activity (e.g. running or jogging) per week. This corresponds with the national results in which nearly 70% of the Norwegian adult population is classified as inactive\textsuperscript{178}. However, in an American population-based cohort, meeting the physical activity guidelines (≥150 min/week) was not associated with incident radiographic or symptomatic and radiographic knee OA\textsuperscript{87}. This adverse effect on joint space narrowing was also found for those with the highest level of LPA (≥300 min/week) in the American study, which corroborates findings of negative knee OA outcomes associated with high levels of LPA. Our definition of high LPA included at least 1 hour/week of high intensity activity; however we did not distinguish between those who participated in 1, 2, or ≥3 hours/week of high intensity LPA. Thus, we could not confirm whether the increased risk was apparent for any level of high intensity activity, or only for those who were the most active. As a result we could not specify the type of LPA or precise dose of LPA that would advocate for or against later hip or knee OA. However, for the majority of participants in our study, engaging in LPA (or lack thereof) did not seem to increase the risk of hip or knee OA or THR/TKR.

Younger age may, as proposed by Cheng et al.\textsuperscript{85}, be a proxy for participation in more vigorous activities and thereby increased risk of injury. They found an interaction between age and LPA. However, in a study of the same cohort, this age-interaction disappeared after adjustments for previous injury\textsuperscript{179}. Further, there was no longer an association between LPA and self-reported hip and knee OA. However, it should be noted that, in this more recent study, the LPA definition used by Cheng and colleagues\textsuperscript{85} was extended to include a joint stress physical activity score based on the frequency, intensity and duration of LPA\textsuperscript{179}. We found no evidence of statistical interaction between age and LPA on the multiplicative scale; however the non-proportional hazards of age indicated that the risk associated with LPA differed depending on age. This was further observed in the age-stratified analysis. We had no information on previous injuries, thus we could not control for this confounder. This has been a limitation in previous large cohort studies investigating the association between LPA
and THR/TKR as well\textsuperscript{73,88,89}. We censored those who received joint replacements secondary to previous meniscal, or ligamentous injury (recorded in NAR), although this might not have completely removed bias from injury prior to baseline. As a result; we may have over- or underestimated the association between LPA and joint replacement. However, in a cohort study of long-distance skiers in Sweden, where participation in multiple, fast ski races was associated with increased risk of THR and TKR\textsuperscript{91}, adjusting for injuries did not substantially change the results. Further, it is important to recognize that injuries occurring after the start of follow-up could be considered mediators in the total effect of LPA on OA or joint replacement, and thus should not be adjusted for.

We found a positive association between LPA and THR, which has not been found in previous studies on the general population, but has been demonstrated in studies related to sport participation and intensive exercise\textsuperscript{69,91}. The link between a high level of physical activity and the risk of hip OA or THR has also been consistently demonstrated in studies investigating occupational workload\textsuperscript{109,110,113,114}. We accounted for physical workload (walking, lifting, construction work, and farming) in our analysis. Therefore, our results represent the effect of LPA independent of occupational activities. The two population-based studies which are most comparable with ours\textsuperscript{88,89}, could not sufficiently adjust for occupational physical activity which may explain the different results across the studies.

An important limitation in our study is that the exposure and covariates were measured at one time point only, at baseline in HUNT. However, exposure to LPA that is important to hip or knee OA etiology may have occurred prior to baseline or during follow-up. Our findings indicated that high LPA increases the risk of THR in both genders and TKR for women only. However as mentioned before, these results may be affected by a healthy selection bias where those who are fit for surgery are the most eligible and willing to undergo THR/TKR in order to maintain an active lifestyle. Active individuals may assert the necessity for, and undergo TJR surgery, at a younger age to retain an active lifestyle both at work and in leisure time. Information in NAR about the ASA (American Society of Anesthesiologists) class (1-5) revealed that about 25% of those receiving a THR or TKR due to primary OA had ASA-class 1 (healthy patient), 50% had ASA-class 2 (mild systemic disease) and approximately 25% had ASA-class 3 (severe systemic disease) at time of surgery. The high number of missing values for LPA may have contributed to this selection bias, and thus limited the generalizability of our results. Multiple testing may have given false positive associations. However, we consistently found significant associations for high LPA only, both
in the main analysis and the sensitivity analysis. We believe we have addressed confounding adequately in paper I; however, as in all observational studies, there might be unmeasured confounding or bias from crude or imprecise measurements of the confounders.

To better understand the relationship between LPA and the risk of THR or TKR, prospective studies are needed with an emphasis on a more detailed description of LPA that incorporates not only the type of activity, but also the mechanical joint-load. We also need more studies to investigate the association between LPA and hip OA (radiographic, symptomatic, arthroplasty). Furthermore, repeated measures of LPA are necessary to assess changes over time in order to create a more accurate picture of the impact of LPA on the risk of THR and TKR.

