"It is better to be vaguely right than exactly wrong."

Carveth Read

(or John Maynard Keynes)

Summary

Mechanical factors such as BMI (body mass index), leisure time physical activity and workload, are of importance in the development of osteoarthritis (OA). Studies showing associations with OA in non-weight-bearing joints indicate that obesity could influence OA beyond mechanical effects (41, 236). OA is also more common in women than in men (43, 202). Thus, systemic mechanisms connected to metabolic, hormonal and gender related factors should be investigated further (125, 188, 202, 224).

Objectives: The overall aim of this thesis was to identify systemic factors that could be associated with end-stage OA, defined as total hip (THR) or knee replacement (TKR) due to primary OA, by addressing the following research questions:

I. Is metabolic syndrome a risk factor of THR or TKR due to OA?
II. Does thyroid function influence the risk of THR or TKR due to OA?
III. Do reproductive history and hormonal factors influence the risk for THR or TKR due to OA?

Methods: We linked baseline data from the Nord-Trøndelag Health Study (HUNT) to the Norwegian Arthroplasty Register (NAR) in order to identify TKR or THR due to primary OA. Cox proportional hazards models were used to estimate hazard ratios (HRs). Included confounders were age, sex, BMI, smoking, physical activity, education and diabetes.

Results and conclusions

I. We found an increased risk of TKR in men <50 years with hypertension, and in both sexes <70 years with increased waist circumference. Apart from this, neither metabolic syndrome nor its components were associated with increased risk of THR or TKR due to primary OA.
II. No association was found between either low or high thyroid function and THR or TKR.
III. We found that higher age at menarche reduced the risk of TKR. Past users of systemic hormone replacement therapy (HRT) were at higher risk of TKR compared to never users. Parity did not increase the risk of THR or TKR.

Summary in Norwegian

Systemiske risikofaktorer for alvorlig artrose i hofte og kne: En epidemiologisk studie fra HUNT og Nasjonalt Register for Leddproteser

Mekaniske faktorer, slik som BMI (body mass index), fysisk aktivitet og arbeidsbelastning, kan påvirke risikoen for å få artrose i hofter og knær. Men noen studier har vist at overvektige også har en økt risiko for å få artrose i ledd som ikke er vektbærende. Det er derfor mulig at overvekt kan påvirke artrose på andre måter enn kun gjennom direkte mekanisk trykk på leddet. Artrose er også mer vanlig hos kvinner. Vi trenger derfor å finne ut mer om hvordan systemiske faktorer, som metabolisme, stoffskifte og kjønn, påviker risikoen for artrose.

Målet med denne doktorgraden var å finne systemiske risikofaktorer som har en sammenheng med alvorlig artrose, definert som totalprotese i hofte eller kne på grunn av artrose. Vi ønsket å finne svar på følgende forskningsspørsmål:

I. Er metabolsk syndrom en risikofaktor for totalprotese i hofte eller kne?
II. Påvirker stoffskifte (thyroideafunksjonen) risikoen for totalprotese i hofte eller kne?
III. Påvirker reproduktiv historie og hormonelle faktorer risikoen for totalprotese i hofte eller kne?

Vi koblet data fra Helseundersøkelsen i Nord-Trøndelag (HUNT) til Nasjonalt Register for leddproteser for å kunne identifisere hvem som senere fikk totalprotese i hofte eller kne på grunn av primær artrose. Analysene ble justert for alder, kjønn, BMI, røyking, fysisk aktivitet, utdanning og diabetes.

Resultater og konklusjoner:

I. Vi fant en økt risiko for totalprotese i kne hos menn under 50 år med høyt blodtrykk, og hos både kvinner og menn under 70 år med økt bukomfang. Bortsett fra dette fant vi ingen sammenheng mellom metabolsk syndrom og totalprotese i hofte eller kne.
II. Vi fant ingen sammenheng mellom hverken lavt eller høyt stoffskifte og totalprotese i hofte eller kne.
III. Vi fant at en høyere alder ved første menstruasjon (menarke) gav en redusert risiko for kneprotese senere i livet. Tidligere bruk av østrogentilskudd økte risikoen for kneprotese. Antall barnefødsler påvirket ikke riskoen for hverken hofte- eller kneprotese.

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Ålesund, January 2018
Alf Inge Hellevik

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Figures and illustrations
All figures and illustrations are by AI Hellevik unless otherwise stated.

List of papers

I. Hellevik AI, Johnsen MB, Langhammer A, Baste V, Furnes O, Storheim K, Zwart JA, Flugsrud GB, Nordsletten L. Metabolic syndrome as risk factor for total hip or knee replacement due to primary osteoarthritis: A prospective cohort study (The HUNT Study and the Norwegian Arthroplasty Register). Clinical Epidemiology. 2018;10: 83-96.

II. Hellevik AI, Johnsen MB, Langhammer A, Fenstad AM, Furnes O, Storheim K, Zwart JA, Flugsrud GB, Nordsletten L. Incidence of total hip or knee replacement due to osteoarthritis in relation to thyroid function: a prospective cohort study (The Nord-Trøndelag Health Study). BMC Musculoskeletal Disorders. 2017;18(1):201

III. Hellevik AI, Nordsletten L, Johnsen MB, Fenstad AM, Furnes O, Storheim K, Zwart JA, Flugsrud GB, Langhammer A. Age of menarche is associated with knee joint replacement due to primary osteoarthritis. (The HUNT Study and The Norwegian Arthroplasty Register). Osteoarthritis Cartilage. 2017;25(10):1654-62.

Acronyms and abbreviations

ADAMTS: A disintegrin and metalloprotease with thrombospondin-like motifs
BMD: Bone mineral density
BMI: Body mass index
cHR: Case-specific hazard ratio
CI: Confidence interval
CVD: Cardiovascular disease
DAG: Directed acyclic graph
DM: Diabetes mellitus
HDL: High density lipoprotein
HR: Hazard ratio
HRT: Hormone replacement therapy
HUNT: The Nord-Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag)
IGT: Impaired glucose tolerance
IL: Interleukin
MMP: Matrix metalloproteinases
MRI: Magnetic resonance imaging
NAR: Norwegian Arthroplasty Register
OA: Osteoarthritis
OC: Oral contraceptives
RR: Relative risk
sHR: Subdistribution hazard ratio
T3: Triiodothyronine
T4: Thyroxine
THR: Total hip replacement
TKR: Total knee replacement
TNF: Tumor necrosis factor
UKR: Unicompartmental knee replacement
VIF: Variance inflation factor

Key concepts

Osteoarthritis (OA), total hip replacement (THR), total knee replacement (TKR), metabolic syndrome, thyroid function, reproductive history.

Background

Osteoarthritis (OA) in the hip and knee is the most common joint disease. It is associated with substantial morbidity (122). The Global Burden of Disease Study 2015 reported that OA had increased the total disability-adjusted life-years by 35% and age-standardized disability-adjusted life-year rates by 4% between 1990 and 2015 (42). Total joint replacement (TJR) reduces OA-related pain and disability as well as health care costs (80). However, the TJR procedure may result in serious complications and the lifespans of the prostheses might vary (64). There is no effective way to prevent the onset or progression of this disease (65, 208), which emphasizes the importance of identifying modifiable risk factors. A better understanding of risk factors could help us to target effective public health strategies and generate new hypotheses about the underlying mechanisms of OA.

Defining OA

Radiographic OA is most commonly graded by the Kellgren-Lawrence (KL) system, which scores OA severity on a scale of 0-4. Definite radiographic OA is defined as KL grade ≥2 (105). Magnetic resonance imaging (MRI) has made it easier to visualize joint structures which are not visible on radiographs. An MRI definition of OA has been proposed, but it has yet not been validated (89).

The definition of symptomatic OA includes the presence of radiographic OA and the symptoms pain, aching or stiffness in the joint. Not all individuals with radiographic OA have symptoms, and thus not symptomatic OA.

Severe OA symptoms, together with manifest radiographic OA with KL grade ≥2, is usually considered an indication for TJR by orthopedic surgeons. This thesis used total hip replacement (THR) or total knee replacement (TKR) due to OA as an indicator of severe OA.

Prevalence and incidence of OA and TJR

The prevalence of OA in Norway has been reported to be 5.5% for the hip and 7.1% for the knee. These figures were obtained by the item: “Have you been diagnosed with osteoarthritis in the hips, knees or hands by a medical doctor or by x-ray?”(70). In a US population, age-standardized prevalence of *radiographic* OA (KL grade ≥2) in people ≥45 years has been reported to be 28% for both knee and hip in the Johnston County Osteoarthritis Project (98, 99). The prevalence of *symptomatic* hip OA and knee OA in people ≥45 years in the Johnston County cohort was 10% and 16%, respectively (98, 99). In the Beijing Osteoarthritis study, the age-standardized prevalence of radiographic hip OA among Chinese elderly subjects was 80-90%

lower than in white US elderly subjects (155). Radiographic knee OA was, however, more prevalent among Chinese women than Caucasian women (46.6% vs. 34.8%) (243).

In a US population, the lifetime risk of symptomatic knee OA has been reported to be around 40% in men and 47% in women (149). The age- and sex-standardized incident rates for symptomatic hip and knee OA have been reported to be 88 and 240 cases per 100 000 person years, respectively. The incidence rates rise markedly after the age of 50, and then level off after 70 years of age (135).

THR or TKR is indicated in patients for whom conservative therapy is no longer sufficient for controlling OA pain (196). In Norway, the lifetime risk of THR due to OA in 2013 was 16.0% for women and 8.3% for men (Figure 1) (3). Correspondingly, the lifetime risk for TKR due to OA in 2013 was 9.7% for women and 5.8% for men (2). Lifetime risk of TKR has also been increasing more rapidly than THR. In 2016, the mean age for receiving a primary TKR was 68.9 years and 69.0 years for a primary THR (Figure 2).

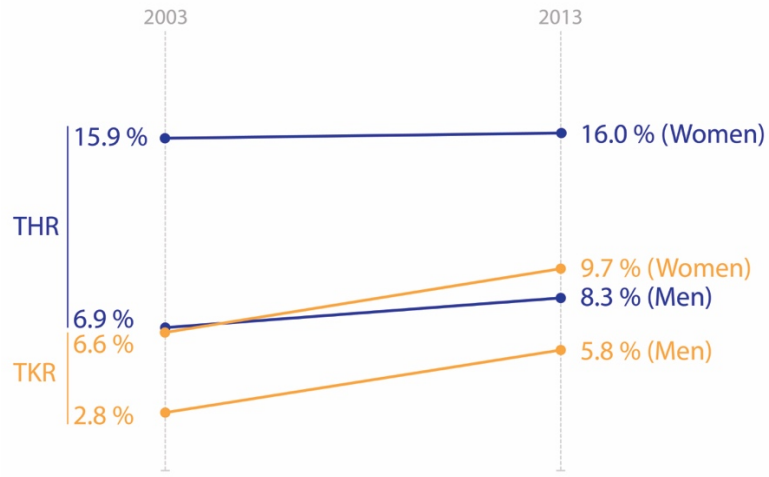


Figure 1: Lifetime risk of THR and TKR in 2003 and 2013 in Norway, by sex. Numbers from Ackerman et al. (2, 3).

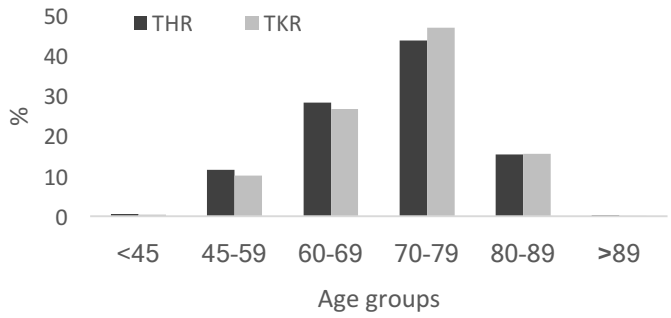


Figure 2: Age distribution in those who received a THR or TKR in Norway between 1995 and 2005. Numbers from NAR.

The incidence of THR or TKR is low for people <50 years of age, but rises sharply thereafter, and decreases again after 70 years of age (Figures 3 and 4). TKR has been performed less often in Norway than the other Nordic countries, and, in contrast to many other Western countries, the incidence of TKR in Norway has been lower than THR. However, the 2017 report from the NAR showed that this relative difference between THR and TKR incidence has diminished in recent years (Figure 5) (1).These trends were also found in a recent study which reported lower incidence of TKR in Norway compared to the other Nordic countries in the period between 1997 and 2012, but an overall increase in TKR incidence in all Nordic countries (Figure 6) (158). It is expected that the incidence will to continue to rise in the coming decades; this could be due to an ageing and more obese population, broadened indications, less acceptance of pain and more active elderly people.

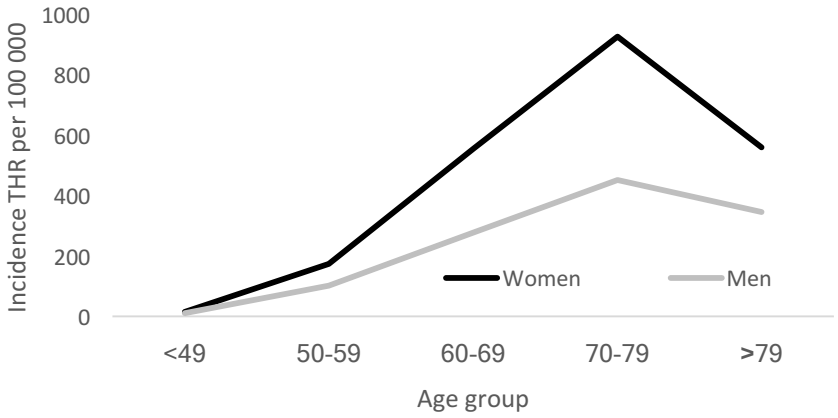


Figure 3: Age and sex specific incidence rates of THR per 100 000 inhabitants in Norway from 1995 to 2006. Numbers from Havelin et al. 2009 (79).

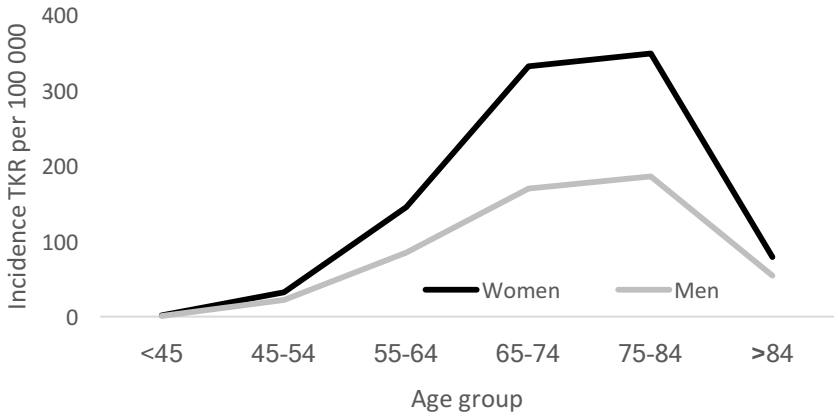


Figure 4: Age and sex specific incidence rates of TKR per 100 000 inhabitants in Norway from 1995 to 2006. Numbers from Robertsson et al. 2010 (179).

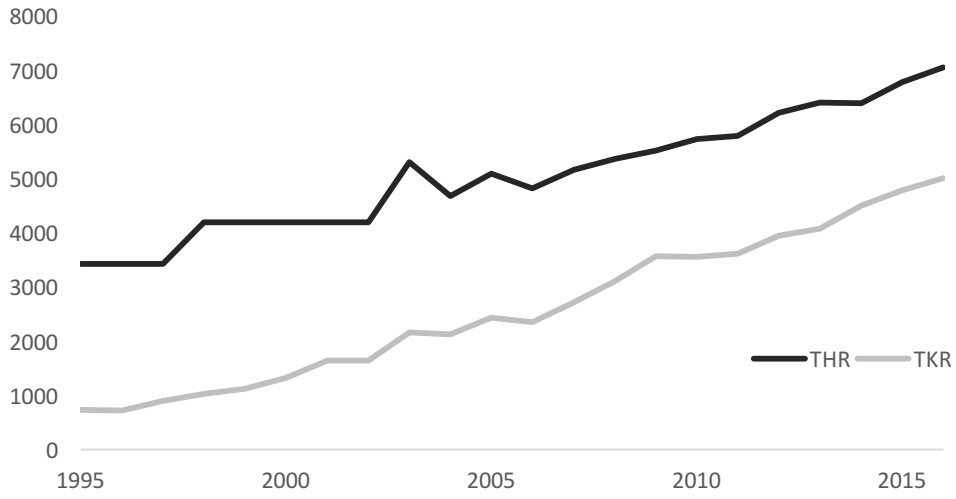


Figure 5: Number of THRs and TKRs due to OA per year in Norway. Numbers from NAR.

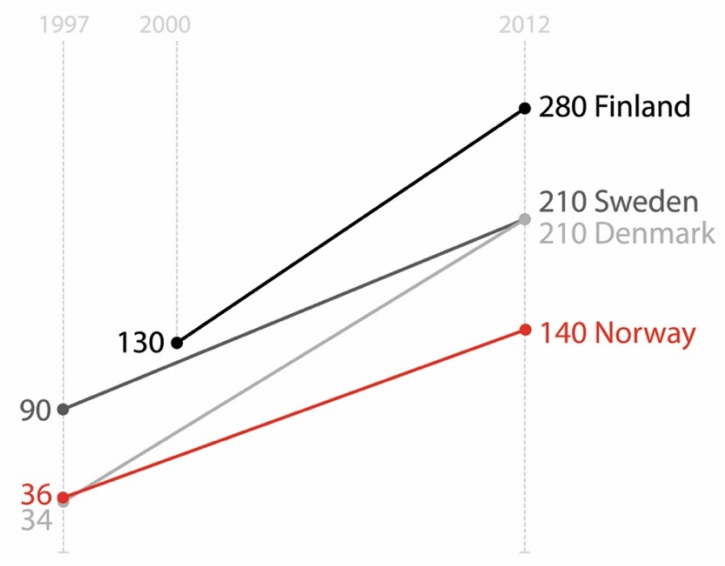


Figure 6: Comparing incidence of TKR + unicompartmental knee replacement per 100 000 inhabitants in Scandinavian countries in persons >30 years between 1997 and 2012. Numbers from Niemelainen et al. 2017 (158).

Risk factors

OA was previously thought to be a normal consequence of ageing, leading to the term degenerative joint disease. OA is now thought to be the result of the complex interplay of several factors (39). These can be divided into systemic factors that act at a systemic level on all relevant

joints, and local factors that act on a particular joint (153, 164). This thesis addresses the factors of sex, metabolic syndrome and thyroid function.

Systemic risk factors

Age

Age is the most important risk factor for OA in both the hip (40) and the knee (194). This could be due to a reduction in the regenerative capacity of joint tissue and a proxy for accumulation of risk factors (153).

Gender

OA is more common in women than in men (43, 202), and the relative risk of developing OA for women compared to men has been reported to be 2.6 after adjustment for age, weight and smoking (43). Women with OA are also more likely to experience rapid structural damage in the joints and undergo total hip arthroplasty (133). There may be biomechanical differences between genders that could contribute to this difference: A wider pelvis and narrower step width in women may increase mechanical loading on the female knee (178).

The increase of OA incidence after menopause has led to the hypothesis that the loss of estrogen unmasks the symptoms of OA by enhancing pain sensitivity (153). However, results have been conflicting: Hormone replacement therapy (HRT) has been shown to have a protective effect on OA in some studies (44, 201, 232), while others have found it to have no effect (48, 103, 154, 242), or even adverse effects (125). Increasing parity has been reported as a risk factor for radiographic OA in the knee (231) as well as THR and TKR (125). However, some studies have not found any association between parity and radiographic joint space narrowing, osteophytes or changes in either cartilage volume or cartilage defects (228). A large, prospective cohort study reported that low age at menarche increased the risk of TKR (125). The use of oral contraceptives has not been associated with OA in most studies (44, 185, 186, 228), except one that reported a possible increased risk of THR (216). The reasons for increased risk of OA and TJR in women remain unclear, and more research is needed to clarify a possible association between reproductive history/hormonal factors and OA.

Obesity

Obesity increases the load on weight-bearing joints and is a more important risk factor for symptomatic OA in the knee than in the hip (26, 52, 175). A meta-analysis showed that the risk of knee OA in obese individuals is 2.96 times higher than in normal-weight individuals (26). Another meta-analysis by Jiang et al. found that BMI was positively associated with knee OA

defined by radiography and/or clinical symptoms (Relative risk (RR) 1.25 and 1.54, respectively). Obesity is also associated with the progression of radiographic knee OA (175), and BMI has been reported to be associated with the risk of THR and TKR due to OA in Norwegian (13, 15, 58), Swedish (129) and Australian cohorts (221).

Metabolic syndrome

Biochemical changes associated with obesity may accelerate OA beyond the direct effect of mechanical loading as described above (115, 171). Obesity could also be associated with both radiographic and symptomatic hand and wrist OA; indicating a systemic effect of obesity on non-weight-bearing joints (32, 163). An association between metabolic syndrome and OA has been reported, and metabolic OA has therefore been hypothesized as a subtype of OA (188, 244).

Metabolic syndrome is a cluster of components associated with increased risk of cardiovascular disease (8). There are various, slightly different definitions, but according to the Joint Interim Statement it includes increased waist circumference, high blood pressure, elevated triglycerides, reduced high-density lipoprotein (HDL) and elevated serum glucose or diabetes (Table 1) (8).

Table 1: Criteria for each component of metabolic syndrome according to the Joint Interim Statement (8).

Component	***Criteria***
Waist circumference (cm)	≥88 in women ≥102 in men
Blood pressure (mmHg)	Systolic blood pressure (SBP) ≥130 or diastolic blood pressure (DBP) ≥85 or hypertensive medication
Triglycerides (mmol/L)	≥1.7
HDL cholesterol (mmol/L)	<1.3 in women <1.0 in men
Fasting serum glucose (mmol/L)	≥5.6 or diabetes

Due to the high prevalence of these components among people with OA, it has been suggested that metabolic syndrome may influence the development of OA independent of BMI (22, 81). This could be explained by shared mechanisms in the etiologies of OA and metabolic syndrome: Inflammation, oxidative stress, common metabolites and endothelial dysfunction

(Table 2) (244). However, OA and metabolic syndrome may simply share common risk factors such as aging and obesity (146).

Table 2: Possible biological mechanisms between each of the metabolic syndrome components and OA. Based on figure from Courties et al. (37).

Obesity	Meta-inflammation (adipokines, cytokines, free fatty acids) Mechanical stress
Hypertension	Subchondral bone vascular ischemia
Dyslipidemia	Cholesterol/high oxidized-LDL (Increased local transformation of growth factor-β (TGF-β) production and synovial macrophages activation)
Impaired glucose tolerance/ Diabetes	Insulin resistance (increased catabolic effect of joint inflammation) High Glucose Exposure (increased oxidative stress, advanced glycation end products (AGEs), cytokines, proteolytic enzymes)

The results of observational studies in humans have been inconsistent. One Australian prospective cohort study found that a cumulative number of metabolic syndrome components, central obesity and hypertension were associated with increased risk of TKR due to OA independent of BMI, but no associations were observed with THR (146). However, the Malmö Diet and Cancer Study found that although central obesity as a component of metabolic syndrome was associated with increased risk of knee OA independent of BMI, metabolic syndrome and its components were not associated with hip OA (47). Other studies have reported that the risk of knee OA increases with the number of metabolic syndrome components (234). In contrast, a recent study reported that, after adjustment for BMI, neither metabolic syndrome nor its components were associated with incident knee OA (159). A meta-analysis including 8 studies with a total of 3202 cases and 20 968 controls found that the available evidence supports the suggestion that metabolic syndrome modestly increases the risk of knee OA (pooled adjusted Odds ratio (OR) 1.05) (218). Nevertheless, due to relatively small numbers in each study, more large-scale prospective cohort studies are needed to further verify this potential association.

Thyroid function

Thyroid hormones play a role in the remodeling and maintenance of bone, and may also influence joints and articular cartilage (230). The pituitary gland releases TSH (thyroid stimulating hormone) which stimulates the thyroid gland to release the thyroid hormones T4/T3 (thyroxine/triiodothyronine), which in turn inhibit the release of TSH through a negative feedback loop (Figure 7). A low level of TSH would therefore indicate hyperthyroidism (high T4/T3), and a high level of TSH would indicate hypothyroidism (low T4/T3). The main hormone

secreted by the thyroid gland is T4, which is converted into the physiologically active T3 in peripheral tissue.

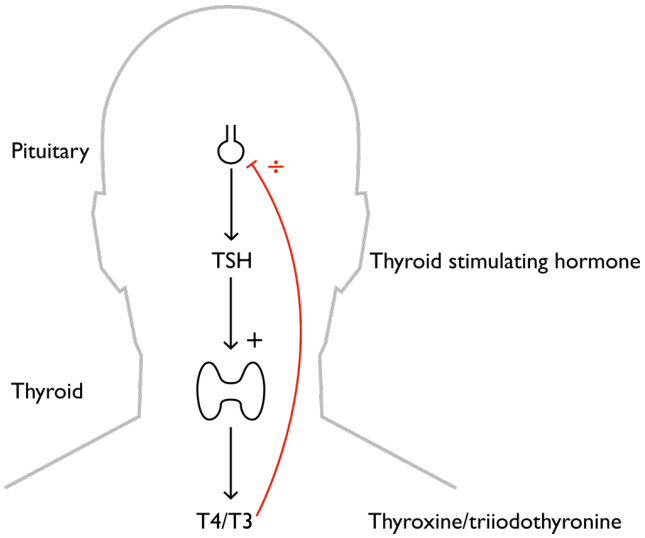


Figure 7: The pituitary – thyroid negative feedback loop.

Genetic studies have suggested that deiodinase-regulated local availability of the active thyroid hormone T3 plays an important role in cartilage maintenance and repair (214). Further data have indicated that increased intracellular T3 availability increases the risk of OA, leading to the hypothesis that reduced T3 availability protects joints from developing OA (223). A phase III clinical trial investigating the use of eprotirome, a thyroid receptor β-agonist, for treatment of hypercholesterolemia (114), found indications of dose-related articular cartilage damage in dogs that had been treated for 12 months (197). This was surprising, as eprotirome is a liver-specific thyroid receptor β-agonist, but it indicates that thyroid hormones have an effect on cartilage (116) and could play a role in the pathogenesis of OA. An older cross-sectional study did not find any association between radiological knee OA and thyroid status measured by TSH (33). To the best of our knowledge, no prospective population study has investigated the association between thyroid function and OA.

Genetics

There is a strong genetic susceptibility for OA (106), accounting for up to half of the risk of its development (85, 200). The heritable component of OA has also been estimated to be stronger for hip than for knee OA (132). Genome-wide association studies, like the Arthritis Research UK Osteoarthritis Genetics (arcOGEN) Consortium, have identified 11 loci associated with OA (16). Pain severity of OA may also have genetic components and genes associated with pain

sensitivity (COMT-gene) have been found to be associated with hip and knee OA (211, 212). Single-nucleotide polymorphism has been associated with several other known risk factors, like hip shape, BMI and bone mineral density (85). Genetic components could therefore influence the risk of OA both through direct effects, and through OA risk factors. Increased pain sensitivity could increase the risk of receiving a TJR.

Bone mineral density (BMD)

High BMD may be associated with increased risk of incident knee OA (73, 156). Low BMD has been associated with reduced hip joint space, as a sign of OA (92). A possible explanation is that individuals with OA may decrease their level of physical activity, which could lead to low BMD. Another explanation for this apparent paradox could be that even if the subchondral bone density in a joint with OA has increased, the whole bone might be less mineralized (123).

Nutrition

The effects of dietary factors have so far been inconclusive. The associations between vitamins C, D, E and K and OA have been conflicting (153). Furthermore, a recent cross-sectional study found no clear association between the antioxidants carotenoid or selenium and radiographic knee OA (124).

Smoking

There is conflicting evidence regarding the associations between smoking and OA, but studies have found a protective effect when using radiographic knee OA (51) and TKR (186) as outcomes. Meta-analyses have shown an inverse association between smoking and OA onset, but no association between smoking and OA progression (88, 167). A recent Mendelian randomization study also showed an inverse relationship between smoking and TJR in current smokers (97).

Joint-level risk factors

Anatomical factors

Hip dysplasia (reduced acetabular coverage of the femoral head) has been associated with increased risk of hip OA (7). Loss of concavity at the anterosuperior head-neck junction (Cam lesion type femoroacetabular impingement) can also increase the risk of developing OA (Figure 8) (5). Subtle abnormalities in hip and femoral head anatomy like less femoral head sphericity, smaller acetabular and femoral neck anteversion and larger acetabular coverage, may also increase the risk of hip OA (238). In the knee, tibial and femoral bone morphology may predict

the development of OA (151). Varus and valgus knee alignment increase the risk of development and progression of OA (54, 189), and leg length inequality of 1 cm or more has been reported to increase the risk of knee OA in the shorter limb (76).

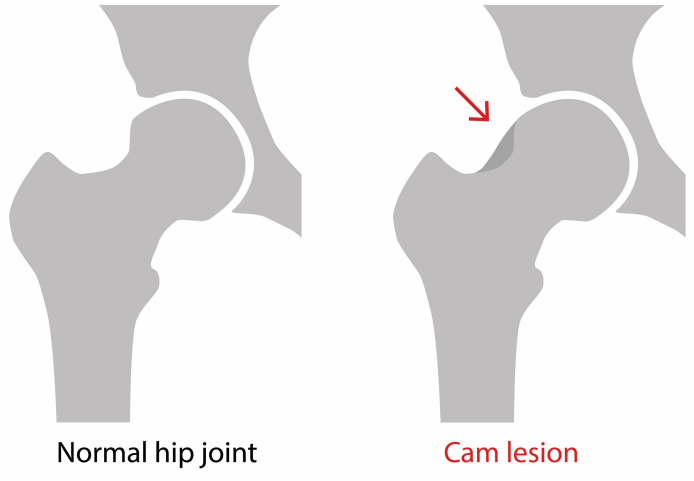


Figure 8: Cam lesion type femoroacetabular impingement.

Injury

Previous injuries increase the risk of OA. Cartilage damage makes joints more susceptible to further injury, and damaged ligaments or meniscus can affect joint biomechanics. Knee injury increases the risk of knee OA by more than four times (150), possibly through thrombin caused by bleeding in the joint that can induce cartilage degradation (63). Abnormalities of the meniscus are also frequently found among patients with OA, but it is common to have no recollection of any knee trauma (91). In 32 persons with symptomatic OA, 75% had meniscal abnormality on MRI (23). The data on hip OA after injury are more limited, although substantial risk of secondary OA after acetabular fractures is well established (210, 215). In a meta-analysis, previous hip joint injury was found to increase the risk of hip OA (177), but the type of hip joint injury was not specified.

Physical activity

Poor quadriceps function can increase the risk of knee OA progression (222). Habitual physical activity has not been shown to affect the risk of radiographic/symptomatic OA (53, 72), but more vigorous physical activity has (139, 143). High intensity activity during adolescence might promote the development of cam-type impingement morphology (6, 191). However, most individuals with abnormal joint biomechanics do not develop OA (5). The results from studies using TKR and THR as outcome measure have been conflicting: One study found that the risk of

TKR increased alongside the level of physical activity, but discovered no such association with THR (220). Other studies found no consistent relationship between physical activity and TKR or THR (4, 14, 59), apart from a possible protective effect on THR in women (4). The results have therefore been inconsistent, and this could partly be due to the different definitions, and types, of physical activity.

Occupation

Some occupational activities may increase the risk of knee OA, especially kneeling and squatting (94, 95). A combination of obesity and heavy physical activity is associated with an enhanced risk of radiological knee OA (139) and TKR/THR (14, 59). A systematic review also found an association between long-term heavy lifting and hip OA (204).

Pathogenesis

It is important to emphasize that OA is a disease of the entire joint and not just the cartilage (127). As the name implies, the pathogenesis of idiopathic OA is still poorly understood, and it is difficult to figure out which of the joint tissues is affected first (cartilage, subchondral bone or synovium). Abnormal or excessive joint loading stimulates joint tissue cells to produce proinflammatory mediators, increasing joint tissue destruction (19, 50). Systemic low-grade chronic inflammation initiated by obesity and metabolic disorders has thus been suggested as a possible pathway to OA, independent of direct weight-bearing (37). The pathogenesis of OA could therefore be thought of as an interplay between systemic and joint-specific inflammatory pathways, with cytokines and adipokines in key signaling roles (Figures 9 and 10).

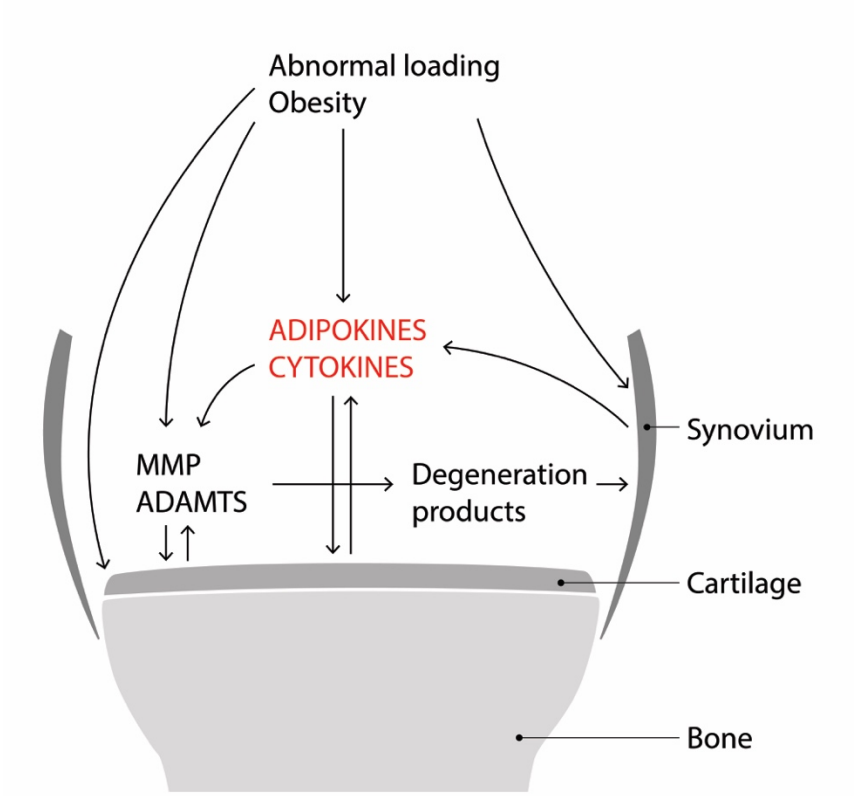


Figure 9: Interplay between systemic, biomechanical and joint-specific inflammatory pathways in early OA. Adipokines play a key role between cartilage and synovium. Figure based on Kluzek et al. (109) and Goldring et al. (66). (MMP: matrix metalloproteinases; ADAMTS: a disintegrin and metalloprotease with thrombospondin-like motifs).

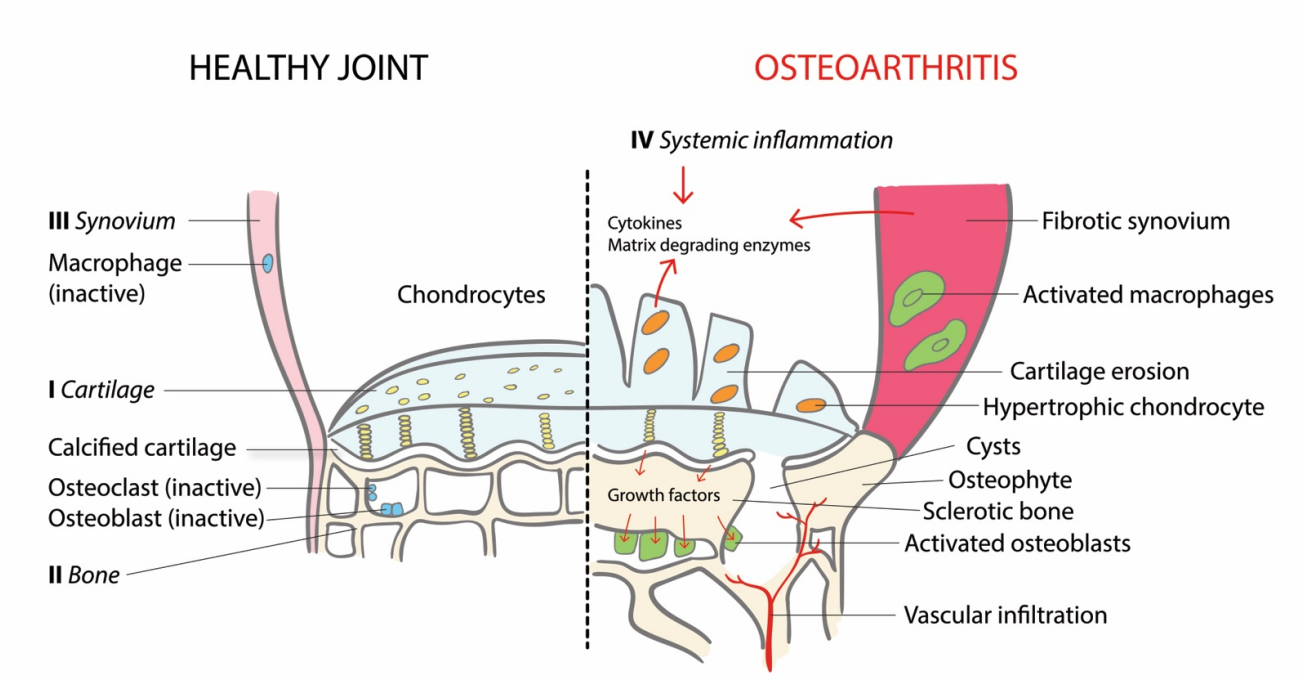


Figure 10: Central components in the pathogenesis of OA: I. Cartilage; II. Subchondral bone; III. Synovium; IV. Systemic inflammation. Based on figure from Glyn-Jones et al. (64).

I. Cartilage

The cartilage enables gliding of the bones in the joint and is a shock absorber. Its main structural protein is type II collagen that provides stabilization and tensile strength. Aggrecan and other proteoglycans drive water into the cartilage to provide compression resistance (64). Chondrocytes respond to the chemical and mechanical environment and regulate the cartilage architecture and biochemical composition (30). Activated, they produce several inflammatory response proteins: Cytokines (IL 1β, IL 6, and TNFα) and matrix-degrading enzymes (matrix metalloproteinases (MMPs) and a disintegrin and metalloprotease with thrombospondin-like motifs (ADAMTS)) (64). The innate immune system is activated in OA, and the expression of complement are abnormally high in OA joints (219). Chondrocytes also express receptors that bind advanced glycation end products, which accumulate in ageing tissues and lead to catabolic processes (128, 173).

II. Subchondral bone

Subchondral bone is highly innervated by sensory nerves and could be one of the main sources of pain in OA. Thickening of the subchondral bone occurs due to increased production of collagen that is improperly mineralized, and is also associated with vascular penetration. Osteophytes form at the joint margins, often at the insertion site of tendons or ligaments. Subchondral bone remodeling might result from directly increased loading through loss of cartilage, or as a response to growth factors as the body attempts to repair cartilage.

III. Synovium

Synovitis and synovial hypertrophy with increased vascularity is common in OA (187). Cells in the synovium produce hyalorunic acid and lubricin that work as lubricants within the joint, but this lubricating effect might be reduced in OA joints (20, 130). Synoviocytes also release inflammatory mediators and degradative enzymes, as described under “Cartilage” (64).

IV. Systemic inflammation

Why obesity is a risk factor for OA in non-weight-bearing joints is not understood (237), but low-grade systemic inflammation may be important in its pathogenesis and symptomatology (96, 203). Adipose tissue increases the levels of systemic inflammation. White adipose tissue produces adipokines (leptin, resistin and chemerin) and inflammatory cytokines (tumor necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6)) (126). Proinflammatory factors could

increase the production of proteolytic enzymes responsible for the degradation of the extracellular matrix that results in joint tissue destruction. This could theoretically be a mechanism mediating the association between cardiovascular diseases, diabetes and metabolic syndrome (87).

Diagnosis

The progression of OA is usually slow, and the problem with using symptoms to define OA is that they appear only when the disease is advanced (17). Symptoms are preceded by preclinical structural changes, and non-surgical interventions are probably most effective in this early stage of the disease. The OA diagnosis can therefore be thought of as a continuum, from the preclinical molecular changes to symptomatic OA and, for those with severe symptoms, THR or TKR (Figure 11).

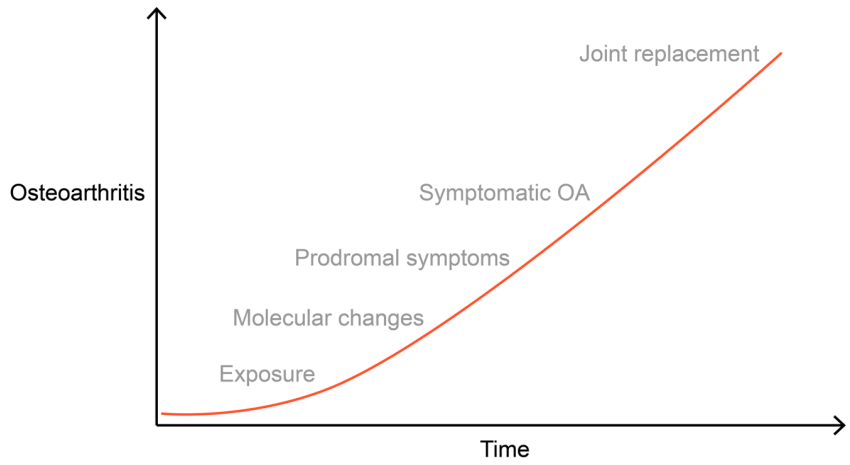


Figure 11: The OA continuum. (Based on diagram from Stefan Lohmander; Lecture 28th of June 2017 at Oslo University Hospital.)

Biochemical markers

Several biochemical markers have been proposed as markers for early OA, like CTX-II (C-terminal telopeptide of collagen type II) in urine and cartilage oligometric matrix protein in serum (213). However, their sensitivity and specificity is lower than imaging (64). When these markers are measured systemically it is difficult to determine which site they originated from since this is in the preclinical stage, and they have so far had little ability to predict symptoms (67).

Imaging

The classic imaging modality for OA diagnostics is plain film radiography. The OA joint is associated with narrowing of the joint space width, osteophyte formation, development of subchondral sclerosis and cysts (Figure 12). As previously described, the degree of radiological OA can be quantified by the Kellgren-Lawrence scoring system (105). The Osteoarthritis Research Society International (OARSI) have also developed an atlas for individual radiographic features in OA (11). Joint space narrowing is, however, the most sensitive radiographic finding in both hip and knee OA, and may be the preferred method for evaluating structural severity of hip and knee OA in clinical trials (68, 69). MRI is more sensitive than radiographs in detecting early structural joint changes (71), and is the recommended modality for assessing cartilage morphology (35). But as asymptomatic structural abnormalities are very common in the older population, it should not be used as a screening tool for OA (71). Ultrasonography is used more often for diagnosing OA, with validity increasing as technology improves (104). CT (computer tomography) has no place in primary OA diagnostics.

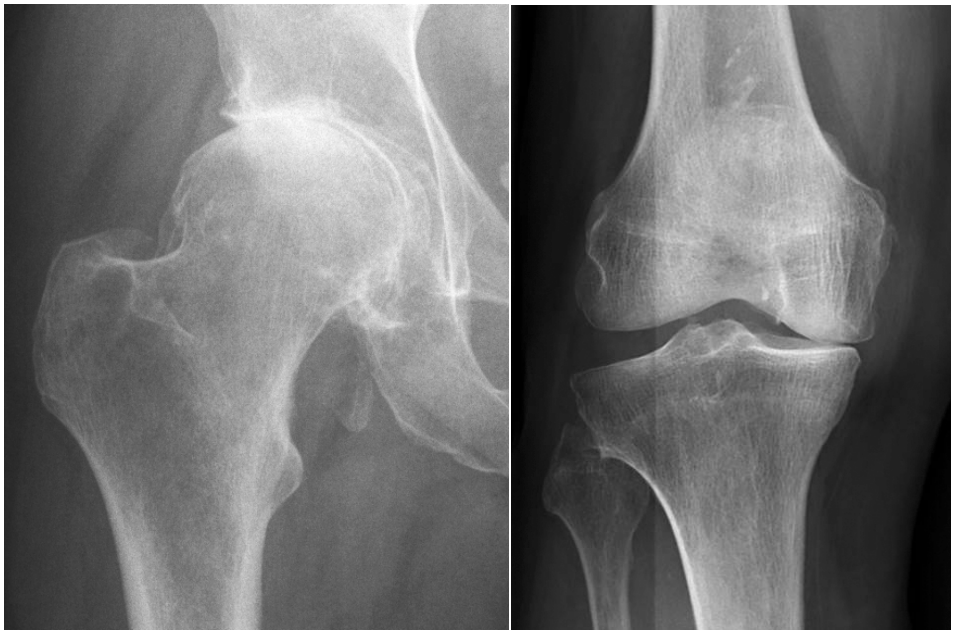


Figure 12: Radiographic hip and knee OA. Copyright Dr. Lars Nordsletten; reproduced with permission.

