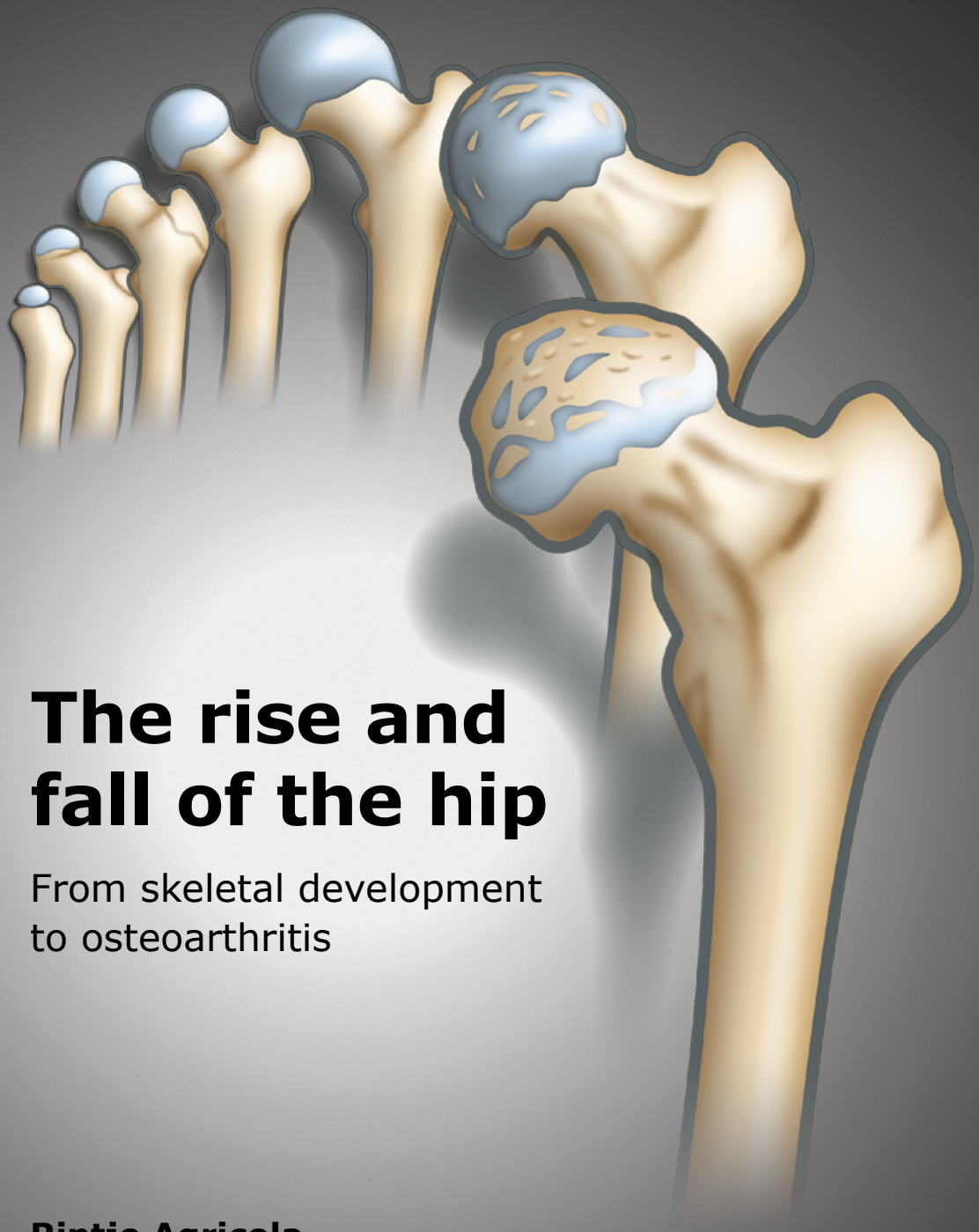

The rise and fall of the hip

From skeletal development to osteoarthritis

Rintje Agricola

The Rise and Fall of the Hip

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The Rise and Fall of the Hip

From Skeletal Development to Osteoarthritis

De ontwikkeling en ondergang van de heup
van botrijping tot artrose

Proefschrift

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In liefdevolle herinnering aan mijn moeder

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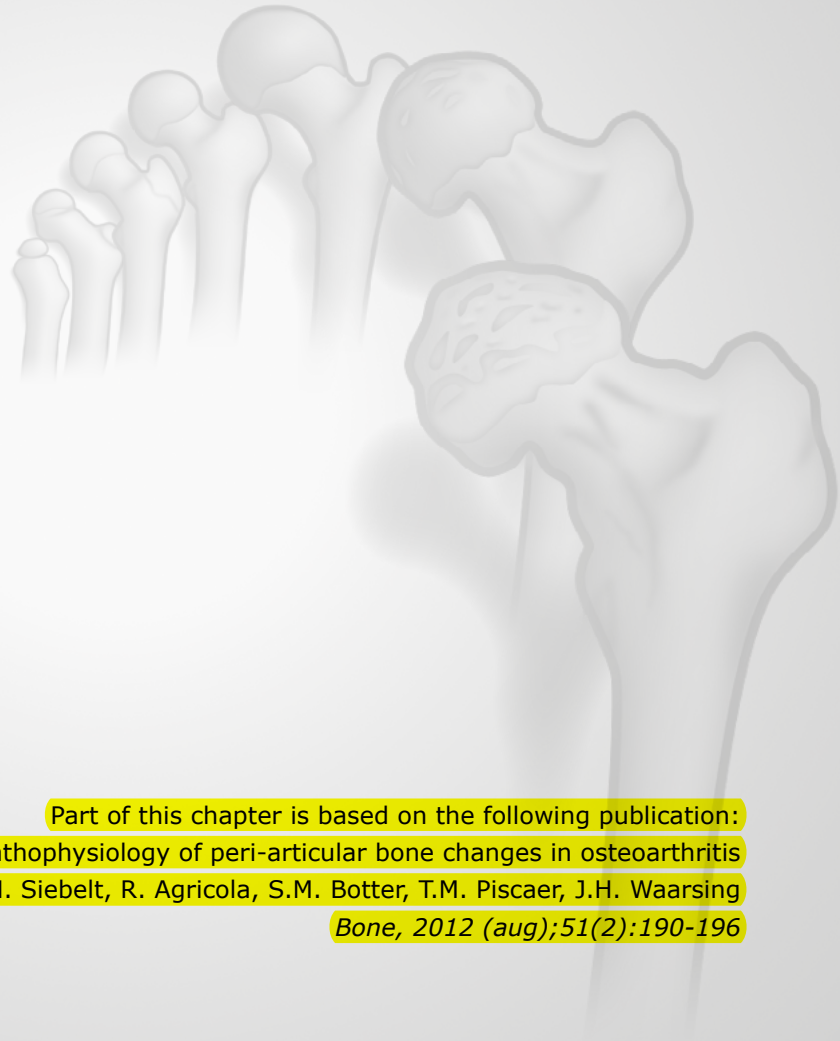
Introduction



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The hip joint

The skeleton provides protection, maintains body shape, and enables movement. Movement of body parts is possible by coupling of bones in joints. The bony anatomy of each specific joint is evolutionary adapted to its specific function.[1] The human hip joint for example, can be simplified as a weightbearing ball (femoral head) and socket (acetabulum) joint, which allows a large range of motion for the upper leg with respect to the pelvis. Articular surfaces of the femoral head and the acetabulum are covered by a layer of shock absorbing hyaline cartilage, which enables them to move easily. The femoral head and acetabulum have intrinsic shortcoming that lead to some instability of the hip and the joint is therefore additionally supported by soft tissue structures. The relatively shallow acetabulum is surrounded by a ring of fibrocartilage (labrum) that deepens the acetabulum. It has been found that the labrum increases acetabular contact surface area from 28.8cm^2 without the labrum to 36.8 cm^2 with the labrum, thereby extending acetabular coverage.[2,3] The stability of the hip is further enhanced by a capsule, which consists of multiple ligaments that run from the pelvis to the femoral neck. Within the capsule, the synovial membrane produces fluid that lubricates the cartilage, thereby virtually eliminating the friction during movement of the hip.[4]

Skeletal development and adaptation of the hip 'the rise'

In infants, the entire proximal end of the femur is composed of cartilage. Between four to seven months after birth, the proximal femoral (secondary) ossification centre appears.[5] From then on, it continues to enlarge until adulthood, when only a thin layer of articular cartilage remains. The greater trochanter also enlarges by appositional cartilage cell proliferation, somewhat later than the femoral head. As a result, three main growth areas are present in the proximal femur during skeletal maturation: the growth plates of the femoral head, the greater trochanter, and the femoral neck isthmus.[6] The proximal femoral growth plate contributes for about 30% to the overall length of the femur. The femoral neck isthmus is a small cartilaginous isthmus between the proximal femoral and trochanteric growth plates along the lateral border of the femoral neck and reflects their previous common origin (figure 1). Probably, it contributes to development of the femoral neck width.

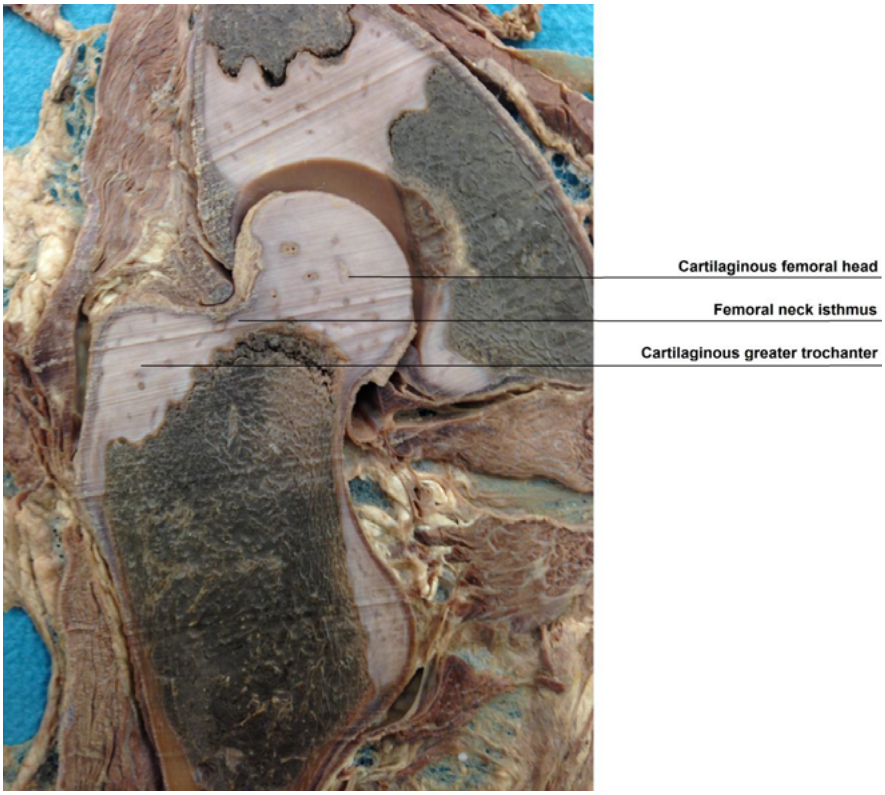


Figure 1: Coronal section of a specimen of a nine year old boy, with unknown cause of death. From the anatomical department (prof G.J. Kleinrensink) of Erasmus Medical Centre, Rotterdam, the Netherlands.

A coordinated growth of these three growth fronts determines the size and shape of the adult proximal femur. A disturbance in any of these growth fronts will lead to alterations in the final shape of the proximal femur.[6]
There are indications that certain shape variants of the hip lead to a higher risk of development of hip OA. It is therefore of great relevance to study if such shape variants are genetically imprinted and thus not modifiable, or whether they are influenced by external (and possibly modifiable) factors. A prerequisite for the latter is that bone can be affected by external factors. It is known that bone is not an indolent tissue, but that it has the capacity to constantly renew itself. This is realized by osteoclasts and osteoblasts working together in structural basic multicellular units (BMUs). Osteoclasts are cells that resorb old bone, which are followed by osteoblasts that deposit the new bone matrix. The possibility for self renewal, or remodeling, is essential for repairing micro-damage in the bone

tissue and fracture healing. During growth, remodeling takes also place to adapt its structure to changing mechanical loads, and is then referred to as modeling. More than a century ago, Roux and Wolff already observed that bone is capable to adapt itself to its mechanical environment.[7,8] This has been well illustrated by the trabecular structure of the proximal femur, which is aligned along the principle loading directions.[9,10] This has led to the idea that external forces as a result of sporting activities, specifically during the period of skeletal growth, can influence bone architecture and bone morphology.

Trabecular bone architecture is often expressed in bone mineral density (BMD) as measured by DEXA scans. Multiple studies using DEXA have shown that athletic activities during growth, and especially those with high impact, stimulate bone formation and lead to a higher BMD. This has been illustrated by studies showing that the dominant arm of professional tennis players has a much higher bone mass than the contra lateral arm.[11-13] In addition, many studies showed a higher bone mass at specific locations in the proximal femur of athletes who participated in high impact sports such as soccer, basketball, and jumping sports.[14-17] Thus, by increasing external loading of the hip, internal bone formation occurs as an adaptive process.[9] Conversely, when the loads applied to bone decrease, an increase in bone resorption and a subsequent decrease in bone formation takes place as in cosmonauts during a space flight or during prolonged bed rest.[18,19]

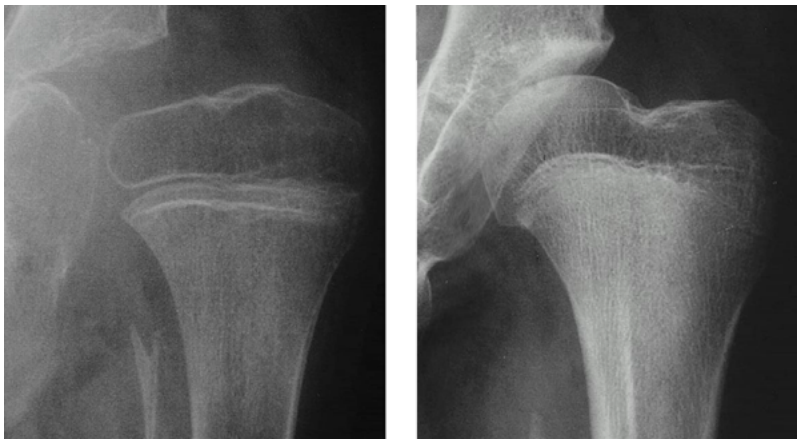


Figure 2. Five weeks after rotationplasty (left) and 7 years postoperatively (right), with increasing centering of what now appears as the femoral head. Note the orientation of the medial part of the growth plate towards the vector of force.