5.2.2 Total and indirect effects of smoking on hip or knee replacement

In paper II, we found a protective effect of smoking on THR and TKR for men. The term ‘effect’ is not used to claim causality, but rather to describe a potential direction of the associations. This result was in line with previous observational studies, with the majority suggesting a protective effect of smoking on hip and knee OA94-97,98,108,180,181. Further, our aim was to decompose the total effect to elucidate potential mechanisms for the observed association. One plausible underlying mechanism of the protective effect of smoking on OA is its indirect effect via BMI. We expected a substantial part of the protective effect of smoking to be mediated through BMI, due to the fact that smoking is known to have an effect on BMI and that BMI has been shown to be a strong risk factor for OA and TJR. However, instead we found that most of the effect of smoking on THR and TKR remained unexplained by BMI. Most consistently, the proportion mediated was related to current vs. never smoking for men, where 6% and 7% of the protective effect of smoking on THR and TKR, respectively, was explained by BMI. The explanation for the modest indirect effect of smoking may be that the protective effect is mainly the result of smoking itself (direct effect), or that the effect is mediated through causal pathways (by other mediators) not known or addressed in our study.

Further, smoking may have a protective effect on OA through nicotine sensitive acetylcholine receptors. The net effect of stimulation of these receptors is anti-inflammatory105. Additionally, it has been suggested that nicotine has a direct effect on the upregulation of glycosaminoglycan and collagen synthetic activity of articular chondrocytes99,100, although this has not been demonstrated conclusively101,102. However,
acetylcholine receptors on neural cells may, when excited, induce musculoskeletal pain\textsuperscript{107}. In line with this, another Norwegian study using the HUNT cohort observed that daily smoking represented a 20\% increase in risk of musculoskeletal complaints (pain and/or stiffness). Although, this was only evident in those <50 years of age\textsuperscript{106}. In our analysis, pain was considered a mediator in the smoking-THR/TKR relationship and was not adjusted for. Pain is an important clinical feature of OA and therefore an important component in the course of the disease. A recent study from the MOST cohort (Multicenter Osteoarthritis Study) found that pressure pain threshold and temporal summation were associated with knee-OA related pain as well as greater knee pain severity\textsuperscript{182}. However, they could not demonstrate an association between duration or severity of radiographic knee OA with these measures. They conclude that lack of association with disease severity might suggest that at least some sensitization and pain sensitivity may be a trait rather than a state of OA, i.e. that some individuals might be predisposed to sensitization irrespective of OA\textsuperscript{182}. Moreover, smoking may protect against OA through a sedentary lifestyle which exerts less stress on weight bearing joints thus reducing cartilage wear and tear\textsuperscript{183}. However, we adjusted for LPA, and therefore a sedentary lifestyle, in our analysis.

In contrast to previous findings, we found that current smoking increased the risk of THR for women. Although other studies have also shown smoking to have stronger effect on men than women\textsuperscript{97,98}, the direction of the association has been similar. Inherent biological and hormonal differences may be plausible mechanisms for the gender difference in the effects of smoking. The increase in incidence of OA among women after menopause has led to suggestions of hormonal influence on articular cartilage, e.g. through estrogen. Estrogen receptors is found in bone and cartilage cells, which may prevent bone loss and increase bone and cartilage volume, and thereby potentially promote the development of OA\textsuperscript{184,185}. Smoking has been suggested to have an anti-estrogenic effect. Further, smokers have lower BMI and less adipose tissue, which is the main determinant of estrogen concentration in postmenopausal women\textsuperscript{186}. Thus, with lower BMI and lower estrogen concentrations one might expect that the risk of OA would decrease in postmenopausal women who smoke. However, estrogen replacement therapy may increase bone metabolism and thereby the mechanical stress on cartilage during joint loading, which, in turn, may increase the susceptibility of OA in women after menopause\textsuperscript{187}, although the opposite effect has also been shown\textsuperscript{184}. In summary, although estrogen may have a modulating effect on cartilage, clinical and epidemiological studies have not completely verified this theory and the mechanisms remain unclear\textsuperscript{15,47,188}. 
Moreover, women may be more likely to self-report pain and OA symptoms and the use of non-radiographic methods tend to exaggerate the sex differences in OA prevalence due to reporting bias\textsuperscript{53}. Thus, the positive association between smoking and THR for women may be influenced by non-biological factors such as health seeking behavior, reporting of pain and symptoms, and willingness to undergo surgery, all of which may increase the difference in risk between genders.