Clinical criteria

Symptoms related to the joint are imperative for the diagnosis of clinical OA. However, despite being a common disease it can be difficult to diagnose. The criteria from the American College of Rheumatology (ACR) (9, 10, 233) use joint pain and radiographic and/or laboratory findings as the basis for defining the diagnosis. These criteria are designed to differentiate between OA and other forms of arthritis (rheumatoid arthritis/ankylosing spondylitis). Self-reported OA had a

sensitivity of 73% and specificity of 96% compared to the ACR criteria for knee OA, and a sensitivity of 81% and specificity of 94% compared to the ACR criteria for hip OA (134, 174).

Osteoarthritis Research Society International (OARSI) Disease State working group further separate between the structural changes that characterize OA at the joint level ("disease") and the patient experience of OA ("illness") (118). This differentiation is, however, most useful in a research setting for designing trials and recruitment.

Treatment

Current medical treatments for OA aim to relieve the pain (symptom modifying drugs), rather than treat the cause of the disease, as no licensed treatments can stop the progression of structural changes within the joint (structure modifying drugs) (229).

There are several evidence-based guidelines for the treatment of OA from the American College of Rheumatology (ACR) (84), European League Against Rheumatism (EULAR) (100, 239) and OARSI (137, 240, 241). Although somewhat different, they are all based on the following principles of prevention and treatment:

1. Primary prevention: Avoiding overweight reduces the risk of OA (13, 15, 60). It is inexpensive and should be the primary prevention strategy in most cases. Physical activity could be important for preventing the development of knee OA, but may need to be modified once structural damage has developed (135).
2. Secondary prevention (non-pharmacological interventions): Weight loss reduces pain and improves function, and might also be associated with a reduced rate of progression of structural damage (55, 90, 117, 140, 209). Cochrane reviews have reported that physiotherapy and exercise programmes for hip and knee OA can improve physical function and reduce pain (61, 62). The combination of exercise and weight loss have an additive effect in pain reduction (140). Exercise has also been shown to delay the need for THR (208).
3. Pharmacological interventions: It is advised to start with topical NSAIDs and/or oral paracetamol (241). Oral NSAIDs are common oral pharmacological agents used for treatment of OA, although they can have side effects like gastrointestinal and cardiovascular complications (135). Intra-articular corticosteroids can only provide short-term pain reduction for around four weeks (18), and long-term use is associated with significantly greater cartilage volume loss (138). Hyaluronic acid was shown to have only a small and clinically irrelevant effect in a recent meta-analysis (184).

Structure modification: Use of agents that could potentially inhibit or reduce the structural progression of OA, like chondroitin sulfate and glucosamine sulfate, have not demonstrated significant effects in meta-analysis (227). Further clinical trials on the possible structure modifying drug strontium ranelate have been limited due to its possible association with cardiovascular morbidity (135). Oral bisphosphonates have been reported to decrease biochemical markers of cartilage degradation, but did not decrease symptoms or slow radiographic progression (24). Intravenous bisphosphonates may reduce knee pain and the areal of bone marrow lesions (an early marker of OA) (121). A recent study also found reduced risk of TKR in knee OA patients who started taking bisphosphonate (152)

4. Surgery

   Arthroscopic knee surgery: Arthroscopic debridement is not indicated as a treatment for knee OA (108, 193), nor with mechanical locking symptoms (192).

   Arthroscopic hip surgery: Recontouring proximal femur to avoid femuroacetabular impingement has been shown to reduce symptoms and may reduce the risk of future OA (34).

   Microfracture or autologous chondrocyte implantation: Both techniques could slightly reduce short-term pain. Unfortunately microfracture produces mechanically inferior fibrocartilage instead of hyaline cartilage, and autologous chondrocyte implantation is an expensive and technically demanding procedure (74).

   Tibial osteotomy: Tibial osteotomy for unloading the compartment of greatest loading reduces symptoms, and may delay the need for a TKR for up to almost 10 years (199).

   Unicompartmental knee replacement (UKR): UKR is appropriate for older patients because it provides pain relief, but forces a reduction in physical activity. A meta-analysis found no difference in complication rates between tibial osteotomy and UKR (199).

THR or TKR: Joint replacement is a highly effective treatment for severe hip and knee OA (Figures 13 and 14) (198). Individuals considering a TJR should be thoroughly informed about the risks of the procedure and potential severe complications. Patient comorbidities and other potential risk factors must be taken into consideration. The criteria for THR or TKR in Norway are long-term OA pain that is not adequately controlled with conservative treatment, pain during rest and reduced function. Harris Hip

Score measures hip function and symptoms in patients with OA (Appendix A) (75), and Oslo University Hospital Ullevål use the following criteria:

Patients <60 years: Harris Hip Score <60

Patients >60 years: Harris Hip Score <70

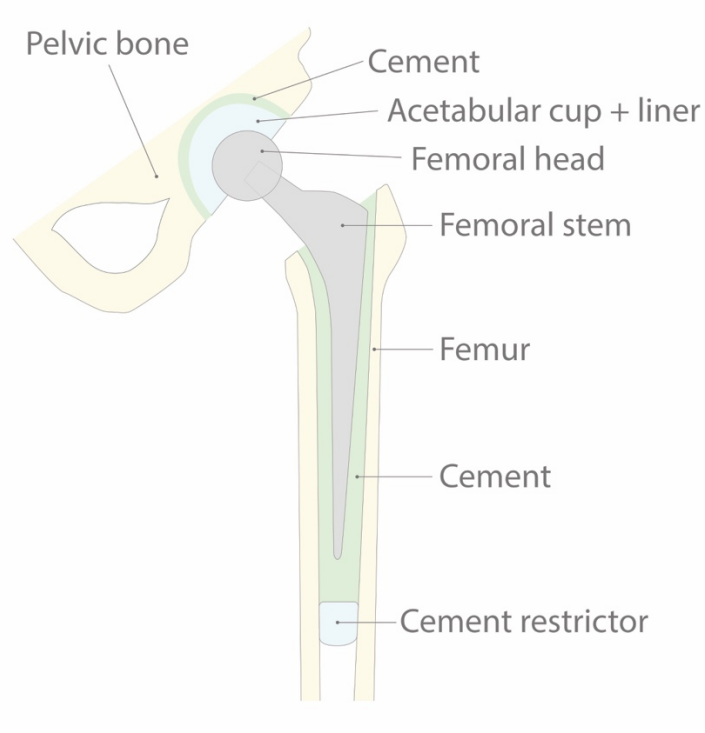


Figure 13: Placement of a cemented total hip replacement (THR); both the acetabular cup and femoral stem can be cemented or uncemented independently.

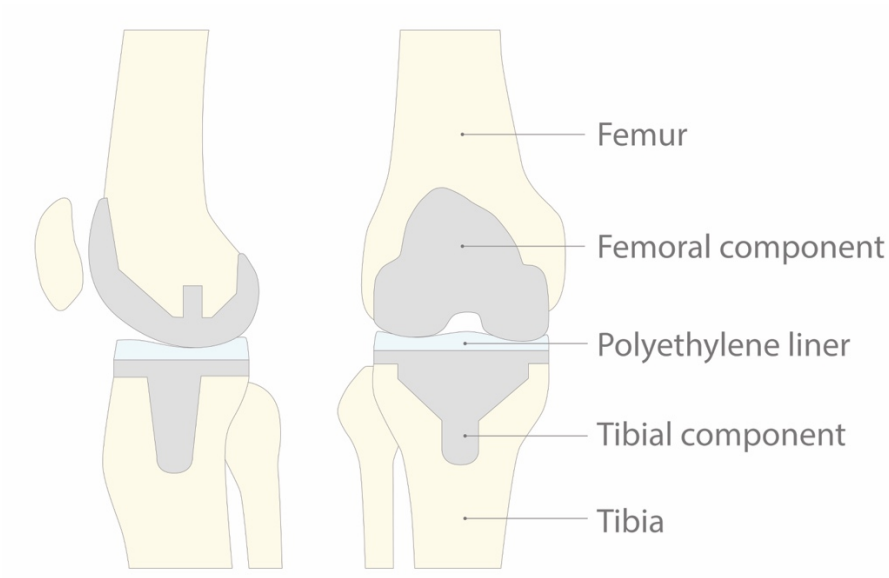


Figure 14: Placement of a total knee replacement (TKR); can be either cemented or uncemented.

Study aims

The main aim of this thesis was to investigate the association between the systemic factors of metabolic syndrome, thyroid function and reproductive and hormonal factors, and the risk of THR or TKR due to primary OA.

Aim of study I: To assess whether metabolic syndrome or its components were risk factors independent of BMI for subsequent THR or TKR due to primary OA.

Aim of study II: To investigate whether thyroid function was associated with subsequent risk of THR or TKR due to primary OA.

Aim of study III: To investigate the association between reproductive history and use of hormonal therapies and the risk of THR or TKR due to OA.

Methods

Study design

All three studies used a prospective study design (Figure 15).

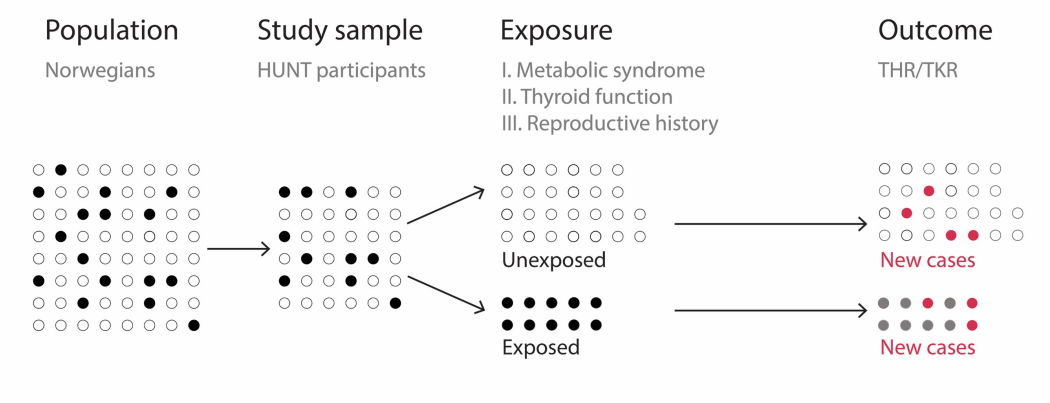


Figure 15: Prospective study design.

Population

In the Nord-Trøndelag Health Study (HUNT) (226) all inhabitants of Nord-Trøndelag county aged 20 years or more were invited to participate in three surveys: HUNT1 (1984-1986), HUNT2 (1995-1997) and HUNT3 (2006-2008) (112) (Figure 16). HUNT4 began in September 2017. HUNT was initially intended to investigate arterial hypertension, diabetes, tuberculosis and quality of life, but the scope of the study expanded over time. The response rate was 89.4% in HUNT1, 69.5% in HUNT2 and 54.1% in HUNT3 (an overview of the non-participants is found in the chapter *Discussion*). This thesis used data from HUNT2 and HUNT3, as HUNT1 did not collect blood samples. The majority of the population is Caucasian, and in 1995 the population was 127 000. The county is mostly rural (86).

The participants filled out self-administered questionnaires (25) (full versions of the questionnaires are available at https://www.ntnu.edu/hunt/data/que). The survey also included a health examination by trained personnel, including height, weight, waist circumference and blood pressure. Analyses of the non-fasting blood samples used for this thesis included high-density lipoprotein cholesterol (HDL), triglycerides and glucose. The survey also collected other data, and a more comprehensive description can be found elsewhere (86, 120).

Figure 16: Map of Norway with the Nord-Trøndelag County.

Study population paper I

There were 65 237 (69.5%) participants at baseline in HUNT2 (112), and 63 617 had measurements of all metabolic syndrome components at baseline. Of these, 956 were excluded (Figure 17) due to previous joint replacement in the hip or knee (n=796), missing date of operation (n=158), or emigration during baseline period (n=2). Thus, a total of 62 661 people (32 990 women and 29 671 men) were included in this study.

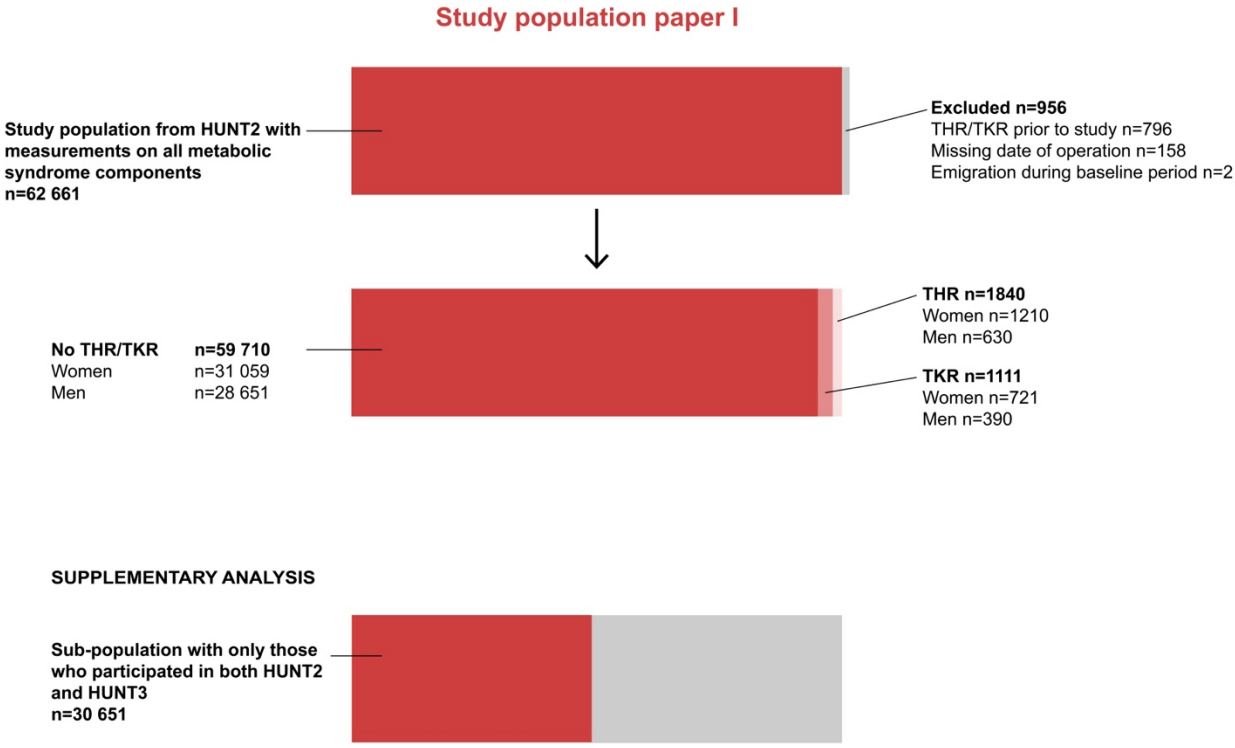


Figure 17: Selection of study population in paper I.

Study population paper II

This study included data from both HUNT2 and HUNT3. In HUNT2 TSH was measured in 35 269 persons; in all women over 40 years old, in a random 50% sample of men over 40 years old and in a random 5% sample of participants aged 20-40 years. In HUNT3, TSH was measured in 49 179 participants. We included 35 269 participants from HUNT2 and 13 132 new participants with TSH measurements from HUNT3 (Figure 18). In persons that participated in both HUNT2 and HUNT3, baseline measurements from HUNT2 were used in the main analyses. Among these 48 401 individuals, 10 510 were excluded from analysis. The exclusion criteria included self-reported thyroid disease (hypothyroidism, hyperthyroidism, goiter, other thyroid disease, use of levothyroxine, carbimazole, previous thyroid surgery or radioiodine therapy) (n=3895), missing information on BMI (n=364), missing information on smoking (n=962), previous THR or TKR (n=644), missing date of operation (n=99), emigration during baseline measurements period (n=1) or self-reported OA at baseline (n=4545). Thus, a total of 37 891 people (22 714 women and 15 177 men) were eligible for follow-up in this study.

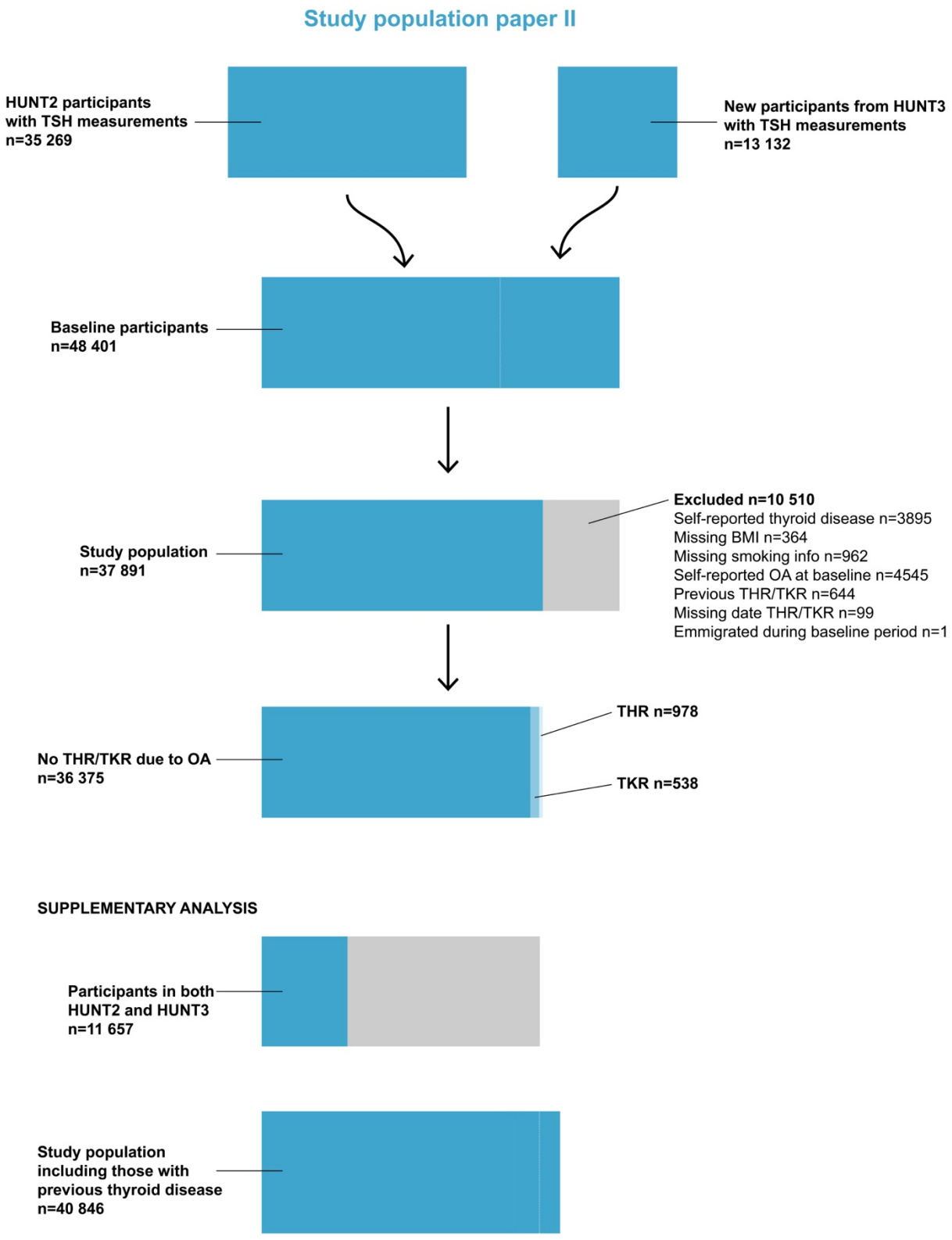


Figure 18: Selection of study population paper II.

Study population paper III

This study used data from both HUNT2 and HUNT3. In total, 35 280 women participated in HUNT2 (75.5% of those invited), and 27 758 in HUNT3 (58.7% of those invited) (112). Our study included baseline data from HUNT2 or HUNT3 as these surveys included questionnaire and interview data on reproductive history and covariates. We included women aged ≥30 years at baseline, and our study population consisted of 11 746 participants from HUNT2, 20 459 participants of both HUNT2 and HUNT3 and 4652 participants from HUNT3 alone (Figure 19). For those who participated in both HUNT2 and HUNT3, we used baseline measurements from HUNT3 in order to include as much information as possible on reproductive history and eventual use of HRT. We excluded women that had undergone bilateral oophorectomy or/and hysterectomy (n=3710). Bilateral oophorectomy in premenopausal women induces premature menopause (190), and women who undergo a hysterectomy with ovarian preservation may almost double their risk of premature menopause compared to women with intact uteri (148). After also excluding 1183 participants with joint replacement before recruitment, 91 with missing date of operation, 436 with missing BMI and 1148 with missing information on smoking, the analyses included 30 289 women.

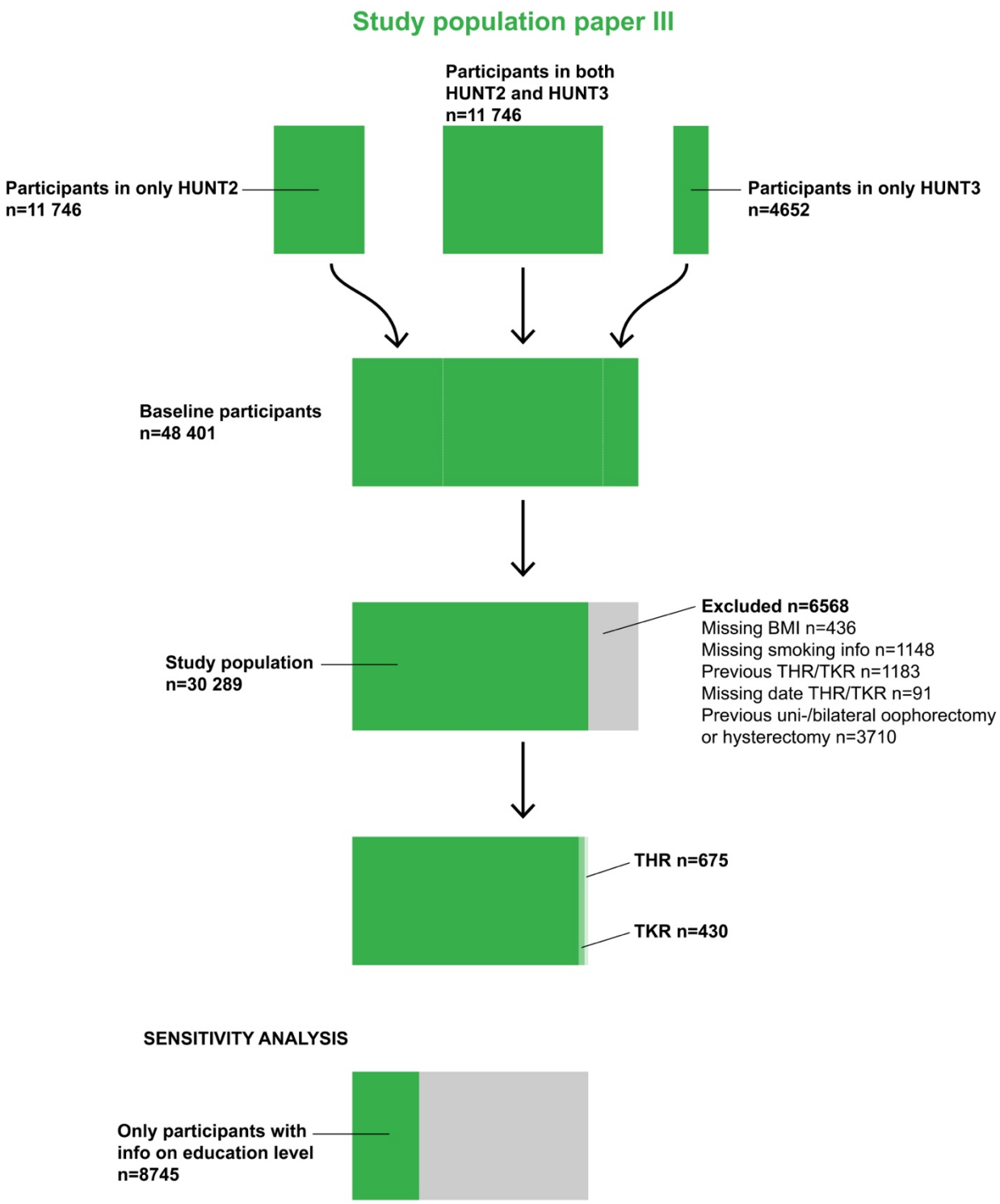


Figure 19: Selection of participants paper III.

Exposures and covariates

Table 3: Exposures paper I

Exposure variables	***Criteria*** [1]	***Measurement***
Waist circumference (cm)	≥88 cm in women or ≥102 cm in men	Waist circumference was measured horizontally at the height of the umbilicus to the nearest centimeter, the participant standing with the arms hanging relaxed.
Blood pressure (mmHg)	Systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg	Blood pressure was measured on the right arm with cuffs adjusted according to the arm circumference, and after the participant had been sitting relaxed for five minutes. Automated measures based on oscillometry were used [2]. Systolic and diastolic blood pressure was then read three times with one minute intervals, and the mean of the second and third readings was used.
Hypertensive medication	Yes/No	Questionnaire: "Are you taking medication for high blood pressure?"
Triglycerides (mmol/L)	≥1.7 mmol/L	Non-fasting blood samples were drawn from each participant. Serum levels of triglycerides, HDL cholesterol and glucose were analysed on a Hitachi 911 Autoanalyser [3].
HDL cholesterol (mmol/L)	<1.3 mmol/L in women or <1.0 mmol/L in men	
Serum glucose (mmol/L)	≥11.1 mmol/L [4]	
Diabetes	Yes/No	Questionnaire: "Do you have, or have you ever had any of the following diseases: Diabetes (….)"
Metabolic syndrome	Presence of ≥3 of the following, based on the criteria above: Increased waist circumference Hypertension or hypertensive medication High triglycerides Low HDL cholesterol Elevated non-fasting serum glucose or diabetes	

[1]According to the Joint Interim Statement (8).

[2]Dinamap 845XT; Critikon, Tampa, FL.

[3]Hitachi, Mito, Japan

[4]The Joint Interim Statement definition of metabolic syndrome is based on fasting blood samples. In lack of this we used a modified definition of metabolic syndrome which was also used in previous studies (136, 145), categorizing elevated glucose as serum glucose ≥11.1 mmol/L. This is, however, likely to be a stricter cut-off since it is intended to identify undiagnosed diabetes (12). The self-reported diagnosis of diabetes in the HUNT study has been validated in a separate study, demonstrating that 96.4% of self-reported diabetes could be verified in medical files (144).

Table 4: Exposures paper II

Exposure variables	***Use***	***Measurement***
Thyroid stimulating hormone (TSH)	The participants were placed in five categories according to their TSH level: One category indicating hyperthyroid function (<0.50 mU/L); three categories within the clinical reference range (0.50-1.49, 1.5-2.49 and 2.5-3.5 mU/L); and one category indicating hypothyroid function (≥3.5 mU/L) (82). TSH was also analyzed as both a continuous variable, and as log-transformed continuous TSH	A non-fasting venous blood sample was drawn from each participant. Concentrations of TSH, free thyroxine (fT4) and total triiodothyronine (T3) were measured. [1]
Free thyroxine (fT4) and triiodothyronine (T3)	Overt hypothyroidism: TSH>4.0 mU/L combined with fT4<8.0 pmol/L) Overt hyperthyroidism: TSH<0.10 mU/L and fT4>20.0 pmol/L and/or total T3>2.7 nmol/L [2]	

[1]Samples in HUNT2 were measured at the Hormone Laboratory, Aker University Hospital, Oslo, using DELFIA hTSH Ultra (sensitivity, 0.03 mU/L; and total analytic variation <5%), DELFIA fT4 (total analytic variation <7%), and AutoDELFIA T3 (total analytic variation <5%), all from Wallac Oy, Turku, Finland. In HUNT3, serum TSH and fT4 were measured at Levanger Hospital, Levanger, Norway, using Architect cSystems ci8200 (sensitivity, 0.01 mU/l; and a total analytic variation <5%), and Architect cSystems ci8200 (total analytic variation <6%), respectively, both from Abbott, Clinical Chemistry, USA. The measurement methods of TSH in HUNT2 and HUNT3 have been compared, with similar results (207), and agreement expressed by Bland-Altman (27) did not reveal any obvious pattern or deviations. The Norwegian population is considered to have sufficient iodine intake (102), and the reference range for clinically normal TSH was defined as 0.50 to 3.5 mU/L based on previous publications from this population (25).

[2]This classification by overt hypo- or hyperthyroidism was made possible by the fT4 measurements taken in people whose TSH levels were <0.20 mU/L or >4.0 mU/L in HUNT2, and in people whose levels were <0.10 mU/L or >3.0 mU/L in HUNT3. Total T3 was only available in HUNT2 and only measured if TSH levels were <0.20mU/L.

Table 5: Exposures paper III

Exposures	***Use***	***Measurement***
Parity	Nulliparous, 1, 2, 3, 4+ births	HUNT2 questionnaire: How many children have you had? HUNT3 interview: If you have been pregnant, how many children have you given birth to? [1]
Age at menarche	≤11, 12, 13, 14, ≥15 years	HUNT2 questionnaire: How old were you when you started menstruating? HUNT3 interview: How old were you when you began menstruating (got your period)? [1]
Menopausal status	Pre/peri- and postmenopausal	HUNT2 questionnaire: Do you still menstruate? [2] HUNT3 interview: How old were you when you stopped menstruating? [1]
Age at menopause	≤48, 49-51, ≥52 years	HUNT2 questionnaire: How old were you when you stopped menstruating? HUNT3 interview: How old were you when you stopped menstruating? [1]
Years of menstruation	Continuous (years)	Age at menopause minus age at menarche
Oral contraceptive (OC) use	Never or ever Duration of use	HUNT2 questionnaire: Have you ever taken birth control pills or the mini pill? [2] For how long did you take contraceptive pills altogether? [2] HUNT3 questionnaire: Do you take or have you taken birth control pills? [2] How many years in total have you taken birth control pills? [2]
Hormone replacement therapy (HRT) use	Never, past and current Local or systemic Duration of use	HUNT2 questionnaire: Hormone treatment (not birth control): Have you taken estrogen in any form? (Tablets/patches and/or estrogen cream/suppositories) If yes: How old were you the first time that you were prescribed estrogen? For about how many years did you use estrogen? If you are currently using estrogen, what is the name of the product? HUNT3 questionnaire: Have you ever used medicines containing estrogen? (Tablets/patches and/or estrogen cream/suppositories) If yes: How old were you when you began? How old are/were you the last time you took/used it?

[1] Asked women between 19 and 55 years old in HUNT3.

[2] Asked women under 70 years.

Table 6: Covariates

Covariate	***Use***	***Measurement***
Age (years)	Continuous	Age at baseline
Body Mass Index (BMI) (kg/m2)	Continuous	HUNT2 Weight: To the nearest half kilogram (kg) Height: Given in whole centimeters (cm) HUNT3 Weight: Given in kg with one decimal Height: Given in cm with one decimal Measurements were taken with the participants wearing light clothes and no shoes.
Physical activity	The two physical activity variables were combined into one variable indicating intensity and duration: None (no activity) Medium (≤2 hours/week light physical activity and/or <1 hour/week hard physical activity) Hard (≥3 hours/week light physical activity and/or ≥1 hour/week hard physical activity)	Questionnaire: "How much of your leisure time have you been physically active in the last year?" Duration of light physical activity (not sweating or out of breath) physical activity (none, <1, 1-2, ≥3 hours/week) Duration of hard (sweating or out of breath) physical activity (none, <1, 1-2, ≥3 hours/week).
Education	Highest level of education: Primary/vocational (<10 years) Secondary (10-12 years) Post-secondary (≥13 years)	Questionnaire: "What is the highest level of education you have achieved?" [1] Primary school 7-10 years, continuation school, folk high school 1-2 years of high school, university qualifying examination, junior college, A levels University or other post-secondary education, less than 4 years University/college, 4 years or more
Osteoarthritis (OA)	Self-reported OA: Yes or no	Questionnaire: HUNT2: "Has a doctor ever said that you have/have had osteoarthritis?" HUNT3: "Have you had or do you have osteoarthritis?"

[1]Only available in HUNT2.

Outcome – The Norwegian Arthroplasty Register (NAR)

Outcome in our studies was primary THR or TKR due to OA, as a proxy for severe OA. We used data from the NAR. Each participant contributed person-years from baseline until a THR or TKR due to OA, THR or TKR due to other causes, migration, death or end of follow-up (December 31, 2013), whichever occurred first (Figure 20).

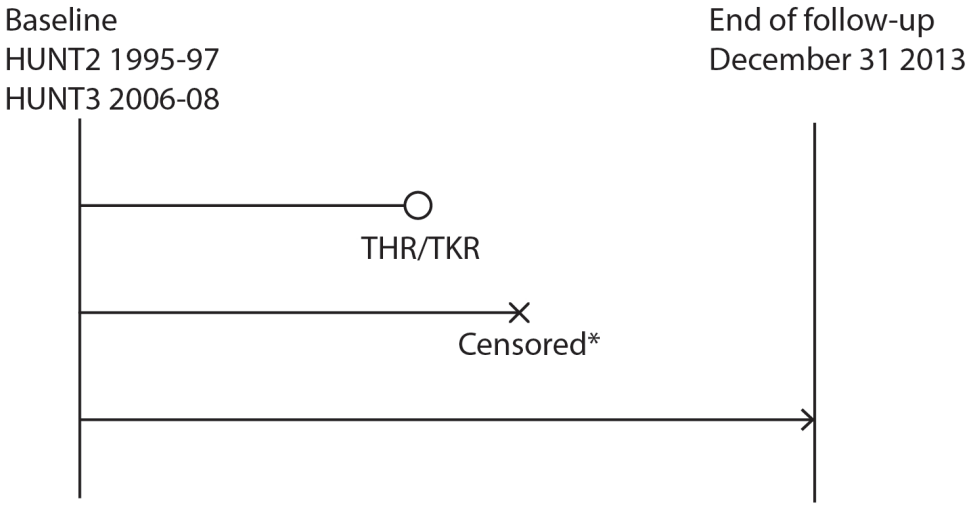


Figure 20: Diagram of timeline for all three studies.
**Censored at date of THR or TKR due to causes other than OA, migration, death or end of follow-up, whichever occurred first.*

The NAR was founded in 1987 by the Norwegian Orthopaedic Association with the intention of detecting inferior implants, cements and techniques (78). Data on THR has been collected since September 1987, and on TKR since 1994 (77). It is a nationwide register with over 95% completeness for primary THRs and TKRs (49). The unique 11-digit identification number of every Norwegian citizen enabled linkage of HUNT data to the NAR. For each arthroplasty performed, the orthopedic surgeon submits a standardized form containing information about the patient, the diagnosis that lead to the arthroplasty, the procedure and the type of implant used (77). THR or TKR due to sequela from fracture, acute fracture, ligament injury, meniscal injury, infection, rheumatoid arthritis, ankylosing spondylitis, Perthes' disease/epiphysiolysis, osteonecrosis of the femoral head or congenital dysplasia were censored. Participants with previous THR or TKR due to any reason or missing date of operation, were excluded from the analysis. Only the first joint replacement counted for participants with more than one THR or TKR during follow-up. The distribution of ages at THR or TKR in our study population were comparable to the nationwide numbers from the NAR (Figures 21 and 22).

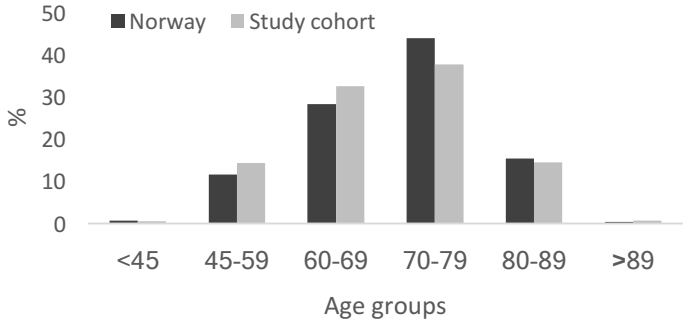


Figure 21: Age distribution in persons receiving a THR; comparing data from the Norwegian Arthroplasty Register (NAR) and our study cohort.

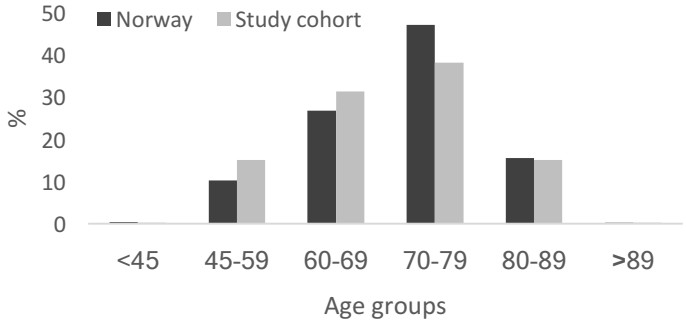


Figure 22: Age distribution in persons receiving a TKR; comparing data from the Norwegian Arthroplasty Register (NAR) and our study cohort.

Choice of confounders

Confounders are associated with both exposures and outcomes, and in our studies they were chosen based on previous literature. We mapped possible casual pathways between variables using directed acyclic graphs (DAGs) (Appendix B) to identify possible confounding pathways (206). Based on these models, the following confounders were included (Table 7):

Paper I: Age (stratified), sex, BMI (continuous), smoking status (never, former, current), physical activity (none, medium, hard) and education (primary, secondary, post-secondary school).

Paper II: Age (continuous), sex, BMI (continuous), smoking status (never, former, current), diabetes (yes or no) and physical activity.

Paper III: Age was used as the time scale. Adjusted for BMI (continuous), smoking (never, former, current), physical activity (none, medium, hard) and other reproductive variables as appropriate for the individual exposures.

Table 7: Confounding variables by paper

Covariate	***Paper I***	***Paper II[1]***	***Paper III[2]***
Age	X	X	X
Sex	X	X	N/A
BMI	X	X	X
Smoking	X	X	X
Physical activity	X	X	X
Education	X		X
Diabetes		X	X
Parity			X
Age at menarche			X
Menopausal status			X
Use of oral contraceptives			X
Use of hormone replacement therapy (HRT)			X

[1]Paper II: Education was not found to be a confounder after analysis in a directed acyclic graph (DAG).

[2]Paper III: Each exposure was analyzed for its interrelationship with other potential hormone-related confounders in a DAG, resulting in a slightly different set of confounders for each exposure (Appendix C).

Characteristics of excluded participants

The 956 participants excluded at baseline in paper I were older, had higher BMIs, lower levels of physical activity, lower education level and more cardiovascular disease than the study population (Table 8). They also had a higher prevalence of metabolic syndrome (37% vs. 20%), and a higher prevalence of the individual components of metabolic syndrome.

In paper II, the 10 510 excluded participants were generally older, had lower levels of physical activity, higher prevalence of diabetes and more were women. Although there was a significant difference in TSH-level between those who were excluded and study participants (2.2 mmol/L and 1.9 mmol/L, respectively), both of these groups are well within the reference range for normal TSH (0.50-3.5 mmol/L).

The same pattern on covariates can also be found in the 6568 excluded participants in paper III, and higher age resulted in a larger proportion of postmenopausal women in this group (91% vs. 56% in the study population). There was also found to be a larger portion of oral

contraception-users in the study population, and a larger portion of HRT-users in the excluded group. However, the groups had similar parity (2.7 vs. 2.6) and age at menarche (13.4 vs. 13.5).

Table 8: Baseline characteristics of excluded and included persons

	Excluded group	***Study population***
Paper I (956 excluded)		
Age (years)	70.6	49.8
Sex (% women)	66.0	52.7
BMI (kg/m^2)	28.2	26.3
Hard physical activity (%)	32.0	40.7
Post-secondary education (%)	6.5	20.0
Cardiovascular disease (%)	19.2	7.7
Increased waist circumference (%)	44.0	20.7
Hypertension (%)	83.8	63.5
High triglycerides (%)	47.9	39.9
Low HDL (%)	26.5	23.1
Impaired glucose tolerance or diabetes (%)	6.5	3.3
Metabolic syndrome (%)	36.7	20.1
Paper II (10 510 excluded)		
Age (years)	62.6	50.7
Sex (% women)	76.8	59.9
BMI (kg/m^2)	27.8	26.5
Hard physical activity (%)	35.0	43.5
Diabetes (%)	7.5	4.0
TSH level (mmol/L)	2.2	1.9
Paper III (6568 excluded)		
Age (years)	66.7	55.7
BMI (kg/m2)	28.0	27.0
Hard physical activity (%)	39.3	46.6
Diabetes (%)	8.2	4.3
Parity (births)	2.7	2.6
Age at menarche (age)	13.5	13.4
Postmenopausal (%)	90.5	56.2
Ever use of oral contraception (%)	50.3	65.7
Ever use of HRT (%)	30.8	17.0

Statistical methods

Cox regression

This thesis used the proportional hazards model, or Cox regression model (38), as the main statistical analysis in all three papers. Cox regression is used for a time-to-event outcome variable; in our case the length of survival of native hip or knee before the event of THR or TKR. All statistical analyses were two-sided with a significance level of $p<0.05$, and the analyses were performed using Stata 14.0/SE (StataCorp LP, College Station, TX, USA).

The effect estimate in Cox regression is called a hazard ratio (HR), and is comparable to the relative risk of TJR at any given time (28). It uses logarithmic transformation to model a linear relationship, which is back-transformed to give a HR. The null value equivalent to a log of zero is 1, and therefore the null value for the HR is 1. HR=1 then indicates no relationship, and in our studies HR<1 indicates a protective relationship and HR>1 indicates an adverse relationship (166).

- When a variable is dichotomous, like hypertension (yes/no), an HR of, for example, 1.41 would mean that people with hypertension have a 41% higher risk of TKR than people without hypertension. (As used in parity, with nulliparous as the reference group with HR=1.0).
- With continuous exposure variables, like TSH, an HR of 1.05 would mean that for each unit of TSH (mmol/L) the HR increased by a factor of 1.05. As this is a logarithmic scale, a change of two units has an increase of 1.05^2, an increase of three units has an increase of 1.05^3 and so on.

Cox regression is also a large sample method, and it is suggested that there should be at least 10 events for each predictor variable (169). It is a semi-parametric statistical model, claiming no assumptions about the shape of the distribution of survival time, but it does require assumptions about proportional hazards. This can be tested graphically:

- Log minus log plot (Figure 23). The assumptions are met if the plots are close to parallel.
- Schoenfeld residual plot (Figure 24). The assumption is met if the regression line is horizontal.

In addition to the graphical assessment, we also performed Schoenfeld residual tests: The assumption about proportional hazards is met if $p\geq0.05$. Age did not meet this assumption in any of the three papers. Therefore, this covariate needed special attention when adjusted for, as described in the following chapter.

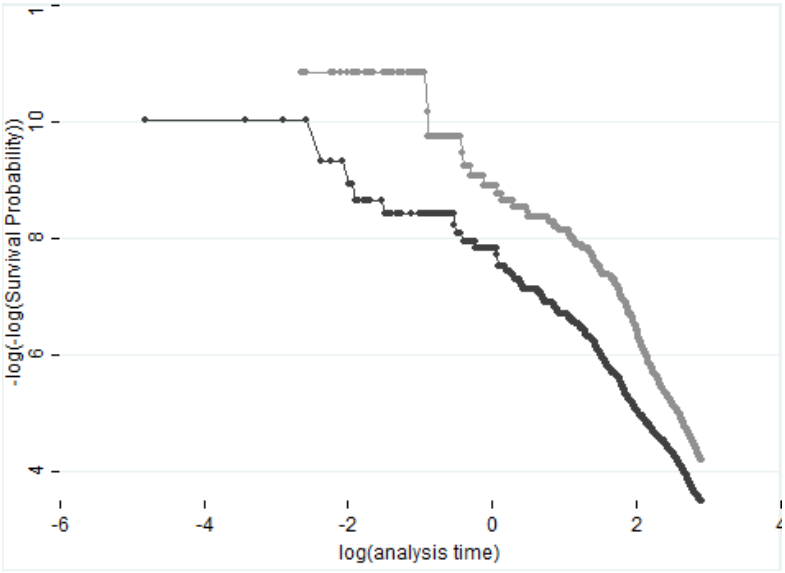


Figure 23: Log minus log plot. The assumption is met if the plots are close to parallel. Here exemplified with waist circumference (dichotomous) as the exposure, and TKR as the outcome.