Bone morphology refers to the surface shape of bones and might be influenced by sporting activities in the same manner as bone architecture, though the actual shape of bones is much less studied. This is primarily due to the radiation load of the radiographs or Computed Tomography (CT) scans needed to study bone morphology in adolescents. Bone is a dynamic tissue and external loads applied to it might largely determine its shape, which is strikingly demonstrated during follow-up after a hip rotationplasty (figure 2).[20] During hip rotationplasty, the femur is completely resected (e.g. due to a malignant tumor) and the proximal tibia is placed into the acetabulum to avoid prosthetic replacement or amputation at the level of the hip. Figure 2 shows that years after this procedure in a 5 years old girl, the bone shape has adapted towards the shape of a proximal femur, despite it was genetically imprinted to become a proximal tibia.

Assuming that the shape of the hip can change resulting from the loads applied to it during skeletal maturation, an abnormal hip morphology might be a result of high impact sporting activities during skeletal growth. This phenomenon has already been demonstrated in other joints: in shoulders of elite baseball players there is more proximal humeral retrotorsion and glenoid retroversion in their throwing than in their nonthrowing arm.[21] Playing soccer during childhood and adolescence is associated with development of genu varum (bowlegs) in the knees.[22] For the hip, there is only one study available that investigates whether different loading conditions, especially those experienced by athletic activities, can influence the shape of the hip.[23]

In 1965 Murray hypothesized a 'tilt deformity' to be a causative factor in hip OA and described the tilt deformity as a slight SCFE.[24] In 1971 it was consequently studied whether this tilt deformity –nowadays known as a cam deformity- might have been a result of chronic stress during the years of adolescence. He investigated three groups of young mature males between 17 and 21 years of age with different athletic backgrounds. The first group were boys at a boarding school well known both for its intellectual standards and athletic successes; the second group attended an identical school, though athletic activities were more voluntary and practiced less; and finally, a third group comprised boys from the same age working in industry, of which many had left state schools at the age of 15, though most had continued with some athletic activity. The prevalence of a tilt deformity on AP radiographs differed significantly between the groups, being 24% in the first group, 9% in the second group, and 15% in the third group. It was suggested that certain forms of sports, especially when undertaken compulsorily during adolescence, might precipitate the abnormality. Another indication that a cam deformity might develop during skeletal growth

was provided by Siebenrock et al., who showed that a cam deformity in adults was associated with an unusual extension of the epiphyseal scar onto the femoral neck.[25] However, prospective studies in adolescents are not available. As recent studies indicate that certain shape variants of the hip pose a higher risk of hip OA, a better knowledge on how these shape variants of the hip develop is required.

Osteoarthritis 'the fall'

OA is the most frequently occurring chronic joint disease worldwide.[26] It is symptomatically characterized by pain, stiffness and loss of function, and on a tissue level by loss of cartilage, osteophyte formation, subchondral sclerosis, and cyst formation (figure 3).

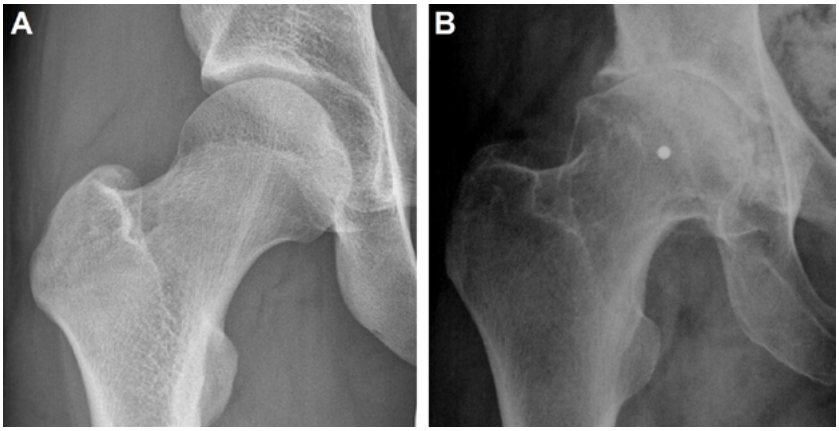


Figure 3. A. A healthy hip without signs of osteoarthritis **B.** A hip with radiographic signs of advanced osteoarthritis including large osteophytes, joint space narrowing (indirect measure of cartilage loss), subchondral sclerosis and joint deformity.

OA has a detrimental impact on quality of life and forms an increasing economic burden.[27] The economic burden consists of both direct and indirect costs. Direct cost is the cost of medical care due to OA and associated comorbidity, and has been estimated to be >$100 billion per year for hip OA alone in the United States (US).[28] Indirect costs are those as a result of OA, but not associated directly with treatment. They include for example the costs of productivity loss and might be 1.5 times the direct cost of OA.[29] The latter is exemplified by the fact that OA is the second cause of work disability after ischaemic heart disease in males >50 years in the US.[30] The costs of hip OA in the Netherlands are unknown, though the indirect costs of conservatively treated patients with knee

OA in the Netherlands have been estimated to be €722 per patient per month.[31] A precise definition of the disease has been difficult to determine and the prevalence of OA is therefore difficult to express in one number. There is often a discrepancy between the clinical presentation and the radiographic evidence of OA. In research, the commonly used definitions of hip OA include 'symptomatic OA' as quantified by the ACR criteria[32], 'radiographic OA' as quantified by for example the Kellgren and Lawrence scale[33], or it is defined by total joint replacement as a result of OA.

OA can affect any synovial joint, but joints most affected by OA are in order of decreasing prevalence the spine (cervical and lumbar), phalanges (distal interphalangeal joint and the first carpometacarpal joint), the knee, and the hip.[34] Besides the definition used, the reported prevalence of hip OA depends largely on the characteristics of the study population such as age, gender, and ethnicity. In the US, the prevalence of radiographic hip OA (K&L>1) in population based studies ranges from 11.9% to 27.6%.[35,36] In the Netherlands, a population based study in the region of Zoetermeer reported a prevalence of around 10% having a K&L grade >1.[34] Another estimation of the incidence of hip OA is provided by the first annual report of the Dutch registry of orthopaedic implants (LROI). In 2011, an incidence of approximately 26.000 total hip replacements due to osteoarthritis was reported.[37] This number is expected to increase in the coming years and there is a trend towards a younger age of patients needing a primary hip replacement.

Risk factors of hip OA

OA is a multifactorial disease with many risk factors involved. The OA population exists of a heterogeneous group of patients that can have very different causes of disease. Multiple pathophysiological pathways can independently lead to the development of OA, though several general risk factors have been identified. Clearly, age is the major risk factor for development of hip OA. Other risk factors of hip OA include genetics, gender, obesity, occupational factors, and physical sporting activities. Finally, the shape of the hip has been increasingly recognized as a biomechanical risk factor for development of hip OA.

The involvement of genetics in OA is indirectly illustrated by the ethnic differences in prevalence of hip OA, which is relatively high in the US and Europe, but rare in Asian countries.[38,39] Although these differences might be influenced by the shape of the hip, which is also known to differ between ethnic groups, some genetic involvement is likely. Furthermore, large GWAS studies have identified several specific loci (SNPs) associated with development of OA.[40,41] For hip OA, gender is

not a clear risk factor in contrast to other types of OA, which are generally more prevalent in females than in males.

The influence of obesity on the risk of developing hip OA is not clear. In contrast to the knee in which BMI is a definite risk factor for OA, obesity is not associated with radiographic hip OA and only moderately associated (OR around 2) with symptomatic hip OA.[42,43] It has therefore even been suggested that obesity can be regarded as a negligible risk factor for hip OA.[44]

There is consistent evidence that occupational factors lead to hip OA.[45] A systematic review reported ORs between 1.1 and 13.8 for heavy physical workload and development of hip OA, when compared with light physical work.[46] Typical examples of people with heavy workload are farmers, dockers and bricklayers.

Sporting activities confer a moderately increased risk for development of hip OA (OR around 2) and a clear dose-response relationship was found.[47] A higher level or frequency of sporting activities raised the OR substantially, and in this subgroup, hip OA also developed at a younger age.[48] A recent Swedish cohort study of over 2000 individuals compared former elite athletes with matched controls.[48] They found that the risk of hip OA was doubled and the risk of total hip replacement (THR) 2.5 times higher amongst the former elite athletes. The OR of both knee OA and total knee replacement (TKR) was 1.6 among the former athletes. Interestingly, when adjusted for soft tissue knee injury, the OR for knee OA and TKR became non significant whereas the OR for hip OA and THR became most pronounced among athletes that had participated in high impact sports (OR around 3-4 for soccer, handball, and ice hockey). This suggests that the association between high level sporting activities and knee OA is primarily explained by a higher prevalence of anterior cruciate ligament injury and meniscal tears, whereas local biomechanical factors probably explain the association between high level (and high impact) sporting activities and hip OA. A possible pathophysiological explanation might be that of a non-optimal shape of the hip.

Hip morphology as a risk factor of hip osteoarthritis

Besides the above-mentioned risk factors, in recent years hip morphology has gained increasing attention as being an important risk factor in the initiation of hip OA. The observation that an abnormal or incongruent shape of the hip might lead to OA was first reported at the beginning of the last century, but was only sporadically reported thereafter.[24,49,50] Some of the most striking morphological problems as seen in sequelae of childhood hip diseases like Perthes' disease,

slipped capital femoral epiphysis (SCFE), and congenital hip dysplasia pose a high risk for early development of hip OA.[51,52] OA as a result of these conditions is therefore also called 'secondary' OA in contrast to primary OA in which the cause is unknown. However, these childhood hip disease are responsible for less than 10% of all primary THR cases.[28] Half a century ago, it was suggested that many cases of 'primary' or 'idiopathic' hip OA are actually the result of previously unrecognized, more subtle shape deformities. This is illustrated by the fact that also mild non-clinical forms of acetabular dysplasia have been associated with development of OA.[53] Furthermore, a non-spherical femoral head was recognized as a potential risk factor for hip OA and first described in the United Kingdom as a 'tilt deformity' by Murray and later in the US as a 'pistol grip deformity' by Stulberg et al.[54] It was not until a decade ago that a non-spherical femoral head became of great interest when the pathomechanism by which it could lead to hip OA was hypothesized by Ganz and colleagues.[55]

Femoroacetabular impingement

A pathophysiological explanation on how subtle shape deformities of the hip might lead to OA was provided by the Swiss group from Ganz and colleagues. In 2001, they published a technique for a safe surgical dislocation of the hip, which allows an almost complete visualisation of the femoral head, and described the observation that acetabular chondrolabral damage often co-existed with a nonspherical shaped femoral head.[56] In 2003 they proposed the mechanism of femoroacetabular impingement (FAI), which can, in turn, cause motion-dependent soft-tissue damage.[55] FAI became of great interest in recent years and is the main topic of the current thesis.

FAI is a condition of a motion dependent abnormal contact between the femoral head-neck junction and the acetabulum, due to a bone shape abnormality on either the femoral or acetabular side. Based on the location of the shape abnormality, two types of FAI can be distinguished: cam impingement (femoral side) and pincer impingement (acetabular side) (figure 4).[57]

Pincer impingement is caused by over coverage of the acetabulum relative to the femoral head, known as a pincer deformity. The hypothesis proposed by Ganz et al. states that the femoral neck causes an abnormal linear contact against the pincer deformity during terminal motion of the hip. It has classically been described to occur primarily in middle-aged women, though no studies are available to confirm this. Initially, labral damage is the main characteristic as the cartilaginous labrum might be crushed between the acetabular bony rim and femoral bony neck. When there are repetitive episodes of pincer impingement,

chondral damage might gradually develop, subsequently leading to hip OA. It was therefore suggested that pincer impingement progresses relatively slow towards hip OA. This hypothesis is supported by intra-operative findings in symptomatic patients with a pincer deformity, where acetabular damage was found throughout the acetabulum in a small thin strip around the acetabulum.[57] However, only retrospective and cross-sectional studies exist which investigate the relationship between a pincer deformity and OA, and the results of these studies are conflicting.[59-66]

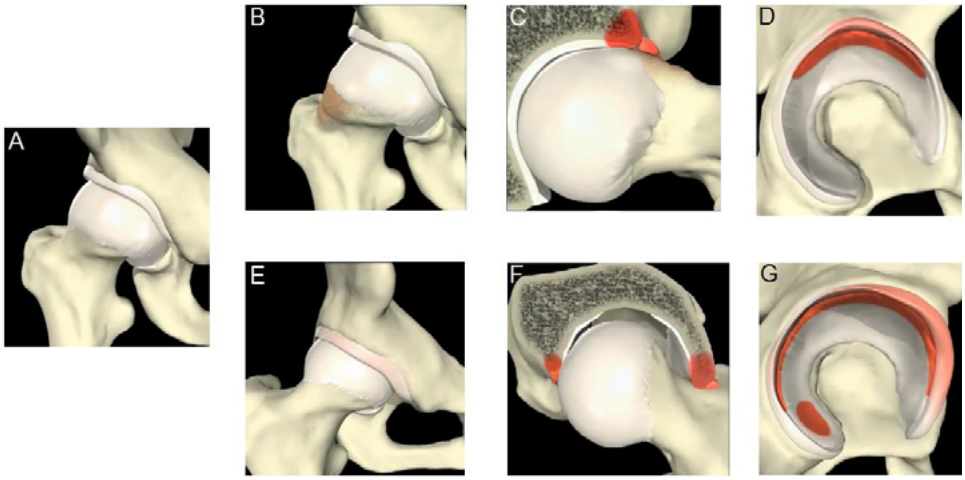


Figure 4. A schematic representation of the hypothesized mechanism of femoroacetabular impingement (FAI).[58] **a.** A spherical femoral head and acetabulum, which is congruent with the femoral head provides the hip a wide range of motion. **b, c, d.** A cam deformity (b) can cause cam impingement against the acetabular rim, especially during flexion and internal rotation of the hip (c) leading to a typical pattern of acetabular chondrolabral damage anterosuperiorely (d). **e, f, g.** A pincer deformity (e) can cause pincer impingement against the femoral neck, especially during terminal flexion of the hip (f) leading to a typical pattern of circumferential acetabular cartilage damage.