Smoking is also associated with increased risk of comorbidity, which may influence the eligibility for surgery. We know that the men in our cohort had a higher burden of smoking (in terms of pack-years) than the women. Comorbidity and mortality associated with higher smoking quantity has shown to contribute more to the burden of disease in men than in women\textsuperscript{189,190}. This is in line with the findings in our cohort. Men were heavier, had more comorbidities and higher mortality. In comparison, a higher proportion of the women who smoked were of normal weight, had less comorbidity and lower mortality. Thus, comorbidity and mortality might to a certain extent explain some of the gender differences in the risk of THR or TKR in our study. Although, including CVD and diabetes in the initial analysis, as measures of comorbidity, did not affect the results. We addressed the competing risk of mortality when we presented the cumulative incidences of THR and TKR. However, we did not include competing risk in the mediation analysis as our intention was to elucidate and estimate a potential mechanism of the smoking-THR/TKR relationship, regardless of other events. For such a connection, the normally derived HR has been suggested as an appropriate and valid measure of risk when the etiology of disease is of interest\textsuperscript{191}.

Important questions still remain concerning the mechanisms behind a possible protective effect of smoking on THR and TKR. Future studies need to disentangle the mediating and direct pathways related to the protective effect of smoking. In addition, futures studies should investigate this association according to gender in order to replicate or reject the gender-effect we discovered in this study.

Using our cross-sectional baseline data, the associations observed in the mediation analysis might not reflect actual causal effects due to the uncertainty of the temporal ordering of the exposure and the mediator, and bias from unmeasured confounders. Thus, inferences about causality cannot be made using this study alone. To further study the potential causal effect of smoking on THR and TKR, we proceeded with another epidemiological approach.
5.2.3 The causal role of smoking on hip or knee replacement

While the intention of paper II was to elucidate a potential mechanism behind the protective effect of smoking on OA, the intention of paper III was to study whether this observed association in previous studies, and in paper II, might be causal.

In line with this, we used a Mendelian randomisation analysis. We replicated the results from paper II and supported the findings from previous epidemiological studies. We identified a difference in the effect of smoking on THR and TKR between genders in paper II. Additionally, the body of evidence supporting a connection between smoking and OA has been found for knee OA. However, due to limited statistical power we were not able to stratify the analyses by either joint-site (hip/knee) or gender.

To our knowledge, this is the first study to investigate the association between smoking and hip or knee OA, or TJR, using an instrumental variable in a Mendelian randomisation analysis. It has been suggested that the contributions of Mendelian randomisation studies are greatest when there is good reason to believe that conventional studies are biased\textsuperscript{128}, for example, in studies on modifiable risk factors such as smoking. Even if all known and established confounders have been included in an observational study, there is still a chance of residual confounding due to imprecise or crude measurement of the confounders or unmeasured confounders. In this situation, it has been suggested that even imperfect evidence from Mendelian randomisation studies strengthens the evidence base\textsuperscript{128}. The principle of Mendelian randomisation relies on the segregation and independent assortment of genetic variants at conception\textsuperscript{158}. Thus, the genetic variants will not be associated with the confounding factors that normally bias conventional observational studies\textsuperscript{62}.

In line this, we found that most of the covariates did not vary across T alleles of the rs1051730 SNP at baseline. However, with each increase in the number of the rs1051730 T alleles, the participants tended to be slightly younger and have a lower BMI. Lower BMI among those who smoke, and with the rs1051730 T allele(s), is to be expected as smoking is inversely associated with BMI\textsuperscript{104,157}. However, the mechanisms through which rs1051730 SNP may exert a positive effect on BMI, independent of smoking, is still speculative\textsuperscript{104}. We addressed the potential impact of age and BMI by adjusting for them. Adjustment for BMI in the Mendelian randomisation analyses had only a minor effect on the estimated association of the rs1051730 T allele and the risk of TJR in current smokers. However, it may indicate that some of the protective effect of smoking may be mediated through BMI, supporting the result we found in the mediation analysis in paper II. It should be stressed that if BMI is a
mediator, adjusting for BMI, as we did in paper III, would be inappropriate, and caution should be used when interpreting the BMI-adjusted results.

Moreover, socioeconomic status is associated both with smoking behavior and the risk of OA and TJR. Socioeconomic status may also influence the possibility of a medical diagnosis, as higher socioeconomic status may be associated with more active health-seeking behavior\textsuperscript{192}. Differences in waiting time were detected for elective primary hip replacements in Norway between 2000-2003; income and waiting time were negatively associated for men, while a higher level of education was associated with lower waiting times amongst women\textsuperscript{193}. It is also possible that higher socioeconomic status increases an individual’s willingness to undergo surgery because of greater knowledge about the procedure and its possible outcome, alongside the wish to retain an active lifestyle. Therefore, studies of risk factors should include rather homogeneous groups according to socioeconomic status\textsuperscript{108}; the HUNT cohort does this, making it suitable for epidemiological studies\textsuperscript{130}. However, as previously mentioned, there is good evidence that the rs1051730 SNP does not associate with confounding factors like socioeconomic status and education level\textsuperscript{103,157}.