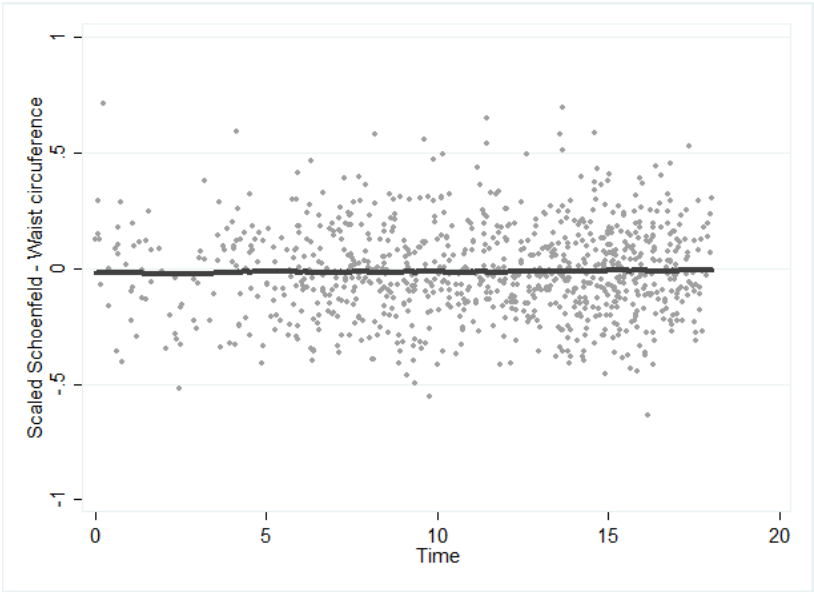


Figure 24: Shoenfeld residuals plot. The assumption is met if the smoothed average is horizontal. Here exemplified with waist circumference (continuous) as the exposure, and TKR as the outcome.

Adjustment for age – different options

The type of time-scale is important as it determines which individuals are considered at risk at a particular time. In cohort studies, time-on-study, adjusted for age as a covariate, is the time-scale normally used. However, age can also be used as the time-scale if the subjects enter the analysis

at their baseline age and exit at their censoring age (31), or age can be converted into a categorical variable to stratify the analyses. Tests of proportional-hazards assumptions were evaluated by Schoenfeld residuals in all covariates, but age did not meet this assumption in any of the three papers. This meant that the risk of THR/TKR did not increase by the same amount for each year of ageing. To solve this problem, we chose different approaches for each of the three papers, all of which will be examined below:

Method A: Time-on-study as the time scale

This model uses time since baseline, with age at baseline included as a covariate. All participants enter the model together at time 0 (baseline) (Figure 25).

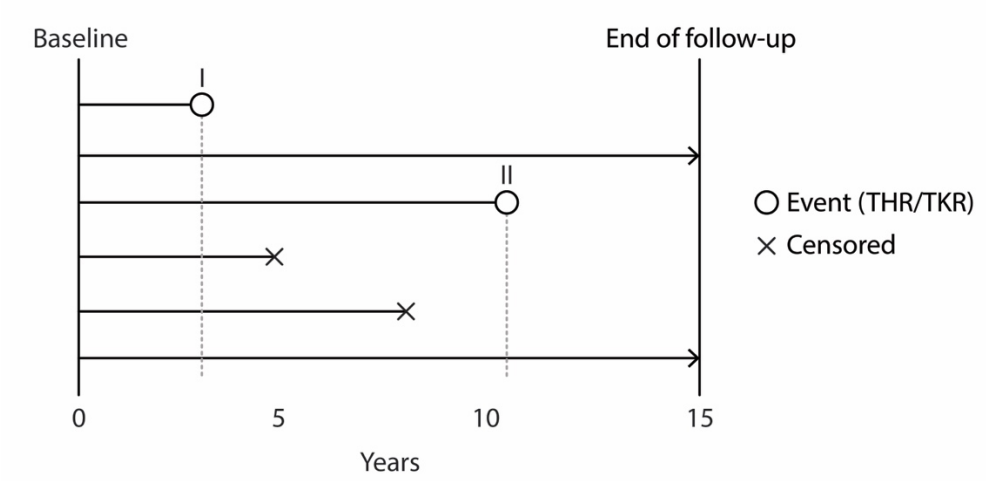


Figure 25: Time-on-study as the time scale.

At the first event (I) all participants are in the risk set, but at the second event (II), only three participants remain in the risk set. This is because three subjects are no longer included in follow-up; one due to an event and two due to censoring (emigration or death). This risk set will include participants of different ages; thus, age is included as a covariate in the model. The effect of age is then modelled linearly, assuming that the risk of THR/TKR increases by the same amount each year. But the underlying risk of THR/TKR associated with age is not linear. In paper II, we did an additional stratified analysis on age, but since this analysis did not show different results age was kept as a continuous variable with time-on-study as the time scale.

Method B: Age as categorical data

The data-set can also be stratified by age without the assumption that the increase in risk of THR/TKR is the same for each year of aging. This method was used in paper I, stratifying the results into age groups <50 years, 50-69.9 years and ≥70 years

Method C: Age as the time-scale

When using age as time-scale, the participants enter the risk set at baseline measurements' age and exit at event or censoring age (Figure 26). Time 0 would then be birth, but they enter the risk set at the age of baseline measurements, provided that they have not been excluded at baseline.

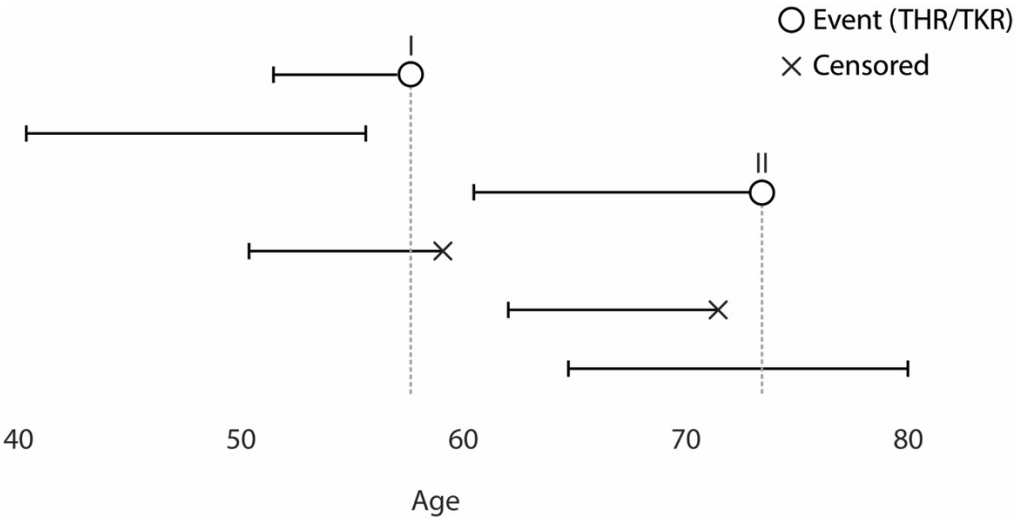


Figure 26: Age as the time scale.

In this example, there are only two participants under follow-up in the risk set at the event (i.e. THR/TKR) at age 58 (I), and two participants under follow-up at the second event (II). The advantage of using age as the time scale is that the event at 58 years of age would not be compared to those at 38 or 78 years (111). A larger difference in risk of THR/TKR is expected between a 38- and a 78-year-old person with similar follow-up times, than between two persons of the same age. Thus, persons with similar risks are in the same risk sets. This method was used in paper III. Retrospectively, this method would also have been the preferable approach in paper II: We therefore re-analyzed the results with this method, but it did not change the results.

Method D: Age as a time-dependent covariate

This model uses time-on-study as the time scale. As noted by Canchola et al. (31): "When the effect of age is modelled linearly, then age as a time-dependent covariate and age as a fixed covariate are equivalent, since if the effect per year of age is constant, then the effect of a given age difference remains the same over time." By definition this approach would therefore give the same results as an analysis with age as covariate. We therefore chose not to use age as a time-dependent covariate in our analyses.

Competing risk

Survival analyses, like the Cox-regression model, analyze the time until a certain event occurs. The Cox model requires independent censoring, meaning that those censored are representative of those under observation at the same time-point (172). However, this assumption is not fulfilled when a study participant experiences an event which prevents the outcome of interest from occurring (Figure 27) (160). This is called competing risk. In this thesis, an example would be the situation when a participant died and was therefore no longer at risk for TJR.

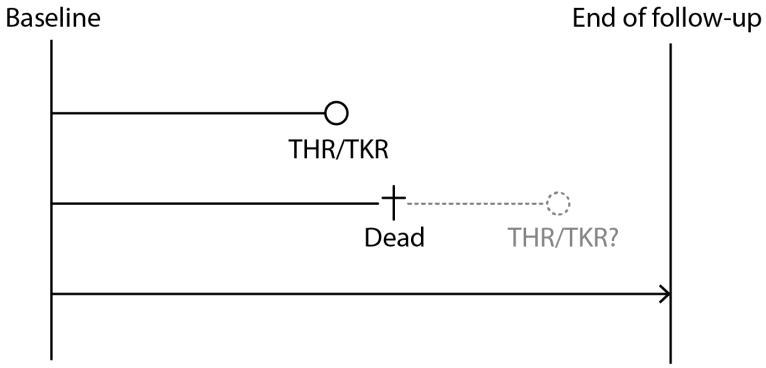


Figure 27: Competing risk of death; an event that could hinder the outcome of THR/TKR.

To decide which method to use for survival analysis in the presence of competing risk, it is essential to separate between aetiological and prognostic research questions: Aetiological research investigates the casual relationship between risk factors and outcome, and prognostic research predicts the probability of an outcome at a given time for an individual patient (160). This thesis aimed to investigate causal relationships, and is thus aetiological research that uses HRs to estimate effect sizes. In this type of research, the Cox regression model is the more appropriate approach, in contrast to the Fine and Gray model used in prognostic research (57). A study from the Swedish Knee Arthroplasty Register found that the parameter estimates from the Fine and Gray model could be misleading if interpreted in terms of relative risk, and the Cox model provided more adequate results (172). For both of these reasons, we chose not to use Fine and Gray models in this thesis.

Other statistical methods

Logistic regression

Logistic regression was used in paper II to investigate the association between TSH level (categorical) and self-reported OA at baseline.

Fisher's exact test

A Fisher's exact test was used in paper II to compare the incidence rate of THR or TKR in participants with and without self-reported thyroid disease at baseline. Although this test was originally intended to be used when expected frequencies are small, the STATA-software makes it possible to apply it to larger data-sets as well. A Pearson's chi-squared test could also be used, and use of this method gave the same results.

Table 9: Overview of statistical methods used in this thesis.

	Paper I	***Paper II***	***Paper III***
Cox regression	X	X	X
Adjustment for age:			
Stratified	X		
Time-on-study as the time scale		X	
Age as the time-scale			X
Logistic regression		X	
Fisher's exact test		X	

Additional analyses

Paper I

To account for potential change in exposure during follow-up, a sensitivity analysis was performed in those who participated in both HUNT2 (1995-1997) and HUNT3 (2006-2008) (n=30 651). By excluding those who changed exposure group between HUNT2 and HUNT3 we were able to do a sensitivity analysis with lower risk of exposure misclassification.

As very few of those between 20 and 30 years of age at baseline were expected to have a primary THR or TKR due to OA, a separate sensitivity analysis also excluded those <30 years in the age group <50 years. Finally, we also did an analysis stratified on both sex and age, to investigate any differences between genders.

Paper II

To investigate whether the change in thyroid function over time was associated with THR/TKR, we did a sub-analysis including only persons that participated in both HUNT2 and HUNT3 (n=19 397). Change in TSH levels between HUNT2 and HUNT3 was used as the exposure

variable. Among these participants, a total of 7740 were excluded due to self-reported thyroid disease (n=2744), missing information on BMI (n=108), missing information on smoking (n=621), previous THR or TKR (n=928), missing date of operation (n=29) or self-reported OA at baseline (n=3310). Thus, a total of 11 657 people was eligible for this sub-analysis. This sub-population was also used in an analysis that investigated whether the results changed when those who started taking thyroid medication after baseline in HUNT2 were excluded.

To see if overt hypo- or hyperthyroidism was associated with THR/TKR, we defined two new exposure groups: One with biochemical hypothyroidism (defined as TSH>4.0 mU/L combined with fT4<8.0 pmol/L), and the other with hyperthyroidism (defined as TSH<0.10 mU/L and fT4>20.0 pmol/L and/or total T3>2.7 nmol/L).

Two additional analyses were performed on the baseline population: First, we investigated the association between TSH level (categorical) and self-reported OA at baseline by using a logistic regression model, adjusting for sex, age, BMI, smoking, physical activity and diabetes. Second, we compared the incidence rate of THR or TKR in participants with and without self-reported thyroid disease at baseline using Fisher's exact test. After excluding participants with missing information on BMI and smoking, previous THR or TKR, missing date of operation or self-reported OA at baseline, 2955 participants reported thyroid disease.

Paper III

Information on education level was only available for 8745 participants from HUNT2. To investigate whether education level affected our results, an additional sensitivity analysis adjusting for education was performed for this group.

Ethics

Participation was voluntary and each participant gave informed, written consent (86). Participants can withdraw from the study at any time. This consent includes linkage to other registries after approval from the Data Inspectorate/Regional Committee for Medical Research Ethics (REK). The HUNT Study is approved by the Data Inspectorate of Norway and REK. All data files for research purposes are de-identified before they are exported to researchers.

NAR has concession from the Data Inspectorate and REK. NAR collects information on diagnosis, date and indication for surgery and information concerning the surgical procedure of arthroplasty. Willingness to be included in NAR does not affect the treatment of the patient. Participants can withdraw from the register at any time, and all data will then be deleted. This PhD project was approved by REK (Ref. nr. 2013/151/REK Sør-øst C).

Results

Paper I

Of the 62 661 participants, 12 593 (20%) were identified as having metabolic syndrome. At baseline, women and men had a mean age of 49.9 years (SD 17.2) and 49.7 (SD 16.7), respectively. Correspondingly, mean age at joint replacement was 69.9 years (SD 9.3) and 69.0 years (SD 9.2). In total, 1840 persons received THR (2.9%), and 1111 persons received TKR (1.8%) during a mean follow-up time of 15.4 (SD 4.3) years.

Metabolic syndrome and THR

No association was found between metabolic syndrome or its individual components and increased risk of THR (Figure 27). In the age group <50 years there was a decreased risk of THR in those with full metabolic syndrome (HR 0.58, 95% CI 0.40-0.83). However, persons with impaired glucose tolerance or diabetes in the groups 50-69.9 and ≥70 years had a significantly decreased risk of THR, with HR 0.65 (95% CI 0.36-0.87) and HR 0.30 (95% CI 0.13-0.67). Participants ≥70 years with hypertension had a decreased risk of THR (HR 0.63, 95 % CI 0.43-0.92). In the youngest age group, <50 years, there was also a decreased risk of THR in those with low HDL (HR 0.72, 95% CI 0.54-0.94).

Metabolic syndrome and TKR

Metabolic syndrome was not associated with the risk of TKR. High waist circumference increased the risk of TKR in the age groups <50 years (HR 1.62, 95% CI 1.10-2.39) and 50-69.9 years (HR 1.43, 95% CI 1.14-1.80) (Figure 28). Hypertension significantly increased the risk of TKR in the age group <50 years (HR 1.38, 95% CI 1.05-1.81). Apart from these findings, none of the other components of metabolic syndrome were associated with increased risk of TKR. However, low HDL was associated with decreased risk of TKR in both those <50 years (HR 0.67, 95% CI 0.49-0.92) and ≥70 years (HR 0.53, 95% CI 0.33-0.86).

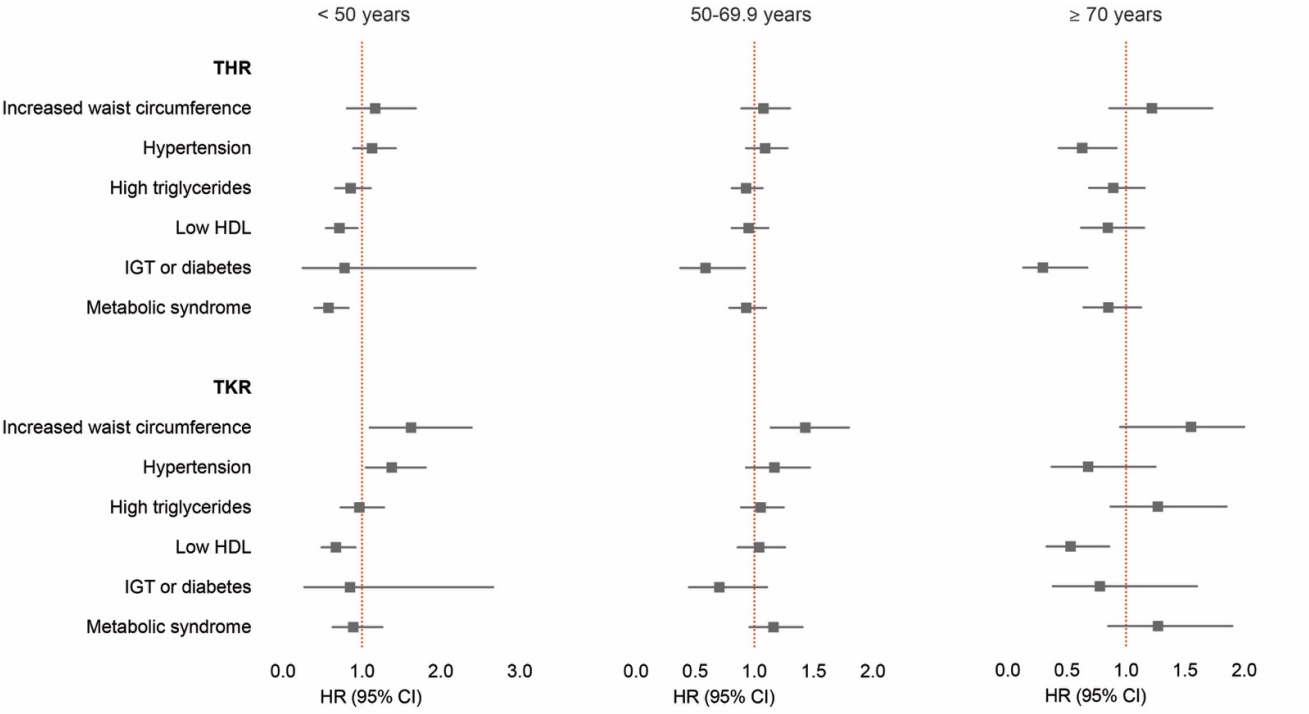


Figure 28: Risk of THR and TKR by metabolic syndrome components and metabolic syndrome. (BMI: Body mass index; HDL: High-density lipoprotein; IGT: Impaired glucose tolerance).

Additional analysis

Of the 30 651 people that participated in both HUNT2 (1995-1997) and HUNT3 (2006-2008), 31.8% changed exposure group from normal to increased waist circumference, and 16.2% changed exposure group from no metabolic syndrome to metabolic syndrome (Figure 29). When analyzing only those who had not changed exposure group in each category, there was no longer a decreased risk of THR in participants <50 years with metabolic syndrome or low HDL. In this analysis, increased waist circumference was also found to be a risk factor for THR in people <50 years (HR 1.80, 95% CI 1.05-3.10), and there continued to be an increased risk of TKR in the age groups <50 years (HR 4.13, 95 % CI 2.15-7.93) and 50-69.9 years (HR 1.43, 95 % CI 1.02-2.01). In contrast to the main analysis, hypertension was no longer a protective factor for THR in persons ≥70 years, nor was impaired glucose tolerance or diabetes protective for THR in persons between 50-69.9 years or ≥70 years.

When stratifying on both sex and age, we found increased risk of TKR only in men >50 years with hypertension (HR 1.65, 95% CI 1.12-2.44). However, there was still an increased risk of TKR in both men and women between 50-69.9 years with increased waist circumference.

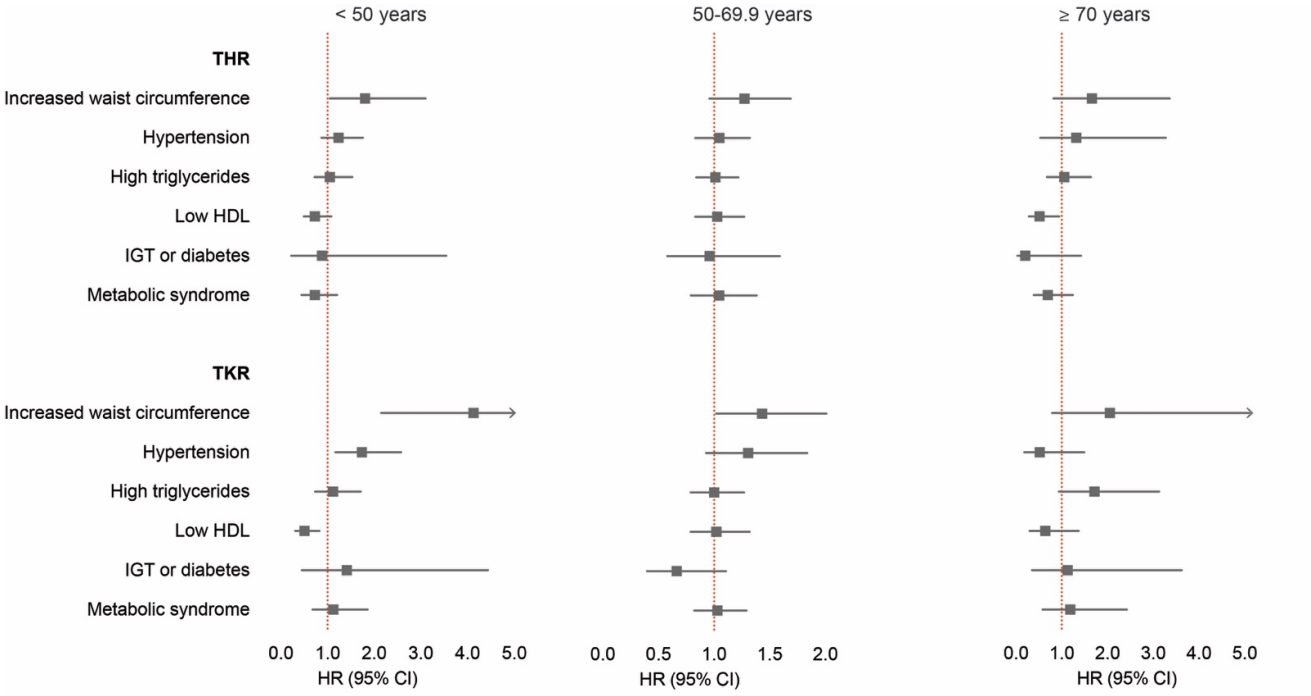


Figure 29: Risk of THR and TKR by metabolic syndrome components and metabolic syndrome including only those who did not change exposure groups during follow-up. Hazard ratios (HRs) adjusted for sex and BMI. (BMI: Body mass index; HDL: High-density lipoprotein; IGT: Impaired glucose tolerance).

Paper II

Of the 37 891 participants, 908 (2.4%) had low TSH (<0.50 mU/l) indicating hyperthyroid function, and 2307 (6.1%) had high TSH (≥3.6 mU/l) indicating hypothyroid function. In total, 978 received THR and 538 received TKR during a median follow-up time of 15.7 years (mean 12.3 years). At baseline, the mean age was 50.7 years (SD 15.8), and the mean ages at THR and TKR were 69.5 years (SD 8.9) and 69.4 years (SD 8.4), respectively.

TSH level did not influence the risk of THR or TKR (Figure 30). Analyses using TSH as a continuous variable did not show any association between TSH and THR or TKR (Figure 31). Additional log-transformation of TSH as a continuous variable did not significantly change these results (data not shown).

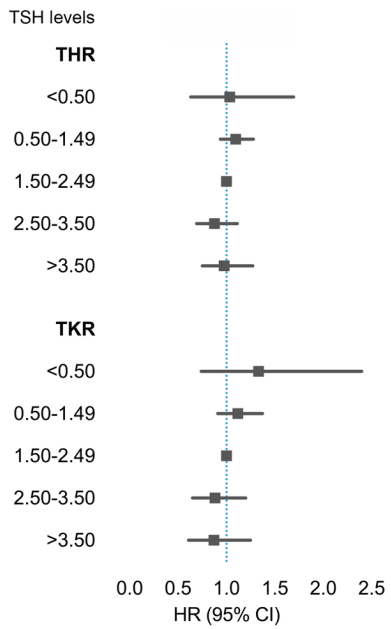


Figure 30: Association between TSH (thyroid stimulating hormone) categories and total hip replacement (THR) or total knee replacement (TKR). Hazard ratios (HRs) adjusted for age, sex, BMI, smoking, physical activity and diabetes.

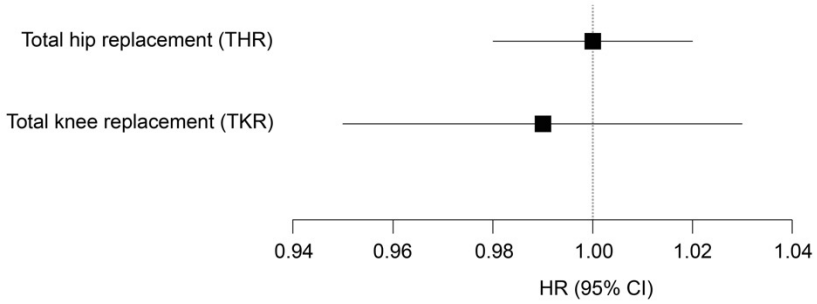


Figure 31: Association between continuous TSH (thyroid stimulation hormone) and total hip replacement (THR) or total knee replacement (TKR).

Paper III

For the 30 289 women included in the study population, the mean age at baseline was 55.7 and mean follow-up time was 8.3 years (SD 4.5). In total, 430 participants had a primary TKR, and 675 had a THR.

Increasing age at menarche was inversely associated with the risk of TKR (p-trend<0.001) (Figure 32). Compared to women with early menarche, those with menarche at 14 years and ≥15 years had a significantly lower risk of TKR (HR 0.64, 95% CI 0.43-0.95; and HR 0.52, 95% CI 0.34-0.80; respectively). The number of years of menstruation between menarche

and menopause was not associated with TKR. Past users of HRT were at higher risk of TKR compared to never users (HR 1.42, 95% CI 1.06-1.90), but only those who used systemic HRT compared to local treatment (HR 1.40, 95% CI 1.03-1.90). Ever users of oral contraceptives had a higher risk of TKR (HR 1.38, 95% CI 1.03-1.84), but this association was only borderline significant in the fully adjusted model (HR 1.36, 95% CI 1.00-1.86).

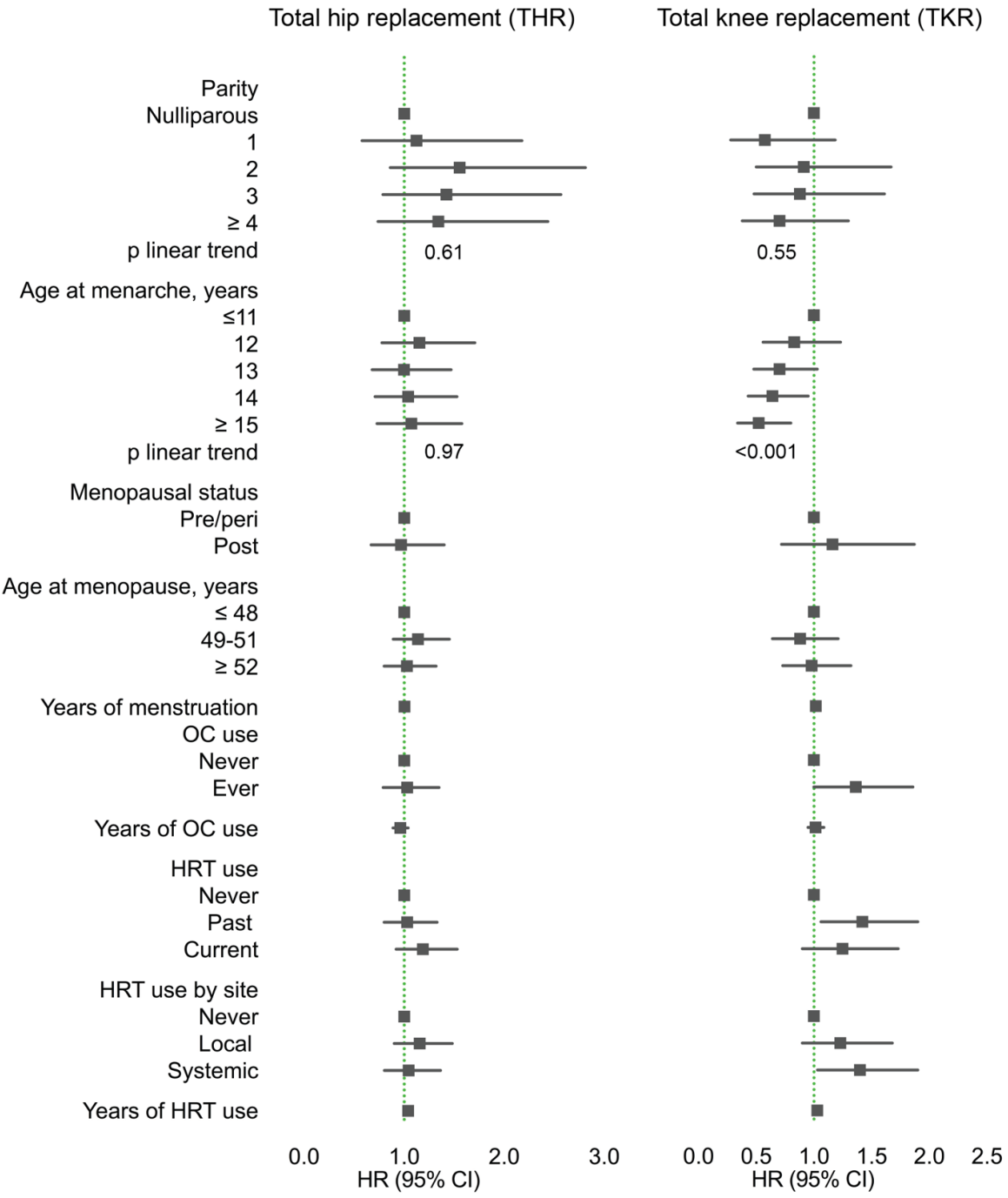


Figure 32: Reproductive history and use of hormonal medication, and risk of THR and TKR. (OC: Oral contraceptives; HRT: Hormone replacement therapy.)

Discussion

This chapter will first discuss the principal finding from each study, and then the methodological challenges that apply to all three studies.

Principal findings

Paper I

We did not find any association between full metabolic syndrome and THR or TKR in the main analysis (Figure 27), except in persons <50 years with metabolic syndrome, who were found to have a decreased risk of THR (HR 0.58, 95% CI 0.40-0.83). However, our study had information on the development of exposure about 10 years after baseline, and that made it possible to account for changes in the exposure status of metabolic syndrome during follow-up: 16.2% of those who participated in both HUNT2 and HUNT3 went from unexposed to exposed. This misclassification of exposure could have affected the results. We therefore did a sensitivity analysis including only those whose exposure status did not change during the first 10 years of follow-up and found that metabolic syndrome was no longer associated with decreased risk of THR in those <50 years. As in the main analysis, in none of the other age strata was metabolic syndrome found to be a risk factor for THR or TKR. We therefore concluded that metabolic syndrome was not an important risk factor for THR or TKR independent of BMI.

We found an increased risk of TKR in participants <50 years with hypertension, and this effect was strongest in men. Hypertension as a risk factor for TKR is consistent with previous findings by Hussain et al. (146). In both the Chingford study from the UK and the ROAD study from Japan, hypertension was found to be associated with OA of the knee independent of BMI (234, 235). A recent study by Niu et al. reported that diastolic blood pressure was related to incident symptomatic OA (159). The prevalence of atherosclerotic risk factors, which include hypertension, has been reported to be higher in individuals with OA (195). It has been hypothesized that vascular pathology of subchondral small vessels could lead to local ischemia and subsequent development of OA (36, 56).

Persons <70 years with increased waist circumference had an increased risk of TKR. Our results were concordant with several previous studies reporting increased central obesity to be a risk factor for OA after adjustment for BMI (129, 146, 221). It may be that the increased amount of abdominal fat tissue releases inflammatory mediators (adipokines, free fatty acids, reactive oxygen species) that in turn affect joints and cartilage (22, 234). Another explanation could be

that a high BMI may be due to either a large muscle/skeletal mass or a large amount of fat tissue. Overweight due to a large muscle mass could be less harmful for the knees than overweight due to a large amount of abdominal fat tissue. Waist circumference may therefore differentiate these two groups.

When analyzing women and men separately, we found that increased waist circumference was a risk factor for TKR in both genders. However, only men with hypertension had an increased risk of TKR. The reasons for this difference are not clear, as one would expect that an underlying biological mechanism of subchondral ischemia was the same in both genders. Further studies on a possible gender-difference regarding hypertension and knee OA are therefore warranted.

Paper II

We did not find any association between thyroid function and the risk of THR or TKR due to OA. Neither were changes in TSH over time, or overt hypo- or hyperthyroidism, associated with incidence of THR or TKR. To the best of our knowledge, this was the first prospective cohort study to investigate the association between thyroid function and risk of OA. In 1996, a cross-sectional study of 577 men and 798 women found no evidence of a significant association between current thyroid status and either chondrocalcinosis or OA (33).

Our findings must be interpreted in relation to recent genetic studies on intracellular T3 availability in joint cartilage. There has been an increased interest in the effect of deiodinase polymorphisms on OA (214). Iodothyronine deiodinases represent a family of proteins involved in local homeostasis of T4 and T3. Three deiodinases have been described, and deiodinase type 2 (D2) and deiodinase type 3 (D3) are detected in bone and cartilage. D2 plays a major role in conversion of T4 to biologically active T3 (110) and thus upregulates local T3 levels. D3 is the main T3-inactivating enzyme and consequently downregulates the local T3 levels. T3 is considered an important regulator of chondrocyte cell growth and differentiation in the endochondral growth plate (180). Local T3 availability, regulated by the opposite functions of D2 and D3, may be a determinant of OA development. D2 has been reported to be upregulated in the cartilage of joints affected by OA compared to joints unaffected by OA (29, 141). However, it is not known if this is a result of the ongoing OA process, or a reflection of the underlying disease pathway. Altogether, these findings suggest that deiodinase regulated local availability of T3 in chondrocytes is a possible factor in the pathophysiology of OA (21, 224). Since our study did not find any association between circulating TSH or T3/T4 levels and OA, it is conceivable

that the serum thyroid hormone levels may be independent of local intracellular T3 levels in joints. Another possible explanation could be that polymorphism in the gene coding for D2 creates a predisposition for non-optimal bone shape (142, 217), leading to increased risk of OA independent of local thyroid hormone levels.

Paper III

This study found that older age at menarche was associated with decreased risk of TKR. We also found an association between past and systemic HRT use and increased risk of TKR. Parity did not increase the risk of TKR or THR.

The observation that increasing age at menarche was inversely related to the risk of TKR has also been reported in a large, prospective study of 1.3 million middle-aged women by Liu et al. (125). The mechanisms underlying these associations are unclear, but there could be several possible explanatory factors. A recent cross-sectional study found an association between early age at menarche and chronic widespread musculoskeletal complaints later in life (113). One may therefore speculate that an increased level of pain from knee OA in this group could lead to a higher incidence of TKR. Early onset of menarche has also been linked to other conditions of ageing such as elevated blood pressure and glucose intolerance, independent of body composition (176). A cross-sectional study by Kalichman et al. demonstrated a negative association between age at menarche and radiological hand OA. They proposed that one possible explanation could be that early menarche was associated with an increased rate of the general ageing process (101). Yet another explanation could be that younger age at menarche may be a marker of other factors such as higher BMI when young (125); weight gain at a young age has been shown to be a significant risk factor for TKR and THR due to OA later in life (13, 15).

Our study did not observe any association between parity and joint replacement. Previous studies on the association between parity and knee OA have shown conflicting results (125, 228, 231). However, the absolute numbers of joint replacements in the nulliparous group in our study were low (n=25 and n=17 for THR and TKR, respectively), which calls the power of this analysis into question. We cannot exclude the possibility that this may have weakened any association. Since both parity and joint replacement are associated with education level, we did a sub-analysis with additional adjustment for education in 8745 participants with data on education level; we revealed a reduced risk of TKR in women with 1 birth or ≥4 births, but there was no significant trend across the categories (p=0.37). This could indicate a complex relationship between parity and TKR/THR that we were unable to clarify further in our study.

Methodological challenges

Error and bias

An epidemiologic study can be viewed as an exercise in measurement, and the aim is to obtain an accurate result (181). Our studies have attempted to find an estimate of the true hazard ratios of the exposures, and major strengths were the large sample size, prospective population-based design, objective measurements and nearly complete registration of outcome variables. Potential sources of error in epidemiological studies can be divided into random and systematic errors (Figure 33).

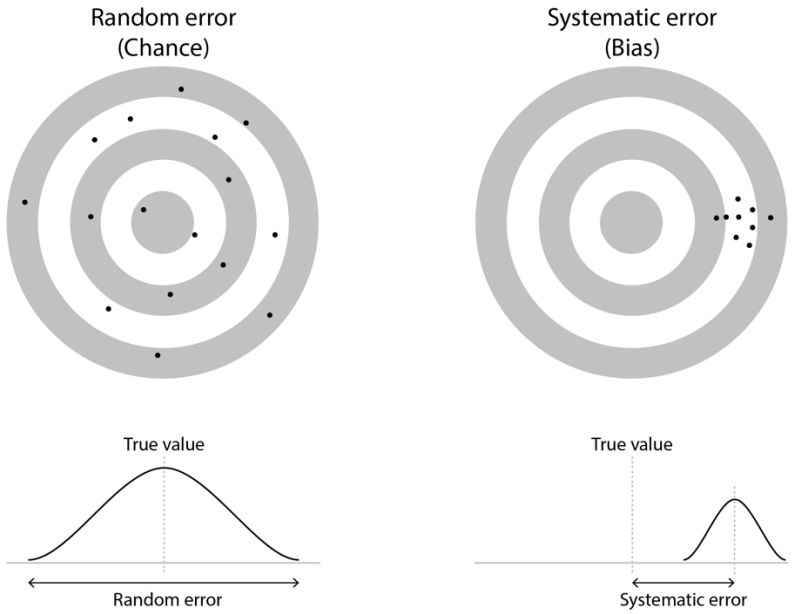


Figure 33: Difference between random and systematic error.

Random error

Random error is the variability in the data that cannot be readily explained, and is also described as random variation or chance (183). The variation in the data-set can be estimated by confidence intervals (CIs), and the width of these intervals describe the amount of random variation and are therefore an estimate of precision. If we increase the sample size, the confidence interval will decrease, and the estimate of the true value will be more precise (Figure 34). An inaccurate blood pressure monitor that provided some measurements that were too high and others that were too low would be an example of random error. Our studies used a relatively large sample size, and therefore had a high precision. But even a large number of participants, and a statistically significant result with a narrow 95% CI, does not necessarily give an estimate of the clinical significance. A statistically significant HR of 1.02, implying a 2% increased risk,

is not necessarily a clinically significant result. In paper III, we found that women with menarche at ≥15 years of age had a significantly lower risk of TKR than those with menarche ≤11 years of age (HR 0.52, 95% CI 0.34-0.80). This would mean a risk reduction of almost 50%, and should be considered to be of clinical significance.

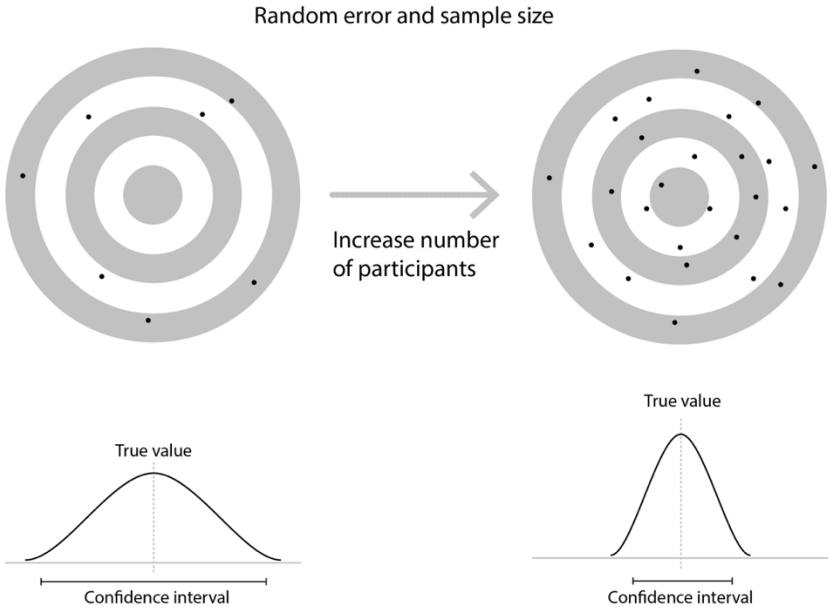


Figure 34: With random error, an increased number of participants will reduce the confidence interval, and thus increase the precision of the estimate.

Systematic error

Systematic error can also be termed bias or a lack of internal validity (183). Since this type of error is not random, a large sample size will not reduce the bias (Figure 35). The large sample size will provide a more precise estimate from the sample, but that does not help since the measurements are systematically wrong. A defect blood pressure monitor that always measured 10 mmHg too high would be an example of systematic error, and increasing the sample size would not affect this error. The aim in epidemiological studies is to reduce this bias for the results to be considered valid (183). There are three main types of systematic error; information bias, selection bias and confounding.

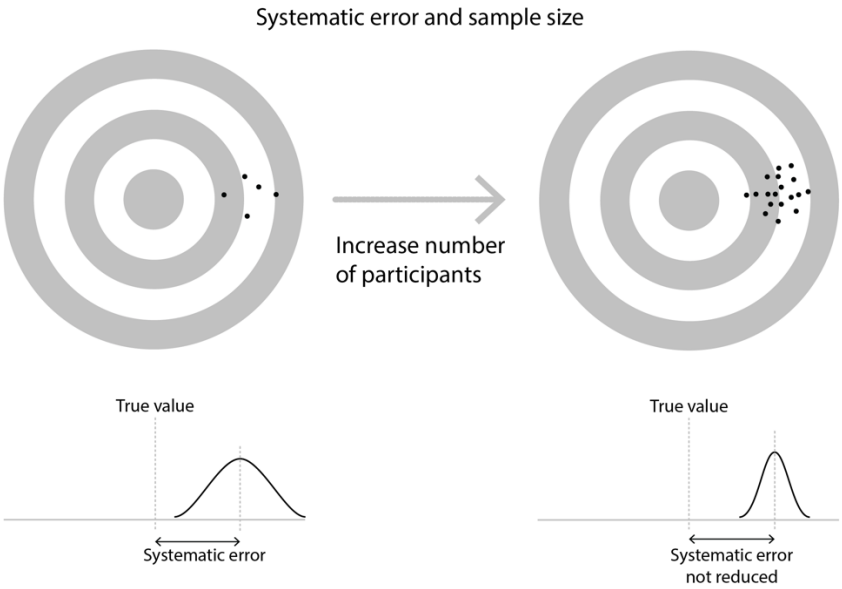


Figure 35: An increased number of participants will not reduce the systematic error.

Information bias

Information bias can be present in a study if the information about a study subject is inaccurate. If the variable is categorical, the participant can be classified into an incorrect category (181). This misclassification can be differential or non-differential. In differential misclassification, the bias is different for exposed and non-exposed participants, or between those experiencing the event or not. Non-differential misclassification is unrelated to corresponding variables (Figure 35) (181).

In paper I, we used objective measurements of height and weight by trained personnel, and thus avoided potential information bias from self-reported BMI (131). However, we did not have information on cholesterol-lowering medication for measurements of HDL and triglycerides. This could have led to differential misclassification as persons on medication were classified as having normal serum levels, thus potentially weakening the association between HDL/triglycerides and joint replacement (Type C, Figure 36). This potential misclassification may explain the apparent reduced risk of TJR in some age groups with low HDL in paper I. But then again, it is still undecided whether a person on medication, and therefore with normal cholesterol, should be classified as exposed or unexposed. In our study, they were classified as unexposed.

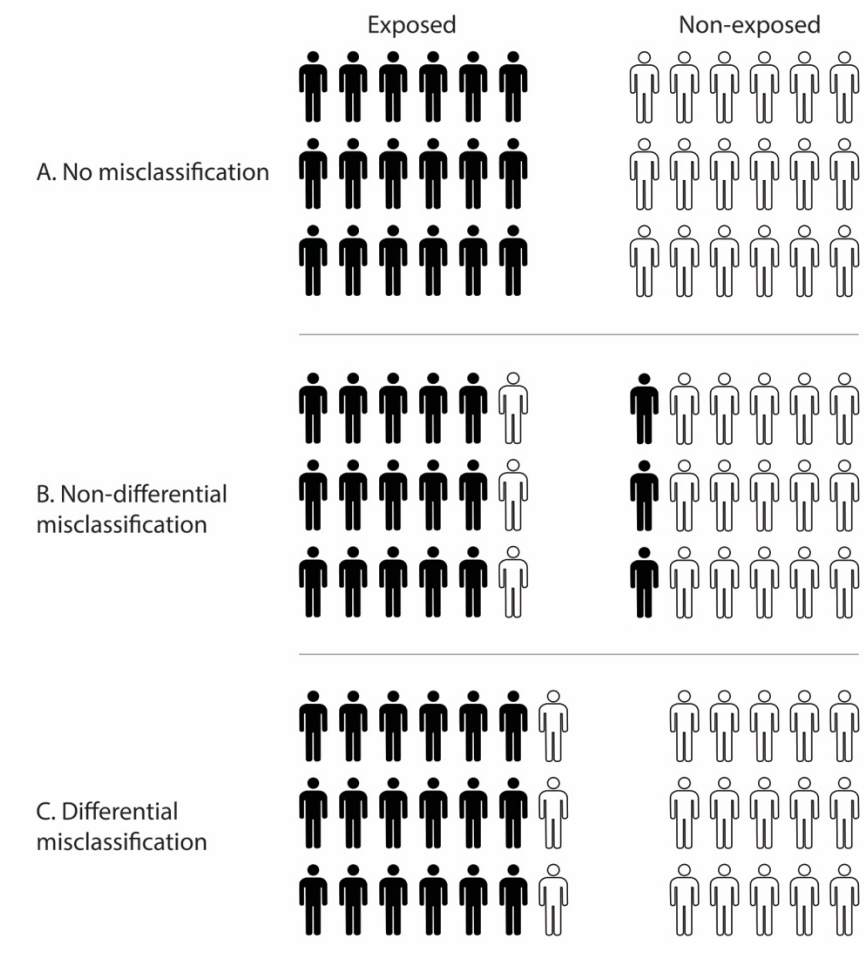


Figure 36: Different types of misclassification bias.