Cam impingement is caused by extra bone formation – a cam deformity – in the anterolateral head-neck junction.[67] This cam deformity may cause impingement against the acetabular rim, especially during flexion and internal rotation of the hip. This type of impingement has classically been described to occur in young athletic males, although this preference of subpopulation has neither been proven. The abnormal contact results in shear forces at the acetabular rim and is typically accompanied by labral tears and detachment of the acetabular cartilage from the subchondral bone. This biomechanically based hypothesis

of cam impingement has been supported by studies showing an association between a cam deformity and limited internal hip rotation as well as hip pain. Furthermore, the explanation of how soft-tissue damage and subsequent OA is caused by cam impingement is also supported by intra-operative findings in symptomatic patients with a cam deformity.[57] Acetabular cartilage delamination has been found in the anterosuperior quadrant of the joint, corresponding to the site where the cam deformity is forced into the acetabulum. These observations suggest a relationship between cam impingement and OA, but again here, epidemiological evidence is scarce and only cross-sectional and retrospective studies are available. These studies do generally show an association between a cam deformity and OA though the strength of association varies between studies. One of the major limitations of these studies is that no conclusions on causality can be drawn, as a non spherical femoral head can also be a results of the advanced OA process itself. When the pathophysiological mechanism between a cam deformity and pain, limited function, and hip OA holds true, a theoretically plausible explanation for development of hip OA is provided. The next interesting questions would then be how a cam deformity develops and whether it can be prevented, as the etiology of the cam deformity itself is still unknown.

Aims and scope of the current thesis

There are indications that the shape of the hip is associated with development of hip OA, though it is unknown which specific shape variants in non-OA hips will lead to the development of hip OA. Recent evidence on this topic points towards an important role of specific shape variants of the acetabulum (pincer deformity) and proximal femur (cam deformity) which may lead to hip OA via a motion dependent process known as FAI. A cam deformity might develop during skeletal maturation of the hip as a result of high impact sporting activities, which would be a promising preventative opportunity for the formation of a cam deformity and subsequent hip OA. In the first part of this thesis we investigate the role of hip shape on development of OA, starting with hip shape in general followed by more specific FAI shape variants. In the second part, we propose both clinical and radiographic definitions of FAI. Finally, in the third part we investigate at which age the formation of a cam deformity begins, how a cam deformity develops in time, and whether its development can be biomechanically explained.

The aims of this thesis are to:

1. investigate the role of hip morphology in the development of hip OA
2. define FAI and the presence of a cam deformity
3. investigate if and how a cam deformity develops during skeletal maturation.

The three parts of this thesis will cover the spectrum from the rise (skeletal development) to the fall (osteoarthritis) of the hip. In order to present the aims of this thesis in a sequence of general morphology to more specific FAI related morphology, the relationship between hip shape and OA will be presented first followed by the definition of FAI and how FAI morphology develops during skeletal maturation.

In **Part I** , we investigated associations between hip morphology and development of hip OA. In **Chapter 2**, we performed a review of the literature to write a state-of-the-art overview of OA, covering epidemiology, pathogenesis, diagnosis, treatment, and prevention. This seminar highlights the importance of hip morphology in the pathogenesis of hip OA. **Chapter 3** is focused on the association between general hip morphology and hip osteoarthritis. Hip morphology was quantified using Statistical Shape Modeling (SSM), which allows to study all shape variants in general within a population and their relationship with development of hip OA, without a predefined hypothesis that concerns a specific morphological parameter. Hip OA was defined by the clinical description as given in the ACR criteria. Several shape variants were found to be predictive of OA development, which forms the basis of the following chapters. In **Chapter 4** we tested how consistent the associated shape variants for development of hip OA are in various populations. To this end we have used one identical shape model for anteroposterior pelvic radiographs in the CHECK and Chingford cohorts. **Chapter 5** describes the relationship between morphological 'abnormalities' of the acetabular side of the hip and development of hip OA. Driven by the finding in chapter 3 that a shallow acetabulum is associated with hip OA, the relationship between acetabular dysplasia and hip OA was studied. Dysplasia was quantified based on an accepted measure in literature (Wiberg angle) on both anteroposterior and lateral radiographs of the hip. Using the same Wiberg angle, acetabular overcoverage, also known as a pincer deformity, was quantified and the subsequent risk for developing OA calculated. The availability of an additional lateral radiographic view of the hip in such a large cohort is unique in the world. **Chapter 6** continues to study more specific shape variants found to be associated with hip OA in chapter 3, now

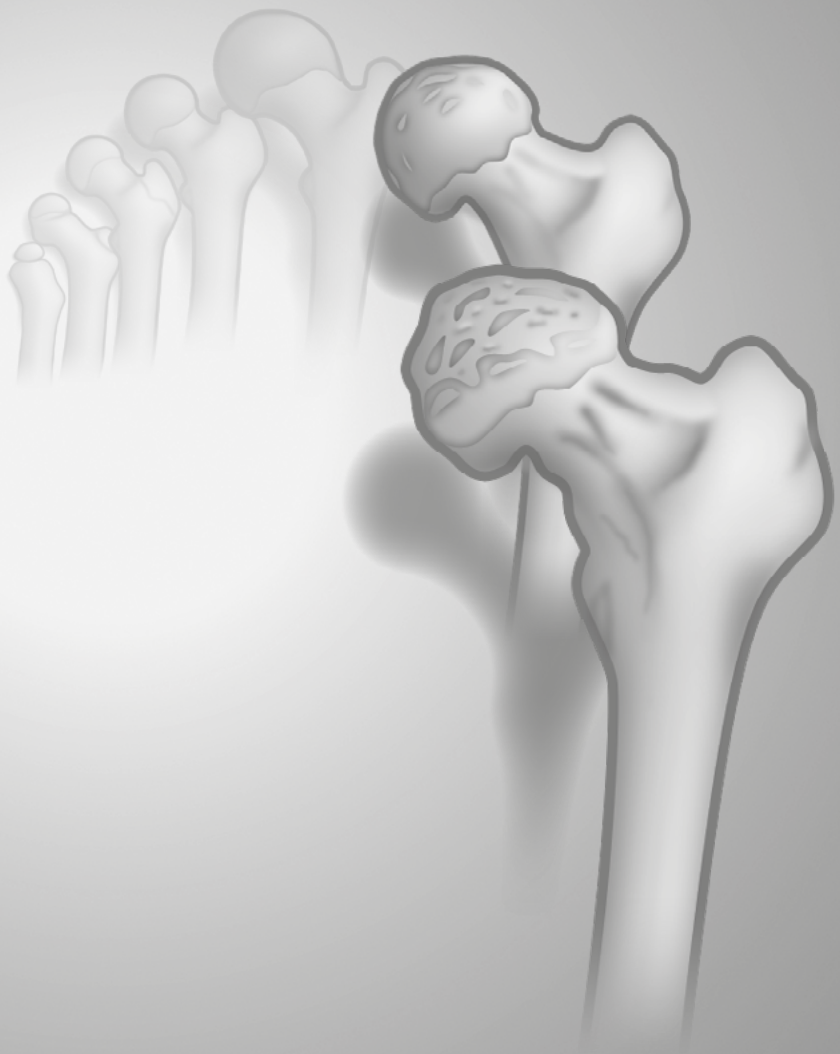
focusing on the femoral side of the hip joint. The association between a cam deformity and cam impingement with hip OA was studied: the first prospective cohort study on this topic in literature.

In **Part II**, we propose a clinical definition of FAI and a radiological definition of a cam deformity. As FAI is a relatively new entity in literature, a proper definition of this condition was formulated in cooperation with a group of investigators that resulted from the first combined American Academy of Orthopaedic Surgeons (AAOS) and Orthopaedic Research Society (ORS) FAI Research Symposium, Chicago 2012. In **Chapter 7**, this definition is provided as well as an overview of the prevalence of FAI and its relation with OA. In **Chapter 8** we propose how to quantify the radiographic presence of a cam deformity by the alpha angle. The alpha angle is a measure mostly used to quantify the extent to which the femoral head deviates from being spherical, though a broad range of threshold values has been used in literature.

In **Part III**, we focused on the development of a cam deformity during skeletal maturation. In **Chapter 9**, we present from which age a cam deformity becomes radiographically visible in young soccer players and we also compared the prevalence of a cam deformity with non athletic controls. In **chapter 10**, we present the prospective two years follow-up of this cohort of young soccer players and investigated if a cam deformity can evolve in time and whether any such evolution continues after skeletal maturation. Additionally, we assessed whether clinical or radiographic parameters were associated with, or predictive for the formation of a cam deformity. Based on the findings of chapter 8 and 9 that a cam deformity only develops during skeletal maturation as a result of a structural adaptation to high impact sporting activities, we investigated in **chapter 11** which specific movements trigger the formation of a cam deformity. Using a finite element (FE) model - a computer model that simulates mechanical load transfer through a (bone) structure - we simulated various loading patterns of the hip and assessed at which locations high mechanical loading and related bone formation occurs in the growing hip. In **chapter 12**, we provide a perspective opinionated article in which we summarize the current knowledge on the etiology of a cam deformity and hypothesize that a cam deformity can be prevented, which may eventually lower the incidence of hip OA. The results of above mentioned chapters are summarized in **Chapter 13**. **Chapter 14** presents the general synthesis, discusses the results of the work performed in the light of the current literature, and comes to the conclusions of this thesis. Potential future research within this field are also presented in this chapter.

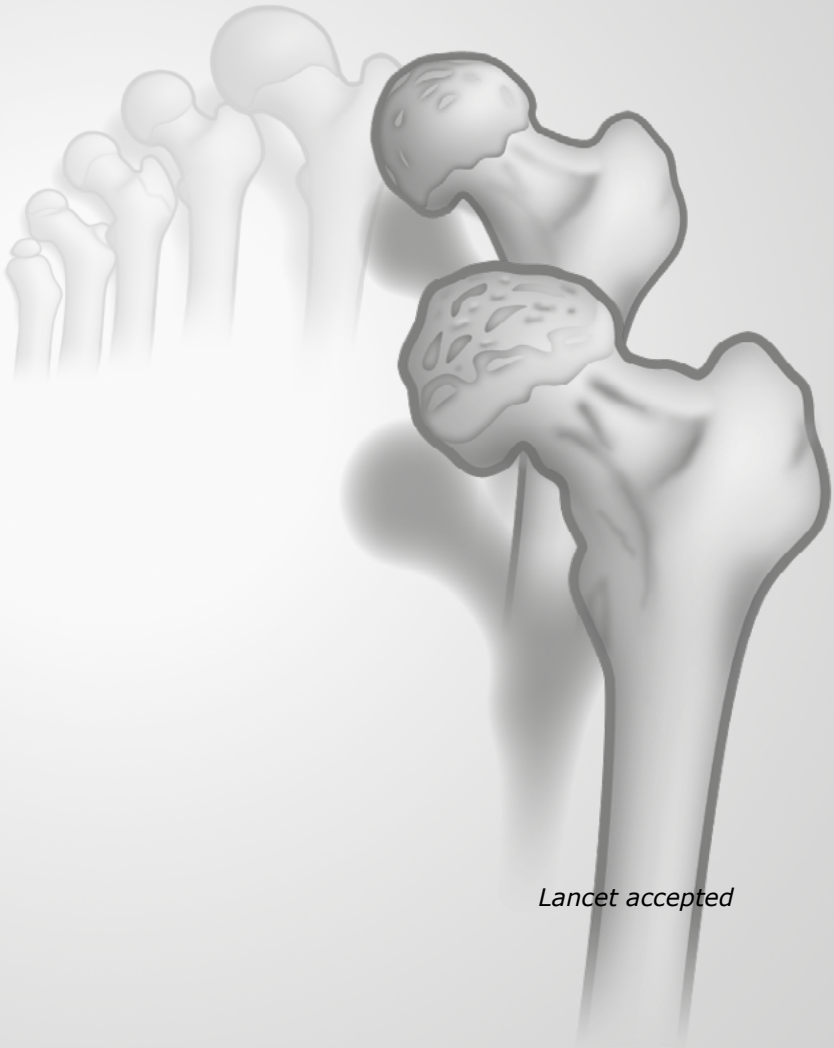
PART 1

Association between hip morphology and development of hip osteoarthritis



Chapter 2

Osteoarthritis: Is it possible to diagnose and treat early disease?



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ABSTRACT

Globally, osteoarthritis is a major source of pain, disability, and socioeconomic cost. The epidemiology of osteoarthritis is complex and multifactorial, with genetic, biological, and biomechanical components. Aetiological factors are also joint specific. Joint replacement is an effective treatment for symptomatic end-stage disease, however, there can be adverse functional outcomes and the lifespan of prostheses is limited. Consequently, there is an increasing shift in focus to disease prevention and the treatment of early osteoarthritis. This is a challenging task given conventional imaging techniques are only able to detect relatively advanced disease and there is a poor correlation between pain and structural degeneration. Nevertheless, recent advances in both imaging and biochemical markers offer potential as diagnostic tools and outcome measures for novel treatments. Joint-preserving interventions under development include lifestyle modification, pharmaceutical and surgical modalities. Some show significant potential, however, at present few demonstrate a proven ability to arrest or delay disease progression.

INTRODUCTION

Osteoarthritis is the most common joint disease world-wide affecting an estimated 10% of males and 18% of females over 60 years of age.[68] The resultant pain and loss of function can be debilitating and in developed countries represents a large socioeconomic burden, costing between 1% and 2.5% of gross domestic product.[69] Osteoarthritis treatment traditionally comprises pain management with joint replacement for end-stage disease.[70-72] This approach does not address the morbidity associated with early disease or the limitations of arthroplasty surgery, which include the possibility of adverse outcomes and the finite lifespan of prostheses. An improved understanding of osteoarthritis pathogenesis combined with superior assays of disease activity is facilitating a shift in focus to the prevention and treatment of early osteoarthritis. Furthermore, identification of different disease phenotypes may allow personalised patient care. This seminar provides an update of recent developments in the prevention and treatment of early disease.