In the Singapore Chinese Health Study, the protective effect of smoking on TKR was quickly lost after smoking cessation\textsuperscript{97}. This study found a dose-dependent relationship between duration of smoking cessation and reduction in TKR risk, with the lowest relative risk found in those who had recently quit smoking (<1 year). A decrease in the protective effect of smoking on OA after smoking cessation may be related to a rapid decrease in the anti-inflammatory effect of smoking. Nicotine is the most physiological active substance in cigarettes\textsuperscript{100}. Since articular cartilage is avascular, it is conceivable that the effects of smoking are mediated by circulating levels of nicotine and are therefore rapidly reversed after smoking cessation\textsuperscript{97}. Further, smoking has been associated with a number of less favorable health outcomes, such as chronic respiratory diseases and CVD\textsuperscript{189,190}. We addressed the potential impact of CVD by adjusting for it in a sensitivity analysis. We considered mortality to represent informative censoring due to higher mortality among smokers compared to non-smokers, therefore, a competing risk analysis was performed by calculating the SHRs\textsuperscript{152}. The main results remained unchanged, which indicated that neither mortality nor CVD could explain the inverse association between the rs1051730 T allele and TJR. These results substantiated the robustness of our findings from the Mendelian randomisation analysis.
When we condition on an observed measure of exposure (e.g. current smoking) it may result in spurious associations between the rs1051730 SNP and confounders of the smoking-TJR association. To test for this, we repeated the analysis of the relationship between the SNP and TJR in the broader strata of never smokers vs. ever smokers (current and former smokers combined). We found a weakened, but protective, effect among ever smokers. This supported the interpretation that the association between the SNP and TJR in current smokers was not a result of collider bias only.

It has been suggested that, when excited, the acetylcholine receptors on neural cells induce musculoskeletal pain\textsuperscript{107}, potentially creating a pleiotropic effect of the rs1051730 SNP. If this was the case, we would expect there to be an association between the SNP and TJR among never smokers, something which we did not find. However, we cannot completely rule out a pleiotropic effect (from pain or other effects), because non-finding may also be due to falsely negative results created by low statistical power.

As previously mentioned, the understanding of causal effects is generally advanced by triangulation from multiple alternative sources\textsuperscript{128}. The result of an inverse association between smoking and TJR have been consistent throughout the use of different approaches; from conventional observational studies\textsuperscript{97,98}, to mediation analysis (paper II) and finally to a Mendelian randomisation analysis (paper III). Thus, our result suggests a causal inverse association between smoking and TJR. The results from the Mendelian randomisation analysis do not provide us with the specific underlying mechanisms of any protective effect. However, they emphasize the importance of finding the mechanisms of this effect.

A limitation of using TJR as a marker of severe OA is that the Mendelian randomisation analysis cannot determine whether the protective effect of smoking results in a reduced risk of OA, or if smoking merely reduces the likelihood of people with OA receiving TJR. Future studies need to investigate whether this inverse association between the SNP and TJR found in our study can be replicated in another sample and with another definition of OA.
6. Conclusions

6.1 Answers to the research questions

In this thesis, the aim was to explore the associations between LPA and smoking on the risk of THR and TKR using different epidemiological methods. The following answers can be given to the specific research questions:

I. A high level of LPA was associated with increased risk of THR in younger women and middle-aged men. For TKR, a high level of LPA was associated with increased risk among middle-aged women only. Less vigorous levels of LPA were not associated with the risk of either THR or TKR (paper I).

II. The total effects showed an inverse association between smoking and THR and TKR for men. On the contrary, smoking was associated with increased risk of THR in women. There was a significant indirect effect of smoking through BMI. However for men, only a small part of this effect was mediated, which indicated that most of the effect of smoking on THR and TKR could not be explained by BMI. The gender differences, may to some extent, be explained by the differences in comorbidity and mortality among smokers (paper II).

III. Mendelian randomisation analysis suggested a causal inverse association between smoking and TJR among current smokers, with the risk of TJR being reduced with each copy of the rs1051730 T allele. This finding was independent of BMI, CVD and the competing risk of mortality. The Mendelian randomisation analysis is not able to further explain the underlying mechanism(s) of this potential causal association (paper III).

6.2 Implications for practice and future research

Findings from our study indicated an increased risk of later THR or TKR associated with a high level of LPA. However, the question still remains as to whether LPA is beneficial or harmful for development and progression of hip and knee OA, since the evidence across studies is inconclusive on dosage, type and timing of activity. Unfortunately, we did not have the comprehensive information on LPA required to resolve these issues. Future studies should incorporate objective measurements of LPA to better quantify and describe LPA.
addition, we need evidence for the relationship between LPA and hip OA, as the body of evidence is on knee OA.

Even though a high level of LPA may increase the risk of later TJR, we do not promote an inactive or sedentary lifestyle. Being physically active is undeniably beneficial for general health. Exercise has been shown to reduce pain and improve physical function in those who have already been diagnosed with hip or knee OA\textsuperscript{40,41}, and possibly to reduce the need for TJR\textsuperscript{32}. However, we do acknowledge the importance of identifying subgroups that might be at higher risk for the development and progression of OA.