A. No misclassification.

B. Non-differential misclassification: Both exposed and unexposed individuals are misclassified. Bias results towards the null.

C. Differential misclassification: The misclassification is dependent on exposure group. (Can occur for exposed or non-exposed groups.)

In paper II, blood samples were not drawn at a set time of day, and it is known that factors like exercise and sleep deprivation influence TSH levels (205). This might have led to non-differential classification bias (Type B, Figure 35). A possible source of non-differential misclassification can also be found in paper III: Since our lower cut-off for age at inclusion was 30 years, the information on reproductive history and use of HRT or oral contraceptives could have changed after baseline for some participants. This is especially relevant when it comes to parity, oral contraceptive use and HRT, and could have led to non-differential misclassification. In both these cases, the results could have been biased towards the null.

Potential information bias and misclassification should also be considered for the outcome variables THR or TKR as surrogate measures of severe OA. Using TJR as an endpoint for severe OA helps distinguish between severe disease and minor disability (45). This also has

the advantage of creating an unambiguous connection with severe disease burden of OA compared to other OA definitions, e.g., radiographic criteria, symptom criteria or OA defined by self-reported diagnosis (107). When investigating the agreement between radiographic and clinical/self-reported methods of diagnosing OA, one recent study found that hip pain was not present in many people with radiographic OA, and many people with hip pain did not have radiographic hip OA (107). In knees, the agreement between radiographic, clinical and self-reported methods of diagnosing OA was only modest (165). Using these outcome-measures could therefore lead to a misclassification of healthy persons being classified as having OA, and vice-versa. However, using TJR as outcome measure is still limited in some respects:

- Patients' health status and potential comorbidities influence orthopedic surgeons' choices regarding operative treatment. This is especially relevant in paper I, where persons with metabolic syndrome would be expected to have a higher prevalence of cardiovascular diseases, and thus be less likely to be recommended for TJR; metabolic syndrome could be a risk factor for OA, but a protective factor for surgery. This could, in part, explain the observed protective effect of impaired glucose tolerance/diabetes on the risk of both THR and TKR and is in line with a study by Nielen et al. that found that risk of severe OA necessitating THR or TKR decreased with increasing diabetes mellitus severity (157).
- Differences between the likelihood of various hospitals and individual orthopedic surgeons recommending surgery.
- Subjects who wish to maintain an active lifestyle may be more motivated to have surgery than less active persons (143), even if they have less severe OA. This potential healthy patient bias could lead to an underestimation of the effect.
- The healthcare system in Norway is publicly funded and free of charge for patients. Although socioeconomic status would not affect access to surgery, it could lead to differences in those seeking surgery. In 2009, Statistics Norway reported that, amongst women with musculoskeletal diseases, those with a higher level of education (university/college level) were more likely to contact specialist health services than those with lower levels of education (high school or lower) (93). A negative association between level of education and the waiting time for THR in Norway has been reported (147), although the income variable was insignificant. Education was found to be a potential confounder in papers I and III, but adjustment for education level did not substantially alter the results.

Validation of OA diagnoses from the NAR has only been done for young adults under 40 years of age undergoing THR due to hip dysplasia (46), and they are therefore inapplicable in our study population. However, numbers from the Danish hip Arthroplasty Registry show a

positive predictive value of 85% regarding the primary hip OA diagnosis (168). The results from the Danish registry are probably comparable to the NAR.

Neither radiographic findings of an OA joint nor the structural changes observed during surgery necessarily correlate well with degree of pain. We are therefore unsure if what we are measuring is the degree of OA or the degree of pain as a response to the disease. From the data available in this thesis, it was not possible to differentiate between these two.

The data collection in the HUNT studies were not initially designed to investigate OA, but is that a problem? To have a large amount of baseline data collected prior to the outcome of interest reduces the risk of recall bias, regardless of what that outcome of interest might be. But there are some adjustments in the baseline measurements that would have improved our studies:

1. Measurements of fasting blood glucose for all participants would have made the measurements more accurate according to the Joint Interim Statement definition of metabolic syndrome. We had to use a stricter cut-off of non-fasting blood glucose of ≥11.1 mmol/L that could have led to an underestimation of the effect due to a larger portion of people with impaired glucose tolerance being classified as normal.
2. Information on cholesterol-lowering medication could also have reduced the risk of misclassification of persons with dyslipidaemia, thus strengthening any association between HDL/triglycerides and joint replacement.

A special type of information bias, recall bias, might have influenced some of the covariates in paper III, especially age at menarche. There is a mean age difference of almost 10 years between the women that reported age at menarche ≤11 years, and those reporting age at menarche ≥15. Adjusting for age may then be insufficient for correcting an eventual systematic recall bias.

Selection bias

Selection bias could be a problem if the relationship between the study variables in the missing data is different from the corresponding relationship in the included data-set (181). One form of selection bias is non-response: Are the non-responders to the HUNT studies different from the responders? The participation rate was 69.5% in HUNT2 and 54.1% in HUNT3, so it is not possible to rule out the risk of selection bias (86). In a non-responder study after HUNT2 (n=685), 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) (119). Non-responders were also found to have a higher prevalence of smoking. Young men had a lower

participation rate. In a non-responder study from HUNT3 the main reason for not participating was lack of time and interest. Non-participants in HUNT3 had lower socio-economic status, higher mortality and higher prevalence of chronic diseases such as cardiovascular disease, diabetes mellitus, fibromyalgia and OA (120). However, only a small proportion (4.7% of women and 2.6% of men) reported illness as a reason for not participating in the HUNT survey. A low participation rate in younger men would probably not have biased our results, since primary THR and TKR are most common in the older population.

Another form of selection bias is missing data about participants, and this is potentially worse for the study than non-participation (181). When investigating the excluded participants in this thesis, they were found to be older, to have higher BMIs, lower physical activity, lower levels of education and more cardiovascular disease (Table 8). The results must therefore be interpreted with caution for people with lower socio-economic status and higher prevalence of chronic diseases. But as discussed under "Generalizability", this will not necessarily represent a problem if we assume an underlying biological mechanism between exposure and TJR.

In paper I, all persons older than 20 years were included in the main analyses. Since TJR due to OA is very uncommon in persons <30 years, we may have included a group of persons that would almost certainly not have an arthroplasty no matter how many risk factors they had, since the threshold for operating this age group is substantially higher. In a separate sensitivity analysis of the age group <50 years, participants <30 years at baseline were excluded. Hypertension was then only borderline significant (HR 1.29, 95% CI 0.98-1.70), but apart from this the results were not substantially different from the main analysis.

Selection bias can also be present in the outcome variable (THR/TKR): Persons with moderate OA who engage in demanding physical activities could be more motivated to have surgery than less active persons, and persons who are generally inactive may be less motivated to have surgery even if they have more severe OA. This could give a healthy patient selection bias with corresponding underestimation of the effect of the exposure.

Confounders

When an effect of an exposure is mixed up with the effect of another variable, it is called confounding (183). In paper II, thyroid function was the exposure and TJR was the outcome. But since BMI is known to be associated with both thyroid function and TJR, BMI may be a confounder on the pathway between thyroid function and TJR (Figure 37). It would then be incorrect not to adjust for BMI, since this would result in residual confounding by BMI.

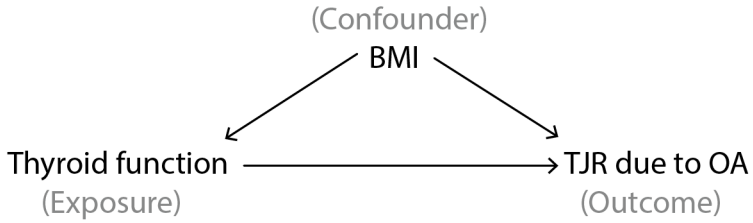


Figure 37: BMI as a confounder.

The ability to adjust for multiple potential confounders was a strength in these studies, and it was important to identify all confounders and their interrelationship before doing the analysis. This was done by setting up a directed acyclic graph (DAG): Associations and their directions are indicated with arrows between the exposure, the outcome and all possible covariates that could affect this casual pathway (Figure 38).

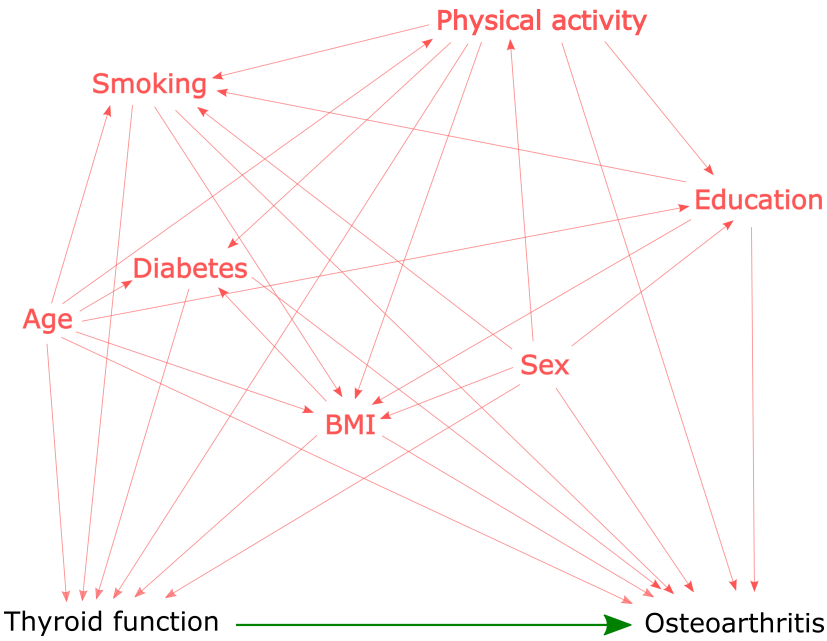


Figure 38: Directed acyclic graph DAG: Analyzing potential confounders on the casual pathway between thyroid function and OA.

The DAG allowed us to assess whether a covariate was a confounder, a mediator or a collider. This is important because adjusting for mediators or colliders can introduce bias (183). This is why adjusting for more covariates is not always better. In our model on thyroid function and TJR, it is also possible to argue that thyroid function leads to changes in BMI, and not the other way around; BMI would then be a mediator (Figure 39). Further, a TJR could affect BMI after an operation, turning BMI into a collider (Figure 40). This is, however, not a possibility in our study, because of its prospective design.

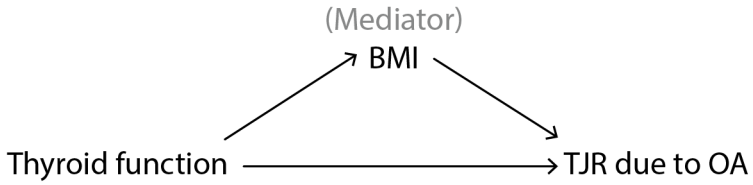


Figure 39: BMI as a mediator.

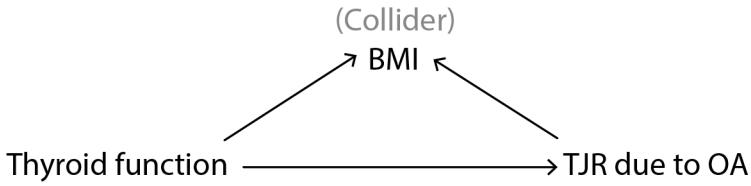


Figure 40: BMI as a collider.

The direction of arrows determines which covariates should be included in the final model. This depends on prior knowledge of associations between covariates – but, like in the case described above, it can present dilemmas. In our final model in paper II, we chose to define BMI as a confounder. (DAGs for papers I and III can be found in Appendix.)

Education was used as an indicator of socioeconomic status in papers I and III, and the HRs did not change significantly after adjusting for this factor. (Education was not found to be a confounder in paper II after the DAG-analysis).

Generalizability

Generalizability, or external validity, determines how valid the results are to populations outside our study population (183). The adult population in Nord-Trøndelag is thought to be fairly representative of Norway when it comes to age, comorbidity and mortality (86). The income and education levels of participants in HUNT2 were slightly lower than in the general Norwegian population (86). The distribution between age groups that received THR or TKR in our study was comparable to the Norwegian population (Figures 21 and 22).

As previously mentioned, since non-participants were more often younger men, and people with lower socio-economic status and more comorbidities, caution should be taken when applying our results to these groups. However, a completely representative sample of the Norwegian population would not necessarily improve the generalizability of our findings – if our

findings have a biological mechanism, it should be applicable to all populations. It is therefore more essential to have a high internal validity; high external validity is more important in studies of the incidence and prevalence of diseases or for opinion surveys (182).

Interaction

An example of interaction could be drunk driving: Both driving and alcohol consumption are risk factors for injury, but their combination is more dangerous than either alone (181). In paper I, high BMI and metabolic syndrome could have not only an additive, but also a synergistic effect on the risk of THR or TKR. Their synergy was tested by including an interaction term between categorical BMI and metabolic syndrome in the logistic regression models. A likelihood ratio test showed no significant difference between the two models, indicating no significant interaction.

Causality

That two variables are associated does not necessarily mean that there is a casual relationship between them. But at what point is it possible for an observed association to become a plausible causation? There are no objective casual criteria, but Sir Austin Bradford Hill proposed a list of "viewpoints" in 1965 to help in the decision-making (83): Strength, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimental evidence and analogy. However, Hill also emphasized that causal inferences could not be based on a set of rules alone (183): "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non *[absolutely essential]*" (Hill, 1965). Although it could be argued that temporality (cause precedes effect) is essential for a causal relationship, Hill's main intention was to help researchers find other ways to explain the association between cause and effect. In paper III, we found an association between age at menarche and TKR, and it is helpful to evaluate this association using Hill's criteria (Table 10).

Table 10: The casual relationship between age at menarche and TKR evaluated by Hill's nine criteria.

Strength	The risk of TKR was HR 0.52 (95% CI 0.34-0.80) in women with menarche at ≥15 years of age compared to those with menarche ≤11 years of age.
Consistency	This finding is consistent with a previous large cohort study (125).
Specificity	Age at menarche is associated with several outcomes other than OA, and thus not especially specific for TKR.
Temporality	Cause (age at menarche) precedes effect (TKR) in time.
Biologic gradient	The trend of the inverse relationship between age at menarche and TKR was highly significant (p=0.001).
Plausibility	A direct effect between age at menarche and TKR is not plausible without considering young age at menarche as an indicator for later risk factors for TKR. These could include increased BMI when young, increased sensitivity to pain or other unidentified intermediate factors.
Coherence	The finding is coherent, or at least not in conflict with, the current understanding of the natural history and biology OA. Although the underlying mechanisms of the association are not clear.
Experimental evidence	No experimental trials have investigated this association, as such a study would be almost impossible to design.
Analogy	Could overlap with "Plausibility": Age at menarche has previously been found to be associated to risk factors for TKR.

As expected, it is difficult to confirm a causal relationship between age at menarche and TKR. But a plausible explanation is that the effect goes through mediators on the casual pathway between the exposure and the outcome, and that these may include increased BMI in adulthood (170), increased sensitivity to musculoskeletal pain (113) or other unidentified intermediate factors.

Onset versus progression of OA

Participants with self-reported OA were excluded in study II. The intention was to separate between risk factors for OA onset and progression. Although the self-reported OA data in HUNT has not been validated, other studies find that self-report of medically diagnosed hip and knee OA had a specificity of >94 % when compared to the ACR criteria (174).

We did not exclude participants with self-reported OA in papers I and III: In paper I, a high number of participants was needed to be able to stratify on both age and sex. By not excluding these participants we had a higher power, but at the expense of not being able to separate between OA onset and progression. In paper III, the information on exposures spanned

from age at menarche to age at menopause. It would therefore not be of any help to exclude prevalent OA at baseline, as many of the exposures may have happened decades earlier.

Collinearity

Collinearity means that there is a high correlation between two covariates, meaning that they roughly measure the same thing. In our data, an example could be waist circumference and BMI in paper I: Estimating the correlation between waist circumference (dichotomous) and BMI (continuous) gave an R^2 of 0.38 in the age group <50 years, 0.43 in the age group 50-69.9 years, and 0.42 in the age group ≥70 years. This corresponded to variance inflation factors (VIF) of 1.62, 1,75 and 1,72, respectively. VIF estimates how much the variance of waist circumference is inflated due to dependence on BMI. Thus, a VIF of 1.62 indicates that the variance of waist circumference is 62% larger than it would be if it was completely unrelated to BMI. There are different opinions on when the correlation is high enough to become a problem, but a VIF <4 may be acceptable (161). However, to estimate the exact effect of increased waist circumference independent of BMI is difficult.

Injury

Previous injuries increase the risk of OA, especially in the knee (149, 162). Only joint replacements due to primary/idiopathic OA were included in our study. We did not have direct information on previous injury, but we excluded all cases in which the operating surgeon reported that the knee joint replacement was due to sequela from fracture, ligament injury, meniscal injury, infection, rheumatoid arthritis or ankylosing spondylitis.

Are HUNT2 and HUNT3 the same population?

Although there was a 10-year period between HUNT2 and HUNT3, they both used the same source population: All inhabitants ≥20 years of age in the county of Nord-Trøndelag. But there could be several reasons why HUNT2 and HUNT3 did not have all the same participants:

- The participation rate in HUNT3 was lower than in HUNT2 (54.1% vs. 69.5%, respectively). Some of the responders in HUNT2 could therefore have been non-responders in HUNT3.
- We would expect some of the older participants in HUNT2 to have died before HUNT3. And people that were too young to participate in HUNT2 could be part of the study population in HUNT3.

The population in Nord-Trøndelag is relatively homogeneous, and few people move in or out of the county (225). So, despite the limitations that arise from using the participants from two consecutive waves of the HUNT health survey, we would argue that the two surveys represent one source population.

During follow-up, the incidence of both THR and TKR increased (Figure 5). But this has probably not substantially altered our results since it is plausible that this increase was the same for both exposed and unexposed groups.

Agreement between measurements in HUNT2 and HUNT3

In papers II and III we used baseline data from both HUNT2 and HUNT3. In the main analyses in paper II, baseline measurements from HUNT2 were used for subjects that participated in both HUNT2 and HUNT3 to increase the follow-up time. In paper III, we used baseline measurements from HUNT3 for persons who participated in both HUNT2 and HUNT3 in order to include as much information as possible on reproductive history and eventual use of HRT. Paper I used data from HUNT3 to identify participants who did not change exposure group during the first 10 years of follow-up. The differences in measurements between HUNT2 and HUNT3 in the respective papers are shown in Table 11 (mean difference in each person).

Table 11: Mean difference between results in HUNT2 and HUNT3 in each person.

Variable	***n persons***	***Mean difference between results from HUNT2 to HUNT3 in each person (SD)***
Paper I		
Waist circumference (cm)	35 998	+9.2 (8.0)
Systolic blood pressure (mmHg)	31 515	-1.4 (18.2)
Diastolic blood pressure (mmHg)	31 527	-5.1 (11.6)
Triglycerides (mmol/L)	35 777	-0.02 (1.0)
HDL (mmol/L)	35 336	-0.04 (0.3)
Non-fasting blood glucose (mmol/L)	35 338	+0.4 (1.7)
BMI (kg/m^2)	35 976	+1.3 (2.3)
Paper II		
TSH (mU/L)	11657	-0.04 (2.2)
Paper III		
Age at menarche (years)	15 893	-0.01 (0.84)

HDL: High-density lipoprotein; TSH: Thyroid stimulating hormone

In paper III, only age at menarche was analyzed. The reason for this was that a low repeatability between the answers regarding other elements of reproductive history would not mean that the answers to the questionnaires were inaccurate: During the 10-year time period between HUNT2 and HUNT3 there would probably be updates on the answers concerning reproductive history or hormonal factors in a large proportion of the population.

Waist circumference increased by around 9 cm, diastolic blood pressure decreased by around 5 mmHg and BMI increased by 1.3 kg/m^2 between HUNT2 and HUNT3. Worth noting is that reported age at menarche did not change; which could indicate that people continued to remember the same age at menarche as they aged, and thus not affecting this potential source of recall bias as discussed above.

Conclusion

Paper I:

We found an increased risk of TKR in men <50 years with hypertension, and people <70 years with increased waist circumference. Apart from this, neither metabolic syndrome nor its components were associated with increased risk of THR or TKR due to primary OA.

Paper II:

We did not find that thyroid function was associated with risk of THR of TKR due to OA. Neither did we find any association between TSH development over time and risk of THR or TKR due to OA.

Paper III:

We found that increasing age at menarche reduced the risk of TKR. Past users and users of systemic hormone replacement therapy (HRT) were at higher risk of TKR compared to never users. Parity did not increase the risk of TKR or THR.

Clinical implications and further research

This thesis was characterized by lack of findings rather than new, significant results. Negative findings may not always be exciting for the researcher or the scientific journal, but they can be good news for the general population and health care system. This research project found evidence that people do not have to worry too much about increased risk of OA if they have metabolic syndrome and are normal weight. And although thyroid dysfunction can increase the risk of osteoporosis and fractures, this thesis could report that this group probably do not have an increased risk of OA. Women still have an increased risk of TJR due to OA, but we found that only age at menarche influenced the risk of TKR. Thus, there are lot of potential risk factors that neither the population and nor the public health service have to worry about – for now – and that is good news.

So keep calm and carry on; the key to idiopathic OA is yet to be found.

References

1. Annual report from the Norwegian Arthroplasty Register. 2017.
2. Ackerman IN, Bohensky MA, de Steiger R, et al. Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis. Osteoarthritis Cartilage. 2017;25(4):455-61.
3. Ackerman IN, Bohensky MA, de Steiger R, et al. Lifetime Risk of Primary Total Hip Replacement Surgery for Osteoarthritis From 2003 to 2013: A Multinational Analysis Using National Registry Data. Arthritis Care Res (Hoboken). 2017;69(11):1659-67.
4. Ageberg E, Engstrom G, Gerhardsson de Verdier M, et al. Effect of leisure time physical activity on severe knee or hip osteoarthritis leading to total joint replacement: a population-based prospective cohort study. BMC Musculoskelet Disord. 2012;13:73.
5. Agricola R, Heijboer MP, Bierma-Zeinstra SM, et al. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Ann Rheum Dis. 2013;72(6):918-23.
6. Agricola R, Heijboer MP, Ginai AZ, et al. A cam deformity is gradually acquired during skeletal maturation in adolescent and young male soccer players: a prospective study with minimum 2-year follow-up. Am J Sports Med. 2014;42(4):798-806.
7. Agricola R, Heijboer MP, Roze RH, et al. Pincer deformity does not lead to osteoarthritis of the hip whereas acetabular dysplasia does: acetabular coverage and development of osteoarthritis in a nationwide prospective cohort study (CHECK). Osteoarthritis Cartilage. 2013;21(10):1514-21.
8. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
9. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum. 1991;34(5):505-14.
10. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8):1039-49.
11. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007;15 Suppl A:A1-56.
12. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2012;35 Suppl 1:S64-71.
13. Apold H, Meyer HE, Espehaug B, et al. Weight gain and the risk of total hip replacement a population-based prospective cohort study of 265,725 individuals. Osteoarthritis Cartilage. 2011;19(7):809-15.
14. Apold H, Meyer HE, Nordsletten L, et al. Risk factors for knee replacement due to primary osteoarthritis, a population based, prospective cohort study of 315,495 individuals. BMC Musculoskelet Disord. 2014;15(1):217.
15. Apold H, Meyer HE, Nordsletten L, et al. Weight gain and the risk of knee replacement due to primary osteoarthritis: a population based, prospective cohort study of 225,908 individuals. Osteoarthritis Cartilage. 2014;22(5):652-8.
16. arc OC, arc OC, Zeggini E, et al. Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet. 2012;380(9844):815-23.
17. Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol. 2006;20(1):3-25.
18. Arden NK, Reading IC, Jordan KM, et al. A randomised controlled trial of tidal irrigation vs corticosteroid injection in knee osteoarthritis: the KIVIS Study. Osteoarthritis Cartilage. 2008;16(6):733-9.
19. Baker K, Grainger A, Niu J, et al. Relation of synovitis to knee pain using contrast-enhanced MRIs. Ann Rheum Dis. 2010;69(10):1779-83.
20. Bastow ER, Byers S, Golub SB, et al. Hyaluronan synthesis and degradation in cartilage and bone. Cell Mol Life Sci. 2008;65(3):395-413.

21. Bay-Jensen AC, Slagboom E, Chen-An P, et al. Role of hormones in cartilage and joint metabolism: understanding an unhealthy metabolic phenotype in osteoarthritis. Menopause. 2013;20(5):578-86.
22. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013;21(1):16-21.
23. Berthiaume MJ, Raynauld JP, Martel-Pelletier J, et al. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis. 2005;64(4):556-63.
24. Bingham CO, 3rd, Buckland-Wright JC, Garnero P, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum. 2006;54(11):3494-507.
25. Bjoro T, Holmen J, Kruger O, et al. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). Eur J Endocrinol. 2000;143(5):639-47.
26. Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2010;18(1):24-33.
27. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.
28. Bland M. An introduction to medical statistics. Fourth edition. ed. Oxford ;: Oxford University Press; 2015.
29. Bos SD, Bovee JV, Duijnisveld BJ, et al. Increased type II deiodinase protein in OA-affected cartilage and allelic imbalance of OA risk polymorphism rs225014 at DIO2 in human OA joint tissues. Ann Rheum Dis. 2012;71(7):1254-8.
30. Burleigh A, Chanalaris A, Gardiner MD, et al. Joint immobilization prevents murine osteoarthritis and reveals the highly mechanosensitive nature of protease expression in vivo. Arthritis Rheum. 2012;64(7):2278-88.
31. Canchola AJ, Stewart SL, Bernstein L, et al. Cox regression using different time-scales. Western users of SAS software annual meeting; 5–7 November 2003; San Francisco, CA, USA: SAS Institute2003.
32. Carman WJ, Sowers M, Hawthorne VM, et al. Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. Am J Epidemiol. 1994;139(2):119-29.
33. Chaisson CE, McAlindon TE, Felson DT, et al. Lack of association between thyroid status and chondrocalcinosis or osteoarthritis: the Framingham Osteoarthritis Study. J Rheumatol. 1996;23(4):711-5.
34. Clohisy JC, St John LC, Schutz AL. Surgical treatment of femoroacetabular impingement: a systematic review of the literature. Clin Orthop Relat Res. 2010;468(2):555-64.
35. Conaghan PG, Hunter DJ, Maillefert JF, et al. Summary and recommendations of the OARSI FDA osteoarthritis Assessment of Structural Change Working Group. Osteoarthritis Cartilage. 2011;19(5):606-10.
36. Conaghan PG, Vanharanta H, Dieppe PA. Is progressive osteoarthritis an atheromatous vascular disease? Ann Rheum Dis. 2005;64(11):1539-41.
37. Courties A, Gualillo O, Berenbaum F, et al. Metabolic stress-induced joint inflammation and osteoarthritis. Osteoarthritis Cartilage. 2015;23(11):1955-65.
38. Cox D. Regression Models and Life Tables. Journal of the Royal Statistic Society. 1972(34):187-202.
39. Creamer P, Hochberg MC. Osteoarthritis. Lancet. 1997;350(9076):503-8.
40. Dagenais S, Garbedian S, Wai EK. Systematic Review of the Prevalence of Radiographic Primary Hip Osteoarthritis. Clin Orthop Relat Res. 2009;467(3):623-37.
41. Dahaghin S, Bierma-Zeinstra SM, Reijman M, et al. Does hand osteoarthritis predict future hip or knee osteoarthritis? Arthritis Rheum. 2005;52(11):3520-7.
42. DALYs GBD, Collaborators H. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1603-58.
43. Davis MA, Ettinger WH, Neuhaus JM, et al. Sex differences in osteoarthritis of the knee. The role of obesity. Am J Epidemiol. 1988;127(5):1019-30.

44. Dennison EM, Arden NK, Kellingray S, et al. Hormone replacement therapy, other reproductive variables and symptomatic hip osteoarthritis in elderly white women: a case-control study. Br J Rheumatol. 1998;37(11):1198-202.
45. Dieppe P. Osteoarthritis: time to shift the paradigm. This includes distinguishing between severe disease and common minor disability. BMJ. 1999;318(7194):1299-300.
46. Engesaeter IO, Lehmann T, Laborie LB, et al. Total hip replacement in young adults with hip dysplasia: age at diagnosis, previous treatment, quality of life, and validation of diagnoses reported to the Norwegian Arthroplasty Register between 1987 and 2007. Acta Orthop. 2011;82(2):149-54.
47. Engstrom G, Gerhardsson de Verdier M, Rollof J, et al. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study. Osteoarthritis Cartilage. 2009;17(2):168-73.
48. Erb A, Brenner H, Gunther KP, et al. Hormone replacement therapy and patterns of osteoarthritis: baseline data from the Ulm Osteoarthritis Study. Ann Rheum Dis. 2000;59(2):105-9.
49. Espehaug B, Furnes O, Havelin LI, et al. Registration completeness in the Norwegian Arthroplasty Register. Acta Orthop. 2006;77(1):49-56.
50. Felson DT. Osteoarthritis as a disease of mechanics. Osteoarthritis Cartilage. 2013;21(1):10-5.
51. Felson DT, Anderson JJ, Naimark A, et al. Does smoking protect against osteoarthritis? Arthritis Rheum. 1989;32(2):166-72.
52. Felson DT, Anderson JJ, Naimark A, et al. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med. 1988;109(1):18-24.
53. Felson DT, Niu J, Clancy M, et al. Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: the Framingham Study. Arthritis Rheum. 2007;57(1):6-12.
54. Felson DT, Niu J, Gross KD, et al. Valgus malalignment is a risk factor for lateral knee osteoarthritis incidence and progression: findings from the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative. Arthritis Rheum. 2013;65(2):355-62.
55. Felson DT, Zhang Y, Anthony JM, et al. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med. 1992;116(7):535-9.
56. Findlay DM. Vascular pathology and osteoarthritis. Rheumatology (Oxford). 2007;46(12):1763-8.
57. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496-509.
58. Flugsrud GB, Nordsletten L, Espehaug B, et al. The impact of body mass index on later total hip arthroplasty for primary osteoarthritis: a cohort study in 1.2 million persons. Arthritis Rheum. 2006;54(3):802-7.
59. Flugsrud GB, Nordsletten L, Espehaug B, et al. Risk factors for total hip replacement due to primary osteoarthritis: a cohort study in 50,034 persons. Arthritis Rheum. 2002;46(3):675-82.
60. Flugsrud GB, Nordsletten L, Espehaug B, et al. Weight change and the risk of total hip replacement. Epidemiology. 2003;14(5):578-84.
61. Fransen M, McConnell S, Harmer AR, et al. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med. 2015;49(24):1554-7.
62. Fransen M, McConnell S, Hernandez-Molina G, et al. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev. 2014(4):CD007912.
63. Furmaniak-Kazmierczak E, Cooke TD, Manuel R, et al. Studies of thrombin-induced proteoglycan release in the degradation of human and bovine cartilage. J Clin Invest. 1994;94(2):472-80.
64. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. Lancet. 2015;386(9991):376-87.
65. Goldring MB, Berenbaum F. Emerging targets in osteoarthritis therapy. Curr Opin Pharmacol. 2015;22:51-63.
66. Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol. 2011;23(5):471-8.
67. Golightly YM, Marshall SW, Kraus VB, et al. Biomarkers of incident radiographic knee osteoarthritis: do they vary by chronic knee symptoms? Arthritis Rheum. 2011;63(8):2276-83.
68. Gossec L, Jordan JM, Lam MA, et al. Comparative evaluation of three semi-quantitative radiographic grading techniques for hip osteoarthritis in terms of validity and reproducibility in 1404 radiographs: report of the OARSI-OMERACT Task Force. Osteoarthritis Cartilage. 2009;17(2):182-7.
69. Gossec L, Jordan JM, Mazzuca SA, et al. Comparative evaluation of three semi-quantitative radiographic grading techniques for knee osteoarthritis in terms of validity and reproducibility in 1759 X-rays: report of the OARSI-OMERACT task force. Osteoarthritis Cartilage. 2008;16(7):742-8.

70. Grotle M, Hagen KB, Natvig B, et al. Prevalence and burden of osteoarthritis: results from a population survey in Norway. J Rheumatol. 2008;35(4):677-84.
71. Guermazi A, Niu J, Hayashi D, et al. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). BMJ. 2012;345:e5339.
72. Hannan MT, Felson DT, Anderson JJ, et al. Habitual physical activity is not associated with knee osteoarthritis: the Framingham Study. J Rheumatol. 1993;20(4):704-9.
73. Hardcastle SA, Dieppe P, Gregson CL, et al. Osteoarthritis and bone mineral density: are strong bones bad for joints? Bonekey Rep. 2015;4:624.
74. Harris JD, Siston RA, Pan X, et al. Autologous chondrocyte implantation: a systematic review. J Bone Joint Surg Am. 2010;92(12):2220-33.
75. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am. 1969;51(4):737-55.
76. Harvey WF, Yang M, Cooke TD, et al. Association of leg-length inequality with knee osteoarthritis: a cohort study. Ann Intern Med. 2010;152(5):287-95.
77. Havelin LI, Engesaeter LB, Espehaug B, et al. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. Acta Orthop Scand. 2000;71(4):337-53.
78. Havelin LI, Espehaug B, Vollset SE, et al. The Norwegian arthroplasty register. A survey of 17,444 hip replacements 1987-1990. Acta Orthop Scand. 1993;64(3):245-51.
79. Havelin LI, Fenstad AM, Salomonsson R, et al. The Nordic Arthroplasty Register Association: a unique collaboration between 3 national hip arthroplasty registries with 280,201 THRs. Acta Orthop. 2009;80(4):393-401.
80. Hawker GA, Badley EM, Croxford R, et al. A population-based nested case-control study of the costs of hip and knee replacement surgery. Med Care. 2009;47(7):732-41.
81. Hawker GA, Stanaitis I. Osteoarthritis year in review 2014: clinical. Osteoarthritis Cartilage. 2014;22(12):1953-7.
82. Hellevik AI, Asvold BO, Bjoro T, et al. Thyroid function and cancer risk: a prospective population study. Cancer Epidemiol Biomarkers Prev. 2009;18(2):570-4.
83. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965;58:295-300.
84. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64(4):465-74.
85. Hochberg MC, Yerges-Armstrong L, Yau M, et al. Genetic epidemiology of osteoarthritis: recent developments and future directions. Curr Opin Rheumatol. 2013;25(2):192-7.
86. Holmen J, Midthjell K, Krüger Ø, et al. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi. 2003;13(1):19-32.
87. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860-7.
88. Hui M, Doherty M, Zhang W. Does smoking protect against osteoarthritis? Meta-analysis of observational studies. Ann Rheum Dis. 2011;70(7):1231-7.
89. Hunter DJ, Arden N, Conaghan PG, et al. Definition of osteoarthritis on MRI: results of a Delphi exercise. Osteoarthritis Cartilage. 2011;19(8):963-9.
90. Hunter DJ, Beavers DP, Eckstein F, et al. The Intensive Diet and Exercise for Arthritis (IDEA) trial: 18-month radiographic and MRI outcomes. Osteoarthritis Cartilage. 2015;23(7):1090-8.
91. Hunter DJ, Zhang YQ, Niu JB, et al. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis Rheum. 2006;54(3):795-801.
92. Jacobsen S, Jensen TW, Bach-Mortensen P, et al. Low bone mineral density is associated with reduced hip joint space width in women: results from the Copenhagen Osteoarthritis Study. Menopause. 2007;14(6):1025-30.
93. Jensen A. Sosiale ulikheter i bruk av helsetjenester 2009 [Available from: https://www.ssb.no/helse/artikler-og-publikasjoner/sosiale-ulikheter-i-bruk-av-helsetjenester - content.
94. Jensen LK. Hip osteoarthritis: influence of work with heavy lifting, climbing stairs or ladders, or combining kneeling/squatting with heavy lifting. Occup Environ Med. 2008;65(1):6-19.

95. Jensen LK. Knee osteoarthritis: influence of work involving heavy lifting, kneeling, climbing stairs or ladders, or kneeling/squatting combined with heavy lifting. Occup Environ Med. 2008;65(2):72-89.
96. Jin X, Beguerie JR, Zhang W, et al. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74(4):703-10.
97. Johnsen MB, Vie GA, Winsvold BS, et al. 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. Osteoarthritis Cartilage. 2017;25(6):817-23.
98. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol. 2007;34(1):172-80.
99. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol. 2009;36(4):809-15.
100. Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003;62(12):1145-55.
101. Kalichman L, Kobyliansky E. Age, body composition, and reproductive indices as predictors of radiographic hand osteoarthritis in Chuvashian women. Scand J Rheumatol. 2007;36(1):53-7.
102. Kapelrud H, Frey H, Theodorsen L. [Excretion of iodine in the urine. A study from 6 different Norwegian districts in 1985]. Tidsskr Nor Laegeforen. 1987;107(15):1320-1, 17.
103. Karlson EW, Mandl LA, Aweh GN, et al. Total hip replacement due to osteoarthritis: the importance of age, obesity, and other modifiable risk factors. Am J Med. 2003;114(2):93-8.
104. Keen HI, Conaghan PG. Ultrasonography in osteoarthritis. Radiol Clin North Am. 2009;47(4):581-94.
105. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16(4):494-502.
106. Kellgren JH, Lawrence JS, Bier F. Genetic Factors in Generalized Osteo-Arthrosis. Ann Rheum Dis. 1963;22:237-55.
107. Kim C, Nevitt MC, Niu J, et al. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. BMJ. 2015;351:h5983.
108. Kise NJ, Risberg MA, Stensrud S, et al. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. BMJ. 2016;354:i3740.
109. Kluzek S, Newton JL, Arden NK. Is osteoarthritis a metabolic disorder? Br Med Bull. 2015;115(1):111-21.
110. Kohrle J. Local activation and inactivation of thyroid hormones: the deiodinase family. Mol Cell Endocrinol. 1999;151(1-2):103-19.
111. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145(1):72-80.
112. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013;42(4):968-77.
113. Kvalheim S, Sandvik L, Winsvold B, et al. Early menarche and chronic widespread musculoskeletal complaints--Results from the HUNT study. Eur J Pain. 2016;20(3):458-64.
114. Ladenson PW, Kristensen JD, Ridgway EC, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. N Engl J Med. 2010;362(10):906-16.
115. Lago F, Gomez R, Conde J, et al. Cardiometabolic comorbidities and rheumatic diseases: focus on the role of fat mass and adipokines. Arthritis Care Res (Hoboken). 2011;63(8):1083-90.
116. Lammel Lindemann J, Webb P. Sobetirome: the past, present and questions about the future. Expert Opin Ther Targets. 2015:1-5.
117. Landsmeer ML, Runhaar J, van der Plas P, et al. Reducing progression of knee OA features assessed by MRI in overweight and obese women: secondary outcomes of a preventive RCT. Osteoarthritis Cartilage. 2016;24(6):982-90.
118. Lane NE, Brandt K, Hawker G, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthritis Cartilage. 2011;19(5):478-82.

119. Langhammer A, Johnsen R, Holmen J, et al. Cigarette smoking gives more respiratory symptoms among women than among men. The Nord-Trondelag Health Study (HUNT). J Epidemiol Community Health. 2000;54(12):917-22.
120. Langhammer A, Krokstad S, Romundstad P, et al. The HUNT study: participation is associated with survival and depends on socioeconomic status, diseases and symptoms. BMC Med Res Methodol. 2012;12:143.
121. Laslett LL, Dore DA, Quinn SJ, et al. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. Ann Rheum Dis. 2012;71(8):1322-8.
122. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008;58(1):26-35.
123. Li B, Aspden RM. Composition and mechanical properties of cancellous bone from the femoral head of patients with osteoporosis or osteoarthritis. J Bone Miner Res. 1997;12(4):641-51.
124. Li H, Zeng C, Wei J, et al. Associations between dietary antioxidants intake and radiographic knee osteoarthritis. Clin Rheumatol. 2016;35(6):1585-92.
125. Liu B, Balkwill A, Cooper C, et al. Reproductive history, hormonal factors and the incidence of hip and knee replacement for osteoarthritis in middle-aged women. Ann Rheum Dis. 2009;68(7):1165-70.
126. Livshits G, Zhai G, Hart DJ, et al. Interleukin-6 Is a Significant Predictor of Radiographic Knee Osteoarthritis The Chingford Study. Arthritis Rheum. 2009;60(7):2037-45.
127. Loeser RF, Goldring SR, Scanzello CR, et al. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum. 2012;64(6):1697-707.
128. Loeser RF, Yammani RR, Carlson CS, et al. Articular chondrocytes express the receptor for advanced glycation end products: Potential role in osteoarthritis. Arthritis Rheum. 2005;52(8):2376-85.
129. Lohmander LS, Gerhardsson de Verdier M, Rollof J, et al. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis. 2009;68(4):490-6.
130. Ludwig TE, McAllister JR, Lun V, et al. Diminished cartilage-lubricating ability of human osteoarthritic synovial fluid deficient in proteoglycan 4: Restoration through proteoglycan 4 supplementation. Arthritis Rheum. 2012;64(12):3963-71.
131. Magnusson K, Haugen IK, Osteras N, et al. The validity of self-reported body mass index in a population-based osteoarthritis study. BMC Musculoskelet Disord. 2014;15:442.
132. Magnusson K, Scurrah K, Ystrom E, et al. Genetic factors contribute more to hip than knee surgery due to osteoarthritis - a population-based twin registry study of joint arthroplasty. Osteoarthritis Cartilage. 2017;25(6):878-84.
133. Maillefert JF, Gueguen A, Monreal M, et al. Sex differences in hip osteoarthritis: results of a longitudinal study in 508 patients. Ann Rheum Dis. 2003;62(10):931-4.
134. March LM, Schwarz JM, Carfrae BH, et al. Clinical validation of self-reported osteoarthritis. Osteoarthritis Cartilage. 1998;6(2):87-93.
135. Martel-Pelletier J, Barr AJ, Cicuttini FM, et al. Osteoarthritis. Nat Rev Dis Primers. 2016;2:16072.
136. Martin RM, Vatten L, Gunnell D, et al. Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway. Cancer Causes Control. 2009;20(7):1181-92.
137. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22(3):363-88.
138. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. JAMA. 2017;317(19):1967-75.
139. McAlindon TE, Wilson PW, Aliabadi P, et al. Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham study. Am J Med. 1999;106(2):151-7.
140. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA. 2013;310(12):1263-73.
141. Meulenbelt I, Bos SD, Chapman K, et al. Meta-analyses of genes modulating intracellular T3 bio-availability reveal a possible role for the DIO3 gene in osteoarthritis susceptibility. Ann Rheum Dis. 2011;70(1):164-7.
142. Meulenbelt I, Min JL, Bos S, et al. Identification of DIO2 as a new susceptibility locus for symptomatic osteoarthritis. Hum Mol Genet. 2008;17(12):1867-75.