EPIDEMIOLOGY

The identification of risk factors is central to understanding disease aetiology and selecting targets for osteoarthritis prevention and treatment. Longitudinal studies of large population cohorts have provided important insights and there is an increasing appreciation that osteoarthritis develops through the action of hostile biomechanics upon a susceptible joint. Biological pathways within a joint are mechanosensitive,[73] and biomechanical factors may be modifiable and offer a potential means of intervention.

Joint biomechanics are dictated by anatomical and functional factors. Anatomical factors include joint morphology. Hip dysplasia, where there is reduced acetabular coverage of the femoral head, is a long established risk factor for osteoarthritis.[74] Femoroacetabular impingement, where there is abnormal contact between the proximal femur and acetabulum can confer up to a 10-fold increased risk of developing end-stage hip osteoarthritis within five years (figure 1 and 2). However, depending on the characteristics of the cohort and definition of abnormal morphology, the positive predictive value ranges from 6-25%, whereas the negative predictive value ranges from 98-99%.[75] Similarly, tibial and femoral bone morphology can predict the development of knee osteoarthritis.[76] Limb alignment also appears to be critical and recent studies provide further evidence that varus and valgus knee alignment increases the risk of osteoarthritis development and progression in the more loaded region of

the joint.[77,78] Furthermore, a leg length inequality of one centimetre or greater is associated with almost twice the prevalence of knee osteoarthritis in the shorter limb.[79] With respect to functional factors, poor quadriceps function may increase the risk of knee osteoarthritis progression.[80] Sporting activity is a recognised but poorly-defined risk factor for hip osteoarthritis,[47] and it may be that high activity levels during adolescence promotes the development of femoroacetabular impingement morphology.[81]

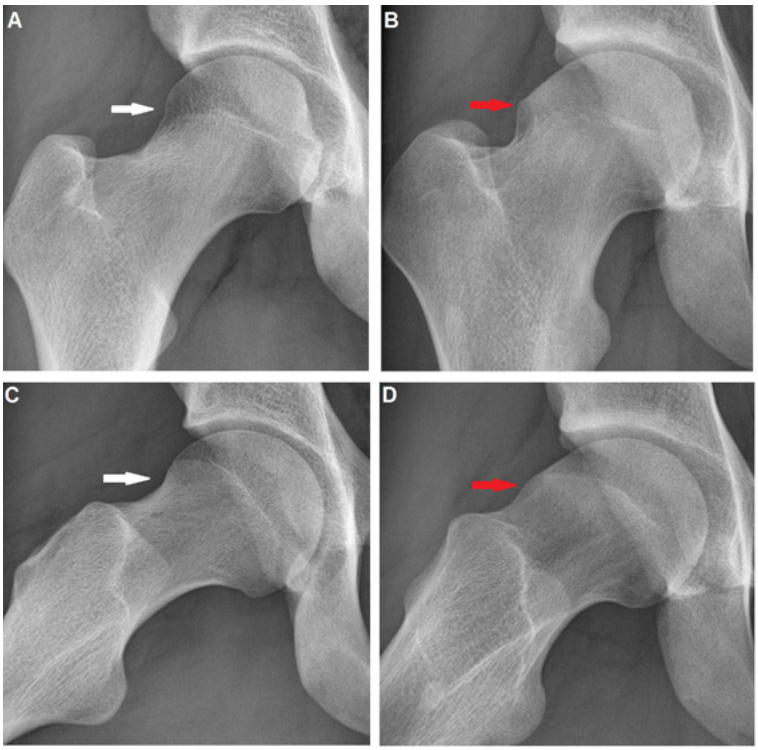


Figure 1: Anteroposterior and Lateral Radiographs of a normal hip (A and C) and a hip with cam lesion femoroacetabular impingement morphology (B and D). In a normal hip, the concavity of the femoral head-neck junction allows an extensive range of hip movement without impingement of the femur against the acetabular rim. In cam lesion femoroactebular impingement, the loss of this concavity at the anterior and superior head-neck junction results in impaction of the femur against the acetabular rim when the hip moves into flexion and internal rotation. This results in damage to the labrum, and may progress to involve the acetabular cartilage with development of osteoarthritis. Surgery to excise bone and reproduce a head-neck concavity is proposed as a means of preventing the development and progression of hip osteoarthritis.

Despite these strong associations, most individuals with abnormal joint biomechanics do not develop osteoarthritis.[75] Susceptibility is, in part, determined

by systemic factors. Age remains the strongest risk factor for osteoarthritis[82] and this may reflect a reduction in regenerative capacity and accumulation of risk factors. Osteoarthritis is also more common in females and although the role of oestrogens has been extensively investigated, the mechanism remains unclear. The material properties of bone may infer some susceptibility. Higher systemic bone mineral density appears to increase the risk of incident osteoarthritis but not disease progression.[83]

Injury may cause bone or cartilage damage that makes the joint more susceptible to further insult, and damage to ligaments or meniscus may adversely affect joint biomechanics. Knee injury confers a greater than four-fold increased risk of developing knee osteoarthritis.[84] Obesity increases the load on weight-bearing joints, but may also increase joint susceptibility through the action of inflammatory adipokines.[85] It confers a three-fold increased risk of developing knee osteoarthritis[86] and accelerates disease progression.[87] It remains a mystery why obesity confers a far smaller risk of developing hip osteoarthritis.[88] Given the increasing prevalence of obesity, this risk factor is responsible for a significant disease burden.

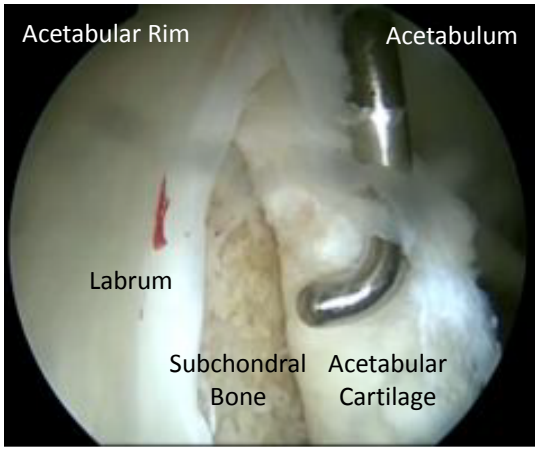


Figure 2: Arthroscopic appearance of the hip of a patient with cam lesion femoroacetabular impingement. The aspherical femoral head enters the acetabulum on hip flexion and internal rotation leading to delamination of the acetabular cartilage from the underlying subchondral bone and the development of osteoarthritis.

The strong genetic basis for osteoarthritis has been recognised for many years through family-based studies. Genome-wide association studies, such as that performed by the Arthritis Research UK Osteoarthritis Genetics (arcOGEN) Consortium,[89] have now identified 11 loci associated with osteoarthritis. The

effect sizes are small (odds ratio 1.11 – 1.21),[89] but consistent with those for other similar complex traits. It is unlikely that genomics alone will reliably identify individuals who will develop disease, but may reveal new biological insights into disease pathogenesis for individual joints. Single-nucleotide polymorphisms have been associated with a number of known risk factors including hip shape, body mass index and bone mineral density.[90]

PATHOGENESIS

Osteoarthritis was once viewed as a disease of purely mechanical cartilage degradation, however, it is now appreciated to be a complex condition involving the whole joint in which the activation of specific matrix proteases plays a pivotal role (figure 3). The possibility that diverse risk factors give rise to osteoarthritis through a common end pathway offers exciting therapeutic potential. It is likely that cartilage, subchondral bone and synovium all play key roles in disease pathogenesis and there may also be an association with systemic inflammation.

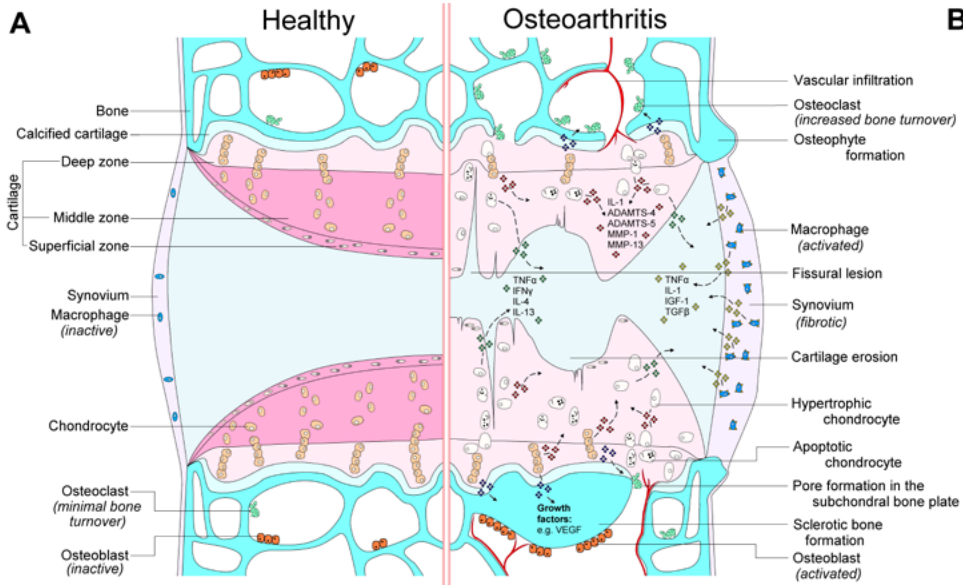


Figure 3: Signalling pathways and structural changes in the development of osteoarthritis.

Cartilage

The main structural protein of cartilage is type II collagen. This provides a meshwork that receives stabilisation from other collagen types and non-

collagenous proteins, such as cartilage oligomeric matrix protein (COMP), and provides cartilage with tensile strength. Aggrecan and other proteoglycans are embedded within this framework, which draw water into the cartilage, providing compressive resistance. Cartilage architecture and biochemical composition are strictly regulated by chondrocytes in response to changes in their chemical and mechanical environment.[91] On activation, they produce a number of inflammatory response proteins such as cytokines, including IL-1β, IL-6 and TNF-α, and matrix degrading enzymes including the metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTSes). Some of these appear to have important pathogenic effects, such as the collagenases (MMP-1, 3 and 13) and aggrecan-degrading-degrading enzymes (ADAMTS-4 and 5). Others may have beneficial matrix remodelling roles in healthy cartilage.[73] Proteases, including ADAMTS-5, are upregulated in a highly mechanosensitive fashion in mice following surgical joint destabilisation, and are downregulated on joint immobilisation.[92] This supports a potential role for addressing hostile joint biomechanics as a preventative strategy.

The innate immune system is activated in osteoarthritis. Chondrocytes express multiple Toll-Like Receptors (TLRs)[93] activated by damage-associated molecular patterns (DAMPs). In osteoarthritis, DAMPS comprise extracellular matrix molecules that include the glycosaminoglycan hyaluronan.[94] Calcium pyrophosphate and sodium urate crystals also bind chondrocyte TLR receptors and may therefore play a role in the aetiology of osteoarthritis.[95] The finding that the expression and activation of complement is abnormally high in human osteoarthritic joints[96] is intriguing. COMP is a potent activator of the alternative complement pathway[97] while proteoglycans such as fibromodulin target the classical pathway.[98] Chondrocytes also express receptors that bind advanced glycation end-products (AGEs)[99] which accumulate in aging tissues. This results in a phenotypic shift to catabolism[100] and may help explain the increasing prevalence of osteoarthritis with age.

Rather than initiating osteoarthritis, responses to extracellular matrix components may simply reflect amplification of established cartilage degradation. Chondrocytes may first be activated by inflammatory signals originating from other joint structures such as synovium or subchondral bone. This warrants elucidation given therapeutic interventions are more likely to be effective when acting further upstream.

Subchondral Bone

Subchondral cortical bone forms an interface between the calcified cartilage below the 'tidemark' and the underlying trabecular bone. Marked changes are seen in the structure and composition of both the cortical plate and trabecular bone in osteoarthritis.[101,102] In fact, aspects of endochondral ossification are reinitiated in osteoarthritis and the tidemark advances with associated vascular penetration. This is accompanied by the formation of osteophytes and subchondral cysts. Advances in imaging now allow bone marrow lesions to be identified on MRI that correlate with a number of histological changes including microfractures at different stages of healing.[103] These lesions localise to areas with the most severe cartilage damage. Whether these pre-date changes in cartilage or occur as a consequence of cartilage damage is unclear. Some studies suggest that changes in subchondral bone and osteophyte formation precede cartilage degeneration,[104,105] but such studies are always biased by the sensitivity of the detection methodology.[106] More recent work demonstrates that like chondrocytes, osteoblasts respond to mechanical stimulation with the expression of inflammatory cytokines and degradative enzymes.[107] These may act directly on cartilage, or changes in the mechanical properties of subchondral bone may have deleterious effects on overlying cartilage. Conversely, subchondral bone remodelling may result from increased loading through loss of cartilage integrity. Being highly innervated, subchondral bone probably contributes to the generation of pain in disease.

Synovium

Synovitis is a frequent feature of osteoarthritis, even in early disease. In established osteoarthritis there is proliferation of resident synoviocytes and tissue hypertrophy, with increased vascularity.[108] Synoviocytes synthesise lubricants such as hyaluronic acid[109] and lubricin.[110] These contribute to optimal joint function but display reduced lubricating capacity in some patients with osteoarthritis.[109,111] Like chondrocytes and osteoblasts, synoviocytes also release inflammatory mediators and degradative enzymes. Activation is likely secondary to inflammatory mediators and cartilage matrix molecules released during an initial insult to the joint, after which synovial tissue appears to drive progressive joint degeneration in a positive feedback cycle.[108] Synovitis predicts the development and progression of symptoms (odds ratio 9.2, 95% CI 3.2 to 26.3)[112] and possibly cartilage loss (odds ratio 2.7, 95% CI 1.4 – 5.1),[113] although the relationship with structural change is less consistent. It is often difficult to compare study findings due to different patient populations and varied methods

of diagnosing synovitis, however, synovitis may represent a rational target for intervention.