Moreover, the effect of smoking on hip and knee OA remains inconclusive. We found smoking to be inversely associated with TJR, both in the mediation analysis and Mendelian randomisation study. The current findings emphasize the importance of finding the mechanisms of this effect. However, due to the numerous health hazards associated with smoking, we do not advocate this behavior in general, but, rather, promote smoking cessation. Future studies should explore the smoking-TJR association according to gender to replicate or reject the gender differences that were present in our data.

OA and the associated costs of joint replacement surgery represent a huge healthcare burden to society in addition to an individual burden on those who are affected by the disease. A better understanding of modifiable risk factors through genotype-phenotype associations can help us to develop new strategies for treatment and early prevention of OA. With progression in epidemiological methods and increasing knowledge about the mechanisms of OA, we have the tools necessary to improve prevention and management and reduce the burden of this disease in the future.
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Appendix I
### HUNT2 questionnaire (Q1): part collecting data on OA, smoking, and physical activity.

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<th><strong>RØYKING</strong></th>
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<td>Røykte noen av de voksne hjemme da du vokste opp?</td>
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<td>Bor du, eller har du bodde, sammen med noen dagligrøykere etter at du fylte 20 år?</td>
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<td>Hvor lenge er du vanligvis daglig til stede i røykfritt rom?</td>
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<td>Sett 0 hvis du ikke oppholder deg i røykfritt rom</td>
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<td>Røyker du selv?</td>
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<td>Sigaretter daglig?</td>
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<td>Sigarer/sigarillos daglig?</td>
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<td>Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet?</td>
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</tr>
<tr>
<td>Hvor mange sigaretter røyker eller røykte du vanligvis daglig?</td>
</tr>
<tr>
<td>Hvor gammel var du da du begynte å røyke daglig?</td>
</tr>
<tr>
<td>Hvor mange år tilsammen har du røykt daglig?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ANDRE PLAGER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>I hvilken grad har du hatt disse plagene i de siste 12 månedene?</td>
</tr>
<tr>
<td>Kvalme</td>
</tr>
<tr>
<td>Brystbrann/eubreoppstøt</td>
</tr>
<tr>
<td>Diarré</td>
</tr>
<tr>
<td>Teg mage</td>
</tr>
<tr>
<td>Hjertebeveg</td>
</tr>
<tr>
<td>Andenød</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ANDRE SYKDOMMER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Har du eller har du noen gang hatt:</td>
</tr>
<tr>
<td>Epilepsi</td>
</tr>
<tr>
<td>Psykiske plager hvor du har søkt hjelp</td>
</tr>
<tr>
<td>Kreftsykdom</td>
</tr>
<tr>
<td>Annen langvarig sykdom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>DAGLIGE FUNKSJONER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv?</td>
</tr>
<tr>
<td>Langvarig: minst ett år</td>
</tr>
<tr>
<td>Hvis ja:</td>
</tr>
<tr>
<td>Hvor mye vil du si at dine funksjoner er nedsatt?</td>
</tr>
<tr>
<td>Litt nedsatt</td>
</tr>
<tr>
<td>Middels nedsatt</td>
</tr>
<tr>
<td>Mye nedsatt</td>
</tr>
<tr>
<td>Er bevegelseshemmet</td>
</tr>
<tr>
<td>Har nedsatt syn</td>
</tr>
<tr>
<td>Har nedsatt hørsel</td>
</tr>
<tr>
<td>Hemmet pga. kroppssyke</td>
</tr>
<tr>
<td>Hemmet pga. psykiske plager</td>
</tr>
</tbody>
</table>

**MENN** fortsetter øverst neste spalte

### BESVARES BARE AV KVINNER

<table>
<thead>
<tr>
<th><strong>FYSISK AKTIVITET</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I FRITID</strong></td>
</tr>
<tr>
<td>Hvor lenge har det fysiske aktivitet i fritida vært det siste året? Tønk deg et ukentlig gjennomsnitt for året.</td>
</tr>
<tr>
<td>Arbeidstid regnes som fritid</td>
</tr>
<tr>
<td>Timer pr. uke</td>
</tr>
<tr>
<td>Leget aktivitet (lige)</td>
</tr>
<tr>
<td>Ingen</td>
</tr>
<tr>
<td>Hard fysisk aktivitet (svett/andpusten)</td>
</tr>
</tbody>
</table>

**UNDER ARBEID**

Hva er arbeidet ditt?

Hvorledes vil du beskrive arbeidet ditt?