143. Michaelsson K, Byberg L, Ahlbom A, et al. Risk of severe knee and hip osteoarthritis in relation to level of physical exercise: a prospective cohort study of long-distance skiers in Sweden. PLoS One. 2011;6(3):e18339.
144. Midthjell K, Holmen J, Bjorndal A, et al. Is questionnaire information valid in the study of a chronic disease such as diabetes? The Nord-Trondelag diabetes study. J Epidemiol Community Health. 1992;46(5):537-42.
145. Moe B, Mork PJ, Holtermann A, et al. Occupational physical activity, metabolic syndrome and risk of death from all causes and cardiovascular disease in the HUNT 2 cohort study. Occup Environ Med. 2013;70(2):86-90.
146. Monira Hussain S, Wang Y, Cicuttini FM, et al. Incidence of total knee and hip replacement for osteoarthritis in relation to the metabolic syndrome and its components: a prospective cohort study. Semin Arthritis Rheum. 2014;43(4):429-36.
147. Monstad K, Engesaeter LB, Espehaug B. Waiting time and socioeconomic status--an individual-level analysis. Health Econ. 2014;23(4):446-61.
148. Moorman PG, Myers ER, Schildkraut JM, et al. Effect of hysterectomy with ovarian preservation on ovarian function. Obstet Gynecol. 2011;118(6):1271-9.
149. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum. 2008;59(9):1207-13.
150. Muthuri SG, McWilliams DF, Doherty M, et al. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. Osteoarthritis Cartilage. 2011;19(11):1286-93.
151. Neogi T, Bowes MA, Niu J, et al. Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the osteoarthritis initiative. Arthritis Rheum. 2013;65(8):2048-58.
152. Neogi T, Li S, Peloquin C, et al. Effect of bisphosphonates on knee replacement surgery. Ann Rheum Dis. 2017.
153. Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am. 2013;39(1):1-19.
154. Nevitt MC, Felson DT, Williams EN, et al. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2001;44(4):811-8.
155. Nevitt MC, Xu L, Zhang Y, et al. Very low prevalence of hip osteoarthritis among Chinese elderly in Beijing, China, compared with whites in the United States: the Beijing osteoarthritis study. Arthritis Rheum. 2002;46(7):1773-9.
156. Nevitt MC, Zhang Y, Javaid MK, et al. High systemic bone mineral density increases the risk of incident knee OA and joint space narrowing, but not radiographic progression of existing knee OA: the MOST study. Ann Rheum Dis. 2010;69(1):163-8.
157. Nielen JT, Emans PJ, Dagnelie PC, et al. Severity of Diabetes Mellitus and Total Hip or Knee Replacement: A Population-Based Case-Control Study. Medicine (Baltimore). 2016;95(20):e3739.
158. Niemelainen MJ, MaKela KT, Robertsson O, et al. Different incidences of knee arthroplasty in the Nordic countries. Acta Orthop. 2017;88(2):173-8.
159. Niu J, Clancy M, Aliabadi P, et al. Metabolic Syndrome, Its Components, and Knee Osteoarthritis: The Framingham Osteoarthritis Study. Arthritis Rheumatol. 2017;69(6):1194-203.
160. Noordzij M, Leffondre K, van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013;28(11):2670-7.
161. O'Brien RM. A caution regarding rules of thumb for variance inflation factors. Quality & Quantity. 2007;41(5):673-90.
162. Oiestad BE, Holm I, Engebretsen L, et al. The prevalence of patellofemoral osteoarthritis 12 years after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2013;21(4):942-9.
163. Oliveria SA, Felson DT, Cirillo PA, et al. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology. 1999;10(2):161-6.
164. Onnerfjord P, Khabut A, Reinholt FP, et al. Quantitative proteomic analysis of eight cartilaginous tissues reveals characteristic differences as well as similarities between subgroups. J Biol Chem. 2012;287(23):18913-24.
165. Parsons C, Clynes M, Syddall H, et al. How well do radiographic, clinical and self-reported diagnoses of knee osteoarthritis agree? Findings from the Hertfordshire cohort study. Springerplus. 2015;4:177.

166. Peacock J, Peacock PJ, ebrary Inc. Oxford handbook of medical statistics. Oxford: Oxford University Press; 2011.
167. Pearce F, Hui M, Ding C, et al. Does smoking reduce the progression of osteoarthritis? Meta-analysis of observational studies. Arthritis Care Res (Hoboken). 2013;65(7):1026-33.
168. Pedersen A, Johnsen S, Overgaard S, et al. Registration in the danish hip arthroplasty registry: completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. Acta Orthop Scand. 2004;75(4):434-41.
169. Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol. 1995;48(12):1503-10.
170. Pierce MB, Leon DA. Age at menarche and adult BMI in the Aberdeen children of the 1950s cohort study. Am J Clin Nutr. 2005;82(4):733-9.
171. Rai MF, Sandell LJ. Inflammatory mediators: tracing links between obesity and osteoarthritis. Crit Rev Eukaryot Gene Expr. 2011;21(2):131-42.
172. Ranstam J, Cook JA. Kaplan-Meier curve. Br J Surg. 2017;104(4):442.
173. Rasheed Z, Akhtar N, Haqqi TM. Advanced glycation end products induce the expression of interleukin-6 and interleukin-8 by receptor for advanced glycation end product-mediated activation of mitogen-activated protein kinases and nuclear factor-kappaB in human osteoarthritis chondrocytes. Rheumatology (Oxford). 2011;50(5):838-51.
174. Ratzlaff C, Koehoorn M, Cibere J, et al. Clinical validation of an Internet-based questionnaire for ascertaining hip and knee osteoarthritis. Osteoarthritis Cartilage. 2012;20(12):1568-73.
175. Reijman M, Pols HA, Bergink AP, et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis. 2007;66(2):158-62.
176. Remsberg KE, Demerath EW, Schubert CM, et al. Early menarche and the development of cardiovascular disease risk factors in adolescent girls: the Fels Longitudinal Study. J Clin Endocrinol Metab. 2005;90(5):2718-24.
177. Richmond SA, Fukuchi RK, Ezzat A, et al. Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. J Orthop Sports Phys Ther. 2013;43(8):515-B19.
178. Ro DH, Lee DY, Moon G, et al. Sex differences in knee joint loading: Cross-sectional study in geriatric population. J Orthop Res. 2017;35(6):1283-9.
179. Robertsson O, Bizjajeva S, Fenstad AM, et al. Knee arthroplasty in Denmark, Norway and Sweden. A pilot study from the Nordic Arthroplasty Register Association. Acta Orthop. 2010;81(1):82-9.
180. Robson H, Siebler T, Stevens DA, et al. Thyroid hormone acts directly on growth plate chondrocytes to promote hypertrophic differentiation and inhibit clonal expansion and cell proliferation. Endocrinology. 2000;141(10):3887-97.
181. Rothman KJ. Epidemiology : an introduction. 2nd ed. New York, NY: Oxford University Press; 2012. viii, 268 p. p.
182. Rothman KJ, Gallacher JE, Hatch EE. Why representativeness should be avoided. Int J Epidemiol. 2013;42(4):1012-4.
183. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Wolters Kluwer Health / Lippincott Williams & Wilkins; 2008. x, 758 p. p.
184. Rutjes AW, Juni P, da Costa BR, et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med. 2012;157(3):180-91.
185. Samanta A, Jones A, Regan M, et al. Is osteoarthritis in women affected by hormonal changes or smoking? Br J Rheumatol. 1993;32(5):366-70.
186. Sandmark H, Hogstedt C, Lewold S, et al. Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. Ann Rheum Dis. 1999;58(3):151-5.
187. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone. 2012;51(2):249-57.
188. Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? Joint Bone Spine. 2013;80(6):568-73.
189. Sharma L, Chmiel JS, Almagor O, et al. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: the MOST study. Ann Rheum Dis. 2013;72(2):235-40.
190. Shuster LT, Rhodes DJ, Gostout BS, et al. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010;65(2):161-6.

191. Siebenrock KA, Kaschka I, Frauchiger L, et al. Prevalence of cam-type deformity and hip pain in elite ice hockey players before and after the end of growth. Am J Sports Med. 2013;41(10):2308-13.
192. Sihvonen R, Englund M, Turkiewicz A, et al. Mechanical Symptoms and Arthroscopic Partial Meniscectomy in Patients With Degenerative Meniscus Tear: A Secondary Analysis of a Randomized Trial. Ann Intern Med. 2016;164(7):449-55.
193. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N Engl J Med. 2013;369(26):2515-24.
194. Silverwood V, Blagojevic-Bucknall M, Jinks C, et al. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015;23(4):507-15.
195. Singh G, Miller JD, Lee FH, et al. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. Am J Manag Care. 2002;8(15 Suppl):S383-91.
196. Singh JA. Epidemiology of knee and hip arthroplasty: a systematic review. Open Orthop J. 2011;5:80-5.
197. Sjouke B, Langslet G, Ceska R, et al. Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomised, double-blind, placebo-controlled phase 3 study. Lancet Diabetes Endocrinol. 2014;2(6):455-63.
198. Skou ST, Roos EM, Laursen MB, et al. A Randomized, Controlled Trial of Total Knee Replacement. N Engl J Med. 2015;373(17):1597-606.
199. Spahn G, Hofmann GO, von Engelhardt LV, et al. The impact of a high tibial valgus osteotomy and unicondylar medial arthroplasty on the treatment for knee osteoarthritis: a meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2013;21(1):96-112.
200. Spector TD, Cicuttini F, Baker J, et al. Genetic influences on osteoarthritis in women: a twin study. BMJ. 1996;312(7036):940-3.
201. Spector TD, Nandra D, Hart DJ, et al. Is hormone replacement therapy protective for hand and knee osteoarthritis in women?: The Chingford Study. Ann Rheum Dis. 1997;56(7):432-4.
202. Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage. 2005;13(9):769-81.
203. Stannus OP, Jones G, Blizzard L, et al. Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. Ann Rheum Dis. 2013;72(4):535-40.
204. Sulsky SI, Carlton L, Bochmann F, et al. Epidemiological evidence for work load as a risk factor for osteoarthritis of the hip: a systematic review. PLoS One. 2012;7(2):e31521.
205. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. J Clin Endocrinol Metab. 2005;90(9):5489-96.
206. Suttorp MM, Siegerink B, Jager KJ, et al. Graphical presentation of confounding in directed acyclic graphs. Nephrol Dial Transplant. 2015;30(9):1418-23.
207. Svare A, Nilsen TI, Bjoro T, et al. Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. Clin Endocrinol (Oxf). 2011;74(6):769-75.
208. Svege I, Nordsletten L, Fernandes L, et al. Exercise therapy may postpone total hip replacement surgery in patients with hip osteoarthritis: a long-term follow-up of a randomised trial. Ann Rheum Dis. 2015;74(1):164-9.
209. Teichtahl AJ, Wluka AE, Tanamas SK, et al. Weight change and change in tibial cartilage volume and symptoms in obese adults. Ann Rheum Dis. 2015;74(6):1024-9.
210. Thomas AC, Hubbard-Turner T, Wikstrom EA, et al. Epidemiology of Posttraumatic Osteoarthritis. J Athl Train. 2017;52(6):491-6.
211. Valdes AM, De Wilde G, Doherty SA, et al. The Ile585Val TRPV1 variant is involved in risk of painful knee osteoarthritis. Ann Rheum Dis. 2011;70(9):1556-61.
212. van Meurs JB, Uitterlinden AG, Stolk L, et al. A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain. Arthritis Rheum. 2009;60(2):628-9.
213. van Spil WE, DeGroot J, Lems WF, et al. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. Osteoarthritis Cartilage. 2010;18(5):605-12.
214. Verloop H, Dekkers OM, Peeters RP, et al. Genetics in endocrinology: genetic variation in deiodinases: a systematic review of potential clinical effects in humans. Eur J Endocrinol. 2014;171(3):R123-35.

215. Vigdorchik JM, Nepple JJ, Eftekhary N, et al. What Is the Association of Elite Sporting Activities With the Development of Hip Osteoarthritis? Am J Sports Med. 2017;45(4):961-4.
216. Vingard E, Alfredsson L, Malchau H. Lifestyle factors and hip arthrosis. A case referent study of body mass index, smoking and hormone therapy in 503 Swedish women. Acta Orthop Scand. 1997;68(3):216-20.
217. Waarsing JH, Kloppenburg M, Slagboom PE, et al. Osteoarthritis susceptibility genes influence the association between hip morphology and osteoarthritis. Arthritis Rheum. 2011;63(5):1349-54.
218. Wang H, Cheng Y, Shao D, et al. Metabolic Syndrome Increases the Risk for Knee Osteoarthritis: A Meta-Analysis. Evid Based Complement Alternat Med. 2016;2016:7242478.
219. Wang Q, Rozelle AL, Lepus CM, et al. Identification of a central role for complement in osteoarthritis. Nat Med. 2011;17(12):1674-9.
220. Wang Y, Simpson JA, Wluka AE, et al. Is physical activity a risk factor for primary knee or hip replacement due to osteoarthritis? A prospective cohort study. J Rheumatol. 2011;38(2):350-7.
221. Wang Y, Simpson JA, Wluka AE, et al. Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: a prospective cohort study. Arthritis Res Ther. 2009;11(2):R31.
222. Wang Y, Wluka AE, Berry PA, et al. Increase in vastus medialis cross-sectional area is associated with reduced pain, cartilage loss, and joint replacement risk in knee osteoarthritis. Arthritis Rheum. 2012;64(12):3917-25.
223. Waung JA, Bassett JH, Williams GR. Adult mice lacking the type 2 iodothyronine deiodinase have increased subchondral bone but normal articular cartilage. Thyroid. 2015;25(3):269-77.
224. Waung JA, Bassett JH, Williams GR. Thyroid hormone metabolism in skeletal development and adult bone maintenance. Trends Endocrinol Metab. 2012;23(4):155-62.
225. Webpage:. HUNT databank [cited 2017 August 15th]. Available from: https://hunt-db.medisin.ntnu.no/hunt-db/.
226. Webpage:. HUNT home page [cited 2017 October 5th]. Available from: https://www.ntnu.edu/hunt.
227. Webpage:. Osteoarthritis: care and management. NICE Guideline CG 177 [cited 2017 November 10th]. Available from: https://www.nice.org.uk/guidance/cg177.
228. Wei S, Venn A, Ding C, et al. The associations between parity, other reproductive factors and cartilage in women aged 50-80 years. Osteoarthritis Cartilage. 2011;19(11):1307-13.
229. Wenham CY, Conaghan PG. New horizons in osteoarthritis. Age Ageing. 2013;42(3):272-8.
230. Williams GR. Thyroid Hormone Actions in Cartilage and Bone. Eur Thyroid J. 2013;2(1):3-13.
231. Wise BL, Niu J, Zhang Y, et al. The association of parity with osteoarthritis and knee replacement in the Multicenter Osteoarthritis Study. Osteoarthritis Cartilage. 2013;21(12):1849-54.
232. Wluka AE, Davis SR, Bailey M, et al. Users of oestrogen replacement therapy have more knee cartilage than non-users. Ann Rheum Dis. 2001;60(4):332-6.
233. Wu CW, Morrell MR, Heinze E, et al. Validation of American College of Rheumatology classification criteria for knee osteoarthritis using arthroscopically defined cartilage damage scores. Semin Arthritis Rheum. 2005;35(3):197-201.
234. Yoshimura N, Muraki S, Oka H, et al. Association of knee osteoarthritis with the accumulation of metabolic risk factors such as overweight, hypertension, dyslipidemia, and impaired glucose tolerance in Japanese men and women: the ROAD study. J Rheumatol. 2011;38(5):921-30.
235. Yoshimura N, Muraki S, Oka H, et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. Osteoarthritis Cartilage. 2012;20(11):1217-26.
236. Yusuf E. Metabolic factors in osteoarthritis: obese people do not walk on their hands. Arthritis Res Ther. 2012;14(4):123.
237. Yusuf E, Nelissen RG, Ioan-Facsinay A, et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis. 2010;69(4):761-5.
238. Zeng WN, Wang FY, Chen C, et al. Investigation of association between hip morphology and prevalence of osteoarthritis. Sci Rep. 2016;6:23477.
239. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2005;64(5):669-81.

240. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage. 2008;16(2):137-62.
241. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010;18(4):476-99.
242. Zhang Y, McAlindon TE, Hannan MT, et al. Estrogen replacement therapy and worsening of radiographic knee osteoarthritis: the Framingham Study. Arthritis Rheum. 1998;41(10):1867-73.
243. Zhang Y, Xu L, Nevitt MC, et al. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing Osteoarthritis Study. Arthritis Rheum. 2001;44(9):2065-71.
244. Zhuo Q, Yang W, Chen J, et al. Metabolic syndrome meets osteoarthritis. Nat Rev Rheumatol. 2012;8(12):729-37.

Appendix and papers I-III

Appendix A: Harris Hip Score (Norwegian version)

SMERTE		Poeng
Ingen		44
Svak	Lett verking/smerte uten innvirkning på funksjon	40
Lett	Noe vondt etter mye aktivitet, behov for reseptfri smertestillende	30
Moderat	Tolerabel, men pasienten plages jevnlig. Kan hemme vanlig aktivitet, kan trenge sterkere smertestillende enn Paracet	20
Sterk	Sterke smerter, men oppegående, hemmer aktivitet betydelig, behov for smertestillende sterkere enn Paracet, noe nattesmerter	10
Invalidiserende	Betydelige nattesmerte, klarer knapt gå på grunn av smertene	0

FUNKSJON		
Trappegang	Normal	4
	Normal, støtte til rekkverk	2
	Ett trinn av gangen ved hjelp av rekkverk	1
	Umulig	0
Transport	Kan bruke kollektivtransport	1
	Kan ikke bruke kollektivtransport	
Sitting	Komfortabel i lav stol >1 time	5
	Komfortabel i høy stol i en halv time	3
	Ikke komfortabel i noen stol	0
Påkledning	Ingen probelemer med sokker/sko	4
	Problemer med sokker/sko	2
	Umulig å ta på sokker/sko	0

GANGFUNKSJON		
Halting	Ingen	11
	Lett	8
	Middels	5
	Svær	0
Støtte	Ingen	11
	Én stokk på lengre tur	7
	Én stokk vanligvis	5
	Én krykke	3
	To stokker eller rullator	2
	To krykker eller umulig å gå	0
Gangdistanse	Ubegrenset	11
	1-1.5 km	8
	<1 km	5
	Kun inne	2
	Seng til stol	0

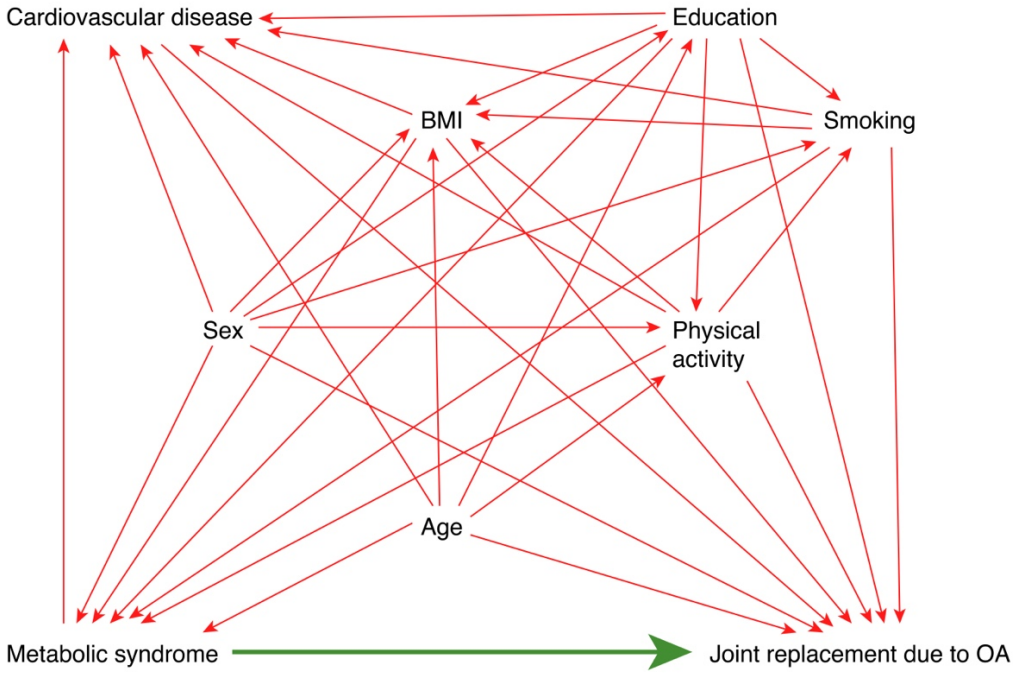
LEDDUTSLAG		
Fleksjon	0° - >90°	3
	0° - 90°	2
	0° - <90°	1
	> 0°	0
Abduksjon	>20°	2
	<20°	1
	0	0

DEFORMITET		
	Ingen	4
	Fleksjonskontraktur >30°	0
	Adduksjonskontraktur >10°	0
	Innadrotasjon >10°	0
	Anisomeli over 3 cm	0

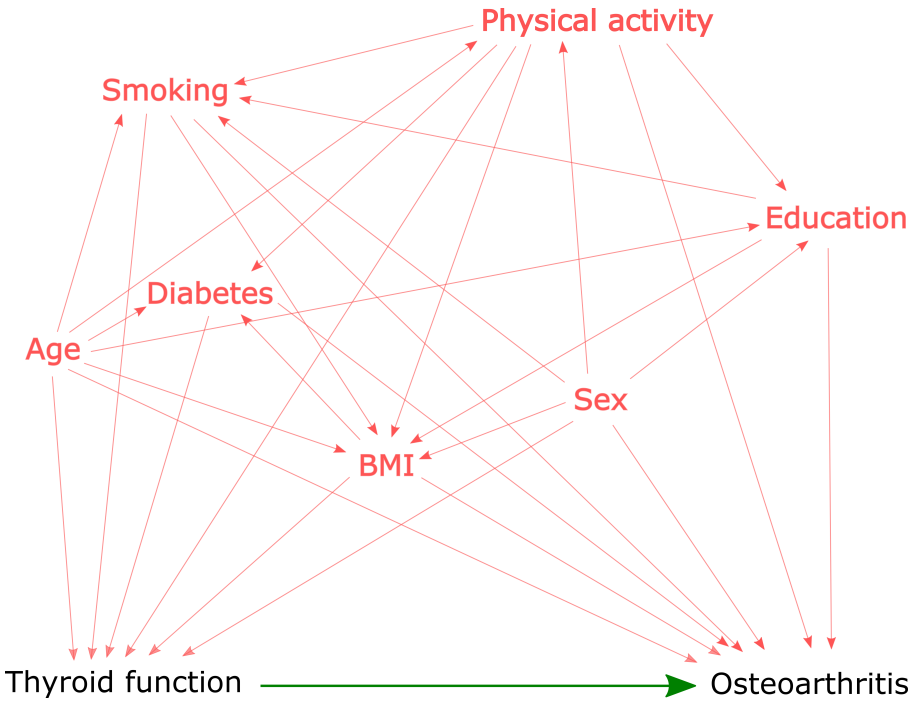
	Total sum

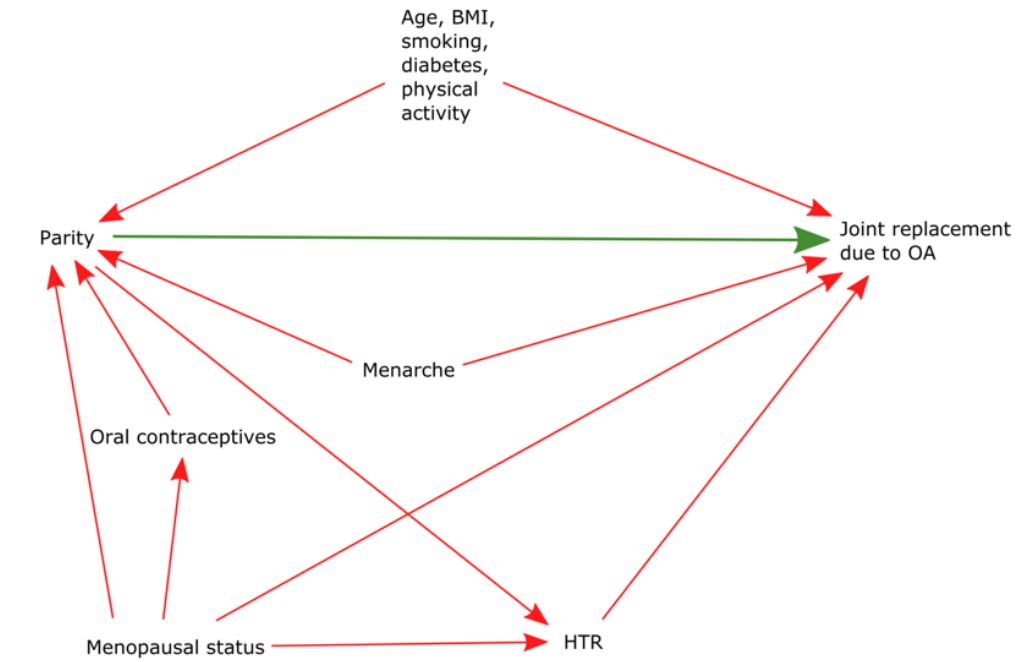
Appendix B: Directed acyclic graphs (DAGs) for each paper.

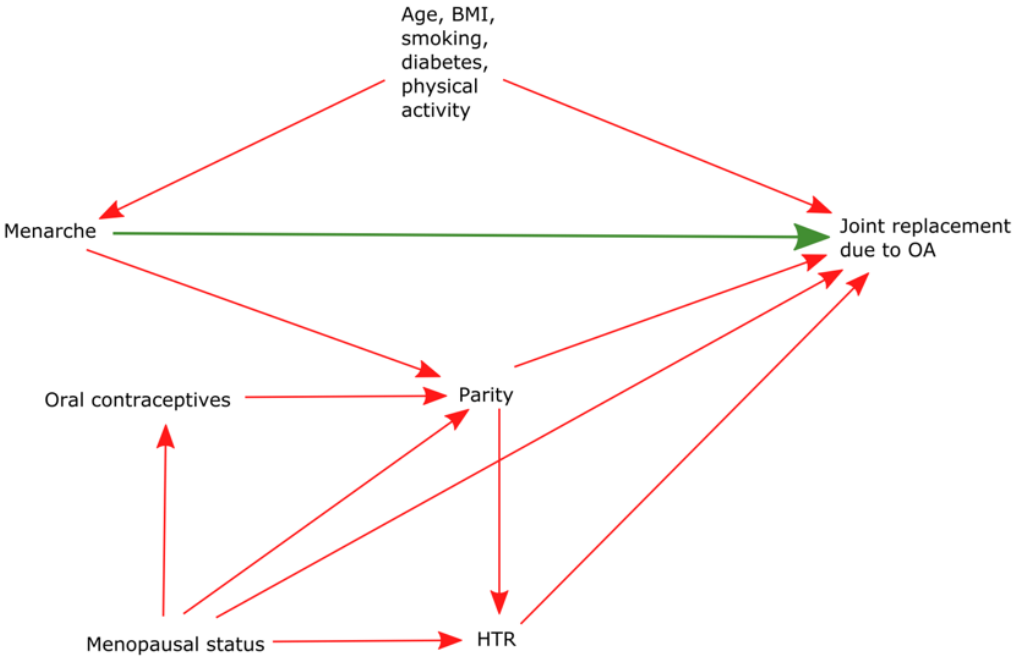
Paper I

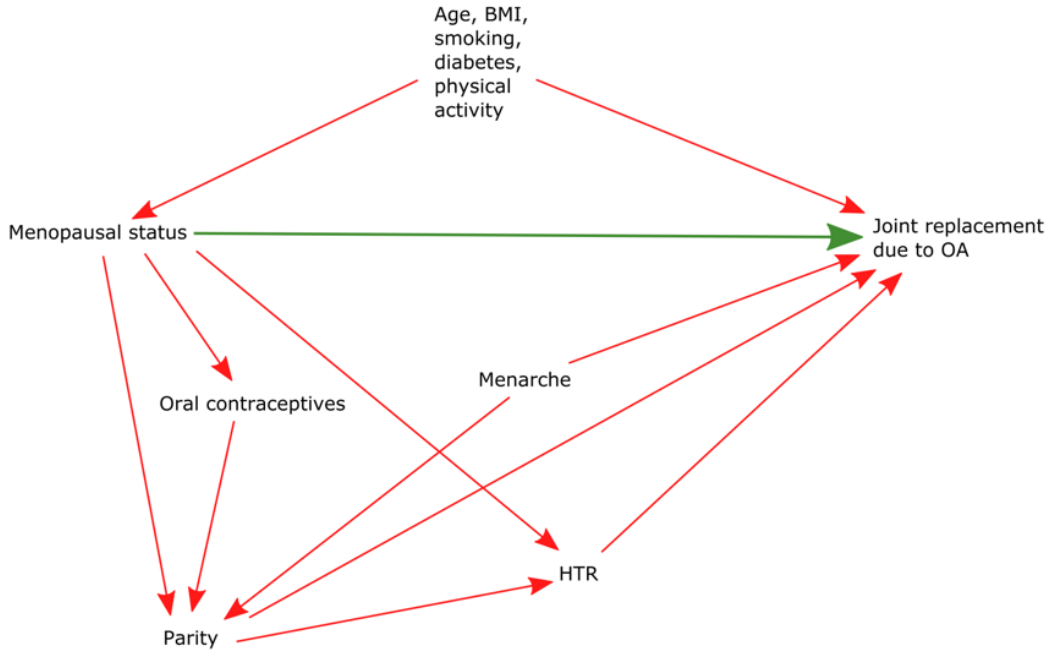


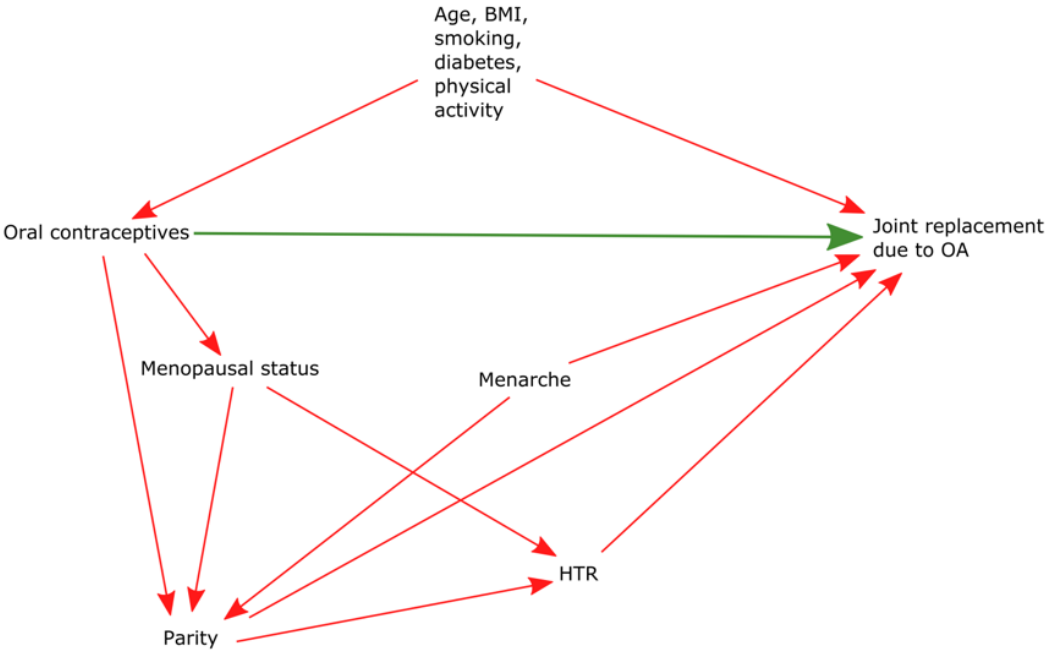
Paper II

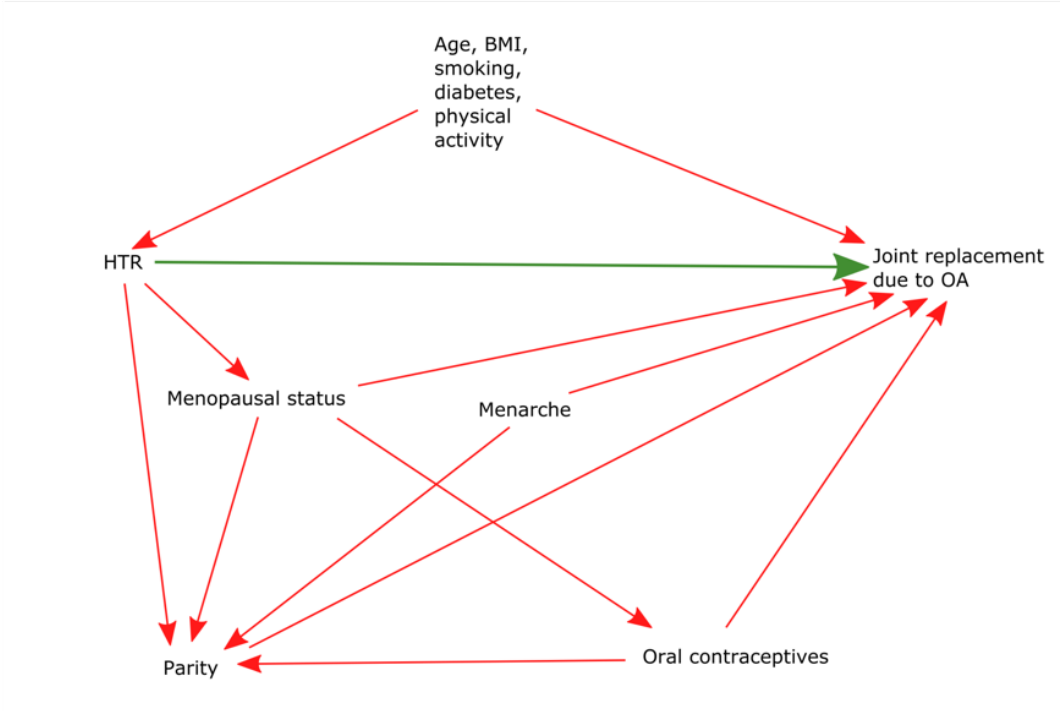



Age, BMI, smoking, diabetes, physical activity
Parity
Joint replacement due to OA
Menarche
Oral contraceptives
Menopausal status
HTR


Age, BMI, smoking, diabetes, physical activity
Menarche
Joint replacement due to OA
Oral contraceptives
Parity
Menopausal status
HTR


Age, BMI, smoking, diabetes, physical activity
Menopausal status
Joint replacement due to OA
Oral contraceptives
Menarche
HTR
Parity


Age, BMI, smoking, diabetes, physical activity
Oral contraceptives
Joint replacement due to OA
Menopausal status
Menarche
HTR
Parity


Age, BMI, smoking, diabetes, physical activity
HTR
Joint replacement due to OA
Menopausal status
Menarche
Parity
Oral contraceptives

Appendix C: Covariates adjusted for in paper III, by exposure.

Exposure variable	***Covariates adjusted for***
Parity	Age, BMI, smoking, physical activity, diabetes, age at menarche, menopausal status, HRT
Age at menarche	Age, BMI, smoking, physical activity, diabetes, menopausal status
Years with menstruation	Age, BMI, smoking, physical activity, diabetes, parity
Menopause status	Age, BMI, smoking, physical activity, parity, age at menarche, HRT
Age at menopause	Age, BMI, smoking, physical activity, parity, age at menarche, HRT
Use of oral contraceptives	Age, BMI, smoking, physical activity, parity, age at menarche, menopausal status
Use of HRT	Age, BMI, smoking, physical activity, parity, menopausal status

Paper I

Clinical Epidemiology

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ORIGINAL RESEARCH

Metabolic syndrome as a risk factor for total hip or knee replacement due to primary osteoarthritis: a prospective cohort study (the HUNT study and the Norwegian Arthroplasty Register)

This article was published in the following Dove Press journal:
Clinical Epidemiology

Alf Inge Hellevik,[1,2] Marianne Bakke Johnsen,[3,4] Arnulf Langhammer,[1] Valborg Baste,[5] Ove Furnes,[6,7] Kjersti Storheim,[3,4] John Anker Zwart,[3,4] Gunnar Birkeland Flugsrud,[2] Lars Nordsletten,[2,4]

[1]The HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Levanger, [2]Division of Orthopaedic Surgery, Oslo University Hospital, Oslo, [3]Research and Communication Unit for Musculoskeletal Health, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, [4]Faculty of Medicine, University of Oslo, Oslo, [5]Uni Research Health, Bergen, [6]The Norwegian Arthroplasty Register, Department of Orthopedic Surgery, Haukeland University Hospital, Bergen, [7]Department of Clinical Medicine, Institute of Medicine and Dentistry, University of Bergen, Bergen, Norway

Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: http://youtu.be/1a6B1V_4t-0

Correspondence: Alf Inge Hellevik
The HUNT Research Centre, Forskningsveien 2
N-7600 Levanger, Norway
Tel +47 4 133 5383
Email alf.hellevik@ntnu.no

Objective: Biochemical changes associated with obesity may accelerate osteoarthritis beyond the effect of mechanical factors. This study investigated whether metabolic syndrome and its components (visceral obesity, hypertension, dyslipidemia and insulin resistance) were risk factors for subsequent total hip replacement (THR) or total knee replacement (TKR) due to primary osteoarthritis.

Design: In this prospective cohort study, data from the second survey of the Nord-Trøndelag Health Study 2 (HUNT2) were linked to the Norwegian Arthroplasty Register for identification of the outcome of THR or TKR. The analyses were stratified by age (<50, 50–69.9 and ≥70 years) and adjusted for gender, body mass index, smoking, physical activity and education.

Results: Of the 62,661 participants, 12,593 (20.1%) were identified as having metabolic syndrome, and we recorded 1,840 (2.9%) THRs and 1,111 (1.8%) TKRs during a mean follow-up time of 15.4 years. Cox regression analyses did not show any association between full metabolic syndrome and THR or TKR, except in persons <50 years with metabolic syndrome who had a decreased risk of THR (hazard ratio [HR] 0.58, 95% CI 0.40–0.83). However, when including only participants whose exposure status did not change during follow-up, this protective association was no longer significant. Increased waist circumference was associated with increased risk of TKR in participants <50 years (HR 1.62, 95% CI 1.10–2.39) and 50–69.9 years (HR 1.43, 95% CI 1.14–1.80). Hypertension significantly increased the risk of TKR in participants <50 years (HR 1.38, 95% CI 1.05–1.81), and this risk was greater for men.

Conclusion: This study found an increased risk of TKR in men <50 years with hypertension and persons <70 years with increased waist circumference. Apart from this, neither metabolic syndrome nor its components were associated with increased risk of THR or TKR due to primary osteoarthritis.

Keywords: osteoarthritis, metabolic syndrome, total hip replacement, total knee replacement

Introduction

Hip and knee osteoarthritis cause significant morbidity and disability in a large proportion of the population.[1] There is no curative treatment for osteoarthritis, and this places the emphasis on identifying preventable risk factors. Increased body mass index (BMI) is a well-established risk factor for osteoarthritis, both in the knee[2–4] and the hip.[5–7] However, biochemical changes associated with obesity may accelerate osteoarthritis beyond the effect of mechanical factors.[8,9] Metabolic osteoarthritis has, therefore, been suggested as a subtype of osteoarthritis, and links between this phenotype and metabolic syndrome have been reported.[10,11]

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Metabolic syndrome is a cluster of components associated with increased risk of cardiovascular disease.[12] These include increased waist circumference, high blood pressure, elevated triglycerides, reduced high-density lipoprotein (HDL) and elevated serum glucose or diabetes. Due to the high prevalence of these components among persons with osteoarthritis, it has been suggested that metabolic syndrome may influence the development of osteoarthritis independent of BMI.[13,14] This could be explained by shared mechanisms in the etiologies of osteoarthritis and metabolic syndrome: inflammation, oxidative stress, common metabolites and endothelial dysfunction.[11] However, it is possible that osteoarthritis and metabolic syndrome simply coexist through their common shared risk factors of age and obesity.[15]

The results of observational studies in humans have been inconsistent. One Australian prospective cohort study found that a cumulative number of metabolic syndrome components, central obesity and hypertension were associated with increased risk of total knee replacement (TKR) due to osteoarthritis independent of BMI, but no associations were observed for total hip replacement (THR).[15] However, the Malmö Diet and Cancer Study found that only central obesity was associated with increased risk of knee osteoarthritis independent of BMI.[16] Metabolic syndrome and its components were not associated with hip osteoarthritis. Other studies have also reported an increased risk of knee osteoarthritis associated with an increase in the number of metabolic syndrome components.[17] In contrast, a recent study reported that, after adjustment for BMI, neither metabolic syndrome nor its components were associated with incident osteoarthritis in the knee.[18] The hypothesis of this study was that metabolic syndrome is a risk factor for THR or TKR due to osteoarthritis.

The aim of this large prospective study was to assess whether metabolic syndrome or its components were risk factors independent of BMI for subsequent THR or TKR due to primary osteoarthritis.

Methods

Study population

Between 1995 and 1997, all inhabitants of Nord-Trøndelag county, aged ≥20 years, were invited to participate in the second wave of the Nord-Trøndelag Health Study 2 (HUNT2).[19] The HUNT studies include three population-based studies: HUNT1 (1984–1986), HUNT2 (1995–1997) and HUNT3 (2006–2008). HUNT was initially intended to investigate arterial hypertension, diabetes, quality of life and to screen for tuberculosis. However, its scope expanded over time.[19] This study included baseline data from HUNT2, as the HUNT1 study did not have information on serum triglycerides and HDL.

A total of 65,237 (69.5%) individuals accepted the invitation to participate in HUNT2.[19] From this group, we included 63,617 participants with measurements of all metabolic syndrome components at baseline. Of these, 956 were excluded (Figure 1) due to previous joint replacement in the hip or knee (n=796), missing date of operation (n=158) or emigration during baseline period (n=2). Thus, a total of 62,661 persons (32,990 women and 29,671 men) were included in this study. Each participant contributed person-time from participation date in HUNT2 (between August 1995 and June 1997) until total hip or knee replacement due to osteoarthritis, total hip

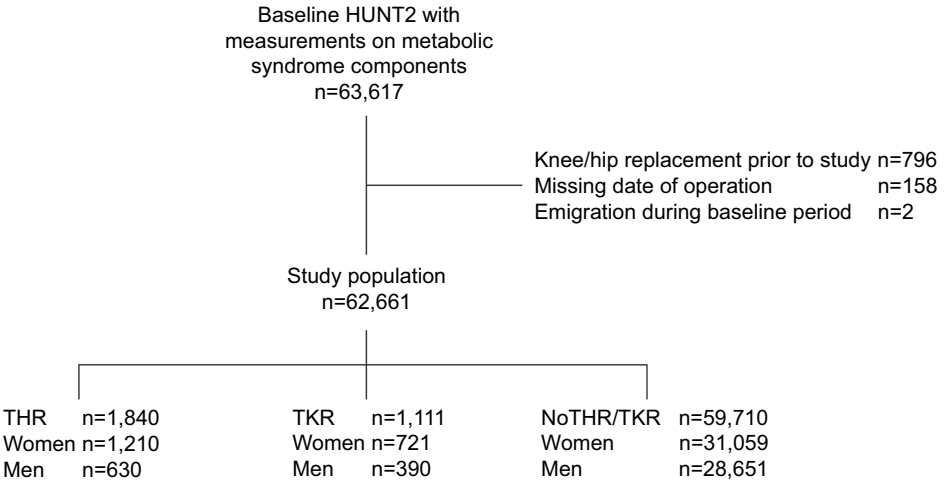

Figure 1 Flowchart.
Abbreviations: HUNT2, the Nord-Trøndelag Health Study 2; THR, total hip replacement; TKR, total knee replacement.

or knee replacement due to other causes, migration, death or the end of follow-up (December 31, 2013), whichever occurred first.

Clinical measurements

The participants were asked to complete a self-administered questionnaire which included a range of health-related questions. Participants were seen once for clinical measurements and blood sampling. The survey included standardized measurement of height, weight, waist circumference and blood pressure by trained nurses or technicians. Weight was measured to the nearest half kilogram with the participants wearing light clothes and no shoes. Waist circumference was measured horizontally at the height of the umbilicus to the nearest centimeter, with the participants standing with their arms hanging relaxed. Blood pressure was measured on the right arm with cuffs adjusted according to the arm circumference, and after the participant had been sitting relaxed for 5 minutes. Measurements based on oscillometry were then taken (Dinamap 845XT; Critikon, Tampa, FL, USA). Systolic and diastolic blood pressure levels were then read three times at 1-minute interval, and the mean of the second and third readings was used in the analysis. Non-fasting blood samples were drawn from each participant. Serum levels of triglycerides, HDL cholesterol and glucose were analyzed on a Hitachi 911 Autoanalyser (Hitachi, Mito, Japan).[20]

According to the Joint Interim Statement, metabolic syndrome is defined as the presence of ≥3 of the following:[12] waist circumference ≥88 cm in women and ≥102 cm in men, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or use of antihypertensive medication, triglycerides ≥1.7 mmol/L, HDL cholesterol <1.3 mmol/L in women and <1.0 mmol/L in men, and glucose >5.6 mmol/L or self-reported diabetes. This definition is based on fasting blood samples. When these were lacking, we used a modified definition of metabolic syndrome also used in previous studies,[21,22] categorizing elevated glucose as serum glucose ≥11.1 mmol/L. This is, however, likely to be a stricter cutoff, since it is intended to identify undiagnosed diabetes.[23] The self-reported diagnosis of diabetes in the HUNT study has been validated in a separate study, demonstrating that 96.4% of self-reported diabetes could be verified in medical files.[24]

To reduce potential confounding, covariates associated with both metabolic syndrome and joint replacement due to osteoarthritis were adjusted for. These covariates included: age (stratified), gender (female/male), BMI (continuous), current smoking status (never, former, current), physical activity (light, medium, hard) and education (primary, secondary, post-secondary). Cardiovascular disease was evaluated to be a mediator, and was therefore not included as a confounder as this could have biased the analyses. The main analysis was done stepwise; the first model was only adjusted for gender and BMI (Model 1) and the second was fully adjusted (Model 2). Age was stratified into the age groups of <50, 50–69.9 and ≥70 years at baseline. Physical activity was categorized by duration of light (not sweating or out of breath) physical activity (none, <1, 1–2, ≥3 hours/week) and/or duration of hard (sweating or out of breath) physical activity (none, <1, 1–2, ≥3 hours/week). The physical activity questions have previously been validated among men between 20 and 39 years.[25] This showed acceptable repeatability and validity for the "hard" physical activity questions, but poor validity for the light questions. The two physical activity variables were combined into one variable indicating intensity and duration: none (no activity), medium (≤2 hours/week light physical activity and/or <1 hour/week hard physical activity) or hard (≥3 hours/week light physical activity and/or ≥1 hour/week hard physical activity). Education was defined as the highest level of completed education (primary/vocational, secondary or post-secondary).