Systemic Inflammation

Osteoarthritis is primarily seen as a local disease confined to the joint and studies investigating the relationship with systemic markers of inflammation have yielded conflicting results. A recent systematic review suggests that serum CRP is associated with symptoms rather than radiographic osteoarthritis[114] and pain may represent a marker of systemic inflammation.[115] It is not understood why obesity remains a risk factor for osteoarthritis in non-weight-bearing joints.[116] Adipokines released from adipose tissue have been proposed as mediators of this effect, however, their role is speculative and not borne out in clinical studies.[117]

DIAGNOSIS

The clinical diagnosis of osteoarthritis requires that patients have symptoms, and the prevention or alleviation of these is the goal of any intervention. Indeed, it is symptoms that prompt patients to seek medical attention outside of screening or research programmes. The difficulty using symptoms to define the presence of osteoarthritis is that they may develop only once there is advanced and likely irreversible disease. This may follow a period of earlier subclinical structural change. With disease modification in mind, symptoms therefore have limited value diagnosing early osteoarthritis when intervention is more likely to be successful. Further limitations are that symptoms fluctuate significantly over time, and are influenced by concurrent pathology and pain pathway modulation.[118]

In this review, we shall define structural osteoarthritis to be present when there is evidence of cartilage loss in the absence of inflammatory or crystal arthropathy, irrespective of whether a patient has symptoms. This definition aims to describe osteoarthritis at an earlier stage. Although cartilage changes might be preceded by changes within synovium and bone, cartilage degeneration appears to be the common endpoint of all osteoarthritis phenotypes. As our understanding of disease pathogenesis improves, measures relating to other joints structures are likely to gain validity. The greatest limitation of addressing structural osteoarthritis is our inability to predict whether it will progress to clinical osteoarthritis.

Interventions employed when patients remain relatively asymptomatic must carry a low risk profile alongside proven efficacy to be ethically acceptable.

Given the poor correlation between symptoms and structure,[119] there is no guarantee that treating structural osteoarthritis will provide clinical benefit. Therefore, studies looking to target the earliest osteoarthritis by modifying structural disease must also take symptoms into account. These are measured quantitatively using validated patient reported outcome measures (PROMs). Structural osteoarthritis is assayed using a rapidly expanding array of biomarkers (figure 4). This expansion has been, driven by advancing technology, an appreciation that osteoarthritis is a condition of the whole joint, and a need to diagnose the earliest disease to facilitate patient selection into clinical trials and to measure treatment efficacy.

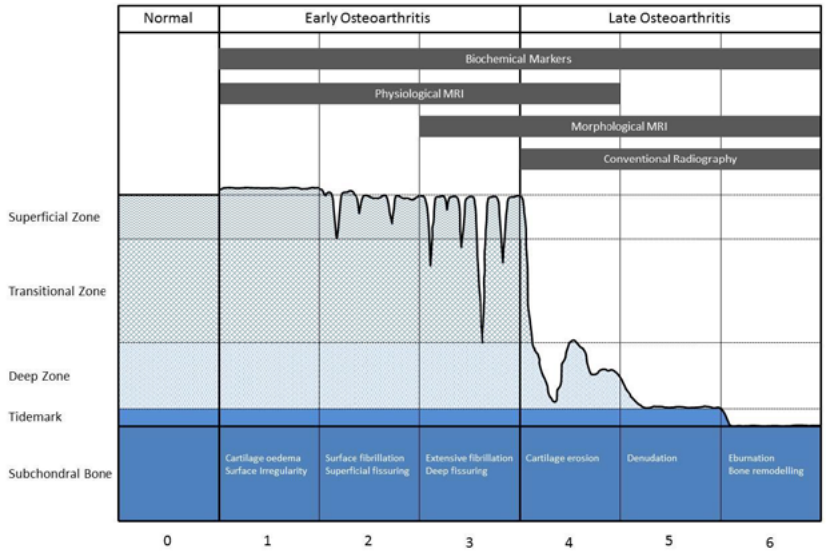


Figure 4: Biochemical markers and imaging modalities offer the ability to evaluate osteoarthritis at different stages of disease, as assessed using the Osteoarthritis Research Society International (OARSI) histological grade. Modified and reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery.[120]

IMAGING

Radiography

Osteoarthritis is traditionally diagnosed using plain film radiography where features include narrowing of the joint space width (JSW), osteophyte formation, and the development of subchondral sclerosis and cysts. Scoring systems include those proposed by Kellgren and Lawrence[33] and Osteoarthritis Research Society International (OARSI)],[121] however, JSW alone is more sensitive and reliable.[122,123]

JSW remains the only structural end-point accepted by the European Medicines Agency and Food and Drug Administration to prove efficacy of disease-modifying osteoarthritis drugs (DMOADs),[124] yet this measure has many limitations.[125] JSW lacks sensitivity and is unable to detect localised cartilage damage[125,126] making it unsuitable for the detection of early osteoarthritis. It also lacks specificity, and in addition to cartilage thickness, JSW in the knee is dependent on the structural integrity of the meniscus and whether it is extruded from the joint space.[127] Standardisation of image acquisition is essential given JSW is strongly influenced by joint positioning.[128] The usually slow progression of osteoarthritis and the limited responsiveness to change means that when JSW is used as an outcome measure, large cohorts are required and ideally patient follow-up should exceed two years,[129] however, this must be balanced against the risk of reduced participant retention. Despite these limitations, radiography is relatively inexpensive and readily available and continues to play a role in both clinical and research settings.

Magnetic Resonance Imaging (MRI)

MRI confers many advantages over radiography and allows the assessment of joint structures in three dimensions and at high resolution.[120] As a result, it is more sensitive at detecting early structural changes[126] and MRI measurements significantly outperform those of radiographs.[130] OARSI now recommend MRI for the assessment of cartilage morphology.[131] Short-term changes in cartilage morphology can reliably predict disease progression in a cohort, but not in an individual.[132] Morphological measurements also fail to take account of functional adaptation[133] or cartilage oedema observed during the very earliest stages of disease.[134]

Physiological MRI permits detection of the earliest osteoarthritis by evaluating the biochemical composition of tissues.[120] Protocols employed to assay glycosaminoglycan content include delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) (figure 5), chemical exchange saturation transfer (CEST), and sodium scanning. dGEMRIC values correlate well with the histological grade of osteoarthritis[135] and statistically significant changes can be detected within 10 weeks of intervention[136] substantiating physiological MRI as a potential outcome measure. However clinical applicability of dGEMRIC is limited by long scanning times and the requirement for intravenous delivery of nephrotoxic contrast agent.[137] CEST and sodium scanning show exciting potential and do not require contrast, but are only possible with ultra-high field strength magnet strengths and dedicated hardware.

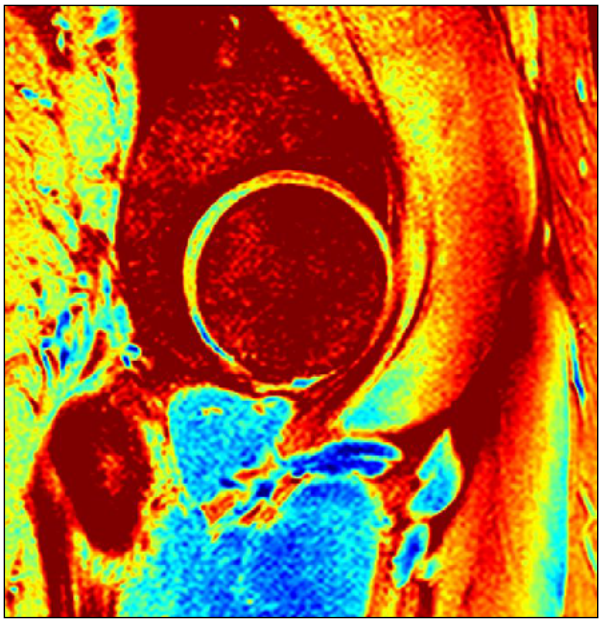


Figure 5: Sagittal dGEMRIC of the hip of a patient with cam lesion femoroacetabular impingement. Although there was no evidence of degenerative change on radiographs, the white arrow highlights a region of glycosaminoglycan depletion within the acetabular cartilage which may indicate early osteoarthritis at the site of impingement.

Other non-invasive MRI protocols that may be of greater clinical relevance and can be used on conventional MRI scanners are under development. They primarily measure collagen orientation and the behaviour of water content, and include T2 mapping, T2* mapping, T1Rho and diffusion techniques. T2 mapping is increasingly used in clinical studies[138] does not require contrast, has acceptable scanning times, and values correlate with histological degeneration.[139] There is evidence that T2 mapping improves sensitivity in the detection of early osteoarthritis cartilage lesions compared with morphological MRI.[140] Some studies also suggest baseline values may predict longitudinal structural degeneration (odds ratios 1.58 – 2.62 for different cartilage regions),[141] however, T2 mapping requires further validation.[138] T2* mapping, T1Rho, diffusion-weighted and diffusion-tensor MRI have been less widely utilised to date, but potential advantages over T2 mapping[142-144] may mean that they play a greater role in the future.

The appreciation that osteoarthritis is a disease of the whole joint has driven imaging of all joint structures. The predictive value of cartilage measurement for disease progression is increased when non-cartilaginous articular pathology

such as bone marrow lesions, meniscal status and synovitis are also taken into account.[145] Scoring systems have been developed for knee, hip and hand osteoarthritis (table 1), which show good reliability and responsiveness in clinical trials.[146]

Table 1: Validated semi-quantitative MRI scoring systems for knee, hip and hand osteoarthritis that assess morphological features of osteoarthritis.[146]

Knee	Whole-Organ Magnetic Resonance Imaging Score (WORMS)
	Knee Osteoarthritis Scoring System (KOSS)
	Boston-Leeds Osteoarthritis Knee Score (BLOKS)
	MRI Osteoarthritis Knee Score (MOAKS)
Hip	Hip Osteoarthritis MRI Scoring System (HOAMS)
Hand	Oslo Hand Osteoarthritis MRI Score (OHOA-MRI)

Ultrasound and Computerised Tomography (CT)

Ultrasound shows increasing potential in the evaluation of osteoarthritis through its ability to assess synovium, particularly in hand and knee osteoarthritis.[147] Computerised tomography (CT) is not widely used to diagnose early osteoarthritis, however, low-dose and dual-energy CT scanners are broadening the musculoskeletal application of this modality.[148]

Biochemical Markers

Biochemical markers can be effector molecules, such a cytokines and enzymes, or extracellular matrix constituents, such as precursors or degradation products of collagen and proteoglycan. Their concentrations reflect tissue metabolism and can be measured in blood, urine, or serum. The BIPED classification stratifies biomarkers into 'burden of disease', 'investigative', 'prognostic', 'efficacy of intervention', or 'diagnostic'.[149] A plethora of biochemical markers have been proposed, but at present none are sufficiently well validated for use in clinical practice. CTX-II (C-terminal telopeptide of collagen type II) and COMP are markers of tissue degradation and remain the most widely investigated and best performing biochemical markers across all BIPED categories.[149]

'Diagnostic' biomarkers aim to identify patients with pathology. Urinary CTX-II and serum COMP are both raised in patients with osteoarthritis compared with healthy controls.[150,151] Sensitivity and specificity are poor for all biochemical markers, and inferior to imaging measures. In knee osteoarthritis diagnosed using the Kellgren-Lawrence Score, the area under the curve (AUC) has been reported as 0.70 (95% CI 0.57 to 0.81) for urinary CTX-II, 0.73 (95% CI 0.58 to 0.86)

for radiographic JSW, and 0.82 (95% CI 0.72 to 0.91) for MRI measurements. Combining CTX-II with MRI measurements gives an AUC of 0.84 (95% CI 0.77 to 0.92).[152] When measured systemically, biochemical markers may originate from any site, hence their value is limited unless disease is confined to the specific joint under investigation, which in practice is rarely the case. Synovial fluid assays overcome this problem, but are limited by acceptability to patients and the potential absence of an effusion. Recent developments suggest that post-translational protein modification may be joint-specific and this warrants further investigation.[153]

The potential value of 'prognostic' biochemical markers is large and may allow the identification of patients most likely to benefit from intervention. Urinary CTX-II and serum COMP perform reasonably well in predicting the incidence and progression of radiographic hip and knee osteoarthritis in longitudinal cohort studies.[154-156] The predictive value of urinary CTX-II (odds ratio 3.2) is greater than JSW (odds ratio 1.4), but lower than MRI measurements (odds ratio 4.8). Combining CTX-II with MRI measurements has the greatest prognostic value for structural knee osteoarthritis progression (odds ratio 5.8).[152] Biochemical markers have only shown a limited ability to predict symptoms.[156] The interpretation of assay results is limited by an incomplete understanding of the biological activity they signify and whether it is relevant to clinical osteoarthritis.[157] Further validation is essential given biochemical markers are already used extensively as outcome measures in clinical studies to assess 'efficacy of intervention'.[158]

The number of 'investigative' biomarkers has increased rapidly with expansion of the field referred to as 'omics' where biological molecules are characterised and quantified. Interesting findings include a proteomic study of cartilage that identified biomarkers that appear to be joint-specific.[159]

The future of biochemical markers is likely to comprise broad-spectrum panels of assays that allow the assessment of osteoarthritis with disease phenotyping to determine the appropriate therapy. Performance may be enhanced if combined with imaging and genotyping. At present, clinical application remains a fairly distant prospect and many challenges remain. Sampling technique is critical and biochemical marker concentrations are influenced by factors including diet, physical activity, and systemic metabolism.

TREATMENT

An improved understanding of disease pathogenesis and advances in the field of biomarkers makes it increasingly possible to identify patients at greatest

risk of disease, diagnose the earliest osteoarthritis, and measure treatment efficacy within a short timeframe. Consequently, a plethora of novel therapeutic strategies have been proposed and tested in clinical trials. Thus far none have been approved by regulatory bodies, which require concurrent structural modification and symptom improvement.[131]

Lifestyle Modification

Many aetiological factors of osteoarthritis are amenable to lifestyle changes. Weight loss in obese patients reduces the risk of developing symptomatic osteoarthritis[160] and improves symptoms once there is evidence of disease.[161] Radiographic structure modification has not been demonstrated, although benefits are evident with dGEMRIC[162] and several biochemical markers.[163] The effects of exercise require further elucidation, but activities focusing on improved muscle strength and aerobic capacity improve symptoms (effect size >0.8)[164] and confer cardiovascular and all-cause mortality benefits.