Bare ett kryss

For det mest stilfellende arbeidet (f.eks. skrivbordsarbeid, montering) | 161 |
Arbeid som krever at du går mye (f.eks. ekspeditørarbeid, lett industriarb, underveis) | 2 |
Arbeid hvor du går og løfter mye (f.eks. postbud, pieier, bygningsarbeid) | 3 |
Tungt kroppsarbeid (f.eks. skogarbeid, tungt jordbruksarbeid, tungt bygningsarbeid) | 4 |
HUNT3 questionnaire (Q1): part collecting data on smoking.

**SKADER**

1. Har du noen gang hatt: 
   
   Ja   Nei   Vet ikke

   Lårhalsbrudd
   Brudd i handledd/underarm ...
   Brudd/sammenfall av ryggvinnler
   Nakkesleng (whiplash)

2. Har du foreldre, sakens eller barn som har, eller har hatt, følgende sykdommer? 
   (Sett ett kryss pr. linje)

   Hjerneslag eller hjerneblodning
   før 60 års alder
   Hjerteinfarkt før 60-års alder
   Astma
   Allergi/haysne/neseallergi
   Kronisk bronkitt/emfysem/KOLS
   Kreftsykdom
   Psykiske plager
   Beinskjærhet (osteoporose)
   Nyresykdom (ikke nyresten, urinvæsinfeksjon, urinlekkasje)
   Diabetes (sukkersyke)

3. Har noen av dine besteforeldre, dine foreldres søskan eller dine søskendebarn fått diagnosen diabetes (type 1 eller type 2)?
   Ja   Nei

**HVORDAN FÖLER DU DEG?**

5. Har du de to siste uker følt deg: 
   (Sett ett kryss pr. linje)

   Trygg og rolig?
   Glad og optimistisk?
   Nervøs og urolig?
   Plaget av angst?
   Irritable?
   Nedfor/deprimert?
   Ensom?

6. Har du noen gang i livet opplevd at noen over lengre tid har forsøkt å kue, fornedre eller ydmyke deg?
   Ja   Nei

**TOBAKK**

1. Røykte noen av de voksne innendørs da du vokste opp?
   Ja   Nei

2. Hvis du aldri har røkt, hopp til spørsmålet 22.
   Nei, jeg har aldri røkt
   Ja, sigaretter 
   Ja, sigarer/sigarillos/pipe

3. Røyker du selv?
   Nei, jeg har sluttet å røyke
   Ja, sigaretter av og til (fest/ferie, ikke daglig)
   Ja, sigarer/sigarillos/pipe av og til
   Ja, sigaretter daglig
   Ja, sigarer/sigarillos/pipe daglig

4. Svar på dette hvis du nå røyker daglig eller tidligere har røkt daglig:

   Hvor mange sigaretter røyker eller røykte du vanligvis daglig?
   Hvor gammel var du da du begynte å røyke daglig?
   Hvis du tidligere har røkt daglig, hvor gammel var du da du sluttet?

5. Svar på dette hvis du røyker eller har røkt av og til, men ikke daglig:

   Hvor mange sigaretter røyker eller røykte du vanligvis i måneden?
   Hvor gammel var du da du begynte å røyke av og til?
   Hvis du tidligere har røkt av og til, hvor gammel var du da du sluttet?

6. Bruker du, eller har du brukt, snus?
   Nei, aldri
   Ja, av og til
   Ja, men jeg har sluttet...
   Hvis du aldri har brukt snus, hopp til spørsmålet 23.

   Hvis ja:
   Hvor gammel var du da du begynte med snus?
   Hvor mange esker snus bruker/brukte du pr. måned?
**HUNT3 questionnaire (Q2): part collecting data on physical activity.**

### AKTIVITET

1. Hvordan har din fysiske aktivitet i fritida vært det siste året? (Tenk deg et utenlig gjennomsnitt for året. Arbeidstid regnes som fritid.)
   - Timer pr. uke
     - Ingen
     - Under 1
     - 1-2
     - 3 el. mer

   **Lett aktivitet**
   - (ikke svett/andetende)
   - Hard fysisk aktivitet
     - (svett/andetende)

2. Hvor lang tid bruker du til sammen daglig foran dataskjerm? (Sett 0 hvis du ikke bruker data)
   - Arbeid: __________ timer
   - Fritid: __________ timer

3. Hvor mange timer ser du på TV/video/DVD daglig?
   - Mindre enn 1 time: __________
   - 1-3 timer: __________
   - Mer enn 6 timer: __________

### KULTUR/LIVSSYN

4. Hvor mange ganger har du i løpet av de siste 6 måneder vært på:
   - (Sett ett kryss pr. linje)
     - Museum, kunstutstillinger
     - Konzerte, teater, kinos
     - Kirker, bedehus
     - Idrettsarrangementer

5. Hvor mange ganger har du i løpet av de siste 6 måneder selv drevet med:
   - (Sett ett kryss pr. linje)
     - Foreningsvirksomhet
     - Musikk, sang, teater
     - Menighetsarbeid
     - Friluftsliv
     - Dans
     - Treningsidrett