To account for potential change in exposure during follow-up, a sensitivity analysis was performed in those who participated in both HUNT2 (1995–1997) and HUNT3 (2006–2008), with n=30,651. By excluding those who changed exposure group between HUNT2 and HUNT3, we were able to do an analysis with a lower risk of misclassification of the exposures.

As very few of those between 20 and 30 years at baseline were expected to have a primary THR or TKR due to osteoarthritis, a separate sensitivity analysis also excluded those <30 years in the age group <50 years. Finally, we also did an analysis stratified on both gender and age to investigate any differences between genders.

Outcome

This study used THR or TKR due to primary osteoarthritis as the outcome. The unique 11-digit identification number of every Norwegian citizen enabled linkage of HUNT data to the Norwegian Arthroplasty Register (NAR). NAR was established in 1987 and includes all artificial joints from 1994 onward. The completeness of THR and TKR registration is over 95%.[26] For each arthroplasty performed, the orthopedic surgeon submits a standardized form containing information about the patient, the diagnosis that led to the arthroplasty, the procedure and the type of implant used.[27] In this paper, primary THR or TKR in patients with primary

or idiopathic osteoarthritis is considered to be an indicator of severe osteoarthritis.

Statistical methods

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% CIs for metabolic syndrome, and its components, for the first recorded primary THR or TKR due to osteoarthritis. Tests of proportional hazards assumption were evaluated by Schoenfeld residuals and log-minus-log plots (Table S1) and were satisfied for all variables, except for age. The analyses were, therefore, stratified into age groups (<50, 50–69.9 and ≥70 years) and adjusted for gender, BMI, smoking, physical activity and education. The analyses were performed using Stata 14/IC (StataCorp LP, College Station, TX, USA).

Ethics approval

This study was approved by the Norwegian Regional Committee for Ethics in Medical Research (REK Sør-Øst C).

Results

Of the 62,661 participants included in this study, 12,593 (20.1 %) were identified as having metabolic syndrome using the modified definition from Joint Interim Statement with a cutoff for non-fasting blood glucose of ≥11.1 mmol/L. The most prevalent components in persons with metabolic syndrome were hypertension, increased triglycerides and low HDL. Members of this group were generally older, had higher BMI, were less physically active, had lower levels of education and higher prevalence of cardiovascular disease than those without metabolic syndrome

Table 1 Baseline characteristics

	Women		Men		Total	
	MetS, n (%)	**No MetS, n (%)**	**MetS, n (%)**	**No MetS, n (%)**	**MetS, n (%)**	**No MetS, n (%)**
Age, years						
19–29	301 (4.3)	4,327 (16.7)	390 (7.0)	3,661 (15.2)	691 (5.5)	7,988 (16.0)
30–39	563 (8.0)	5,392 (20.8)	727 (13.1)	4,623 (19.2)	1,290 (10.2)	10,015 (20.0)
40–49	1,037 (14.7)	5,952 (22.9)	1,084 (19.5)	5,372 (22.3)	2,121 (16.8)	11,324 (22.6)
50–59	1,287 (18.3)	4,337 (16.7)	1,058 (19.0)	4,203 (17.4)	2,345 (18.7)	8,540 (17.1)
60–69	1,558 (22.2)	2,911 (11.2)	1,038 (18.7)	3,148 (13.0)	2,596 (20.6)	6,059 (12.1)
70–79	1,663 (23.6)	2,280 (8.8)	956 (17.2)	2,434 (10.1)	2,619 (20.8)	4,714 (9.4)
≥80	626 (8.9)	756 (2.9)	305 (5.5)	672 (2.8)	931 (7.4)	1,428 (2.8)
Gender						
Women					7,035 (55.9)	25,955 (51.8)
BMI, kg/m^2						
<18.5	7 (0.1)	328 (1.3)	4 (0.1)	109 (0.5)	11 (0.1)	437 (0.9)
18.5–24.99	696 (9.9)	13,739 (52.9)	499 (9.0)	9,853 (40.8)	1,195 (9.5)	23,592 (47.1)
25–29.99	2,794 (39.7)	9,400 (36.2)	2,710 (48.7)	12,244 (50.8)	5,504 (43.7)	21,644 (43.2)
≥30	3,538 (50.3)	2,488 (9.6)	2,345 (42.2)	1,907 (7.9)	5,883 (46.7)	4,395 (8.8)
Smoking						
Never	3,536 (52.1)	11,958 (47.1)	1,715 (31.5)	9,274 (39.1)	5,251 (42.9)	21,232 (43.2)
Former	1,492 (22.0)	5,546 (21.8)	2,305 (42.4)	7,457 (31.4)	3,797 (31.1)	13,003 (26.5)
Current	1,763 (25.9)	7,899 (31.1)	1,419 (26.1)	7,007 (29.5)	3,182 (26.0)	14,906 (30.3)
Missing	244	552	119	375	363	927
Physical activity						
None	791 (14.4)	1,442 (6.1)	575 (11.7)	1,620 (7.3)	1,366 (13.1)	3,062 (6.7)
Medium	3,169 (57.7)	12,749 (54.3)	2,623 (53.2)	10,375 (46.5)	5,792 (55.6)	23,124 (50.5)
Hard	1,530 (27.9)	9,291 (39.6)	1,729 (35.1)	10,321 (46.2)	3,259 (31.3)	19,612 (42.8)
Missing	1,545	2,473	631	1,797	2,176	4,270
Education						
Primary/vocational	5,415 (86.5)	16,127 (64.8)	4,077 (78.7)	16,321 (70.5)	9,492 (83)	32,448 (67.6)
Secondary	297 (4.7)	3,034 (12.2)	315 (6.1)	1,969 (8.5)	612 (5.3)	5,003 (10.4)
Post-secondary	552 (8.8)	5,719 (23)	788 (15.2)	4,866 (21.0)	1,340 (11.7)	10,585 (22.0)
Missing	771	1,075	378	957	1,149	2,032
Increased WC	5,444 (77.4)	3,444 (13.3)	2,883 (51.8)	1,221 (5.1)	8,327 (66.1)	4,665 (9.3)
Hypertension	6,439 (91.5)	11,771 (45.4)	5,393 (97)	16,208 (67.2)	11,832 (94.0)	27,979 (55.9)
High triglycerides	6,335 (90.1)	4,189 (16.1)	5,383 (96.9)	9,083 (37.7)	11,718 (93.1)	13,272 (26.5)
Low HDL	5,019 (71.3)	4,040 (15.6)	3,705 (66.7)	1,692(7.0)	8,724 (69.3)	5,732 (11.5)
IGT or diabetes	806 (11.5)	202 (0.8)	713 (12.8)	333 (1.4)	1,519 (12.1)	535 (1.1)

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; MetS, metabolic syndrome; WC, waist circumference.

(Table 1). At baseline, women and men had a mean age of 49.9 years (SD 17.2) and 49.7 years (SD 16.7), respectively. Correspondingly, mean age at joint replacement was 69.9 years (SD 9.3) and 69.0 years (SD 9.2). In total, 1,840 persons received THR (2.9%), and 1,111 persons received TKR (1.8%) during a mean follow-up time of 15.4 (SD 4.3) years.

Metabolic syndrome and THR

No association was found between metabolic syndrome or its individual components and increased risk of THR (Table 2). In the age group <50 years, there was a decreased risk of THR in those with the full metabolic syndrome (HR 0.58, 95% CI 0.40–0.83). There was no substantial difference in the analyses in Model 1 and the fully adjusted Model 2. However, persons with impaired glucose tolerance or diabetes in the groups 50–69.9 and ≥70 years had a significantly decreased risk of THR, with HR 0.65 (95% CI 0.36–0.87) and HR 0.30 (95% CI 0.13–0.67). Participants ≥70 years with hypertension had a decreased risk of THR (HR 0.63, 95 % CI 0.43–0.92). In the youngest age group, <50 years, there was also a decreased risk of THR in those with low HDL (HR 0.72, 95% CI 0.54–0.94).

Metabolic syndrome and TKR

Metabolic syndrome was not associated with the risk of TKR. High waist circumference increased the risk of TKR in the age groups <50 years (HR 1.62, 95% CI 1.10–2.39) and 50–69.9 years (HR 1.43, 95% CI 1.14–1.80), as shown in Table 2. Hypertension significantly increased the risk of TKR in the age group <50 years (HR 1.38, 95% CI 1.05–1.81). Apart from these findings, none of the other components of metabolic syndrome were associated with increased risk of TKR. However, low HDL was associated with decreased risk of TKR in both those <50 years (HR 0.67, 95% CI 0.49–0.92) and ≥70 years (HR 0.53, 95% CI 0.33–0.86).

Additional analysis

Of the 30,651 persons who participated in both HUNT2 (1995–1997) and HUNT3 (2006–2008), 31.8% changed the exposure group during the follow-up period from normal to increased waist circumference and 16.2% changed the exposure group during the follow-up period from no metabolic syndrome to metabolic syndrome (Table 3). When analyzing only those who had not changed the exposure group in each category, there was no longer a decreased risk of THR in participants <50 years with metabolic syndrome or low HDL (Figure 2). In this analysis, increased waist circumference was

Table 3 Number of participants who switched the exposure groups during follow-up, including only those who participated in both HUNT2 (1995–1997) and HUNT3 (2006–2008) (N=30,651)

	From unexposed to exposed group, n (%)	From exposed to unexposed group, n (%)
Waist circumference	9735 (31.8)	274 (0.9)
Hypertension	3955 (12.9)	3303 (10.8)
High triglycerides	4767 (15.6)	4296 (14.0)
Low HDL	3175 (10.4)	2331 (7.6)
IGT or diabetes	1115 (3.6)	13 (0.04)
Metabolic syndrome	4971 (16.2)	1428 (4.7)

Abbreviations: HDL, high-density lipoprotein; HUNT2, the Nord-Trøndelag Health Study 2; IGT, impaired glucose tolerance.

Table 2 Risk of THR or TKR by metabolic syndrome components and metabolic syndrome

	Model 1[a]			Model 2[b]		
	<50 years	50–69.9 years	≥70 years	<50 years	50–69.9 years	≥70 years
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
THR						
Increased waist circumference	1.25 (0.88–1.77)	0.98 (0.83–1.16)	1.19 (0.90–1.57)	1.17 (0.81–1.68)	1.08 (0.89–1.30)	1.22 (0.86–1.73)
Hypertension	1.24 (0.98–1.55)	1.16 (1.00–1.35)	0.63* (0.46–0.87)	1.13 (0.89–1.43)	1.09 (0.93–1.28)	0.63* (0.43–0.92)
High triglycerides	0.92 (0.72–1.17)	0.95 (0.84–1.07)	0.86 (0.70–1.07)	0.86 (0.66–1.11)	0.93 (0.81–1.07)	0.89 (0.69–1.16)
Low HDL	0.71* (0.54–0.93)	0.99 (0.86–1.14)	0.82 (0.64–1.04)	0.72* (0.54–0.94)	0.95 (0.81–1.12)	0.85 (0.62–1.15)
IGT or diabetes	0.73 (0.23–2.29)	0.60* (0.41–0.87)	0.33* (0.18–0.61)	0.78 (0.25–2.44)	0.65* (0.36–0.87)	0.30* (0.13–0.67)
Metabolic syndrome	0.64* (0.46–0.90)	0.94 (0.81–1.09)	0.82 (0.65–1.04)	0.58* (0.40–0.83)	0.93 (0.79–1.10)	0.83 (0.65–1.14)
TKR						
Increased waist circumference	1.62* (1.12–2.36)	1.43* (1.16–1.76)	1.45 (0.98–2.15)	1.62* (1.10–2.39)	1.43* (1.14–1.80)	1.55 (0.95–2.53)
Hypertension	1.44* (1.11–1.88)	1.12 (0.91–1.37)	0.76 (0.45–1.30)	1.38* (1.05–1.81)	1.17 (0.93–1.47)	0.68 (0.37–1.25)
High triglycerides	0.97 (0.74–1.27)	1.03 (0.88–1.20)	1.17 (0.86–1.59)	0.97 (0.73–1.28)	1.05 (0.89–1.25)	1.27 (0.87–1.85)
Low HDL	0.62* (0.46–0.84)	0.94 (0.78–1.12)	0.66* (0.46–0.93)	0.67* (0.49–0.92)	1.04 (0.86–1.26)	0.53* (0.33–0.86)
IGT or diabetes	1.01 (0.37–2.73)	0.73 (0.50–1.09)	0.79 (0.45–1.40)	0.85 (0.27–2.66)	0.70 (0.45–1.11)	0.78 (0.38–1.60)
Metabolic syndrome	0.94 (0.68–1.30)	1.07 (0.90–1.28)	1.25 (0.91–1.73)	0.89 (0.63–1.26)	1.16 (0.96–1.41)	1.27 (0.85–1.90)

Notes: *Significant at $p<0.05$. [a]Model 1, HR adjusted for gender and BMI. [b]Model 2, HR adjusted for gender, BMI, smoking, physical activity and education.
Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HR, hazard ratio; IGT, impaired glucose tolerance; THR, total hip replacement; TKR, total knee replacement.

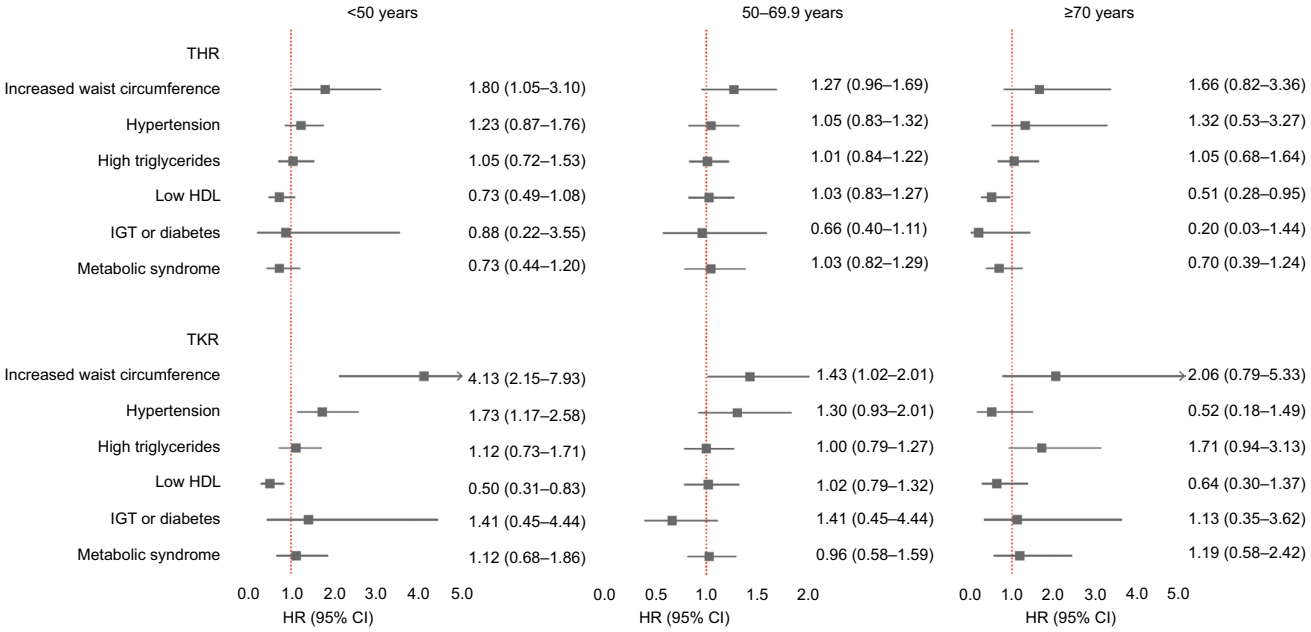

Figure 2 Risk of THR or TKR by metabolic syndrome components and metabolic syndrome including only those patients who did not change exposure groups during follow-up.

Note: HRs adjusted for gender and BMI.

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HR, hazard ratio; IGT, impaired glucose tolerance; THR, total hip replacement; TKR, total knee replacement.

also found to be a risk factor for THR in persons <50 years (HR 1.80, 95% CI 1.05–3.10), and there continued to be an increased risk of TKR in the age groups <50 years (HR 4.13, 95% CI 2.15–7.93) and 50–69.9 years (HR 1.43, 95% CI 1.02–2.01). In contrast to the main analysis, hypertension was no longer a protective factor for THR in persons >70 years, nor was impaired glucose tolerance or diabetes protective for THR in persons between 50 and 69.9 years or >70 years of age.

In a separate sensitivity analysis of the age group <50 years, participants <30 years at baseline were excluded. Hypertension was then only borderline significant (HR 1.29, 95% CI 0.98–1.70); but apart from this, the results were not substantially different from the main analysis (Figure 3).

When stratifying on both gender and age, we found increased risk of TKR only in men <50 years with hypertension (HR 1.90, 95% CI 1.16–3.11), as shown in Table S2. However, there was still an increased risk of TKR in both men and women between 50 and 69.9 years with increased waist circumference.

Discussion

In this large prospective study with over 60,000 participants, we found no increased risk of THR or TKR in persons with metabolic syndrome. There was a reduced risk of THR in participants <50 years with metabolic syndrome, but this association was no longer significant when excluding those who changed exposure group during follow-up. We found an increased risk of TKR in participants <70 years with increased waist circumference and in those <50 years with hypertension. Apart from these findings, neither metabolic syndrome nor its components increased the risk of THR or TKR due to osteoarthritis.

In the main analysis (Table 2), we did not find any association between the full metabolic syndrome and THR or TKR, except in persons <50 years with metabolic syndrome, who were found to have a decreased risk of THR (HR 0.58, 95% CI 0.40–0.83). However, our study had information on the development of exposure about 10 years after baseline, and this made it possible to account for changes in the exposure status of metabolic syndrome during follow-up: 16.2% of those who participated in both HUNT2 and HUNT3 went from unexposed to exposed. This misclassification of exposure could have affected the results. We, therefore, did a sensitivity analysis including only those whose exposure status did not change during the first 10 years of follow-up and found that metabolic syndrome was no longer associated with decreased risk of THR in those <50 years. As in the main analysis, in none of the other age strata was metabolic syndrome found to be a risk factor for THR or TKR. We, therefore, conclude that metabolic syndrome is not an important risk factor for THR or TKR independent of BMI.

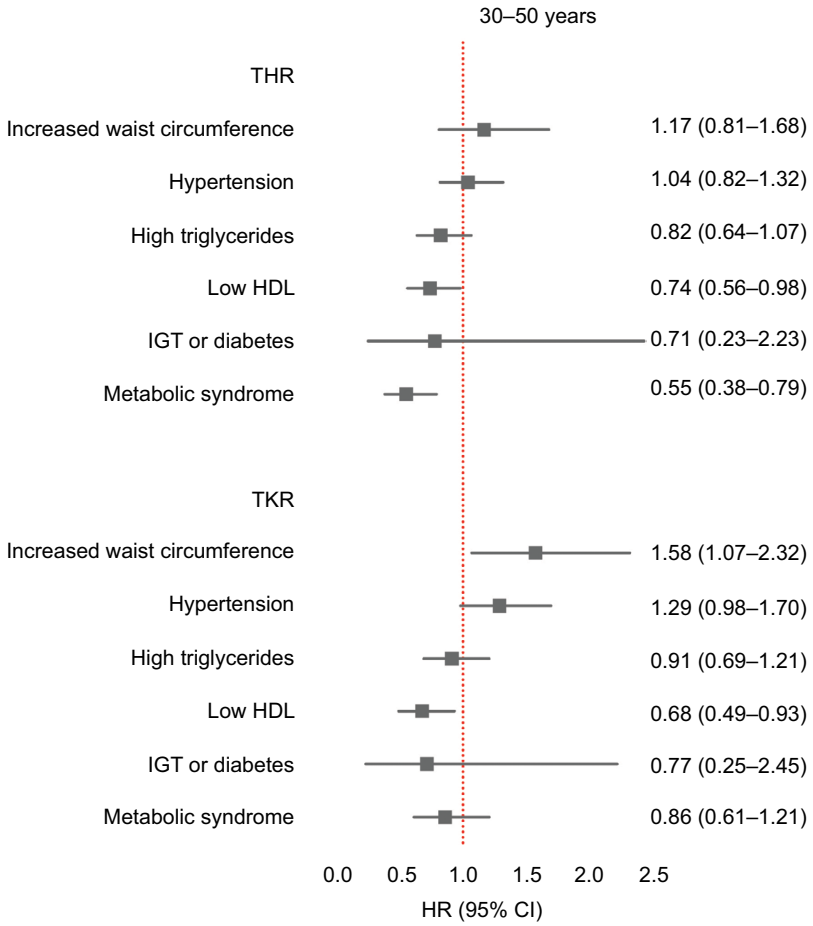

Figure 3 Risk of THR or TKR by metabolic syndrome components and metabolic syndrome in participants <50 years after excluding participants <30 years at baseline.
Note: HRs adjusted for gender, BMI, smoking, physical activity and education.
Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HR, hazard ratio; IGT, impaired glucose tolerance; THR, total hip replacement; TKR, total knee replacement.

The high number of participants allowed for stratification by age, and thereby the investigation of how some components of metabolic syndrome could have different effects on risk of total joint replacement in younger and older age groups. This could help explain some of the previous conflicting results regarding the association between metabolic syndrome and total joint replacement; what may be a risk factor in those <50 years, such as hypertension or increased waist circumference, may not be a risk factor in those ≥70 years (Table 2). The mechanisms behind this are not clear, but it is possible that components of metabolic syndrome could be seen as a relative contraindication to joint replacement surgery to a higher degree in the old, compared to the young. Thus, these components could be protective against surgery, but not necessarily osteoarthritis, in the old. Using THR and TKR as indicators of osteoarthritis had the advantage of being an unambiguous indicator of severe disease burden compared to other osteoarthritis definitions, for example, radiographic criteria, symptom criteria or osteoarthritis defined by self-reported diagnosis.[28] Using total joint replacement as an endpoint for osteoarthritis also helps distinguish between severe disease and common minor disability.[29] However, there are several important limitations to this approach. Firstly, persons with moderate osteoarthritis who engage in demanding physical activities could be more motivated to have surgery than less active persons. Secondly, the metabolic syndrome risk factors could influence the orthopedic surgeon's choice regarding treatment, giving a healthy patient selection bias with corresponding underestimation of the effect of possible risk factors. This effect could have been what we observed when we observed that hypertension and increased waist circumference were not found to be risk factors in those ≥70 years. Our findings are also in line with a study by Nielen et al which found that risk of severe osteoarthritis necessitating THR or TKR decreased with increasing severity of diabetes mellitus.[30] This could help explain the apparent protective effect of impaired glucose tolerance or diabetes in the two older age groups.

We found an increased risk of TKR in participants <50 years with hypertension, and this effect was strongest in men. Hypertension as a risk factor for TKR is consistent with previous findings by Monira Hussain et al.[15] In both the Chingford study from the UK and the ROAD study from Japan, hypertension was found to be associated with osteoarthritis of the knee, independent of BMI.[17,31] A recent study by Niu et al reported that diastolic blood pressure was related to incident symptomatic osteoarthritis.[18] The prevalence of atherosclerotic risk factors, which include hypertension, has been reported to be higher in individuals with osteoarthritis.[32] It has been hypothesized that vascular pathology of subchondral small vessels could lead to local ischemia and subsequent development of osteoarthritis.[33,34] Le Clanche et al summarized a possible pathologic pathway between hypertension and osteoarthritis in a recent review[35] and attributed the connection to a reduced capacity of cells to produce nitric oxide, as hypertension causes a narrowing of the blood vessels.[36] This again leads to reduced blood flow in the subchondral bone, and thereby a compromised exchange of nutrients and oxygen and degradation of cartilage.[34] This subchondral ischemia could also induce osteocyte apoptosis in the subchondral bone, which again could lead to osteoclast recruitment and subchondral bone loss.[37]

Persons <70 years with increased waist circumference had an increased risk of TKR. Our results were concordant with several previous studies reporting increased central obesity to be a risk factor for osteoarthritis after adjustment for BMI.[4,15,38] It may be that the increased amount of abdominal fat tissue releases inflammatory mediators (adipokines, free fatty acids, reactive oxygen species) that, in turn, affect the joints and cartilage.[13,17,39] Another explanation could be that a high BMI may be due to either a large muscle/skeletal mass or a large amount of fat tissue. Overweight due to a large muscle mass could, therefore, be less harmful for the knees than overweight due to a large amount of abdominal fat tissue. Waist circumference may, therefore, differentiate these two groups.

Strengths and limitations

To the best of our knowledge, this is the largest prospective population study addressing the association between metabolic syndrome and total joint replacement due to primary osteoarthritis. In most cases, the metabolic syndrome components were measured many years prior to joint replacement. The ability to adjust for multiple potential confounders was a strength in this study. Even though the participation rate in HUNT2 was fairly high compared to most other surveys, there is always a potential for selection bias.[20] In particular, men from young age groups had a lower participation rate. However, since primary THR and TKR are most common in the elderly population, the effect of this selection bias in our study population should be minimal.

Information on potential change in exposure group during follow-up was also a strength in this study. When excluding participants who switched the exposure group during the first 10 years of follow-up, there was no longer an association between hypertension and THR in persons >70 years, nor was impaired glucose tolerance or diabetes associated with THR in persons between 50 and 69.9 years or >70 years. The apparent protective effects of these exposures in the main analyses could, therefore, have been due to misclassification of exposure.

When analyzing women and men separately, we found that increased waist circumference was a risk factor for TKR in both genders. However, only men with hypertension had an increased risk of TKR. The reason for this difference is not clear, as one would expect that an underlying biologic mechanism of subchondral ischemia was the same in both genders. Further studies on a possible gender difference in hypertension and knee osteoarthritis are, therefore, warranted.

THR or TKR is very uncommon in persons <30 years, and including this group in the analysis could have distorted the results. In a sensitivity analysis excluding those <30 years, we found that the risk of TKR in participants with hypertension was weakened (HR 1.29, 95% CI 0.98–1.70). This could indicate that including young participants could lead to overestimation of the effect of hypertension on TKR, and this should be taken into account in further studies.

Participants taking antihypertensive medication and/or with known diabetes were accounted for in the analysis by including them in the hypertensive and impaired glucose tolerance groups, respectively. However, we did not have information on cholesterol-lowering medication, and this could have resulted in differential misclassification of exposure as persons on medication were classified as having normal serum levels, thus potentially weakening the association between HDL/triglycerides and joint replacement. This possible misclassification may explain the reduced risk of THR or TKR in persons with low HDL in both the highest and lowest age strata (Table 2; Figure 2).

As previously described, a limitation in this study was that we only had information on non-fasting serum blood glucose. Our cutoff level of serum glucose ≥11.1 mmol/L is likely to be a stricter definition of impaired glucose tolerance,[23] and may thus have resulted in an underestimation of

any association between impaired glucose tolerance/diabetes and joint replacement.

Many participants may have had metabolic syndrome for some time before entering the study. This could have led to a bias in estimation resulting from studying prevalent exposure rather than new exposure.[40] We were not able to differentiate between new and prevalent cases, and thus, the effect of this prevalent cohort bias could have led to an underestimation of any association between metabolic syndrome and total joint replacement.

Waist circumference and BMI are correlated. Estimating the correlation between waist circumference (dichotomous) and BMI (continuous) gave an R^2 of 0.38 in the age group <50 years, 0.43 in the age group 50–69.9 years and 0.42 in the age group ≥70 years. This corresponded to a variance inflation factor (VIF) of 1.62, 1.75 and 1.72, respectively. VIF estimates how much the variance of waist circumference is inflated because of dependence on BMI. Thus, a VIF of 1.62 indicates that the variance of waist circumference is 62% larger than it would be if it was completely unrelated to BMI. There are different opinions on when the correlation is high enough to become a problem, but a VIF <4 may be acceptable.[41] However, it is difficult to exactly estimate the effect of increased waist circumference, independent of BMI.

Education is used as an indicator of socioeconomic status, and the HRs did not change significantly after adjusting for this factor. In addition to this, the hospital care in Norway is publicly financed and free of charge for patients. Therefore, we do not think that socioeconomic factors represented a major confounder in this material.

Previous injuries increase the risk of osteoarthritis, especially in the knee.[42,43] Even though we did not have direct information on previous injury, the operating surgeon had to report whether the knee joint replacement was due to primary/idiopathic osteoarthritis or a sequela from fracture, ligament injury, meniscal injury, infection, rheumatoid arthritis or ankylosing spondylitis. We only included joint replacement due to primary/idiopathic osteoarthritis.

Validation of diagnoses from the NAR has only been done for young adults <40 years of age undergoing THR due to hip dysplasia,[44] and is therefore inapplicable to our study population. However, numbers from the Danish Hip Arthroplasty Registry show a positive predictive value of 85% regarding the primary hip osteoarthritis diagnosis.[45] The results from the Danish registry are probably comparable to the Norwegian registry.

The main clinical implication of this study was that we did not find any increased risk of osteoarthritis in participants with metabolic syndrome. Metabolic syndrome may, therefore, not be an effective screening tool for identifying individuals with increased risk of THR or TKR. It is, however, possible to identify two groups that should receive special attention in reducing the risk of TKR due to osteoarthritis: persons <70 years with increased waist circumference and persons <50 years with hypertension. The clinical focus should still be mainly on weight reduction, as this is also an important first step in the treatment and prevention of hypertension.[46] However, treatment for the other metabolic syndrome components is, of course, still advisable due to their association with increased risk of cardiovascular disease.

Conclusion

This study found an increased risk of TKR in men <50 years with hypertension and in persons <70 years with increased waist circumference. Apart from this, neither metabolic syndrome nor its components were associated with increased risk of THR or TKR due to primary osteoarthritis.

Acknowledgments

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Author contributions

AIH participated in the study concept and design, obtained funding, performed the analysis, interpreted the data and drafted the manuscript. LN, MBJ, AL, GF, OF, KS and JAZ were involved in the conception and design of the study. OF was also involved in data collection of THR and TKR. VB contributed with statistical expertise. All authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

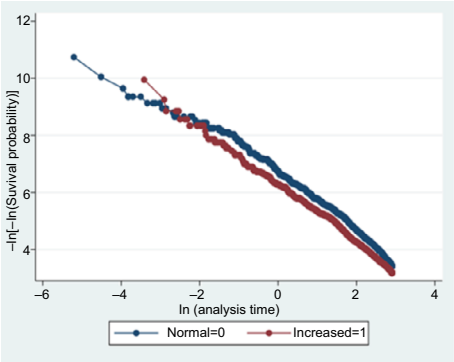
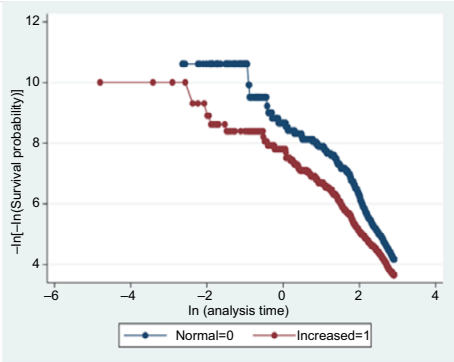
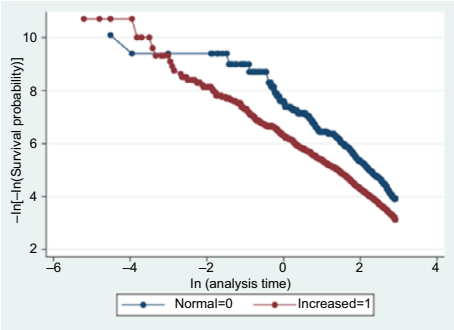
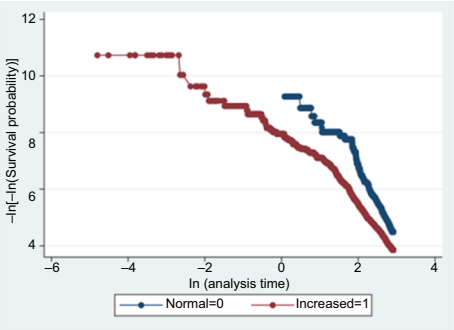
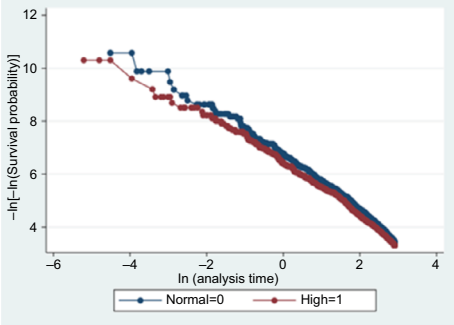
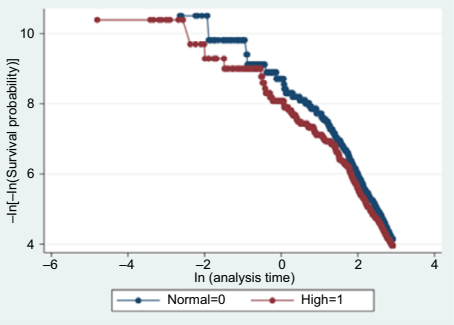
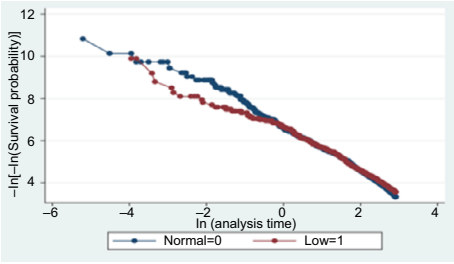
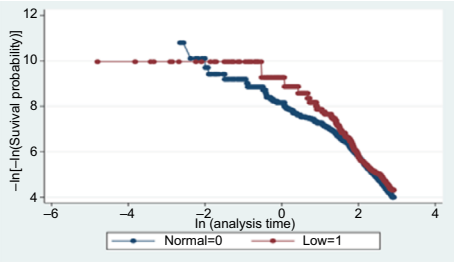
References

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2163–2196.
2. Apold H, Meyer HE, Nordsletten L, Furnes O, Baste V, Flugsrud GB. Risk factors for knee replacement due to primary osteoarthritis, a population based, prospective cohort study of 315,495 individuals. *BMC Musculoskelet Disord*. 2014;15(1):217.
3. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. *Ann Intern Med.* 1988;109(1):18–24.
4. Lohmander LS, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Engstrom G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. *Ann Rheum Dis*. 2009;68(4):490–496.
5. Apold H, Meyer HE, Espehaug B, Nordsletten L, Havelin LI, Flugsrud GB. Weight gain and the risk of total hip replacement a population-based prospective cohort study of 265,725 individuals. *OsteoarthritisCartilage*. 2011;19(7):809–815.
6. Flugsrud GB, Nordsletten L, Espehaug B, Havelin LI, Engeland A, Meyer HE. The impact of body mass index on later total hip arthroplasty for primary osteoarthritis: a cohort study in 1.2 million persons. *Arthritis Rheum.* 2006;54(3):802–807.
7. Flugsrud GB, Nordsletten L, Espehaug B, Havelin LI, Meyer HE. Risk factors for total hip replacement due to primary osteoarthritis: a cohort study in 50,034 persons. *Arthritis Rheum*. 2002;46(3):675–682.
8. Rai MF, Sandell LJ. Inflammatory mediators: tracing links between obesity and osteoarthritis. *Crit Rev Eukaryot Gene Expr*. 2011;21(2):131–142.
9. Lago F, Gomez R, Conde J, Scotece M, Gomez-Reino JJ, Gualillo O. Cardiometabolic comorbidities and rheumatic diseases: focus on the role of fat mass and adipokines. *Arthritis Care Res (Hoboken).* 2011;63(8):1083–1090.
10. Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? *Joint Bone Spine.* 2013;80(6):568–573.
11. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol.* 2012;8(12):729–737.
12. Alberti KG, Eckel RH, Grundy SM, et al; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120(16):1640–1645.
13. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis Cartilage.* 2013;21(1):16–21.
14. Hawker GA, Stanaitis I. Osteoarthritis year in review 2014: clinical. *Osteoarthritis Cartilage.* 2014;22(12):1953–1957.
15. Monira Hussain S, Wang Y, Cicuttini FM, et al. Incidence of total knee and hip replacement for osteoarthritis in relation to the metabolic syndrome and its components: a prospective cohort study. *Semin Arthritis Rheum.* 2014;43(4):429–436.
16. Engstrom G, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Lohmander LS. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study. *Osteoarthritis Cartilage.* 2009;17(2):168–173.
17. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Association of knee osteoarthritis with the accumulation of metabolic risk factors such as overweight, hypertension, dyslipidemia, and impaired glucose tolerance in Japanese men and women: the ROAD study. *J Rheumatol.* 2011;38(5):921–930.
18. Niu J, Clancy M, Aliabadi P, Vasan R, Felson DT. Metabolic syndrome, its components, and knee osteoarthritis: the framingham osteoarthritis study. *Arthritis Rheumatol.* 2017;69(6):1194–1203.
19. Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. *Int J Epidemiol.* 2013;42(4):968–977.
20. Holmen J, Midthjell K, Krüger Ø, et al. The Nord-Trøndelag Health Study 1995–1997 (HUNT 2): objectives, contents, methods and participation. *Norsk Epidemiologi.* 2003;13(1):19–32.
21. Moe B, Mork PJ, Holtermann A, Nilsen TI. Occupational physical activity, metabolic syndrome and risk of death from all causes and cardiovascular disease in the HUNT 2 cohort study. *Occup Environ Med.* 2013;70(2):86–90.
22. Martin RM, Vatten L, Gunnell D, Romundstad P, Nilsen TI. Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway. *Cancer Causes Control*. 2009;20(7):1181–1192.
23. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2012;35(Suppl 1):S64–S71.
24. Midthjell K, Holmen J, Bjorndal A, Lund-Larsen G. Is questionnaire information valid in the study of a chronic disease such as diabetes? The Nord-Trondelag diabetes study. *J Epidemiol Community Health.* 1992;46(5):537–542.
25. Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trøndelag Health Study (HUNT 2). *Eur J Epidemiol.* 2007;22(6):379–387.
26. Espehaug B, Furnes O, Havelin LI, Engesaeter LB, Vollset SE, Kindseth O. Registration completeness in the Norwegian Arthroplasty Register. *Acta Orthop.* 2006;77(1):49–56.
27. Havelin LI, Engesaeter LB, Espehaug B, Furnes O, Lie SA, Vollset SE. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. *Acta Orthop Scand.* 2000;71(4):337–353.
28. Kim C, Nevitt MC, Niu J, et al. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. *BMJ.* 2015;351:h5983.
29. Dieppe P. Osteoarthritis: time to shift the paradigm. This includes distinguishing between severe disease and common minor disability. *BMJ.* 1999;318(7194):1299–1300.
30. Nielen JT, Emans PJ, Dagnelie PC, et al. Severity of diabetes mellitus and total hip or knee replacement: A Population-Based Case-Control Study. *Medicine (Baltimore)*. 2016;95(20):e3739.
31. Yoshimura N, Muraki S, Oka H, et al. Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. *Osteoarthritis Cartilage.* 2012;20(11):1217–1226.
32. Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. *Am J Manag Care*. 2002;8(15 Suppl):S383–S391.
33. Conaghan PG, Vanharanta H, Dieppe PA. Is progressive osteoarthritis an atheromatous vascular disease? *Ann Rheum Dis.* 2005;64(11):1539–1541.
34. Findlay DM. Vascular pathology and osteoarthritis. *Rheumatology (Oxford).* 2007;46(12):1763–1768.
35. Le Clanche S, Bonnefont-Rousselot D, Sari-Ali E, Rannou F, Borderie D. Inter-relations between osteoarthritis and metabolic syndrome: a common link? *Biochimie.* 2016;121:238–252.
36. Huang PL, Huang Z, Mashimo H, et al. Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature.* 1995;377(6546):239–242.
37. Aguirre JI, Plotkin LI, Stewart SA, et al. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. *J Bone Miner Res*. 2006;21(4):605–615.
38. Wang Y, Simpson JA, Wluka AE, et al. Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: a prospective cohort study. *Arthritis Res Ther.* 2009;11(2):R31.

39. Courties A, Gualillo O, Berenbaum F, Sellam J. Metabolic stress-induced joint inflammation and osteoarthritis. *OsteoarthritisCartilage.* 2015;23(11):1955–1965.
40. Heaton B, Applebaum KM, Rothman KJ, et al. The influence of prevalent cohort bias in the association between periodontal disease progression and incident coronary heart disease. *Ann Epidemiol.* 2014;24(10):741–746.
41. O'Brien RM. A caution regarding rules of thumb for variance inflation factors. *Qual Quant*. 2007;41(5):673–690.
42. Oiestad BE, Holm I, Engebretsen L, Aune AK, Gunderson R, Risberg MA. The prevalence of patellofemoral osteoarthritis 12 years after anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(4):942–949.
43. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum*. 2008;59(9):1207–1213.
44. Engesaeter IO, Lehmann T, Laborie LB, Lie SA, Rosendahl K, Engesaeter LB. Total hip replacement in young adults with hip dysplasia: age at diagnosis, previous treatment, quality of life, and validation of diagnoses reported to the Norwegian Arthroplasty Register between 1987 and 2007. *Acta Orthop*. 2011;82(2):149–154.
45. Pedersen A, Johnsen S, Overgaard S, Soballe K, Sorensen HT, Lucht U. Registration in the danish hip arthroplasty registry: completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. *Acta Orthop Scand.* 2004;75(4):434–441.
46. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2003;42(5):878–884.

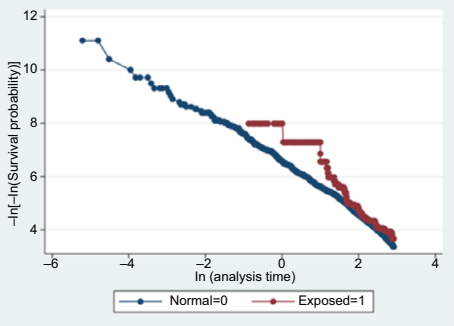
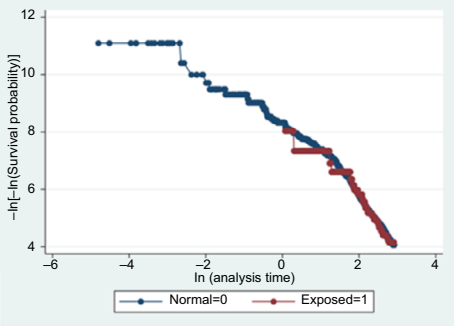
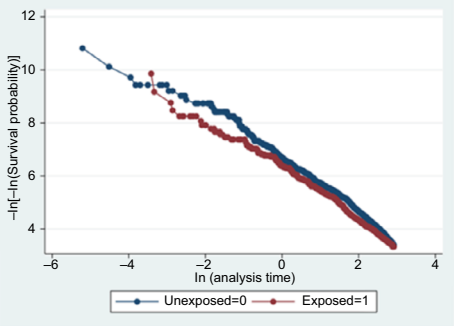
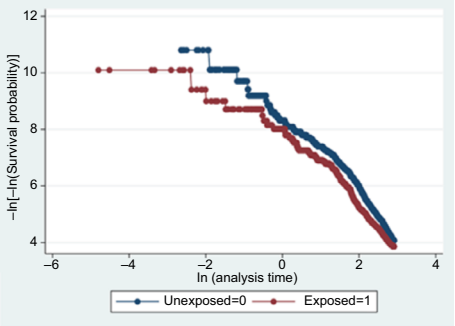
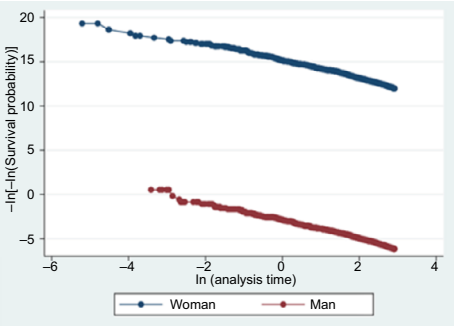
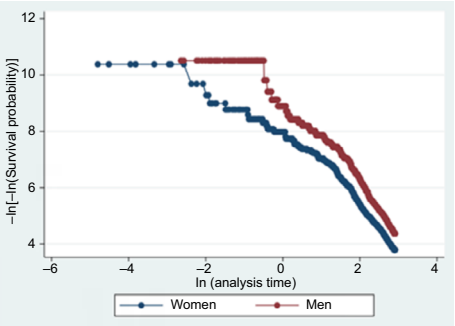
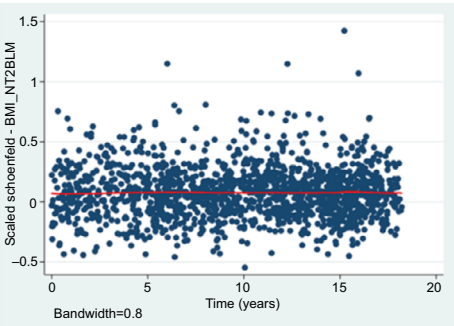
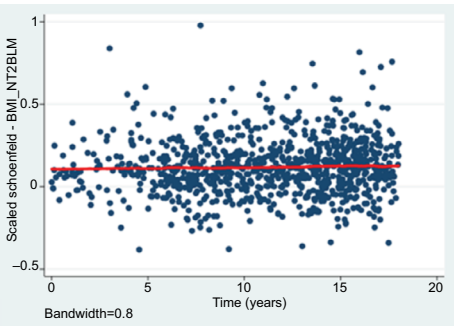
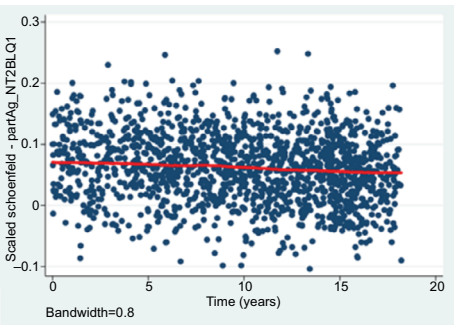
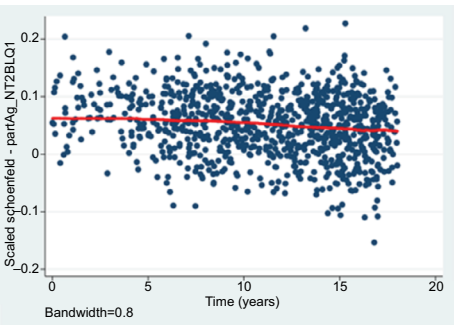
Supplementary materials

Table S1 Graphical evaluation of proportional hazards assumption for Cox regression, using log-minus-log plot for categorical variables and Schoenfeld residual plot for continuous variables

	THR	TKR
Waist circumference		
Blood pressure		
Triglycerides		
HDL		

(*Continued*)

Table S1 (*Continued*)

	THR	TKR
Diabetes or impaired Glucose tolerance		
Metabolic syndrome		
Gender		
BMI		
Age		

Abbreviation: BMI, body mass index; HDL, high-density lipoprotein; THR, total hip replacement; TKR, total knee replacement.