Surgery

i) Correction of Aetiological Factors

Some aetiological factors may be amenable to surgery. The progression of osteoarthritis secondary to hip dysplasia is successfully delayed by reorientating the acetabulum. In addition to sustained symptomatic improvement, hip survival rates exceed 80% at 10 years.[165] More recently, arthroscopic hip surgery to recontour the proximal femur (figure 6) and prevent femoroacetabular impingement has shown symptomatic benefit beyond five years and may modify the long-term risk of developing osteoarthritis,[166] however, evidence to date is confined to small cohort studies. Knee alignment predicts the development of osteoarthritis in the compartment of greatest loading, hence unloading this compartment offers therapeutic potential. In an interesting study, temporary surgical joint distraction produced symptomatic and structural improvement in end-stage knee osteoarthritis and suggests reparative potential remains in osteoarthritis.[167] Periarticular osteotomies to correct the mechanical axis of the knee show promise, and prospective studies demonstrate symptomatic improvement extending beyond 10 years.[168] However, in general, evidence for the efficacy of these interventions is limited. Randomised controlled trials with long-term follow-up are required to determine whether these joint-preserving operations prevent clinical and structural osteoarthritis progression.[169]

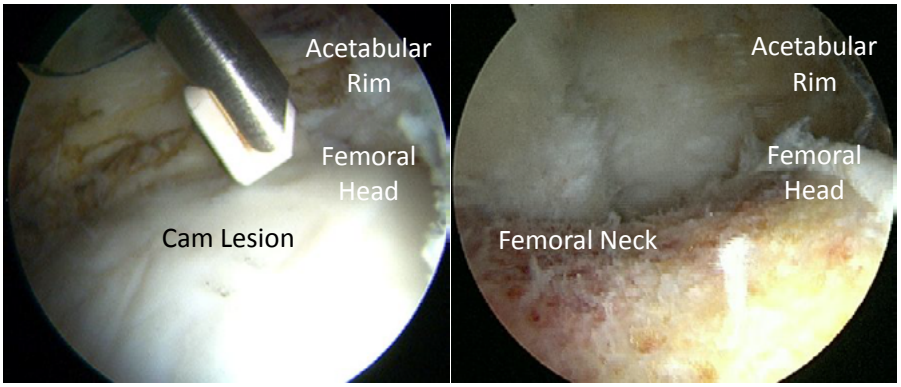


Figure 6: Arthroscopic appearance of the femoral head-neck junction in a patient with cam lesion femoroacetabular impingement before and after surgical correction of the deformity. The pre-operative image (a) shows the cam lesion (illustrated with a red arrow on figure 1) adjacent to the acetabular rim, above which a radiofrequency ablation device is held. The post-operative image (b) shows the head-neck junction after resection of the cam lesion using a burr to recreate the normal concavity of a head-neck junction (illustrated with a white arrow on figure 4). The aim of recreating this concavity is to prevent impaction against the acetabular rim that is thought to be a major cause of hip osteoarthritis. It is therefore hoped that this procedure might prevent or delay the development of osteoarthritis.

ii) Cartilage Repair and Regeneration Techniques

Research continues into a variety of surgical techniques which aim to repair localised cartilage lesions.[170] These can be divided into techniques that transplant autologous cartilage and those that seek to stimulate cartilage regeneration.

Mosaicplasty and osteochondral grafting describe procedures where autologous plugs of cartilage and underlying subchondral bone are transplanted from healthy non-loadbearing regions of a joint to areas of damage. They are technically demanding and rely on the availability of healthy cartilage.

Microfracture seeks to stimulate generation of new cartilage at sites of focal full-thickness defects. It involves traumatising subchondral bone using a pick to release chondroprogenitor cells. Although these differentiate into mechanically inferior fibrocartilage rather than hyaline cartilage,[170] the technique is inexpensive and easy to perform, and is the most widely used regenerative approach.

Limitations in the above procedures have driven the field of tissue engineering and the development of more advanced regenerative techniques. Autologous chondrocyte implantation (ACI) has been in development since the 1980s where chondrocytes are arthroscopically harvested and cultured, before implantation

into the cartilage defect several weeks later. The technique has undergone several iterations, but to date it remains unclear whether ACI confers improved clinical outcomes over more simple techniques such as microfracture.[171] Latest developments comprise alternative sources of cell, including mesenchymal and embryonic stem cells, utilisation of growth factors, and the implantation of cells into three-dimensional scaffolds or matrices that support growth, differentiation, and maintenance of a chondrogenic phenotype (figure 7).[172]

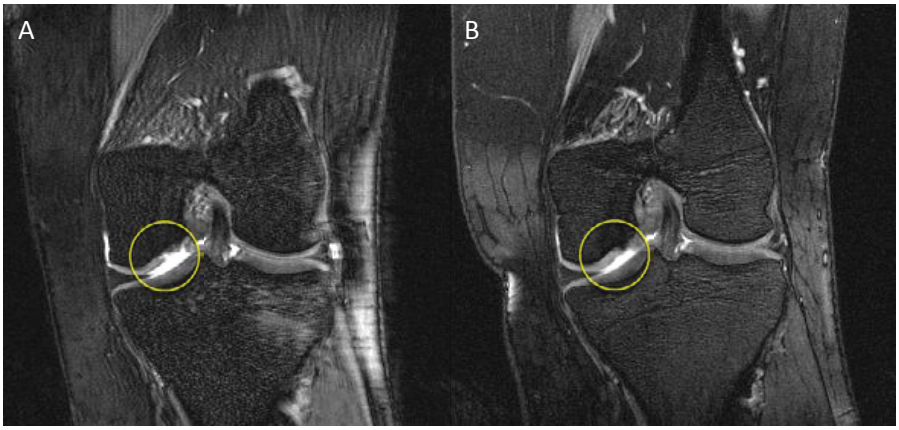


Figure 7: Osteochondral lesion before and after matrix-induced autologous chondrocyte implantation (MACI). A) Isolated osteochondral lesion in the lateral aspect of the medial femoral condyle. B) Structural changes 14 months post reconstruction with MACI graft showing partial infill of lesion with cartilage repair tissue. There was an associated improvement in clinical symptoms.

There is little evidence that the above techniques modify the development of osteoarthritis. Cartilage repair is unlikely to be successful if the joint environment remains biologically or mechanically hostile, but may provide an important adjunct to the correction of aetiological factors.

Pharmaceuticals

Many patients who develop osteoarthritis do not have identifiable risk factors amenable to intervention. Furthermore, it is not known whether the correction of risk factors is sufficient to reverse a catabolic tissue phenotype. Pharmaceutical agents already play a key role in symptom control, particularly paracetamol and non-steroidal anti-inflammatories,[172,173] but an increasing number of drugs are also under investigation as DMOADs. None to date have been approved by regulatory bodies.

i) Supplementation

Chondroitin and glucosamine have demonstrated anti-inflammatory and anti-catabolic properties in vitro[174] and their ability to improve symptoms or delay structural progression of osteoarthritis has been extensively investigated in clinical trials. Results have been conflicting, purportedly due to different study designs and patient populations, investigator bias, or the use of different drug formulations. Studies tend to report more positive findings when using glucosamine sulphate rather than glucosamine hydrochloride, however, assuming glucosamine is the active ingredient, there is no available rationale to explain this effect.[175] Overall the literature does not indicate that chondroitin or glucosamine confer a clinically relevant benefit[176] and they are not recommended in guidelines published by international bodies.[176-178] However, it is noteworthy that both have safety profiles comparable with placebo.

Hyaluronic acid is a glycosaminoglycan found in synovial fluid that acts as a lubricant, but concentrations decline in osteoarthritis.[109] Hyaluronic acids have been widely used in osteoarthritis as viscosupplementation administered via intra-articular injections, however, debate over efficacy and safety continues. A recent meta-analysis concludes that there is no clinically relevant benefit with respect to pain or function,[178] neither is there is convincing evidence of structural benefit. Lubricin is a glycoprotein that acts synergistically with hyaluronic acid to provide lubrication,[179] but exhibits reduced lubricating capacity in a subset of patients with osteoarthritis.[111] Supplementation restores normal joint lubrication and may be chondroprotective,[111,180] offering potential therapeutic benefit.

ii) Enzyme Inhibition

An alternative strategy is to target degradative enzymes. Doxycycline is a potent MMP inhibitor and randomised controlled trials have demonstrated reduced JSW narrowing compared with placebo, but little improvement in pain or function.[181] This small potential benefit appears to be outweighed by adverse events.[181] Other broad MMP inhibitors have not demonstrated structural or symptomatic benefit and frequently result in musculoskeletal toxicity.[182] Upstream intracellular signalling molecules, such as inducible nitric oxide synthase (iNOS), have also been targeted with disappointing results.[183]

iii) Bone Metabolism:

Bisphosphonates have been used in an attempt to reverse subchondral bone changes seen in osteoarthritis through their inhibition of osteoclast activity. Randomised controlled trials have investigated the effect of risedronate in knee

osteoarthritis where a reduction in urinary CTX-II was demonstrated compared with placebo, but without a reduction in JSW narrowing over two years.[184,185] Furthermore, the symptomatic improvement seen in one cohort[184] was not reproduced in a larger multi-national study.[185] More recently, a single dose of zoledronic acid was shown to improve pain and the size of bone marrow lesions at six months.[186] Strontium ranelate, in addition to osteoclast inhibition and osteoblast stimulation, enhances chondrocyte matrix production in vitro.[187] A randomised controlled trial showed that strontium ranelate therapy for three years reduces radiographic joint space narrowing over placebo, accompanied by a modest improvement in symptoms and a reduction in urinary CTX-II.[188] Further studies of strontium ranelate may be indicated, however, side effect profiles are likely to limit its clinical utility in osteoarthritis.

iv) Anti-Inflammatory Therapy:

A number of proposed therapeutic agents target inflammation. Intra-articular steroid injections are widely used to improve symptoms, but do not modify structure.[189] Methotrexate is also under investigation in patients with significant synovitis.[190] It is hoped biologic agents targeting components of the inflammatory cascade might transform the treatment of osteoarthritis in the same manner as for rheumatoid osteoarthritis,[191] but unfortunately results to date are disappointing.

Anakinra, a recombinant IL-1 receptor antagonist, improved symptoms in patients with knee osteoarthritis compared with placebo, but the effect was not sustained beyond four days post intra-articular injection.[192] When AMG 108, a monoclonal antibody against the IL-1 receptor, was administered subcutaneously or intravenously in patients with knee osteoarthritis there was no clinical benefit and the death of a patient was attributed to neutropenia secondary to this agent.[193]

Anti-TNF therapy has also been trialled in osteoarthritis.[194] Adalimumab, a monoclonal antibody to TNF-α, has not demonstrated a therapeutic effect in hand osteoarthritis,[195] however, promising results have been reported in inflammatory knee osteoarthritis.[196]

Given the adverse effects of biologic therapies, systemic treatment is perhaps best justified when disease affects several joints, such as in hand osteoarthritis, whereas single joint osteoarthritis of the knee or hip may be best approached with an intra-articular injection of slow release medication.[197]

Table 2: Summary table of treatment strategies that have demonstrated potential disease-modifying properties.

Class of Intervention	Intervention	Outcome	Additional Comments
Lifestyle Modification	Weight Loss	Studies have demonstrated reduction in pain.	Disease modification not examined. Largely examined in early disease or as primary prevention strategy.
	Exercise (Strength and Aerobic Capacity)		
Surgery (i) Modification of joint biomechanics	Joint distraction (6 -12 weeks)	Significant and sustained reduction in pain and improvement in joint function. Regeneration of cartilage	Early studies show perhaps the best evidence (MRI) to date that cartilage can regenerate in an osteoarthritic joint
	Debridement of FAI lesions	Improvement in pain with possible disease modification	Small cohort studies only
	Osteotomy	Established technique for reduction of pain.	Recent studies have shown cartilage regeneration.
(ii) Stimulating regeneration	Cell based therapies e.g. autologous chondrocyte implantation	Studies have shown fairly consistent improvement in pain and defect filling.	Generally not well controlled. Patients are highly selected (usually focal cartilage defects only). Very expensive procedure with biological concerns e.g. of infection and malignancy.
	Microfracture of subchondral bone	Modest improvements in pain and defect filling in old studies.	Often used as a comparator in cell based repair studies. Generally thought to produce fibro- rather than hyaline cartilage.
Pharmaceutical Targeting cartilage degradation	Glucosamine sulphate Chondroitin sulphate	Modest reduction in pain compared to placebo. Inconsistent improvement in structure.	Meta analyses have failed to demonstrate an overall improvement over placebo (high in nutraceutical studies).
	Doxycycline	Some structure modification but no change in pain	Limited by side effects
	FGF18 (intra articular)	Reduction in pain and evidence for structure modification	Primary endpoint not reached but secondary endpoints were.
Targeting bone remodelling	Strontium Ranelate	Modest structure modification and symptom improvement	Likely to be limited by side effects.

v) Stem Cell Therapy

Stem cell therapy may have an application in osteoarthritis and multipotent mesenchymal stem cells are found in healthy and diseased cartilage. Kartogenin is a molecule that promotes differentiation of chondrocytes. In animal models, kartogenin reverses established osteoarthritis by promoting repair of cartilage lesions.[198] Whether this or similar molecules will translate to the clinical arena remains to be seen.

DISCUSSION

An improved understanding of osteoarthritis aetiology and pathogenesis has yielded an increasing array of potential targets for the prevention of disease development and progression. Furthermore, advances in the fields of imaging and biochemical markers have facilitated the diagnosis of earlier disease, and may provide sensitive assays for treatment efficacy. But despite these advances, effective preventative strategies have not been readily forthcoming.

Of all the interventions investigated to date, lifestyle modifications show the greatest benefit. Promoting the maintenance of an optimum weight and participation in regular exercise are cost-effective and also reduce all-cause mortality. Results are eagerly awaited from ongoing trials investigating the effects of surgically correcting adverse joint biomechanics.[169] Interestingly, the disease-modifying effect of doxycycline was negated in knees that were varus aligned.[199] Interventions to modify risk factors may on their own prove inadequate if joint tissues have already shifted to a catabolic phenotype. Combining surgical intervention with pharmaceutical agents may represent an optimum strategy.