6. Hvilket livssyn vil du si ligger nærmest opp til ditt eget? (Sett ett kryss)
   - Kristent livssyn
   - Ateistisk livssyn
   - Humanistisk livssyn
   - Annet livssyn

7. Når det skjer vondt ting i livet mitt, tenker jeg: "det er et øyemed med det".
   - Ja
   - Nei
   - Vet ikke

   - Aldri
   - Av og til
   - Ofte

### PERSONLIGHET

9. Beskriv deg selv slik du vanligvis er:
   - Ja
   - Nei

10. Har du vært plaget av hodepine det siste året?
    - Ja
    - Nei
    - Hvis ja, gå til spørsmål 24.

11. Hvis ja:
    - Migrener
    - Hva slags hodepine: Annen hodepine

12. Omtrent antall dager pr. måned med hodepine:
    - Mindre enn 1 dag
    - 1-3 dager
    - 4-6 dager
    - 7-14 dager
    - Mer enn 14 dager

13. Hvor sterk er hodepinas vanligvis?
    - Mild (hemmer ikke aktivitet)
    - Moderat (hemmer aktivitet)
    - Sterk (forhinder aktivitet)

14. Hvor lenge varer hodepinas vanligvis?
    - Mindre enn 4 timer
    - 1-3 dager
    - 4-6 dager
    - Mer enn 3 dager

15. Er hodepinas vanligvis preget av eller ledsaget av:
    - (Sett ett kryss pr. linje)
      - Bankende/dunkende smerte?
      - Pressende smerte?
      - Ensidig smerte (høyre eller venstre)?
      - Forværing ved moderat fysisk aktivitet?
      - Kalme og/eller oppkast?
      - Lys- og lydskyrbest?

16. Får eller under hodepinas; kan du ha forbigående:
    - Ja
    - Nei

17. Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine:
    - dager
Appendix II
Registration form for total hip replacements in the Norwegian Arthroplasty Register

Navn: ..........................................................
(Skriv lydlig ev. pasient klistrelapp - spesifiser sykehus.)

Sykehus: ..........................................................

BENTAP VED REVISJON (Paprosky's klassifisering se baksiden)

Acetabulum □ I □ II □ III □ IV □ V □ VI □ VII □ VIII □ IX □ X

Femur □ I □ II □ III □ IV □ V □ VI □ VII □ VIII □ IX □ X

PROTESEKOMPONENTER (Bruk klistrelapp på baksiden, eller spesifiser nøyaktig)

Acetabulum

Navn/Type ..........................................................
ev. katalognummer .............................................
□ Med hydrokysapattit □ Uten hydrokysapattit
□ Sement med antibiotika – Navn ..........................................................
□ Sement uten antibiotika – Navn ...........................
□ Utementent ....................................................
□ Resurfacing ...................................................

Caput
□ Fastsittende caput ............................................
□ Separat caput - Navn/Type .................................
ev. katalognummer .............................................
Diameter .........................................................

SYSTEMISK ANTIBIOTIKA
□ Nei □ Ja: ..........................................................
□ Behandling ....................................................
Navn .............................................................
Dosing ...........................................................
Varighet i timer (døgn): ........................................

Medikament 1 ......................................................
Dosing opr.dag..............................................
Dosing videre ............................................... Varighet ....... døgn
Medikament 2 ......................................................
Dosing ..........................................................
Varighet ....... døgn

Fast antiokagulasjon

□ Nei □ Ja, type ....................................................

FIBRINOLOYSEHEMMER
□ Nei □ Ja, medikament: ........................................

OPERASJONSTID (hud til hud) ................. min

PEROPERATIV KOMPLIKASJON
□ Nei □ Ja, hvilke(n): ........................................

ASA KLASSE (se baksiden for definisjon)
□ Frisk □ Asymptomatisk tilstand som gir økt risiko □ Symptomatisk sykdom □ Livstruende sykdom □ Moribund

Legge: .................................................................
Legger som har fylt ut skjemaet (navnet registreres ikke i databasen).
Registration form for total knee replacements in the Norwegian Arthroplasty Register

Navn: 
(Skriv tydelig ev. pasient klistrelapp – spesifiser sykehus.)
Sykehus: 

PROTESE KNE (Bruk klistrelapper på baksiden, eller spesifiser nøytaklig) 

PROTESETYPE 

\[ \text{Totalprotese} \]
\[ \text{Hemi/protese} \]
\[ \text{Enkomponentprotese} \]

PROSKIMAL KOMPONENT 

Navn/Type/Str 

\[ \text{ev. katalognummer} \]

\[ \text{Femur komponent} \] 
\[ \text{Navn/Type/Str} \]

\[ \text{ev. katalognummer} \]

\[ \text{Patella komponent} \] 
\[ \text{Navn/Type/Str} \]

\[ \text{ev. katalognummer} \]

\[ \text{Distal komponent} \]
\[ \text{Navn/Type/Str/Diameter} \]

\[ \text{ev. katalognummer} \]

Legen som har fylt ut skjemaet (navnet registreres ikke i databasen)

11.02.2011

KNEPROTESER og andre leddproteser

Insetting, skifting eller fjerning av protese eller protesedeler, samt bleddesvisjoner for infisert protese.