Table S2 Risk of THR or TKR by metabolic syndrome components and metabolic syndrome stratified on gender and age[a]

	Women			Men		
	<50 years	50–69.9 years	≥70 years	<50 years	50–69.9 years	≥70 years
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
THR						
Increased waist circumference	1.35 (0.88–2.08)	1.05 (0.83–1.32)	1.25 (0.81–1.92)	0.78 (0.39–1.58)	1.15 (0.83–1.59)	1.15 (0.63–2.09)
Hypertension	1.25 (0.94–1.66)	1.10 (0.90–1.35)	0.54* (0.33–0.88)	0.92 (0.62–1.38)	1.09 (0.82–1.45)	0.77 (0.42–1.43)
High triglycerides	0.94 (0.68–1.32)	1.00 (0.84–1.19)	1.04 (0.74–1.44)	0.74 (0.50–1.10)	0.82 (0.66–1.01)	0.66 (0.43–1.01)
Low HDL	0.75 (0.54–1.03	0.96 (0.79–1.16	0.91 (0.63–1.31)	0.62 (0.36–1.07)	0.93 (0.70–1.23)	0.71 (0.40–1.25)
IGT or diabetes	No exposed cases	0.48* (0.25–0.93)	0.34* (0.12–0.92)	2.31 (0.73–7.32)	0.65 (0.35–1.18)	0.24* (0.06–0.99)
Metabolic syndrome	0.61* (0.39–0.95)	0.96 (0.78–1.18)	0.92 (0.64–1.32)	0.51* (0.27–0.94)	0.86 (0.65–1.14)	0.68 (0.40–1.16)
TKR						
Increased waist circumference	1.48 (0.90–2.43)	1.34* (1.01–1.78)	1.59 (0.86–2.94)	1.76 (0.94–3.30)	1.65* (1.12–2.44)	1.51 (0.65–3.50)
Hypertension	1.15 (0.81–1.62)	1.09 (0.83–1.43)	0.62 (0.28–1.37)	1.90* (1.16–3.11)	1.40 (0.92–2.14)	0.80 (0.31–2.08)
High triglycerides	0.77 (0.51–1.16)	1.17 (0.94–1.45)	1.26 (0.78–2.02)	1.19 (0.79–1.80)	0.87 (0.65–1.15)	1.35 (0.71–2.58)
Low HDL	0.69 (0.47–1.02)	1.17 (0.93–1.48)	0.72 (0.43–1.20)	0.62 (0.36–1.06)	0.77 (0.53–1.12)	0.16* (0.04–0.68)
IGT or diabetes	0.94 (0.40–2.18)	0.28* (0.12–0.68)	0.94 (0.40–2.18)	0.67 (0.09–4.84)	1.38 (0.81–2.35)	0.52 (0.13–2.17)
Metabolic syndrome	0.86 (0.54–1.37)	1.28* (1.01–1.63)	1.46 (0.89–2.40)	0.87 (0.51–1.47)	0.95 (0.67–1.34)	1.01 (0.50–2.07)

Notes: *Significant at $p<0.05$. [a]HRs adjusted for BMI, smoking, education and physical activity.

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HR, hazard ratio; IGT, impaired glucose tolerance; THR, total hip replacement; TKR, total knee replacement.

Paper II

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RESEARCH ARTICLE Open Access

Incidence of total hip or knee replacement due to osteoarthritis in relation to thyroid function: a prospective cohort study (The Nord-Trøndelag Health Study)

Alf Inge Hellevik[1,2*], Marianne Bakke Johnsen[3,6], Arnulf Langhammer[1], Anne Marie Fenstad[4], Ove Furnes[4,5], Kjersti Storheim[3,6], John Anker Zwart[3,6], Gunnar Flugsrud[2] and Lars Nordsletten[2,6]

Abstract

Background: To study whether thyroid function was associated with risk of hip or knee replacement due to primary osteoarthritis.

Methods: In a prospective cohort study, data from the second and third survey of the Nord-Trøndelag Health Study were linked to the Norwegian Arthroplasty Register in order to identify total hip or knee replacement as a result of primary osteoarthritis.

Results: Among 37 891 participants without previously known thyroid disease we recorded 978 total hip replacements (THRs) and 538 total knee replacements (TKRs) during a median follow-up time of 15.7 years. The analyses were adjusted for sex, age, BMI (body mass index), smoking, physical activity and diabetes. We did not find any association between TSH (thyroid stimulating hormone) and THR or TKR due to osteoarthritis. Neither were changes in TSH over time, or overt hypo- or hyperthyroidism, associated with incidence of THR or TKR.

Conclusion: No association was found between thyroid function and hip or knee joint replacement due to osteoarthritis.

Keywords: Thyroid function, Thyroid stimulating hormone, Osteoarthritis, Hip joint replacement, Knee joint replacement

Background

Osteoarthritis in the hip and knee is a major health problem and leads to significant morbidity [1]. Several drugs have been evaluated, but so far only exercise has been found to effectively prevent or delay the onset of osteoarthritis [2, 3]. This finding emphasizes the importance of identifying modifiable risk factors. Thyroid hormones play a role in the remodelling and maintenance of bone, and recent studies also indicate the potential importance of thyroid hormones in joints and articular cartilage [4]. Genetic studies have suggested that deiodinase-regulated local availability of the active thyroid hormone triiodothyronine (T3) plays an important role in cartilage maintenance and repair [5]. Further data have indicated that increased intracellular T3 availability increases the risk of osteoarthritis, leading to the hypothesis that reduced tissue T3 availability protects joints from development of osteoarthritis [6]. A phase III clinical trial investigating the use of eprotirome, a thyroid receptor β-agonist, for treatment of hypercholesterolemia [7], was terminated due to indications of dose related articular cartilage damage in dogs which had been treated with eprotirome for 12 months [8]. This was surprising, as eprotirome is a liver-specific thyroid receptor β-agonist, but it indicates that thyroid hormones influence cartilage [9] and could play a role in the pathogenesis of osteoarthritis.

* Correspondence: alf.hellevik@ntnu.no
[1]The HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Levanger, Norway
[2]Division of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway
Full list of author information is available at the end of the article

No prospective population studies have investigated the association between thyroid function and osteoarthritis. An older cross-sectional study did not find any association between radiological knee osteoarthritis and thyroid status measured by thyroid stimulating hormone (TSH) [10]. In this prospective cohort study of 37 891 individuals without previously known thyroid disease, the aim was to assess whether thyroid function was associated with subsequent risk of hip or knee replacement due to primary osteoarthritis.

Methods

In the Nord-Trøndelag Health Study (HUNT) all inhabitants of Nord-Trøndelag county ≥ 20 years of age were invited to participate in three surveys: HUNT1 (1984–1986), HUNT2 (1995–1997) and HUNT3 (2006–2008) [11]. This study only included data from the HUNT2 and HUNT3 surveys, as the HUNT1 study did not collect blood samples. HUNT2 had 65 237 participants (69.5% of those invited), and HUNT3 had 50 807 participants (54.1% of those invited) [12].

In HUNT2, TSH was measured in 35 269 persons; in all women over 40 years old, in a random 50% sample of men over 40 years old and in a random 5% sample of participants aged 20–40 years. In HUNT3, TSH was measured in all 49 179 participants. We included 35 269 participants from HUNT2 and 13 132 new participants with TSH measurements from HUNT3. In persons that participated in both HUNT2 and HUNT3, baseline measurements from HUNT2 were used in the main analyses. Among these 48 401 individuals, 10 510 were excluded from analysis (Fig. 1). The exclusion criteria included self-reported thyroid disease (hypothyroidism, hyperthyroidism, goitre, other thyroid disease, use of levothyroxine, carbimazole, previous thyroid surgery or radioiodine therapy) ($n = 3895$), missing information on BMI ($n = 364$), missing information on smoking ($n = 962$), previous THR or TKR ($n = 644$), missing date of operation ($n = 99$), emigration during baseline measurements period ($n = 1$) or self-reported osteoarthritis at baseline ($n = 4545$). Thus, a total of 37 891 people (22 714 women and 15 177 men) were eligible for follow-up in this study. Each participant contributed person-years from baseline (either between August 1995 and June 1997 or between October 2006 and June 2008) until a THR or TKR due to osteoarthritis, THR or TKR due to other causes, migration, death or end of follow-up (December 31, 2013), whichever occurred first.

Measurements

The participants filled out a self-administered questionnaire, including history of thyroid disease [13]. The survey also included measurements of height and weight by trained personnel. Weight was measured while the participants were wearing light clothing without shoes.

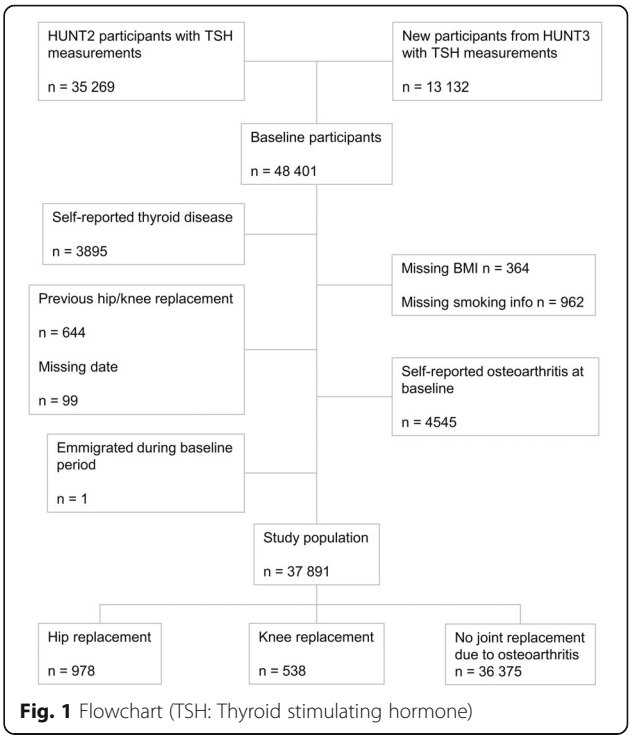

Fig. 1 Flowchart (TSH: Thyroid stimulating hormone)

BMI was calculated as weight in kilograms divided by squared height in metres.

A non-fasting venous blood sample was drawn from each participant. Concentrations of TSH, free thyroxine (fT4) and total triiodothyronine (T3) in HUNT2 were measured at the Hormone Laboratory, Aker University Hospital, Oslo, using DELFIA hTSH Ultra (sensitivity, 0.03 mU/L; and total analytic variation <5%), DELFIA fT4 (total analytic variation <7%), and AutoDELFIA T3 (total analytic variation <5%), all from Wallac Oy, Turku, Finland. In HUNT3, serum TSH and fT4 were measured at Levanger Hospital, Levanger, Norway, using Architect cSystems ci8200 (sensitivity, 0.01 mU/l; and a total analytic variation <5%), and Architect cSystems ci8200 (total analytic variation <6%), respectively, both from Abbott, Clinical Chemistry, USA. The measurement methods of TSH in HUNT2 and HUNT3 have previously been compared, with similar results [14], and agreement expressed by Bland-Altman [15] did not reveal any obvious pattern or deviations. The Norwegian population is considered to have sufficient iodine intake [16], and reference range for clinically normal TSH was defined as 0.50 to 3.5 mU/l based on previous publications from this population [13].

Covariates

The covariates were chosen based on previous literature, and had to be associated with both thyroid function and osteoarthritis. We mapped possible casual

pathways between all variables using a directed acyclic graph model (DAG) (Appendix) to visually identify possible confounding pathways [17]. Based on this DAG-model, the possible confounders included in this analysis were sex, age (continuous), BMI (continuous), current smoking status (never, former or current), diabetes (yes or no) and physical activity. Physical activity was categorized by duration of light physical activity (none, <1, 1–2, ≥3 h/week), and/or duration of hard physical activity (none, <1, 1–2, ≥3 h/week). The physical activity questions have been previously validated among men, where especially hard physical activity correlated well with more objective measures [18]. These two variables were combined into one physical activity variable indicating intensity and duration: None (no activity), medium (≤2 h/week light physical activity and/or < 1 h/week hard physical activity), hard (≥ 3 h/week light physical activity and/or ≥ 1 h/week hard physical activity).

Osteoarthritis at baseline was based on an affirmative answer to the question: "Has a doctor ever said that you have/have had osteoarthritis?" from HUNT2 participants, and "Have you had or do you have osteoarthritis?" from HUNT3 participants.

Outcome

In this study, primary total hip or knee replacement was considered to be a surrogate measure of severe osteoarthritis; and we used primary total hip or knee replacement due to primary osteoarthritis as outcome. The 11-digit identification numbers assigned to every Norwegian citizen enabled linkage to the Norwegian Arthroplasty Register (NAR). For each arthroplasty performed, the orthopaedic surgeon submits a standardized form containing information about the patient, the diagnosis that led to the arthroplasty, the procedure and the type of implant used [19]. NAR was established in 1987 and includes all artificial joints from 1994 onwards. The completeness of hip and knee replacement registration is over 95% [20].

Statistical methods

The participants were placed in five categories according to their TSH level: One category indicating hyperthyroid function (<0.50 mU/l); three categories within the clinical reference range (0.50–1.49, 1.5–2.49 and 2.5–3.5 mU/l); and one category indicating hypothyroid function (≥3.5 mU/l) [21]. Hazard ratios (HRs) of THR or TKR by category of TSH were estimated using a Cox proportional hazards model with 95% confidence interval (CI); TSH 1.5–2.49 mU/l was chosen as a reference. TSH was also analysed as both a continuous variable, and as log-transformed continuous TSH. The HRs were adjusted for age, sex, BMI and smoking. An additional analysis also adjusted for physical activity and diabetes. We treated THR and TKR both as separate outcomes and combined in one outcome variable of total joint replacement (TJR).

A sub-analysis included only persons that participated in both HUNT2 and HUNT3 (n = 19 397). TSH levels at HUNT3 were then subtracted from the TSH levels in HUNT2 to estimate the change in TSH during the intervening decade. Information on the other baseline covariates was taken from HUNT3. Among these participants a total of 7740 were excluded due to self-reported thyroid disease (n = 2744), missing information on BMI (n = 108), missing information on smoking (n = 621), previous THR or TKR (n = 928), missing date of operation (n = 29) or self-reported osteoarthritis at baseline (n = 3310). Thus, a total of 11 657 people were eligible for this sub-analysis. This sub-population was also used in an analysis that investigated whether the results changed when those who had started on thyroid medication after baseline in HUNT2 were excluded.

In a sensitivity analysis people were divided into two groups, one with biochemically manifest (overt) hypothyroidism (defined as TSH >4.0 mU/L combined with fT4 < 8.0 pmol/L), and the other with overt hyperthyroidism (defined as TSH <0.10 mU/L and fT4 > 20.0 pmol/L and/or total T3 > 2.7 nmol/L). This classification by overt hypo- or hyperthyroidism was made possible by the fT4 measurements taken in people whose TSH levels were <0.20 mU/l or >4.0 mU/l in HUNT2, and in people whose levels were <0.10 mU/l or >3.0 mU/l in HUNT3. Total T3 was only available in HUNT2 and only measured if TSH levels were <0.20mU/L.

Two additional analyses were performed on the baseline population: First, we investigated the association between TSH level (categorical) and self-reported osteoarthritis at baseline by using a logistic regression model, adjusting for sex, age, BMI, smoking, physical activity and diabetes. Second, we compared the incidence rate of THR or TKR in participants with and without self-reported thyroid disease at baseline using Fisher's Exact test. After excluding participants with missing information on BMI and smoking, previous THR or TKR, missing date of operation or self-reported osteoarthritis at baseline, 2955 participants reported thyroid disease.

Proportional hazards assumptions were evaluated by Schoenfeld residuals tests. They showed proportional hazards on all covariates, except for age. Thus we did an additional stratified analysis on age, but it did not show different results (data not shown). Age was therefore kept as a continuous variable in all our analyses. All statistical analyses were two-sided with a significance level of $p < 0.05$. The analyses were performed using Stata 14.0/SE (StataCorp LP, College Station, TX, USA).

Results

Of the 37 891 participants, 908 (2.4%) had low TSH (<0.50 mU/l) indicating hyperthyroid function, and 2307 (6.1%) had high TSH (≥3.6 mU/l) indicating hypothyroid function (Table 1). Among the women, 6.9% had high TSH, compared to 4.8% of men. Participants with high TSH were generally older and were less likely to be current smokers than participants in the reference group (TSH 1.5–2.4 mU/l). No clear trend was seen in relation to physical activity.

In total, 978 received THR and 538 received TKR during a median follow-up time of 15.7 years (mean 12.3 years). At baseline, the mean age was 50.7 years (SD 15.8), and the mean ages at THR and TKR were 69.5 years (SD 8.9) and 69.4 years (SD 8.4), respectively.

TSH level did not influence the risk of THR or TKR in the unadjusted analysis or the analysis adjusted for gender, age, BMI and smoking (Table 2). Neither additional adjustment for physical activity and diabetes (Table 2), nor collapsing the outcome variable into total joint replacement (TJR) (Table 3), altered these results. Analyses using TSH as a continuous variable did not show any association between TSH and THR or TKR (Fig. 2). Additional log-transformation of TSH as a continuous variable did not significantly change these results (data not shown).

In a separate analysis studying the change in TSH (delta-TSH) during the time between HUNT2 and HUNT3, 11 657 participants were included. Of these, 200 received THR and 102 received TKR during a mean follow-up time of 6.1 years. No association was seen between changes in TSH and risk of THR or TKR (Fig. 3). Additional adjustment for baseline TSH did not substantially alter these results. The same sub-population was also used to identify persons with no thyroid disease or treatment at baseline in HUNT2 who still had no thyroid disease or treatment at HUNT3. However, no association between TSH and THR (HR 1.00, 95% CI 0.97–1.02) or TKR (HR 0.98, 95% CI 0.94–1.03) was found.

In a sensitivity analysis neither overt hypo- nor hyperthyroid function was found to influence the risk of THR or TKR, (HR 0.91, 95% CI 0.40–2.04) and (HR 2.01, 95% CI 0.75–5.4) respectively. Also, no association was found between overt hypothyroid function and TKR (HR 1.03, 95% CI 0.38–2.78). There were no cases of TKR amongst the overtly hyperthyroid, so no analysis could be performed in this subgroup.

In additional analyses on the baseline population, there was no association between TSH levels and self-reported osteoarthritis at baseline (data not shown). Those with self-reported thyroid disease at baseline had an incidence rate of 0.0027 THR per person-year and 0.0015 TKR per person-year. Our main study population (excluding those with self-reported thyroid disease) had an incidence rate of 0.0021 THR per person-year and 0.0012 TKR per person-year. This gave and incidence rate ratio of 1.28 (95% CI 1.04–1.56) for THR, and 1.27 (95% CI 0.95–1.95) for TKR, and indicated a slightly higher incidence rate for THR in those with self-reported thyroid disease, but no significant difference in the incidence rate for TKR, compared to participants without self-reported thyroid disease.

Discussion

In this large prospective study we did not find any association between thyroid function and the risk of THR or

Table 1 Study population characteristics in relation to thyroid stimulating hormone (TSH) categories

	Serum TSH										Total	
	<0.50		*0.50–1.49*		*1.5–2.49*		*2.5–3.49*		*≥3.5*			
Participants (%)	908	(2.4)	17675	(46.7)	13228	(34.9)	3773	(10.0)	2307	(6.1)	37891	
Women (%)	651	(2.9)	10405	(45.8)	7738	(34.1)	2346	(10.3)	1574	(6.9)	22714	(60.0)
Men (%)	257	(1.7)	7270	(47.9)	5490	(36.2)	1427	(9.4)	733	(4.8)	15177	(40.0)
Age (SD)	50.7	(16.7)	48.2	(15.3)	51.6	(15.6)	54.9	(15.9)	58.3	(15.3)	50.7	(15.8)
BMI (SD)	25.9	(4.4)	26.1	(4.1)	26.8	(4.2)	27.1	(4.4)	27.2	(4.5)	26.5	(4.2)
Smoking status (%)												
Never	335	(36.9)	6778	(38.3)	6080	(46.0)	1869	(49.5)	1167	(50.6)	16229	(42.8)
Former	236	(26.0)	4683	(26.5)	3768	(28.5)	1120	(29.7)	723	(31.3)	10530	(27.8)
Current	337	(37.1)	6214	(35.2)	3380	(25.5)	784	(20.8)	417	(18.1)	11132	(29.4)
Physical activity (%) (missing = 6826)												
Low	46	(6.5)	862	(6.0)	719	(6.6)	232	(7.4)	151	(8.2)	2010	(6.5)
Medium	371	(52.8)	7226	(49.9)	5454	(50.0)	1555	(49.7)	921	(50.1)	15527	(50.0)
High	286	(40.7)	6394	(44.1)	4738	(43.4)	1344	(42.9)	766	(41.7)	13528	(43.6)
Diabetes (%) (missing = 56)	55	(6.1)	613	(3.5)	559	(4.2)	173	(4.6)	115	(5.0)	1515	4.0

Table 2 Association between TSH categories and hip or knee replacement due to osteoarthritis

TSH (mU/L)	Persons (n)	Cases (n)	HR[a]	(95% CI)	HR[b]	(95% CI)	HR[c]	(95% CI)
THR								
< 0.50	908	21	0.98	(0.63–1.53)	0.99	(0.64–1.53)	1.04	(0.63–1.69)
0.50–1.49	17675	411	0.93	(0.81–1.08)	1.07	(0.93–1.24)	1.09	(0.94–1.28)
1.5–2.49	13228	359	1	Reference	1	Reference	1	Reference
2.5–3.49	3773	105	0.98	(0.79–1.22)	0.85	(0.68–1.05)	0.88	(0.69–1.11)
> 3.5	2307	82	1.22	(0.96–1.55)	0.96	(0.76–1.22)	0.98	(0.75–1.27)
TKR								
< 0.50	908	14	1.26	(0.73–2.16)	1.32	(0.76–2.26)	1.33	(0.74–2.4)
0.50–1.49	17675	224	0.97	(0.80–1.18)	1.15	(0.95–1.40)	1.12	(0.91–1.37)
1.5–2.49	13228	191	1	Reference	1	Reference	1	Reference
2.5–3.49	3773	64	1.12	(0.84–1.48)	0.94	(0.71–1.25)	0.88	(0.65–1.20)
> 3.5	2307	45	1.24	(0.90–1.72)	0.98	(0.70–1.35)	0.87	(0.61–1.25)

(*THR* total hip replacement, *TKR* total knee replacement)
[a]Unadjusted
[b]Adjusted for age, sex, BMI and smoking
[c]Adjusted for age, sex, BMI, smoking, physical activity and diabetes

TKR due to osteoarthritis. Neither were changes in TSH over time, or overt hypo- or hyperthyroidism, associated with incidence of THR or TKR.

Few previous population studies have investigated the association of thyroid function with risk of osteoarthritis. In 1996, a cross-sectional study of 577 men and 798 women found no evidence of a significant association between current thyroid status and either chondrocalcinosis or osteoarthritis [10]. However, that study only investigated prevalent osteoarthritis with a concurrent serum TSH concentration and could not take into account development in TSH or later treatment for abnormal thyroid function. Since our study could use data from both the second and third waves of the HUNT-survey, we were able to investigate the development of TSH over a median time of 11.2 years (SD 0.6). Change in TSH over time was however not associated with osteoarthritis development resulting in the need for joint replacement.

Previous or current thyroid disease at baseline was an exclusion criterion in our study. Nonetheless, all participants with TSH levels suggesting hypothyroid or hyperthyroid function may have received medical treatment for thyroid disease during the follow-up period, as participants with biochemical indication of pathological thyroid function were recommended to contact their general practitioners [22]. This could have weakened any association between TSH and osteoarthritis. We therefore did a sub-analysis of persons that participated in both HUNT2 and HUNT3, and excluded participants that reported use of thyroid medication or thyroid disease in HUNT3. This did not significantly alter the results.

Our findings must be interpreted in relation to recent genetic studies on intracellular T3 availability in joint cartilage. There has been an increased interest in the effect of deiodinase polymorphisms on osteoarthritis [5]. Iodothyronine deiodinases represent a family of proteins involved in local homeostasis of thyroxine (T4) and triiodothyronine (T3). Three deiodinases have been described and, of these, the deiodinase type 2 (D2) and deiodinase type 3 (D3) are

Table 3 Association between TSH categories and total joint replacement (TJR) in the hip or knee due to osteoarthritis

TSH (mU/L)	Persons (n)	Cases (n)	HR[a]	(95% CI)	HR[b]	(95% CI)	HR[c]	(95% CI)
<0.50	908	35	1.08	(0.77–1.52)	1.10	(0.78–1.55)	1.15	(0.79–1.67)
0.50–1.49	17675	635	0.95	(0.84–1.06)	1.10	(0.98–1.23)	1.10	(0.97–1.25)
1.5–2.49	13228	550	1	Reference	1	Reference	1	Reference
2.5–3.49	3773	169	1.03	(0.87–1.22)	0.88	(0.74–1.05)	0.88	(0.73–1.06)
>3.5	2307	127	1.23	(1.01–1.49)	0.97	(0.80–1.17)	0.94	(0.76–1.16)

[a]Unadjusted
[b]Adjusted for age, sex, BMI and smoking
[c]Adjusted for age, sex, BMI, smoking, physical activity and diabetes

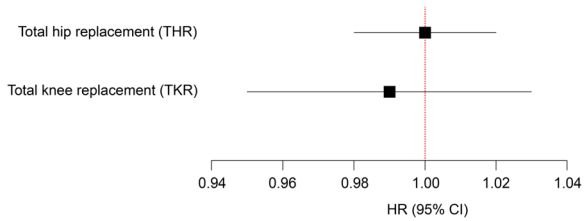

Fig. 2 Association between continuous TSH and total hip replacement (THR) or total knee replacement (TKR) due to osteoarthritis. (Adjusted for age, sex, BMI, smoking, physical activity and diabetes)

detected in bone and cartilage. D2 plays a major role in conversion of T4 to biologically active T3 [23] and thus upregulates local T3 levels. Deiodinase type 3 (D3) is the main T3-inactivating enzyme and consequently downregulates the local T3 levels. T3 is considered an important regulator of chondrocyte cell growth and differentiation in the endochondral growth plate [24]. Local T3 availability, regulated by the opposite functions of D2 and D3, may be a determinant of osteoarthritis development. D2 has been reported to be upregulated in the cartilage of joints affected by osteoarthritis compared to joints unaffected by osteoarthritis [25, 26]. However, it is not known if this is a result of the ongoing osteoarthritis process, or a reflection of the underlying disease pathway. Taken together, these findings suggest that deiodinase regulated local availability of T3 in chondrocytes is a possible factor in the pathophysiology of osteoarthritis [27, 28]. Since our study did not find any association between circulating TSH, T3/T4 levels and osteoarthritis, it is conceivable that the serum thyroid hormone levels may be independent of local intracellular T3 levels in joints. Another possible explanation could be that polymorphism in the gene coding for D2 creates a predisposition for non-optimal bone shape [29, 30], leading to increased risk of osteoarthritis independent of local thyroid hormone levels.

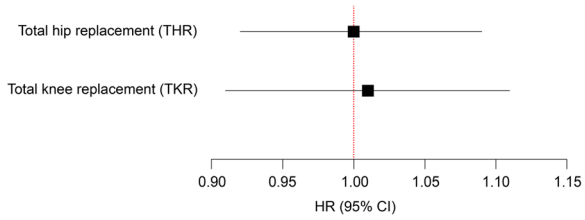

Fig. 3 Association between change in TSH (delta TSH) and total hip replacement (THR) or total knee replacement (TKR) due to osteoarthritis. (Adjusted for age, sex, BMI and smoking)

Strengths and limitations

Our study included over 37 000 persons without known thyroid disease at baseline, and in most cases thyroid function was measured many years prior to joint replacement. To the best of our knowledge, this is the first prospective population study addressing the association between thyroid function and joint replacement due to primary osteoarthritis. The prospective design and longitudinal data on TSH measurements are strengths of this study. By excluding participants with self-reported osteoarthritis at baseline it was possible to differentiate between risk of osteoarthritis development and progression.

Our study used joint replacement due to primary osteoarthritis as a surrogate measure of severe osteoarthritis. Validation of the osteoarthrosis diagnosis from the Norwegian Arthroplasty Register has not been done in an unselected population [31]. However, the Danish hip Arthroplasty Registry has reported a positive predictive value of 85% regarding primary hip osteoarthritis diagnosis [32], and it is likely that these results are comparable to the Norwegian Arthroplasty Register. The advantage of using joint replacement as a proxy for osteoarthritis is its unambiguous connection with disease burden of osteoarthritis compared to other osteoarthritis definitions, e.g., radiographic criteria, symptom criteria or osteoarthritis defined by self-reported diagnosis [33]. However, this outcome measure is still limited in some respects, most importantly, that patients' health status and potential comorbidities influence orthopaedic surgeons' choices regarding operative treatment. Secondly, persons with moderate osteoarthritis who engage in demanding physical activities could be more motivated to have surgery than less active persons. Persons who are generally inactive may be less motivated to have surgery even if they have more severe osteoarthritis. This could give a healthy patient selection bias with corresponding underestimation of the effect of thyroid function.

Previous injuries increase the risk of knee osteoarthritis [34, 35], but only joint replacements due to primary/idiopathic osteoarthritis were included in our study. We did not have direct information on previous injury, but we excluded all cases in which the operating surgeon reported that the knee joint replacement was due to sequela from fracture, ligament injury, meniscal injury, infection, rheumatoid arthritis or ankylosing spondylitis.

The interrelationship between BMI and thyroid function is complex and BMI could be treated as either a confounder or a mediator in our model [36]. The reason we chose to define it as a confounder was that we wanted to investigate the direct effect of thyroid function on joint replacement, independent of BMI. Potential

confounding by other unmeasured factors could not be excluded. But these factors should then be associated with both thyrotropin level and osteoarthritis. Therefore, we did not adjust for level of education in this study (Appendix).

The participation rate in the HUNT-surveys was fairly high compared to most other surveys, but there is always a potential risk of selection bias that cannot be adjusted for in the statistical analysis [37]. Blood samples were not drawn at a set time of the day, and it is known that other factors like exercise and sleep deprivation influence TSH levels [38]. This might have led to non-differential classification bias, thus weakening any associations. We also only had data on fT4 and T3 in subpopulations. Therefore, the absolute numbers of participants with overt hypo- or hyperthyroidism were small, reducing the power to detect any association between them and euthyroid subject and should thus be interpreted with caution.

This study focused on the relationship between thyroid function and osteoarthritis. However, there may also be an association between autoimmune thyroid disease and osteoarthritis [39]. As thyroid autoantibody not necessarily correlate with thyroid function, an association between thyroid function and osteoarthritis trough autoimmune factors could be missed in our study.

The exclusion of participants who reported hypo- or hyperthyroidism in their answers regarding use of treatment or medication might have caused misclassification since radioiodine is used in the treatment of cancer and T4 in the medical treatment of goitre. However, these treatments are infrequent, and it is unlikely that they substantially altered our results.

In the analysis comparing incidence rate of THR in people with and without self-reported thyroid disease we found a small, but significant, increased risk of THR in people reporting thyroid disease. And since we excluded participants with self-reported thyroid disease, this might have led to an underestimation of the effect on THR. We therefore did an additional analysis including those with self-reported thyroid disease: This showed no association between TSH levels and THR in a Cox-regression model (data not shown), and thus confirmed the findings from the primary analysis.

Conclusion

In this prospective study of 37 891 participants without previously known thyroid disease, we did not find that thyroid function was associated with risk of hip or knee joint replacement due to osteoarthritis. Neither did we find any association between TSH development over time and risk of hip or knee joint replacement due to osteoarthritis.

Appendix

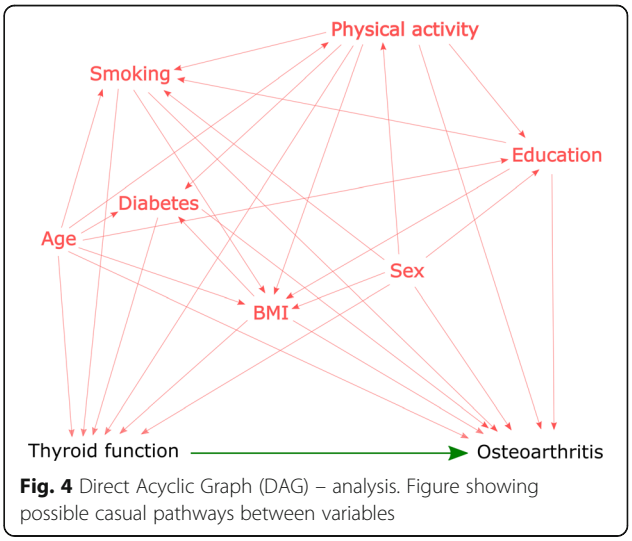

Fig. 4 Direct Acyclic Graph (DAG) – analysis. Figure showing possible casual pathways between variables

Abbreviations

BMI: Body mass index; D2: Deiodinase type 2; D3: Deiodinase type 3; DAG: Directed acyclic graph; fT4: Free thyroxine; HR: Hazard ratio; HUNT: The Nord-Trøndelag Health study; NAR: Norwegian Arthroplasty Register; OA: Osteoarthritis; SD: Standard deviation; T3: Triiodothyronine; T4: Thyroxine; THR: Total hip replacement; TKR: Total knee replacement; TSH: Thyroid stimulating hormone

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Availability of data and materials

Ethical and legal restrictions prohibit the authors from making datasets available outside the HUNT database, which is available by contacting the HUNT administration. Please see https://www.ntnu.edu/hunt/data for details on how to obtain all relevant data.

Authors' contributions

AL conceived of the idea for this study. AlH participated in the study concept and design, obtained funding, performed the analysis, interpreted the data and drafted the manuscript. LN, MBJ, AL, GBF, OF, KS and JAZ were involved in the conception and design of the study. OF was also involved in the collection of hip and knee replacement data. AMF contributed statistical expertise. All the authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The participants signed written informed consent for participation in HUNT, NAR and linkage of data to national health registries. This study was approved by the Norwegian Regional Committee for Ethics in medical Research (2013/151/REK Sør-Øst C).

Publisher's Note

Author details
[1]The HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Levanger, Norway. [2]Division of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway. [3]Research and Communication Unit for Musculoskeletal Health, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway. [4]The Norwegian Arthroplasty Register, Department of Orthopedic Surgery, Haukeland University Hospital, Bergen, Norway. [5]Department of Clinical Medicine, Institute of Medicine and Dentistry, University of Bergen, Bergen, Norway. [6]Faculty of Medicine, University of Oslo, Oslo, Norway.

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References

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163–96.
2. Goldring MB, Berenbaum F. Emerging targets in osteoarthritis therapy. Curr Opin Pharmacol. 2015;22:51–63.
3. Svege I, Nordsletten L, Fernandes L, Risberg MA. Exercise therapy may postpone total hip replacement surgery in patients with hip osteoarthritis: a long-term follow-up of a randomised trial. Ann Rheum Dis. 2015;74(1):164–9.
4. Williams GR. Thyroid Hormone Actions in Cartilage and Bone. European Thyroid J. 2013;2(1):3–13.
5. Verloop H, Dekkers OM, Peeters RP, Schoones JW, Smit JW. Genetics in endocrinology: genetic variation in deiodinases: a systematic review of potential clinical effects in humans. Eur J Endocrinol. 2014;171(3):R123–135.
6. Waung JA, Bassett JH, Williams GR. Adult mice lacking the type 2 iodothyronine deiodinase have increased subchondral bone but normal articular cartilage. Thyroid. 2015;25(3):269–77.
7. Ladenson PW, Kristensen JD, Ridgway EC, Olsson AG, Carlsson B, Klein I, Baxter JD, Angelin B. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. N Engl J Med. 2010;362(10):906–16.
8. Sjouke B, Langslet G, Ceska R, Nicholls SJ, Nissen SE, Ohlander M, Ladenson PW, Olsson AG, Hovingh GK, Kastelein JJ. Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomised, double-blind, placebo-controlled phase 3 study. Lancet Diabetes Endocrinol. 2014;2(6):455–63.
9. Lammel Lindemann J, Webb P. Sobetirome: the past, present and questions about the future. Expert Opin Ther Targets. 2016;20(2):145–9.
10. Chaisson CE, McAlindon TE, Felson DT, Naimark A, Wilson PW, Sawin CT. Lack of association between thyroid status and chondrocalcinosis or osteoarthritis: the Framingham Osteoarthritis Study. J Rheumatol. 1996;23(4):711–5.
11. HUNT home page [http://www.ntnu.no/hunt]. Accessed 15 Nov 2016
12. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013;42(4):968–77.
13. Bjoro T, Holmen J, Kruger O, Midthjell K, Hunstad K, Schreiner T, Sandnes L, Brochmann H. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). Eur J Endocrinol. 2000;143(5):639–47.
14. Svare A, Nilsen TI, Bjoro T, Asvold BO, Langhammer A. Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. Clin Endocrinol (Oxf). 2011;74(6):769–75.
15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307–10.
16. Kapelrud H, Frey H, Theodorsen L. [Excretion of iodine in the urine. A study from 6 different Norwegian districts in 1985]. Tidsskr Nor Laegeforen. 1987;107(15):1320–1. 1317.
17. Suttorp MM, Siegerink B, Jager KJ, Zoccali C, Dekker FW. Graphical presentation of confounding in directed acyclic graphs. Nephrol Dial Transplant. 2015;30(9):1418–23.
18. Kurtze N, Rangul V, Hustvedt B-E, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trøndelag Health Study (HUNT 2). Eur J Epidemiol. 2007;22(6):379–87.
19. Havelin LI, Engesaeter LB, Espehaug B, Furnes O, Lie SA, Vollset SE. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. Acta Orthop Scand. 2000;71(4):337–53.
20. Espehaug B, Furnes O, Havelin LI, Engesaeter LB, Vollset SE, Kindseth O. Registration completeness in the Norwegian Arthroplasty Register. Acta Orthop. 2006;77(1):49–56.
21. Hellevik AI, Asvold BO, Bjoro T, Romundstad PR, Nilsen TI, Vatten LJ. Thyroid function and cancer risk: a prospective population study. Cancer Epidemiol Biomarkers Prev. 2009;18(2):570–4.
22. HUNT databank [https://hunt-db.medisin.ntnu.no/hunt-db/]. Accessed 15 Nov 2016.
23. Kohrle J. Local activation and inactivation of thyroid hormones: the deiodinase family. Mol Cell Endocrinol. 1999;151(1-2):103–19.
24. Robson H, Siebler T, Stevens DA, Shalet SM, Williams GR. Thyroid hormone acts directly on growth plate chondrocytes to promote hypertrophic differentiation and inhibit clonal expansion and cell proliferation. Endocrinology. 2000;141(10):3887–97.
25. Bos SD, Bovee JV, Duijnisveld BJ, Raine EV, van Dalen WJ, Ramos YF, van der Breggen R, Nelissen RG, Slagboom PE, Loughlin J, et al. Increased type II deiodinase protein in OA-affected cartilage and allelic imbalance of OA risk polymorphism rs225014 at DIO2 in human OA joint tissues. Ann Rheum Dis. 2012;71(7):1254–8.
26. Meulenbelt I, Bos SD, Chapman K, van der Breggen R, Houwing-Duistermaat JJ, Kremer D, Kloppenburg M, Carr A, Tsezou A, Gonzalez A, et al. Meta-analyses of genes modulating intracellular T3 bio-availability reveal a possible role for the DIO3 gene in osteoarthritis susceptibility. Ann Rheum Dis. 2011;70(1):164–7.
27. Waung JA, Bassett JH, Williams GR. Thyroid hormone metabolism in skeletal development and adult bone maintenance. Trends Endocrinol Metab. 2012;23(4):155–62.
28. Bay-Jensen AC, Slagboom E, Chen-An P, Alexandersen P, Qvist P, Christiansen C, Meulenbelt I, Karsdal MA. Role of hormones in cartilage and joint metabolism: understanding an unhealthy metabolic phenotype in osteoarthritis. Menopause. 2013;20(5):578–86.
29. Waarsing JH, Kloppenburg M, Slagboom PE, Kroon HM, Houwing-Duistermaat JJ, Weinans H, Meulenbelt I. Osteoarthritis susceptibility genes influence the association between hip morphology and osteoarthritis. Arthritis Rheum. 2011;63(5):1349–54.
30. Meulenbelt I, Min JL, Bos S, Riyazi N, Houwing-Duistermaat JJ, van der Wijk HJ, Kroon HM, Nakajima M, Ikegawa S, Uitterlinden AG, et al. Identification of DIO2 as a new susceptibility locus for symptomatic osteoarthritis. Hum Mol Genet. 2008;17(12):1867–75.
31. Engesaeter IO, Lehmann T, Laborie LB, Lie SA, Rosendahl K, Engesaeter LB. Total hip replacement in young adults with hip dysplasia: age at diagnosis, previous treatment, quality of life, and validation of diagnoses reported to the Norwegian Arthroplasty Register between 1987 and 2007. Acta Orthop. 2011;82(2):149–54.
32. Pedersen A, Johnsen S, Overgaard S, Soballe K, Sorensen HT, Lucht U. Registration in the danish hip arthroplasty registry: completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. Acta Orthop Scand. 2004;75(4):434–41.
33. Kim C, Nevitt MC, Niu J, Clancy MM, Lane NE, Link TM, Vlad S, Tolstykh I, Jungmann PM, Felson DT, et al. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. BMJ. 2015;351:h5983.
34. Oiestad BE, Holm I, Engebretsen L, Aune AK, Gunderson R, Risberg MA. The prevalence of patellofemoral osteoarthritis 12 years after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2013;21(4):942–9.
35. Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, Dragomir A, Kalsbeek WD, Luta G, Jordan JM. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum. 2008;59(9):1207–13.
36. Pearce EN. Thyroid hormone and obesity. Curr Opin Endocrinol Diabetes Obes. 2012;19(5):408–13.

37. Holmen J, Midthjell K, Krüger O, Langhammer A, Holmen TL, Bratberg G, Vatten LG. L-LP: The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi. 2003;13(1):19–32.
38. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. J Clin Endocrinol Metab. 2005;90(9):5489–96.
39. Soy M, Guldiken S, Arikan E, Altun BU, Tugrul A. Frequency of rheumatic diseases in patients with autoimmune thyroid disease. Rheumatol Int. 2007; 27(6):575–7.