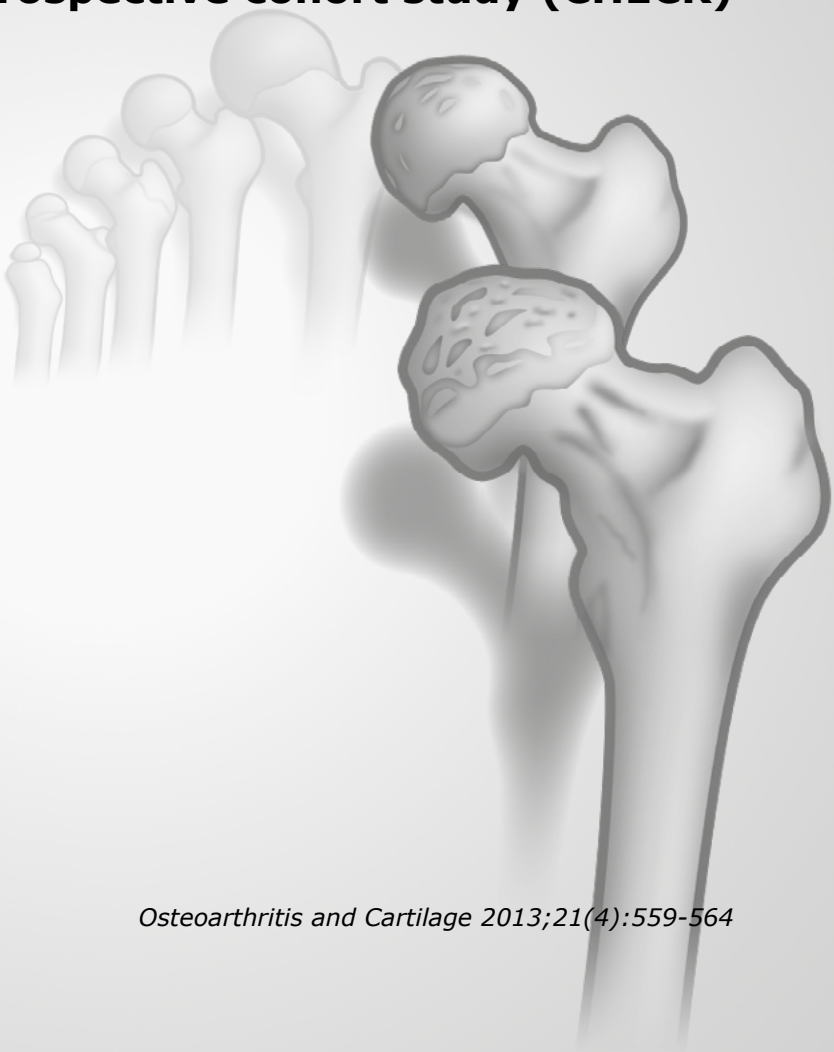
Key challenges are to define and standardise outcome measures, and to understand why there is a poor correlation between structural degradation and symptoms.[119] A better understanding of peripheral and central pain pathways, aided by tools such as functional MRI, may help to unravel this enigma.[200] The limitations of targeting pain alone are highlighted by trials targeting nerve growth factor (NGF). Tanezumab and fulranumab are monoclonal antibodies to NGF, which in randomised controlled trials showed impressive improvements in pain and function compared with placebo.[191] However, a small minority of patients developed rapidly progressive osteoarthritis[200] raising the concern that increased joint loading permitted by improved analgesia worsens disease.

Osteoarthritis has several disease phenotypes[201] and identifying and specifically targeting these is likely to prove critical for the successful development of novel therapies. Clinical trials investigating the efficacy of an intervention that targets

a particular aspect of disease pathogenesis, such as synovitis, are less likely to yield positive results in large unselected populations. Accurately defined disease phenotypes enable a personalised approach to treatment. Improved accuracy of predictive models may also permit selection of minimally symptomatic individuals for early intervention. In the meantime, symptom management in early and moderate disease and arthroplasty surgery for advanced disease remain the mainstay of treatment.

Chapter 3

Total hip replacement but not clinical osteoarthritis can be predicted by the shape of the hip: a prospective cohort study (CHECK)



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ABSTRACT

Objective To investigate the association between baseline hip shape and both clinical hip osteoarthritis (OA) and total hip replacement (THR) at 5-year follow-up.

Design Individuals from the Cohort Hip and Cohort Knee (CHECK) study, with early symptomatic OA, having standardized anteroposterior pelvic radiographs at baseline and 5-year follow-up (n=723) were included. Hip shape on the radiographs was assessed using statistical shape modelling (SSM). Hips fulfilling the American College of Rheumatology (ACR) criteria at follow-up were classified as clinical OA. The association between each mode of shape variation and both outcome measures was calculated by Generalized Estimating Equations (GEE).

Results The included individuals comprised 575 females and 148 males (mean age 55.9 ± 5.2 years). At baseline, 8% fulfilled the ACR criteria, 76% had no radiographic hip OA [Kellgren & Lawrence (K&L) = 0] and 24% had doubtful OA (K&L = 1). At follow-up, 147 hips (10.4%) fulfilled the ACR criteria and 35 hips (2.5%) had received THR. Five shape variants (modes) at baseline associated significantly with THR within 5 years. When combined in one GEE model, these shape variants resulted in a predictive power indicated by an area under the curve of 0.81. No shape variants associated with the presence of clinical OA at follow-up.

Conclusion The shape of the hip as quantified by an SSM has a good predictive value for THR, whereas variation in shape cannot predict clinical OA. Minor shape variants may be used as a radiographic biomarker to predict the future risk of THR.

INTRODUCTION

Osteoarthritis (OA) is often present in multiple joints, but hip OA frequently occurs in isolation, suggesting that local factors are important in its development.[202] There is growing evidence that morphology of the hip joint is one such a risk factor. Morphological abnormalities of the hip probably predispose to OA by an altered biomechanical behavior of the hip.[55] This seems plausible for hips with an evident non-optimal shape as seen in (congenital) hip dysplasia, Perthes disease, and slipped capital femoral epiphysis.[51,53] Recently however, the more prevalent cam-type deformities have also been recognized as a causative factor for end-stage OA, with a positive predictive value as high as 52%.[203] Thus, the morphology of the hip appears promising for prediction of hip OA before the actual onset of OA.[101,204]

Obvious shape abnormalities are usually quantified by predefined measures such as the centre-edge angle for dysplasia and the alpha angle for cam-type deformity. However, subtle morphological variation might also play an important role, but these are difficult to capture by predefined measures.

By using statistical shape modeling (SSM), a sophisticated technique which identifies independent shape variants, it is possible to quantitatively describe the total morphology of the hip.[205,206] An SSM describes all variation in shape that exists in the study population, and is therefore a method which can identify shapes 'at risk' for OA without any assumptions.

Hip OA is usually defined by clinical symptoms such as pain and decreased function, or radiographically by structural alterations as seen on radiographs. However, a poor association between clinical and radiographic definitions for hip OA has been reported.[207] Previously, it has been shown in cross-sectional and case-control studies that subtle shape variants of the proximal femur associate with radiographic OA.[63,101,206,208,209] However, it is unknown whether hip shape associates with OA as defined by clinical criteria. Possibly, 'at risk' shapes are different for both definitions, as it has been shown that those shape variants that associated with radiographic hip OA were different from those that associated with pain.[209]

We investigated whether minor shape variants of hips without definite radiographic signs of OA at baseline, can be predictive in people with first onset hip or knee pain for the development of hip OA after 5 years, as classified either by the American College of Rheumatology (ACR) criteria for clinical OA or by total hip replacement (THR).

METHODS

Study cohort

All individuals were participants of the Cohort Hip and Cohort Knee (CHECK) cohort. CHECK is a nationwide prospective cohort study of 1002 individuals with early symptomatic OA of knee or hip. On entry, all participants had pain or stiffness of knee or hip and were aged 45-65 years; they had not yet consulted their general practitioner (GP) for these symptoms, or the first consultation was within 6 months before entry. Participants with a pathological condition other than early OA that could explain the symptoms were not included in the cohort (for hip: trauma, rheumatoid arthritis, congenital dysplasia, Perthes disease, subluxation, osteochondritis dissecans, fracture, septic arthritis, Kellgren & Lawrence (K&L) grade 4 or total hip replacement, previous hip surgery, and individuals having only symptoms of bursitis or tendinitis).[210]

Radiographs, serum samples, and clinical examination were obtained from eleven (general and university) hospitals at baseline and at five year follow-up. Individuals were recruited either by GPs who were invited to refer eligible persons to one of those centres and by advertisements in local newspapers. The 723 of the 1002 individuals who had anteroposterior (AP) pelvic radiographs of sufficient quality obtained both at baseline and at five year follow-up were included [the mean (sd) follow-up was 5.06 (0.17) years. Of the initial 1002 individuals, 137 subjects did not have pelvic radiographs at both baseline and follow-up, of the remaining individuals, 124 subjects had AP hip instead of AP pelvic radiographs at baseline, and 18 subjects did not have radiographs of sufficient quality at baseline to add them to the SSM. Excluded individuals did not differ on any baseline characteristic from the included individuals. The study was approved by the medical ethics committees of all participating centres, and written informed consent was obtained from all participants.

Radiographs and SSM

Weight bearing AP pelvic radiographs were obtained according to a standardized protocol. Feet were positioned such that the medial side of the distal part of the first phalanx touched and a wedge was used to assure 15° internal rotation. The tube to film distance was 120 cm, and the beam was centered on the superior part of the pubic symphysis.

From these radiographs at baseline the shape of the proximal femur and pelvis was outlined using SSM software (ASM tool kit, Manchester University, Manchester, UK).[205] The shape model was created by a set of 75 landmark

points that were positioned along the surface of the bone in the image by three investigators, who were unaware of any clinical or radiographic outcomes. Each point is always positioned on the same anatomical landmark (e.g., most lateral point of greater trochanter, most distal point of ischial bone etc.) of the outline, to allow comparison between the shapes (Figure 1).

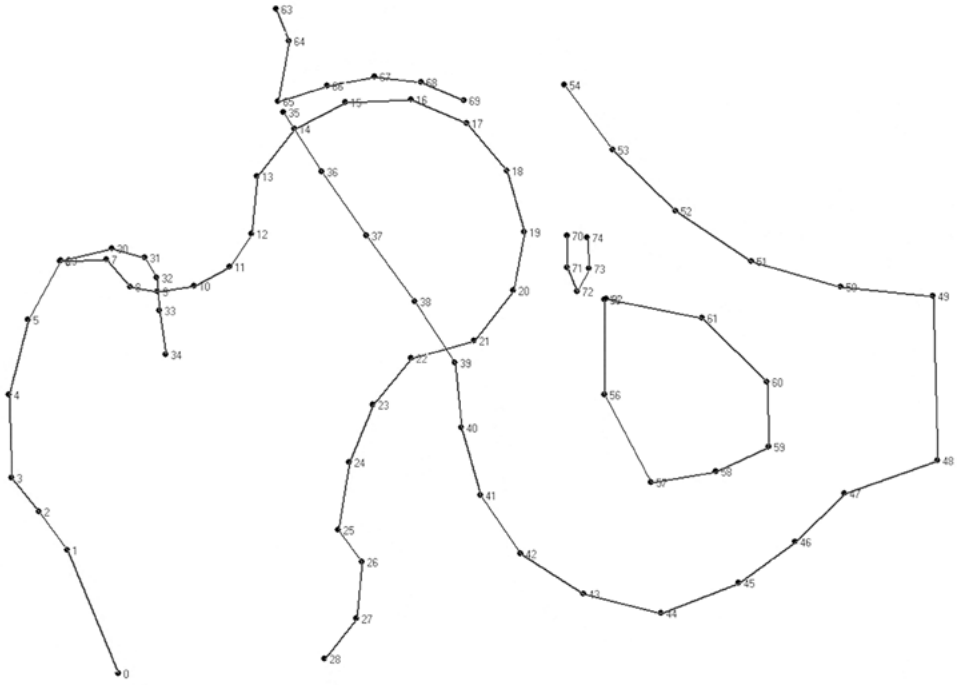


Figure 1. The statistical shape model which consisted of 75 points.

Principal component analysis was used to transform the set of points into an SSM, which consists of a number of modes that together describe the total variation in shape in the study population. Shape variants which are correlated are captured in one mode such that each single mode represents independent shape variants. Each mode is quantitatively described as the mean, which corresponds with 0, and the positive or negative deviation from the mean as expressed in the number of SDs.[205]

To examine the inter-observer reliability of the modes obtained, the point set was positioned by each investigator in 24 randomly selected radiographs. Intra-observer reliability was tested in 10 randomly selected radiographs with an interval of 2 months.

We retained enough modes to explain 90% of the variation in hip morphology of the included individuals. Further, all radiographs were scored for radiographic OA according to K&L classification at baseline and 5-year follow up, independent of the positioning of the SSM point set.[211]

Outcome measures

The primary outcome measures were meeting the clinical ACR criteria for hip OA at 5-year follow-up, and hips having received a THR within 5 years.[32] In short, a prerequisite for meeting the ACR criteria is hip pain, either together with internal hip rotation <15° and an erythrocyte sedimentation rate ≤45 mm/h, or together with hip internal rotation ≥15°, and pain on internal rotation, and morning stiffness of the hip ≤60 minutes, and age >50 years. Secondary outcome measures were two items of the ACR criteria separately; amount of hip pain and decreased internal hip rotation (<15°) at 5-year follow-up. The severity of pain in the previous 48 h was assessed per hip using the Visual Analog Scale (VAS). This scale runs from 0 to 10, where 0 equals no pain and 10 very intense pain. Internal hip rotation was measured according to a standardized protocol in sitting position by a goniometer in 90° of flexion, which previously showed satisfactory reliability[212].

Statistical analysis

Reliability of positioning the point set was assessed using intra-class correlation coefficient (ICC). Univariable differences in baseline characteristics between hips that developed OA and normal hips were evaluated by the Mann-Whitney test for continuous variables, by chi-square test for sex, and by Generalized Estimating Equations (GEE) for K&L score.

To analyze whether a mode was predictive for the various outcome measures, regression models using GEE were constructed. All modes were corrected for age, gender, and BMI. In order to account for the many modes (24) tested, an effect was considered significant at a P-value smaller than 0.002 (p=0.05 / 24 modes). From these predictive models, odds ratios (OR) were calculated for each mode to describe the strength for each independent predictive mode. The predictive power of the GEE model including all significant modes was tested by the area under the ROC curve (AUC). All statistical analyses were performed in SPSS version 17.0.