LOKALISASJON, AKTUELL OPERASJON

\[ \begin{array}{|c|c|}
\hline
\text{Kne} & \text{Håndled} \\
\text{Ankel} & \text{Fingre (ang. ledd)} \\
\text{Tær (ang. ledd)} & \text{Annet} \\
\text{Skulder} & \text{Rygg (ang. nivå)} \\
\text{Albe} & \text{ } \\
\hline
\end{array} \]

AKTUELLE SIDE (ett kryss) (Bilateral opr. = 2 skjema)

\[ \begin{array}{|c|c|}
\hline
\text{Høyre} & \text{Venstre} \\
\hline
\end{array} \]

TIDLIGERE OPERASJON I AKTUELLE LEDD (ev. flere kryss)

\[ \begin{array}{|c|c|}
\hline
\text{Nei} & \text{ } \\
\text{Osteosynthese for intraartikulær lednhard fraktur} & \text{ } \\
\text{Osteotomi} & \text{ } \\
\text{Artrodese} & \text{ } \\
\text{Protese} & \text{ } \\
\text{Synektomi} & \text{ } \\
\text{Annet (f.eks menisk og leddbåndopp.)} & \text{ } \\
\hline
\end{array} \]

OPERASJONSDATO (dd.mm.åå)

\[ \begin{array}{|c|c|}
\hline
\text{AKTUELLE OPERASJON} (ett kryss)
\hline
\text{Primæraperasjon} & \text{Reoperasjon (protese tidligere)} \\
\hline
\end{array} \]

ÅRSAK TIL AKTUELLE OPERASJON (KRYSS AV ENTIEN A ELLER B)

A. Primæraperasjon, pga (ev. flere kryss)

\[ \begin{array}{|c|c|}
\hline
\text{Idiopathisk afrose} & \text{ } \\
\text{Rheumatoid artritt} & \text{ } \\
\text{Rakforsel/sequelle} & \text{ } \\
\text{Mr. Bechterew} & \text{ } \\
\text{Sequele ligamentskade} & \text{ } \\
\text{Sequele meniskskade} & \text{ } \\
\text{Akut fraktur} & \text{ } \\
\text{Infeksjonsequelle} & \text{ } \\
\text{Spondyloide} & \text{ } \\
\text{Sequele prolapso kirurgi} & \text{ } \\
\text{Degenerativ skivesykdom} & \text{ } \\
\text{Annet} & \text{ } \\
\hline
\end{array} \]

\[ \text{Hvileken} \]

\[ \text{Progresjon av artrose} \]

\[ \text{Annet (f.eks tid for fjerning protese)} \]

\[ \text{Bytte el. innsættelse av distal komponent} \]

\[ \text{Bytte el. innsættelse av proximal komponent} \]

\[ \text{Bytte el. innsættelse av hele prosese} \]

\[ \text{Insættelse av patellakomp.} \]

\[ \text{Bytte av patellaprote} \]

\[ \text{Bytte av plastføring} \]

\[ \text{Artrodese} \]

\[ \text{Amputasjon} \]

BENTRANSPLANTASJON (ev. flere kryss)

\[ \begin{array}{|c|c|}
\hline
\text{Proximal} & \text{Nei} \quad \text{Ja} \quad \text{Benpakking} \\
\text{Distal} & \text{Nei} \quad \text{Ja} \quad \text{Benpakking} \\
\hline
\end{array} \]

SYSTEMISK ANTIBIOTIKA

\[ \begin{array}{|c|c|}
\hline
\text{Navn} & \text{Dosing} & \text{Varighet i timer (døgn)} \\
\hline
\text{Medikament 1} & \text{Timer (…døgn)} & \text{ } \\
\text{Medikament 2} & \text{Timer (…døgn)} & \text{ } \\
\text{Medikament 3} & \text{Timer (…døgn)} & \text{ } \\
\hline
\end{array} \]

TROMBOSEPROFYLAKSE

\[ \begin{array}{|c|c|}
\hline
\text{Døring oper.dag} & \text{Døring videre} & \text{Varighet (…døgn)} \\
\hline
\end{array} \]

\[ \text{Fibrinolysehemmer} \]

\[ \text{DREK} \]

\[ \text{Operasjonstid (hvor tidlig)} \]

\[ \text{Peroperativ komplikasjoner} \]

\[ \text{Legen} \]

\[ \text{Legen som har fylt ut skjemaet (navnet registreres ikke i databasen)} \]

\[ \text{F.eks. caput humeri) \]

\[ \text{ev. katalognummer} \]