Paper III

Osteoarthritis and Cartilage 25 (2017) 1654–1662

Osteoarthritis and Cartilage

Age of menarche is associated with knee joint replacement due to primary osteoarthritis (The HUNT Study and the Norwegian Arthroplasty Register)

A.I. Hellevik † ‡ *, L. Nordsletten ‡ §, M.B. Johnsen § ||, A.M. Fenstad ¶, O. Furnes ¶ #, K. Storheim § ||, J.A. Zwart § ||, G. Flugsrud ‡, A. Langhammer †

† The HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Levanger, Norway
‡ Division of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway
§ Faculty of Medicine, University of Oslo, Norway
|| Research and Communication Unit for Musculoskeletal Health, Division of Clinical Neuroscience, Oslo University Hospital, Oslo, Norway
¶ The Norwegian Arthroplasty Register, Department of Orthopedic Surgery, Haukeland University Hospital, Bergen, Norway
# Department of Clinical Medicine, Institute of Medicine and Dentistry, University of Bergen, Bergen, Norway

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SUMMARY

Objective: To investigate whether parity, age at menarche, menopausal status, age at menopause, use of oral contraceptives (OC) or use of hormone replacement therapy (HRT) were associated with total knee replacement (TKR) or total hip replacement (THR) due to primary osteoarthritis.
Method: In a prospective cohort study of 30,289 women from the second and third surveys of the Nord-Trøndelag Health Study, data were linked to the Norwegian Arthroplasty Register (NAR) in order to identify TKR or THR due to primary osteoarthritis. Cox proportional hazards models were used to estimate the hazard ratios (HRs).
Results: We observed 430 TKRs and 675 THRs during a mean follow-up time of 8.3 years. Increasing age at menarche was inversely associated with the risk of TKR (P-trend < 0.001). Past users and users of systemic HRT were at higher risk of TKR compared to never users (HR 1.42 (95% confidence interval (CI) 1.06–1.90) and HR 1.40 (95% CI 1.03–1.90), respectively). No association was found between parity, age at menarche, menopausal status, age at menopause, oral contraceptive use or HRT use and THR.
Conclusion: We found that increasing age at menarche reduced the risk of TKR. Past users and users of systemic HRT were at higher risk of TKR compared to never users. Parity did not increase the risk of THR or TKR.

Introduction

Osteoarthritis is probably the result of a complex interplay between genetic, cellular and biomechanical factors. A better understanding of the risk factors and, thereby, groups at risk, would make it possible to target effective public health preventions[1].

There is a rise in osteoarthritis prevalence in women after menopause[2]. The findings from epidemiologic studies on reproductive history (parity, age at menarche, menopausal status and age at menopause) and hormonal factors (oral contraceptives (OC) and hormone replacement therapy (HRT)) in relation to osteoarthritis have been conflicting. Increasing parity has been reported as a risk factor for radiographic osteoarthritis in the knee[3] as well as total knee replacement (TKR) and total hip replacement (THR)[4]. However, some studies have not found any association between parity and radiographic joint space narrowing, osteophytes or changes in either cartilage volume or cartilage defects[5]. A large,

* Address correspondence and reprint requests to: A.I. Hellevik, HUNT Research Centre, Forskningsveien 2, N-7600 Levanger, Norway.
E-mail addresses: alf.hellevik@ntnu.no (A.I. Hellevik), lars.nordsletten@medisin.uio.no (L. Nordsletten), m.b.johnsen@medisin.uio.no (M.B. Johnsen), anne.marie.fenstad@helse-bergen.no (A.M. Fenstad), ove.furnes@helse-bergen.no (O. Furnes), kjersti.storheim@medisin.uio.no (K. Storheim), j.a.zwart@medisin.uio.no (J.A. Zwart), gbflugsrud@gmail.com (G. Flugsrud), arnulf.langhammer@ntnu.no (A. Langhammer).

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prospective cohort study reported that low age at menarche increased the risk of TKR[4], but this finding has not yet been confirmed by other studies. The use of OC has not been associated with osteoarthritis in most studies[5–8], except one that reported a possible increased risk of THR[9]. HRT has been shown to have a protective effect on osteoarthritis in some studies[7,10,11], while others have found it to have no effect[12–15] or even adverse effects[4].

The aim of this study was to investigate the association between reproductive history and use of hormonal therapies and the risk of TKR or THR due to osteoarthritis in a prospective cohort study.

Methods

In the Nord-Trøndelag Health Study (HUNT)[16] all inhabitants of Nord-Trøndelag county ≥ 20 years of age were invited to participate in three surveys: HUNT1 (1984–1986), HUNT2 (1995–1997) and HUNT3 (2006–2008)[17]. In total, 35,280 women participated in HUNT2 (75.5% of those invited), and 27,758 in HUNT3 (58.7% of those invited)[17]. Our study only included baseline data from HUNT2 or HUNT3 as these surveys included questionnaire and interview data on reproductive history and covariates. We included women aged ≥30 years at baseline, and our study population consisted of 11,746 participants from HUNT2, 20,459 participants of both HUNT2 and HUNT3 and 4652 participants from HUNT3 alone. For those who participated in both HUNT2 and HUNT3, we used baseline measurements from HUNT3 in order to include as much information as possible on reproductive history and eventual use of HRT. In this study we defined reproductive history as parity, age at menarche, years of menstruation and age at menopause. Hormonal therapies included use of OC and use of HRT. Height and weight were measured by trained personnel. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in metres. Bilateral oophorectomy in premenopausal women induces premature menopause[18], and women who undergo a hysterectomy with ovarian preservation may almost double their risk of premature menopause compared to women with intact uteri[19]. We therefore chose to exclude both of these groups at baseline (n = 3710). After also excluding 1183 participants with joint replacement before recruitment, 91 with missing date of operation, 436 with missing BMI and 1148 with missing information on smoking, the analyses included 30,289 women (Fig. 1).

For follow-up, we identified cases with a TKR or THR due to primary osteoarthritis, according to the operating surgeon, using information from the Norwegian Arthroplasty Register (NAR). This linkage was conducted using the 11-digit personal identification number that is unique to each Norwegian citizen. NAR contains a record of over 95% of all TKRs and THRs in Norway[20]. If a person had more than one arthroplasty, only the first procedure was considered as the event.

Cox proportional hazards models were used to estimate the hazard ratios (HRs) of TKR and THR according to parity (nulliparous, 1, 2, 3, 4+ births), age at menarche (≤11, 12, 13, 14, 15+ years), menopausal status (pre/peri- and postmenopausal), age at menopause (≤48, 49–51, 52+ years), years of menstruation (age at menopause minus age at menarche), oral contraceptive use (never or ever, and duration of use) and HRT use (never, past, current; local or systemic and duration of use). Age was used as the time scale in the analyses. Model 1 adjusted for BMI

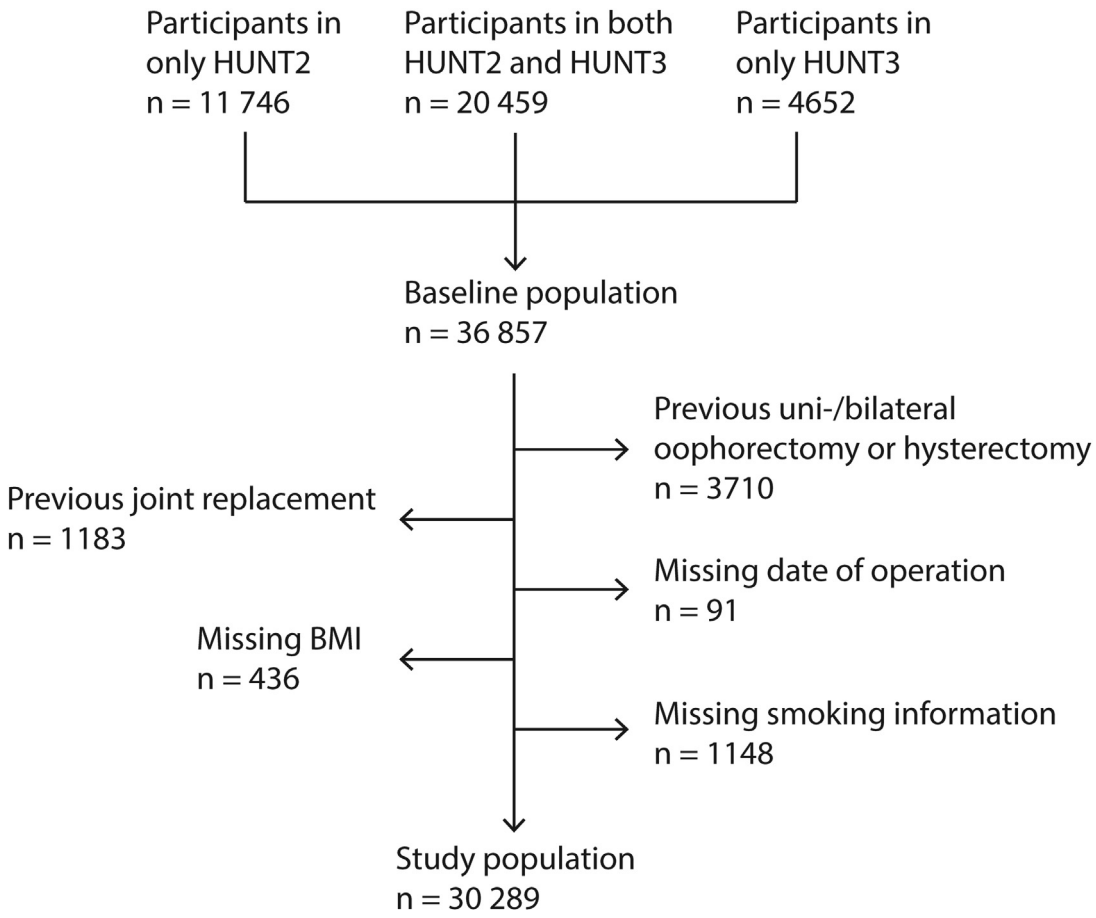

Fig. 1. Flowchart.

(continuous) and smoking (never, former or current). The fully adjusted model 2 also adjusted for physical activity (none, medium, hard) and other reproductive variables as appropriate for the individual exposures. Each exposure was analysed for its interrelationship with other potential hormone-related confounders in a direct acyclic graph (DAG), resulting in a slightly different set of confounders for each exposure (Table A, Appendix). In these DAG analyses, diabetes was only found to be a potential confounder to parity and age at menarche, and thus only adjusted for in these two analyses.

Information on education level was only available for 8745 participants from HUNT2, and an additional sensitivity analysis adjusting for education was performed on this group. Education level was evaluated to be a confounder to parity, oral contraceptive use and HRT (Tables B and C, Appendix), and was defined as the highest level of completed education (primary/vocational, secondary or post-secondary).

The analyses examining age at menopause were limited to postmenopausal women who had never used HRT. The tests for linear trends were based on the categorical variables scored as the mean of each category. All statistical analyses were two-sided with a significance level of $P < 0.05$. The analyses were performed using Stata 14.0/SE (StataCorp LP, College Station, TX, USA). Tests based on Cox regression methods showed no evidence that proportional hazard assumptions were violated.

Ethics

The participants signed written informed consent for participation in HUNT, NAR and linkage of data to national health registries. This study was approved by the Norwegian Regional Committee for Ethics in Medical Research (2013/151/REK Sør-Øst C).

Results

For the 30,289 women included in the study population, the mean age at baseline was 55.7 and mean follow-up time was 8.3 years (SD 4.5). In total, 430 participants had a primary TKR, and 675 had a THR, due to primary osteoarthritis.

Women who reported age at menarche of ≤11 years were older at baseline than those who reported menarche at ≥15 years (Table I). Never users of OC were older than ever users, and past or current users of HRT were older than never users. BMI slightly decreased with increasing age at menarche. A lower portion of the women with higher age at menarche smoked. There was a higher prevalence of diabetes in women who were never oral contraceptive users. Hard physical activity was more prevalent in premenopausal women and oral contraceptive users. Women that received a TKR or THR during follow-up were older, and there were a higher percentage of past or current HRT users than among those who did not get a joint replacement (Table II).

Increasing age at menarche was inversely associated with the risk of TKR (P-trend < 0.001) (Table III). Compared to women with early menarche, those with menarche at 14 years and ≥15 years had a significantly lower risk of TKR (HR 0.64, 95% confidence interval (CI) 0.43–0.95; and HR 0.52, 95% CI 0.34–0.80; respectively). The number of years of menstruation between menarche and menopause was not associated with TKR. Past users of HRT were at higher risk of TKR compared to never users (HR 1.42, 95% CI 1.06–1.90), but only those who used systemic HRT compared to local treatment (HR

Table I
Study population characteristics at baseline (OC: Oral contraceptives; HRT: Hormone replacement therapy)

	n	%	Mean age	SD	BMI	SD	Current smokers (%)	Diabetes (%)	Hard physical activity (%)
All women								missing = 28	missing = 6253
Parity									
Nulliparous	1168	4.0	58.2	18.9	27.0	5.1	28.4	4.8	36.4
1	2966	10.3	53.6	16.2	26.9	5.2	33.4	3.9	44.2
2	10,649	36.8	52.7	14.2	26.6	4.6	29.9	3.3	49.3
3	8818	30.5	55.0	14.2	26.9	4.7	27.5	4.0	48.5
≥4	5322	18.4	63.6	14.1	27.9	4.9	25.8	7.0	39.3
Missing	1366		54.9	16.5	27.1	5.6	22.2	4.3	53.7
Age at menarche, years*									
≤11	2683	9.2	50.7	12.9	28.5	5.4	33.7	5.6	49.9
12	5502	18.9	52.2	14.1	27.6	5.0	29.7	4.4	47.2
13	7554	26.0	53.2	14.5	27.0	4.7	29.4	3.4	48.2
14	7227	24.8	57.2	15.2	26.6	4.6	27.8	4.2	47.0
≥15	6129	21.1	60.5	15.4	26.2	4.5	26.1	4.6	43.9
Missing/unknown	1194		64.4	16.6	27.1	4.9	20.8	5.2	34.4
Menopausal status†									
Pre/peri	10,336	40.9	41.9	6.9	26.5	4.9	32.1	1.4	50.5
Post	14,922	59.1	65.8	10.2	27.4	4.7	25.0	6.2	44.6
Missing/unknown	2855		63.2	16.7	27.0	5.0	31.5	6.6	32.6
Age at menopause, years‡									
≤48	4815	32.3	64.7	11.2	27.3	4.9	48.2	5.7	42.7
49–51	5090	34.1	66.6	10.4	27.3	4.6	31.6	6.3	44.1
≥52	5017	33.6	65.9	9.0	27.6	4.7	20.3	6.6	47.0
OC use§									
Never	6202	34.2	56.7	9.7	27.4	5.0	29.8	4.6	46.3
Ever	11,924	65.8	46.0	9.8	26.5	4.7	31.4	1.9	52.4
Missing	5733		50.1	11.1	26.9	5.0	37.7	3.1	42.1
HRT use									
Never	22,203	83.0	52.3	14.5	26.9	4.9	29.2	3.5	48.4
Past	2536	9.5	64.4	9.5	27.1	4.6	24.2	5.3	48.0
Current	2003	7.5	64.4	10.2	27.1	4.4	23.0	5.4	46.4
Missing	3547		65.5	16.5	27.1	4.9	29.8	7.6	30.9

* Asked of women who were between 19 and 55 years old in HUNT3, but asked of all women in HUNT2.
† Excluded those with amenorrhoea after surgery or radiotherapy ($n = 2176$).
‡ Only in postmenopausal women.
§ Only information in women ≤ 70 years.

Table II
Study population characteristics at baseline in all women, and those who received a total knee replacement (TKR) or total hip replacement (THR)

	All women $n = 30,289$	TKR $n = 430$	THR $n = 675$
Mean age, years (SD)	55.7 (15.2)	64.3 (10.6)	65.6 (10.5)
BMI, mean (SD)	27.0 (4.8)	30.8 (5.3)	28.7 (4.8)
Current smokers, *n* (%)	8613 (28.4)	83 (19.3)	159 (23.6)
Diabetes, *n* (%)	1293 (4.3)	23 (5.4)	33 (4.9)
Hard physical activity, n (%)	11,200 (37.0)	139 (39.8)	232 (42.3)
Parity, mean (SD)	2.6 (1.3)	2.9 (1.4)	2.9 (1.5)
Age at menarche, mean (SD)*	13.4 (1.5)	13.2 (1.5)	13.6 (2.0)
Years of menstruation, mean (SD)	36.0 (4.6)	36.6 (4.7)	36.2 (4.6)
Postmenopausal, *n* (%)†	14,922 (59.1)	341 (88.1)	515 (88.8)
Age at menopause, mean (SD)‡	49.6 (4.4)	49.8 (4.4)	49.9 (4.0)
Ever users of oral contraceptives, *n* (%)§	11,924 (65.8)	103 (44.2)	133 (40.8)
Past users of HRT, *n* (%)	2536 (9.5)	69 (18.7)	88 (15.3)
Current users of HRT, *n* (%)	2003 (7.5)	57 (15.5)	95 (16.6)

* Asked of the women who were between 19 and 55 years old in HUNT3, but asked of all women in HUNT2.
† Excluded those with amenorrhoea after surgery or radiotherapy ($n = 2176$).
‡ Only in postmenopausal women.
§ Only information in women $\leq$ 70 years.

Table III
Reproductive history and use of hormonal medication, and risk of total knee replacement (TKR) (OC: Oral contraceptives; HRT: Hormone replacement therapy)

	Population at risk	Person years	Cases	Model 1*		Model 2†	
				HR	95% CI	HR	95% CI
Parity							
Nulliparous	1168	12,610	17	1	Ref	1	Ref
1	2966	26,173	27	0.79	(0.43–1.45)	0.57	(0.28–1.19)
2	10,649	86,907	127	1.20	(0.72–2.00)	0.91	(0.50–1.67)
3	8818	71,050	134	1.28	(0.77–2.12)	0.88	(0.48–1.61)
≥4	5322	44,731	111	1.04	(0.62–1.73)	0.7	(0.38–1.30)
P linear trend				0.55		0.55	
Age at menarche, years							
≤11	2683	21,502	48	1	Ref	1	Ref
12	5502	45,203	83	0.81	(0.56–1.15)	0.83	(0.56–1.23)
13	7554	62,328	105	0.77	(0.55–1.09)	0.70	(0.48–1.03)
14	7227	59,988	104	0.68	(0.48–0.96)	0.64	(0.43–0.95)
≥15	6129	50,698	78	0.58	(0.40–0.84)	0.52	(0.34–0.80)
P linear trend				0.002		0.001	
Menopausal status							
Pre/peri	10,336	91,247	46	1	Ref	1	Ref
Post	14,922	112,668	341	0.95	(0.63–1.44)	1.16	(0.72–1.87)
Age at menopause, years							
≤48	4815	37,504	111	1	Ref	1	Ref
49–51	5090	38,187	105	0.92	(0.70–1.20)	0.88	(0.64–1.21)
≥52	5017	36,976	125	0.99	(0.77–1.29)	0.98	(0.73–1.32)
Years of menstruation	14,386	250,254	430	1.01	(0.99–1.04)	1.02	(0.99–1.04)
OC use							
Never	6202	56,109	130	1	Ref	1	Ref
Ever	11,924	96,117	103	1.37	(1.03–1.84)	1.36	(1.00–1.86)
Years of OC use	11,488	90,646	94	0.99	(0.93–1.06)	1.01	(0.95–1.09)
HRT use							
Never	22,203	175,094	243	1	Ref	1	Ref
Past	2536	18,035	69	1.45	(1.10–1.90)	1.42	(1.06–1.90)
Current	2003	16,964	57	1.36	(1.02–1.82)	1.25	(0.90–1.73)
HRT use by site							
Never	22,203	175,094	243	1	Ref	1	Ref
Local	2197	16,539	62	1.33	(1.00–1.76)	1.23	(0.90–1.68)
Systemic	2342	18,460	64	1.49	(1.13–1.98)	1.40	(1.03–1.90)
Years of HRT use	3370	22,306	99	1.02	(0.99–1.05)	1.03	(1.00–1.06)

* Adjusted for age, BMI and smoking.
† Adjusted for age, BMI, smoking and physical activity in all analyses. Additional adjustment for diabetes, parity, menarche, menopausal status, oral contraceptives and hormone replacement therapy as appropriate in each DAG analysis.

1.40, 95% CI 1.03–1.90). Ever users of OC had a higher risk of TKR (HR 1.38, 95% CI 1.03–1.84), but this association was only borderline significant in the fully adjusted model (HR 1.36, 95% CI 1.00–1.86).

No association was found between parity, age at menarche, postmenopausal status or oral contraceptive use and THR (Table IV). Current HRT users had increased risk of THR after adjustment for age, BMI and smoking, but this association was no longer significant in the fully adjusted model. There was, however, an increased risk of THR associated with years of HRT use (HR 1.04, 95% CI 1.01–1.07). The vast majority of past/current HRT users were postmenopausal women ($n = 4046$), compared to pre/perimenopausal women ($n = 329$) (data not shown).

Table IV
Reproductive history and use of hormonal medication, and risk of total hip replacement (THR) (OC: Oral contraceptives; HRT: Hormone replacement therapy).

	Population at risk	Person years	Cases	Model 1*		Model 2†	
				HR*	95% CI	HR†	95% CI
Parity							
Nulliparous	1168	12,610	25	1	Ref	1	Ref
1	2966	26,173	55	1.17	(0.73–1.88)	1.12	(0.58–2.18)
2	10,649	86,907	209	1.43	(0.94–2.17)	1.56	(0.86–2.81)
3	8818	71,050	186	1.30	(0.85–1.97)	1.42	(0.79–2.57)
≥4	5322	44,731	184	1.29	(0.85–1.97)	1.34	(0.74–2.44)
P linear trend				0.57		0.61	
Age at menarche, years							
≤11	2683	21,502	49	1	Ref	1	Ref
12	5502	45,203	118	1.04	(0.75–1.45)	1.15	(0.78–1.71)
13	7554	62,328	155	0.96	(0.70–1.33)	1.00	(0.68–1.47)
14	7227	59,988	177	0.93	(0.67–1.28)	1.04	(0.71–1.53)
≥15	6129	50,698	163	0.92	(0.67–1.28)	1.07	(0.73–1.58)
P linear trend				0.352		0.968	
Menopausal status							
Pre/peri	10,336	91,247	65	1	Ref	1	Ref
Post	14,922	112,668	515	0.99	(0.70–1.41)	0.97	(0.67–1.40)
Age at menopause, years							
≤48	4815	37,504	156	1	Ref	1	Ref
49–51	5090	38,187	185	1.13	(0.92–1.40)	1.14	(0.89–1.45)
≥52	5017	36,976	174	1.04	(0.83–1.29)	1.03	(0.80–1.32)
Years of menstruation	14,386	236,732	667	1.01	(0.99–1.03)	1	(0.98–1.03)
OC use							
Never	6202	56,109	193	1	Ref	1	Ref
Ever	11,924	96,117	133	1.11	(0.87–1.42)	1.03	(0.79–1.35)
Years of OC use	11,488	90,646	120	0.94	(0.87–1.01)	0.96	(0.89–1.04)
HRT use							
Never	22,203	175,094	391	1	Ref	1	Ref
Past	2536	18,035	88	1.12	(0.88–1.41)	1.03	(0.80–1.33)
Current	2003	16,964	95	1.32	(1.05–1.66)	1.19	(0.92–1.53)
HRT use by site							
Never	22,203	175,094	391	1	Ref	1	Ref
Local	2197	16,539	100	1.26	(1.01–1.58)	1.16	(0.90–1.48)
Systemic	2342	18,460	83	1.16	(0.91–1.48)	1.05	(0.80–1.36)
Years of HRT use	3370	22,306	116	1.04	(1.01–1.07)	1.04	(1.01–1.07)

* Adjusted for age, BMI and smoking.
† Adjusted for age, BMI, smoking and physical activity in all analyses. Additional adjustment for diabetes, parity, menarche, menopausal status, oral contraceptives and hormone replacement therapy as appropriate in each DAG analysis.

In a sensitivity analysis of 8745 participants from HUNT2 on parity, oral contraceptive use, and HRT use, adjusted for education level, we found a reduced risk of TKR in women reporting 1 birth (HR 0.15, 95% CI 0.09–0.78) or ≥ 4 births (HR 0.18, 95% CI 0.22–0.97) compared to nulliparous women, but there was no significant trend across the categories ($P = 0.37$) (Table B, Appendix). Years of HRT use slightly increased the risk of THR, but past or current use of HRT was not associated with THR (Table C, Appendix).

Discussion

This prospective cohort study of over 30,000 women found that older age at menarche was associated with decreased risk of TKR. We also found an association between past and systemic HRT use and increased risk of TKR. Parity did not increase the risk of TKR or THR.

The observation that increasing age at menarche was inversely related to the risk of TKR has also been reported in a large prospective study of 1.3 million middle-aged women by Liu *et al.*[4]. The mechanisms underlying these associations are unclear, but there could be several possible explanatory factors. A recent cross-sectional study found an association between early age at menarche and chronic widespread musculoskeletal complaints later in life[21]. One may therefore speculate that an increased level of pain from knee osteoarthritis in this group could lead to a higher incidence of TKR. Early onset of menarche has also been linked to other conditions of ageing such as elevated blood pressure and glucose intolerance, independent of body composition[22]. A cross-sectional study by Kalichman *et al.* demonstrated a negative association between age at menarche and radiological hand osteoarthritis. They proposed that one possible explanation could be that early menarche was associated with an increased rate of the general ageing process[23]. Yet another explanation could be that younger age at menarche may be a marker of other factors such as higher BMI when young[4]; weight gain at a young age has been shown to be a significant risk factor for TKR and THR due to osteoarthritis later in life[24,25].

Systemic use of HRT increased the risk of TKR, and although we did not find any association between current use of HRT and joint replacement, our finding of increased risk of TKR in women with past use of HRT is in agreement with the results by Liu *et al.*[4]. They reported that past or current use of postmenopausal hormone therapy was associated with a significant increase in the incidence of THR and TKR. However, clinical and epidemiological studies have shown conflicting results, and a systematic review found no clear association between HRT and osteoarthritis[26]. Heterogeneity between the hormones used and outcome measurements also made statistical data pooling impossible. They concluded that the relationship was, perhaps, too complex, or that other factors play a role in the increased incidence of osteoarthritis in women aged >50.

Our study did not observe any association between parity and joint replacement. Previous studies on the association between parity and knee osteoarthritis have shown conflicting results[3–5].

However, the absolute numbers of joint replacements in the nulliparous group in our study were low ($n = 25$ and $n = 17$ for THR and TKR, respectively), which calls the power of this analysis into question. We cannot exclude the possibility that this may have weakened any association. Since both parity and joint replacement are associated with education level, we did a sub-analysis with additional adjustment for education in 8745 participants with data on education level; we revealed a reduced risk of TKR in women with 1 birth or ≥4 births, but there was no significant trend across the categories ($P = 0.37$). This could indicate a complex relationship between parity and TKR/THR that we were unable to clarify further in our study.

The healthcare system in Norway is publicly funded and free of charge for patients. Although socioeconomic status would not affect access to surgery, it could lead to a difference in those seeking surgery. In 2009, Statistics Norway reported that amongst women with musculoskeletal diseases, those with a higher level of education (university/college level) were more likely to contact specialist health services than those with lower levels of education (high school or lower)[27]. A negative association between the level of education and the waiting time for THR in Norway has been reported[28], although the income variable was insignificant.

Ever use of OC did not significantly increase the risk of TKR or THR in the fully adjusted model, although the point estimate of the *P* value was borderline significant for TKR, $P = 0.053$ (HR 1.36, 95% CI 1.00–1.86). Menopausal status and age at menopause were not associated with THR or TKR.

Strengths and limitations

Major strengths of this study were the large sample size, prospective population-based design, objective measurements and nearly complete registration of TKR and THR.

Our study used objective measurements of height and weight by trained personnel, and thus avoided potential information bias. The study by Liu *et al.*[4] used self-reported BMI. Self-reported BMI may be biased, and a recent study showed limited agreement with actual height and weight in overweight and obese individuals with clinical osteoarthritis[29].

At the time between HUNT2 (1995–1997) and HUNT3 (2006–2008) studies reported an association between HRT and coronary heart disease[30,31], and HRT and breast/gynaecological cancers[32–34]. The proportion of women using HRT could therefore have been lower in the HUNT3 study. In our data-set we found that 19% of participants in HUNT2 were past or current HRT users, compared to 16.3% in HUNT3. Therefore, HRT prescription did not differ substantially between the two surveys, and should not have greatly affected our results.

The design of this study is prospective since the baseline information was recorded prior to an eventual joint replacement. However, we cannot exclude the possibility that recall bias might have influenced some of the covariates, especially age at menarche. Table I shows a mean age difference of almost 10 years between the women that reported age at menarche ≤11 years, and those reporting age at menarche ≥15. As well, a Danish study from 2009 showed significantly earlier breast development among girls born more recently during a 15-year period[35]. This could indicate that the age at menarche may have decreased over time in our study population, thus creating a cohort effect. Adjusting for age may then be insufficient for correcting an eventual systematic information bias and a cohort effect bias.

At baseline, the mean age of our study population was 55.7, and 62.1% of the women in our study were postmenopausal. However, since our lower cut-off for age at inclusion was 30 years, the information on reproductive history and use of HRT or OC could have changed for some participants after baseline. This is especially relevant when it comes to parity, oral contraceptive use and HRT, and could have led to non-differential misclassification and thus weakened any associations. To increase the information on lifetime reproductive history and eventual use of HRT, we chose to use baseline measurements from HUNT3 for those that participated in both HUNT2 and HUNT3, even if this reduced follow-up time after baseline; the 9468 participants with baseline measurements from HUNT2 had a mean follow-up time of 13.0 years compared to 6.1 years for the 20,821 participants with baseline measurement from HUNT3. Lower incidences of TKR (1.2 %) and THR (1.8%) in the HUNT3 group, compared to TKR (1.8%) and THR (3.2%) in the HUNT2 group, might contribute to lower precision and underestimation of any associations.

A previous study from the HUNT2 material reported that women who had undergone unilateral oophorectomy entered menopause around 1 year earlier than women with two intact ovaries[36] (Separation between uni- vs bilateral oophorectomy was only available from HUNT2, as the HUNT3 questionnaire only asked about bilateral oophorectomy). We chose not to exclude participants that had had only one ovary surgically removed ($n = 776$), and additional adjustment for unilateral oophorectomy when analysing age at menarche did not change the results (data not shown).

In HUNT2 we had information on type of HRT medication in 2601 participants. Of these participants, 1456 (56%) used a combination of oestrogen and progesterone, and 1145 used oestrogen without progesterone. HUNT3 did not have information about the precise type of HRT used by each individual. A previous publication on HRT from HUNT3 reported that data from the Norwegian Prescription Database showed that during the time frame and region of the HUNT3 study, 83.5% of HRT users were prescribed a combination of oestradiol and/or oestriol and progesterone, 9.0% either oestradiol or oestriol without progesterone and 7.5% used the synthetic oestrogen tibolone[37,38].

Although there was a 10-year period between HUNT2 and HUNT3, they both used the same source population: All inhabitants ≥20 years of age in the county of Nord-Trøndelag in Norway. But there could be several reasons why HUNT2 and HUNT3 did not have all the same participants:

- The participation rate in HUNT3 was lower than in HUNT2 (58.7% and 75.5%, respectively). Some of the responders in HUNT2 could therefore have been non-responders in HUNT3.
- We would expect some of the older participants in HUNT2 to have died before HUNT3. And people that were too young to participate in HUNT2 could be part of the study population in HUNT3.

The population in Nord-Trøndelag is relatively homogeneous, with less than 3% non-Caucasian, and is relatively stable, with few people moving in or out of the county[39]. So despite the limitations that arise from using the participants from two consecutive waves of the HUNT health survey, we would argue that the two surveys represent one source population.

The osteoarthrosis diagnoses from the NAR have not been validated[40]. However, the Danish Hip Arthroplasty Registry has reported a positive predictive value of 85% regarding primary hip osteoarthritis diagnosis[41], and it is likely that these results are comparable to the NAR.

Previous injuries increase the risk of osteoarthritis, especially in the knee[42,43]. However, the operating surgeon reports whether each joint replacement is due to primary/idiopathic osteoarthritis, or due to other specified causes. We only included joint replacement due to primary/idiopathic osteoarthritis.

We used joint replacement as an indicator of severe osteoarthritis. Joint replacement is the most definitive treatment for osteoarthritis in the hip or knee, and has the advantage of being a strong indicator of severe clinical disease compared to other definitions of osteoarthritis[44]. Using total joint replacement as an endpoint also helps to identify the burden of severe disease, and is therefore relevant for health economics[45]. The decision to do a total arthroplasty does, however, rely on several factors: the severity of pain, radiographic findings, comorbidities and the patient's motivation for undergoing surgery. Subjects who wish to maintain an active lifestyle may be more motivated to have surgery than less active persons[46], even if they have less severe osteoarthritis. This potential healthy patient bias could lead to an underestimation of the effect of reproductive and hormonal therapies on osteoarthritis.

We found that increasing age at menarche reduced the risk of TKR. Past users and users of systemic HRT were at higher risk of TKR compared to never users. Parity did not increase the risk of TKR or THR.

Contributors

AIH participated in the study concept and design, obtained funding, performed the analysis, interpreted the data and drafted the manuscript. LN, MBJ, AL, GBF, OF, KS and JAZ were involved in the conception and design of the study. OF was also involved in the collection of THR and TKR data. AMF contributed with statistical expertise. All the authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

Conflict of interest

None.

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Appendix

Table A
Covariates adjusted for in Model 1 and Model 2 (BMI: Body Mass Index; HRT: Hormone replacement therapy)

Exposure variable	Covariates adjusted for in Model 1	Additional covariates adjusted for in Model 2
Parity	Age, BMI, smoking	Diabetes, physical activity, age at menarche, menopausal status, HRT
Age at menarche	Age, BMI, smoking	Diabetes, physical activity, parity, menopausal status
Years of menstruation	Age, BMI, smoking	Diabetes, physical activity, parity
Menopausal status	Age, BMI, smoking	Physical activity, parity, age at menarche, HRT
Age at menopause	Age, BMI, smoking	Physical activity, parity, age at menarche, HRT
Use of oral contraceptives	Age, BMI, smoking	Physical activity, parity, age at menarche, menopausal status
Use of HRT	Age, BMI, smoking	Physical activity, parity, menopausal status

Table B
Parity, oral contraceptives (OC), hormone replacement therapy (HRT) and risk of total knee replacement (TKR); sensitivity analysis with additional adjustment for education

	Population at risk	Person years	Cases	HR*	95% CI	HR†	95% CI
Parity							
Nulliparous	797	9743	14	1	Ref	1	Ref
1	961	13,486	10	0.52	(0.23–1.18)	0.15	(0.09–0.78)
2	2602	36,701	40	0.83	(0.45–1.53)	0.20	(0.27–1.12)
3	2131	29,165	40	0.87	(0.47–1.60)	0.20	(0.26–1.11)
≥4	1913	22,874	46	0.77	(0.42–1.41)	0.18	(0.22–0.97)
P linear trend				0.97		0.37	
OC use							
Never	2119	30,002	59	1	Ref	1	Ref
Ever	2176	35,524	21	0.92	(0.52–1.62)	0.95	(0.50–1.78)
Years of OC use	1883	30,955	16	1.04	(0.95–1.13)	1.05	(0.95–1.16)
HRT use							
Never	4897	67,037	81	1	Ref	1	Ref
Past	414	5172	10	1.05	(0.54–2.03)	1.06	(0.50–2.23)
Current	704	8760	22	1.38	(0.86–2.24)	1.36	(0.79–2.36)
HRT use by site							
Never	4897	67,037	81	1	Ref	1	Ref
Local	544	6269	20	1.50	(0.91–2.48)	1.56	(0.88–2.76)
Systemic	574	7662	12	0.99	(0.54–1.83)	0.93	(0.46–1.89)
Years of HRT use	319	3740	16	0.96	(0.81–1.14)	0.96	(0.80–1.14)

* Adjusted for age, BMI, smoking and education level.
† Adjusted for age, BMI, smoking, physical activity and education level in all analyses. Additional adjustment for diabetes, parity, menarche, menopausal status, oral contraceptives and hormone replacement therapy as appropriate in each DAG analysis.

Table C
Parity, oral contraceptives (OC), hormone replacement therapy (HRT) and risk of total hip replacement (THR); sensitivity analysis with additional adjustment for education

	Population at risk	Person years	Cases	HR*	95% CI	HR†	95% CI
Parity							
Nulliparous	797	9743	21	1	Ref	1	Ref
1	961	13,486	21	0.83	(0.45–1.53)	1.02	(0.44–2.33)
2	2602	36,701	77	1.16	(0.72–1.89)	1.53	(0.77–3.02)
3	2131	29,165	61	0.97	(0.59–1.59)	1.17	(0.58–2.36)
≥4	1913	22,874	81	1.03	(0.64–1.67)	1.1	(0.55–2.23)
P linear trend				0.87		0.88	
OC use							
Never	2119	30,002	91	1	Ref	1	Ref
Ever	2176	35,524	33	0.97	(0.62–1.52)	1.01	(0.63–1.62)
Years of OC use	1883	30,955	25	0.96	(0.87–1.05)	0.95	(0.86–1.04)
HRT use							
Never	4897	67,037	144	1	Ref	1	Ref
Past	414	5172	14	0.77	(0.45–1.34)	0.85	(0.47–1.51)
Current	704	8760	35	1.04	(0.72–1.52)	1.03	(0.68–1.57)
HRT use by site							
Never	4897	67,037	144	1	Ref	1	Ref
Local	544	6269	26	0.98	(0.64–1.49)	1.07	(0.67–1.71)
Systemic	574	7662	23	0.92	(0.59–1.43)	0.86	(0.53–1.41)
Years of HRT use	319	3740	17	1.13	(1.03–1.25)	1.18	(1.05–1.33)

* Adjusted for age, BMI, smoking and education level.
† Adjusted for age, BMI, smoking, physical activity and education level in all analyses. Additional adjustment for diabetes, parity, menarche, menopausal status, oral contraceptives and hormone replacement therapy as appropriate in each DAG analysis.

References

1. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol 2014;28:5–15.
2. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthr Cartil 2005;13:769–81.
3. Wise BL, Niu J, Zhang Y, Felson DT, Bradley LA, Segal N, *et al.* The association of parity with osteoarthritis and knee replacement in the Multicenter Osteoarthritis Study. Osteoarthr Cartil 2013;21:1849–54.
4. Liu B, Balkwill A, Cooper C, Roddam A, Brown A, Beral V, *et al.* Reproductive history, hormonal factors and the incidence of hip and knee replacement for osteoarthritis in middle-aged women. Ann Rheum Dis 2009;68:1165–70.
5. Wei S, Venn A, Ding C, Martel-Pelletier J, Pelletier JP, Abram F, *et al.* The associations between parity, other reproductive factors and cartilage in women aged 50-80 years. Osteoarthr Cartil 2011;19:1307–13.
6. Samanta A, Jones A, Regan M, Wilson S, Doherty M. Is osteoarthritis in women affected by hormonal changes or smoking? Br J Rheumatol 1993;32:366–70.
7. Dennison EM, Arden NK, Kellingray S, Croft P, Coggon D, Cooper C. Hormone replacement therapy, other reproductive variables and symptomatic hip osteoarthritis in elderly white women: a case-control study. Br J Rheumatol 1998;37:1198–202.
8. Sandmark H, Hogstedt C, Lewold S, Vingard E. Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. Ann Rheum Dis 1999;58:151–5.
9. Vingard E, Alfredsson L, Malchau H. Lifestyle factors and hip arthrosis. A case referent study of body mass index, smoking and hormone therapy in 503 Swedish women. Acta Orthop Scand 1997;68:216–20.
10. Wluka AE, Davis SR, Bailey M, Stuckey SL, Cicuttini FM. Users of oestrogen replacement therapy have more knee cartilage than non-users. Ann Rheum Dis 2001;60:332–6.
11. Spector TD, Nandra D, Hart DJ, Doyle DV. Is hormone replacement therapy protective for hand and knee osteoarthritis in women? The Chingford Study. Ann Rheum Dis 1997;56:432–4.
12. Erb A, Brenner H, Gunther KP, Sturmer T. Hormone replacement therapy and patterns of osteoarthritis: baseline data from the Ulm Osteoarthritis Study. Ann Rheum Dis 2000;59:105–9.
13. Zhang Y, McAlindon TE, Hannan MT, Chaisson CE, Klein R, Wilson PW, *et al.* Estrogen replacement therapy and worsening of radiographic knee osteoarthritis: the Framingham Study. Arthritis Rheum 1998;41:1867–73.
14. Karlson EW, Mandl LA, Aweh GN, Sangha O, Liang MH, Grodstein F. Total hip replacement due to osteoarthritis: the importance of age, obesity, and other modifiable risk factors. Am J Med 2003;114:93–8.
15. Nevitt MC, Felson DT, Williams EN, Grady D. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: the Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2001;44:811–8.
16. http://www.ntnu.edu/hunt. Cited January 2017.
17. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, *et al.* Cohort profile: the HUNT Study, Norway. Int J Epidemiol 2013;42:968–77.
18. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. Maturitas 2010;65:161–6.
19. Moorman PG, Myers ER, Schildkraut JM, Iversen ES, Wang F, Warren N. Effect of hysterectomy with ovarian preservation on ovarian function. Obstet Gynecol 2011;118:1271–9.
20. Espehaug B, Furnes O, Havelin LI, Engesaeter LB, Vollset SE, Kindseth O. Registration completeness in the Norwegian Arthroplasty Register. Acta Orthop 2006;77:49–56.
21. Kvalheim S, Sandvik L, Winsvold B, Hagen K, Zwart JA. Early menarche and chronic widespread musculoskeletal complaints–results from the HUNT Study. Eur J Pain 2016;20:458–64.
22. Remsberg KE, Demerath EW, Schubert CM, Chumlea WC, Sun SS, Siervogel RM. Early menarche and the development of cardiovascular disease risk factors in adolescent girls: the Fels Longitudinal Study. J Clin Endocrinol Metab 2005;90:2718–24.
23. Kalichman L, Kobyliansky E. Age, body composition, and reproductive indices as predictors of radiographic hand

osteoarthritis in Chuvashian women. Scand J Rheumatol 2007;36:53–7.
24. Apold H, Meyer HE, Espehaug B, Nordsletten L, Havelin LI, Flugsrud GB. Weight gain and the risk of total hip replacement a population-based prospective cohort study of 265,725 individuals. Osteoarthr Cartil 2011;19:809–15.
25. Apold H, Meyer HE, Nordsletten L, Furnes O, Baste V, Flugsrud GB. Weight gain and the risk of knee replacement due to primary osteoarthritis: a population based, prospective cohort study of 225,908 individuals. Osteoarthr Cartil 2014;22:652–8.
26. de Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, *et al*. No clear association between female hormonal aspects and osteoarthritis of the hand, hip and knee: a systematic review. Rheumatology (Oxford) 2009;48:1160–5.
27. Sosiale ulikheter i bruk av helsetjenester (in Norwegian); 2009 cited January 2017. Available from: https://www.ssb.no/helse/artikler-og-publikasjoner/sosiale-ulikheter-i-bruk-av-helsetjenester#content.
28. Monstad K, Engesaeter LB, Espehaug B. Waiting time and socioeconomic status–an individual-level analysis. Health Econ 2014;23:446–61.
29. Magnusson K, Haugen IK, Osteras N, Nordsletten L, Natvig B, Hagen KB. The validity of self-reported body mass index in a population-based osteoarthritis study. BMC Musculoskelet Disord 2014;15:442.
30. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
31. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, *et al*. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523–34.
32. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000;92:328–32.
33. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000;283:485–91.
34. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, *et al*. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA 2003;290:1739–48.
35. Aksglaede L, Sorensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. Pediatrics 2009;123:e932–9.
36. Bjelland EK, Wilkosz P, Tanbo TG, Eskild A. Is unilateral oophorectomy associated with age at menopause? A population study (the HUNT2 Survey). Hum Reprod 2014;29:835–41.
37. Norwegian Prescription Database http://www.norpd.no. Cited May 2017.
38. Pintzka CW, Haberg AK. Perimenopausal hormone therapy is associated with regional sparing of the CA1 subfield: a HUNT MRI study. Neurobiol Aging 2015;36:2555–62.
39. HUNT Databank https://www.ntnu.edu/hunt/databank. Cited January 2017.
40. Engesaeter IO, Lehmann T, Laborie LB, Lie SA, Rosendahl K, Engesaeter LB. Total hip replacement in young adults with hip dysplasia: age at diagnosis, previous treatment, quality of life, and validation of diagnoses reported to the Norwegian Arthroplasty Register between 1987 and 2007. Acta Orthop 2011;82:149–54.
41. Pedersen A, Johnsen S, Overgaard S, Soballe K, Sorensen HT, Lucht U. Registration in the Danish hip arthroplasty registry: completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. Acta Orthop Scand 2004;75:434–41.
42. Oiestad BE, Holm I, Engebretsen L, Aune AK, Gunderson R, Risberg MA. The prevalence of patellofemoral osteoarthritis 12 years after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 2013;21:942–9.
43. Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, *et al*. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008;59:1207–13.
44. Kim C, Nevitt MC, Niu J, Clancy MM, Lane NE, Link TM, *et al*. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. BMJ 2015;351:h5983.
45. Dieppe P. Osteoarthritis: time to shift the paradigm. This includes distinguishing between severe disease and common minor disability. BMJ 1999;318:1299–300.
46. Michaelsson K, Byberg L, Ahlbom A, Melhus H, Farahmand BY. Risk of severe knee and hip osteoarthritis in relation to level of physical exercise: a prospective cohort study of long-distance skiers in Sweden. PLoS One 2011;6:e18339.