RESULTS

Participants

Of the 723 individuals (1411 hips), 575 were women and 148 were men with a mean age of 55.9 years (± 5.2 years). At baseline, 8% of the included hips fulfilled the ACR criteria whereas 92% did not meet the clinical criteria of hip OA. Radiographically, 76% of the included individuals had no signs of radiographic hip OA (K&L = 0) and 24% had doubtful radiographic hip OA (K&L = 1). Additional baseline characteristics are presented in Table 1, stratified for the presence or absence of THR and clinical OA at follow-up

Outcome measures

A total of 147 (10.4%) hips fulfilled the ACR criteria for clinical OA at 5-year follow-up and 35 hips (2.48%) underwent THR within 5-year follow-up. At follow-up, 23 hips (1.63%) had internal hip rotation less than 15°.

Predictive modes

A total of 24 modes were extracted from the SSM, which together explained 90% of the total variance in shape. We could not identify any mode at baseline, which was predictive for OA at 5-year follow-up ($p<0.05$) as defined by the ACR criteria. When corrected for age, sex, and BMI, five modes (modes 7, 11, 12, 15, and 22) independent of each other associated significantly with THR within 5 years. The p-values, OR, and ICC scores of these modes are summarized in table 2. Although a mode does not represent only one single aspect of variation in shape, but is a combination of various correlated aspects of variation in shape, we described the most obvious patterns in shape variation that the predictive modes represent (Figure 2). Modes with a p-value less than 0.05, but greater than 0.002 are also presented in table 2 and illustrated in figure 3. Combining the five significant modes in the GEE model for calculating the area under the ROC curve, resulted in a predictive value of 0.81.

Although no modes were found to be significantly predictive for the ACR criteria at follow-up, we found modes, which could predict severity of pain and limited internal rotation at follow-up when analyzed separately. For pain, mode 9 was nearly significantly associated with the VAS scores (p-value of 0.007). Higher values of mode 7 were almost significantly predictive for internal rotation <15° (p-value of 0.003). The association between all modes and the secondary outcome measures is given in table 3.

Table 1. Baseline characteristics of the participants stratified by the absence or presence of clinical OA and THR at 5-year follow-up.

	Total (1411 hips)	Absence of THR (1376 hips)	Presence of THR (35 hips)	P-value Absence vs presence of THR	Absence of clinical OA (1264 hips)	Presence of clinical OA (147 hips)	p-value Absence vs presence of clinical OA
Age in years: mean (SD)	55.9 (5.20)	55.9 (5.2)	57.7 (4.1)	0.052	56.0 (5.2)	55.1 (5.4)	0.041
Women, No. (%)	1120 (79)	1097 (80)	23 (66)	0.030	1001 (79)	119 (81)	0.67
BMI, kg/m²: mean (SD)	26.1 (4.1)	26.1 (4.2)	25.7 (4.1)	0.56	26.1 (4.2)	26.3 (3.6)	0.16
Height in cm: mean (SD)	169.9 (8.2)	169.8 (8.2)	170.2 (8.5)	0.88	169.8 (8.2)	170.4 (7.9)	0.42
Weight in kg: mean (SD)	75.3 (13.6)	75.3 (13.7)	74.6 (13.3)	0.99	75.1 (13.7)	76.6 (13.4)	0.19
K&L grade				<0.001			0.006
Grade 0, No (%)	1058 (76)	1048 (77)	10 (29)		964 (77)	94 (65)	
Grade 1, No (%)	331 (24)	306 (23)	25 (71)		280 (23)	51 (35)	

Abbreviations: BMI; body mass index, K&L; Kellgren and Lawrence.

Table 2. The strength of the relation, reliability, and reproducibility of the modes which significantly associated with THR within 5 years.

	Relation with THR at follow-up				Relation with Clinical OA				Reliability and reproducibility (ICC)	
Modes	**OR (95% CI)**	**P-value**	**aOR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**aOR (95% CI)**	**P-value**	**Range intra observer**	**Inter observer**
Mode 2	**1.78 (1.27-2.47)**	**0.001**	1.73 (1.19-2.51)	0.004	1.00 (0.84-1.19)	0.99	1.03 (0.85-1.25)	0.77	0.96-0.98	0.97
Mode 4	**1.98 (1.32-2.98)**	**0.001**	2.01 (1.27-3.16)	0.003	1.06 (0.87-1.30)	0.55	1.08 (0.88-1.31)	0.47	0.74-0.96	0.81
Mode 5	0.69 (0.50-0.97)	0.033	0.64 (0.45-0.91)	0.012	1.10 (0.91-1.32)	0.33	1.08 (0.90-1.30)	0.41	0.88-0.93	0.82
Mode 6	0.75 (0.54-1.03)	0.072	0.69 (0.49-0.97)	0.034	1.16 (0.96-1.41)	0.12	1.17 (0.97-1.41)	0.11	0.61-0.87	0.43
Mode 7	**0.52 (0.37-0.74)**	**<0.001**	**0.54 (0.38-0.78)**	**0.001**	0.95 (0.78-1.15)	0.60	0.94 (0.77-1.14)	0.52	**0.62-0.87**	**0.76**
Mode 11	**1.71 (1.23-2.36)**	**0.001**	**1.78 (1.28-2.47)**	**0.001**	0.97 (0.83-1.13)	0.68	0.95 (0.82-1.11)	0.54	**0.74-0.92**	**0.76**
Mode 12	**2.01 (1.42-2.85)**	**<0.001**	**2.10 (1.46-3.04)**	**<0.001**	1.03 (0.87-1.22)	0.72	1.05 (0.88-1.25)	0.59	**0.63-0.91**	**0.84**
Mode 13	0.58 (0.40-0.84)	0.004	0.58 (0.40-0.84)	0.003	0.99 (0.84-1.17)	0.91	1.00 (0.84-1.18)	0.98	0.01-0.87	0.83
Mode 15	**1.95 (1.41-2.71)**	**<0.001**	**1.90 (1.39-2.59)**	**<0.001**	1.09 (0.91-1.30)	0.35	1.11 (0.93-1.33)	0.26	**0.59-0.93**	**0.86**
Mode 16	0.58 (0.39-0.85)	0.005	0.63 (0.44-0.91)	0.014	0.99 (0.82-1.20)	0.92	0.97 (0.80-1.18)	0.77	0.42-0.93	0.68
Mode 22	**0.56 (0.40-0.77)**	**<0.001**	**0.59 (0.42-0.81)**	**0.001**	0.88 (0.74-1.04)	0.13	0.88 (0.74-1.05)	0.14	**0.67-0.92**	**0.84**

aOR were adjusted for age, sex, and body mass index at baseline. The presented OR represent every increase in one SD.
(a)OR; (adjusted) odds ratio, CI; Confidence interval.

Table 3. Strength of the relation between all modes and secondary outcome measures pain and decreased internal rotation

	Relation with Pain (VAS) at follow-up				Relation with decreased internal rotation (<15°) at follow-up			
Modes	**OR (95% CI)**	**P-value**	**aOR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**aOR (95% CI)**	**P-value**
Mode 0	0.85 (0.74-0.98)	0.02	0.90 (0.78-1.04)	0.15	1.87 (1.19-2.94)	0.007	1.68 (0.97-2.92)	0.06
Mode 1	1.12 (0.96-1.32)	0.16	1.12 (0.95-1.32)	0.19	1.26 (0.59-2.71)	0.55	1.71 (0.80-3.68)	0.17
Mode 2	0.99 (0.87-1.13)	0.90	1.09 (0.95-1.25)	0.24	0.87 (0.46-1.64)	0.67	0.72 (0.40-1.29)	0.27
Mode 3	1.17 (1.01-1.35)	0.04	1.08 (0.93-1.27)	0.32	0.87 (0.52-1.48)	0.61	1.03 (0.51-2.05)	0.94
Mode 4	0.96 (0.83-1.12)	0.62	0.99 (0.86-1.15)	0.90	1.00 (0.66-1.50)	0.98	1.00 (0.65-1.54)	0.99
Mode 5	1.02 (0.89-1.16)	0.80	1.05 (0.93-1.20)	0.44	1.20 (0.80-1.80)	0.39	1.24 (0.81-1.90)	0.33
Mode 6	1.03 (0.91-1.17)	0.63	1.06 (0.94-1.21)	0.35	0.77 (0.45-1.32)	0.34	0.79 (0.44-1.45)	0.79
Mode 7	0.92 (0.80-1.07)	0.30	0.96 (0.82-1.11)	0.55	1.92 (1.26-2.93)	0.002	**1.77 (1.22-2.56)**	**0.003**
Mode 8	0.97 (0.86-1.11)	0.97	0.97 (0.85-1.11)	0.65	0.66 (0.39-1.10)	0.11	0.77 (0.48-1.26)	0.30
Mode 9	1.17 (1.03-1.33)	0.01	**1.19 (1.05-1.36)**	**0.007**	1.03 (0.69-1.53)	0.90	1.00 (0.64-1.55)	0.98
Mode 10	0.86 (0.76-0.97)	0.01	**0.87 (0.76-0.98)**	**0.022**	1.76 (1.00-3.08)	0.05	1.62 (0.94-2.82)	0.08
Mode 11	0.90 (0.79-1.02)	0.10	0.89 (0.78-1.01)	0.07	0.98 (0.65-1.46)	0.91	1.11 (0.79-1.57)	0.54
Mode 12	0.93 (0.81-1.07)	0..32	0.92 (0.80-1.06)	0.23	1.63 (1.12-2.39)	0.011	**1.59 (1.05-2.41)**	**0.028**
Mode 13	1.02 (0.89-1.17)	0.75	1.04 (0.91-1.19)	0.56	0.96 (0.62-1.51)	0.87	0.93 (0.61-1.42)	0.75
Mode 14	0.96 (0.84-1.09)	0.49	0.98 (0.86-1.12)	0.73	1.08 (0.75-1.58)	0.67	1.11 (0.75-1.65)	0.60
Mode 15	1.06 (0.92-1.22)	0.43	1.03 (0.89-1.18)	0.74	1.47 (1.08-2.00)	0.015	**1.46 (1.09-1.94)**	**0.011**
Mode 16	1.08 (0.94-1.23)	0.30	1.07 (0.93-1.22)	0.35	1.10 (0.71-1.70)	0.68	0.59 (0.71-1.82)	0.59
Mode 17	0.94 (0.83-1.08)	0.38	0.95 (0.83-1.08)	0.41	0.61 (0.40-0.92)	0.019	**0.57 (0.36-0.88)**	**0.012**
Mode 18	1.03 (0.90-1.18)	0.65	1.01 (0.88-1.16)	0.89	1.29 (0.76-2.17)	0.35	1.25 (0.73-2.14)	0.42
Mode 19	0.98 (0.86-1.11)	0.73	0.99 (0.87-1.12)	0.85	1.04 (0.61-1.78)	0.88	1.17 (0.69-2.00)	0.56
Mode 20	1.00 (0.88-1.15)	0.97	1.03 (0.90-1.17)	0.71	0.78 (0.53-1.14)	0.20	0.78 (0.52-1.16)	0.22
Mode 21	0.96 (0.84-1.09)	0.53	0.98 (0.86-1.11)	0.72	1.40 (0.96-2.04)	0.08	1.46 (0.99-2.16)	0.06
Mode 22	1.04 (0.92-1.18)	0.51	1.02 (0.90-1.15)	0.80	0.99 (0.67-1.46)	0.96	0.99 (0.65-1.51)	0.98
Mode 23	0.93 (0.83-1.05)	0.24	0.92 (0.82-1.04)	0.17	0.66 (0.43-1.02)	0.06	0.64 (0.41-1.00)	0.05

aOR were adjusted for age, sex, and body mass index at baseline. The presented OR represent every increase in one SD.
(a)OR; (adjusted) odds ratio, CI; Confidence interval, VAS; Visual Analog Scale, as a continuous measure (0-10).

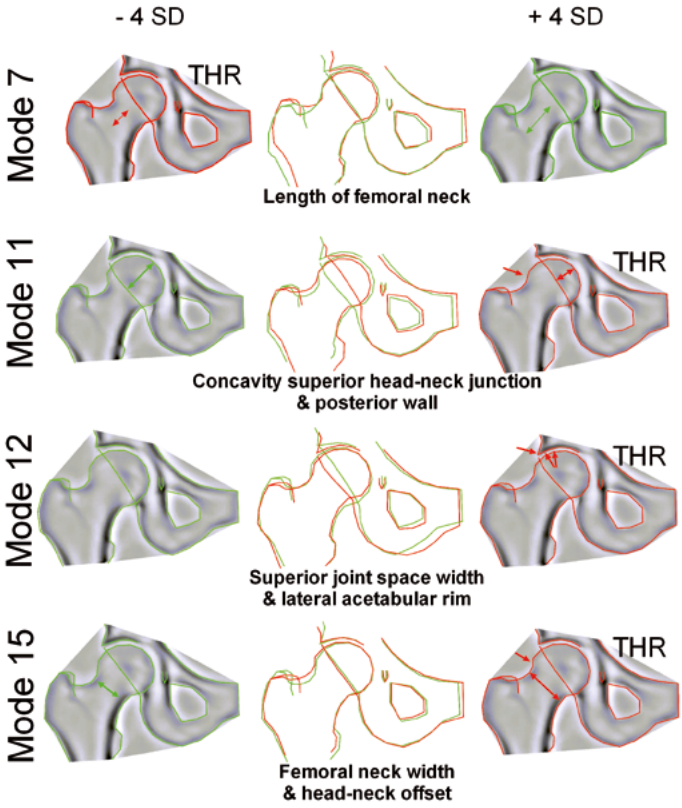


Figure 2. Modes which were significantly predictive for THR are shown. The shapes corresponding with the -4 and +4 standard deviations of the mean are illustrated on the left and right side respectively. The middle column shows the overlapping shapes of the -4 and +4 standard deviations; the extremes which are predictive for THR are shown in red. Mode 7 represents variation in the length of the femoral neck, mode 11 represents variation in the concavity of the superior head-neck junction together with variation of the posterior wall, mode 12 represents variation in the superior joint space width together with the femoral head coverage by the lateral acetabular rim, and mode 15 represents variation in the femoral neck width, together with the resulting variation in head-neck offset.

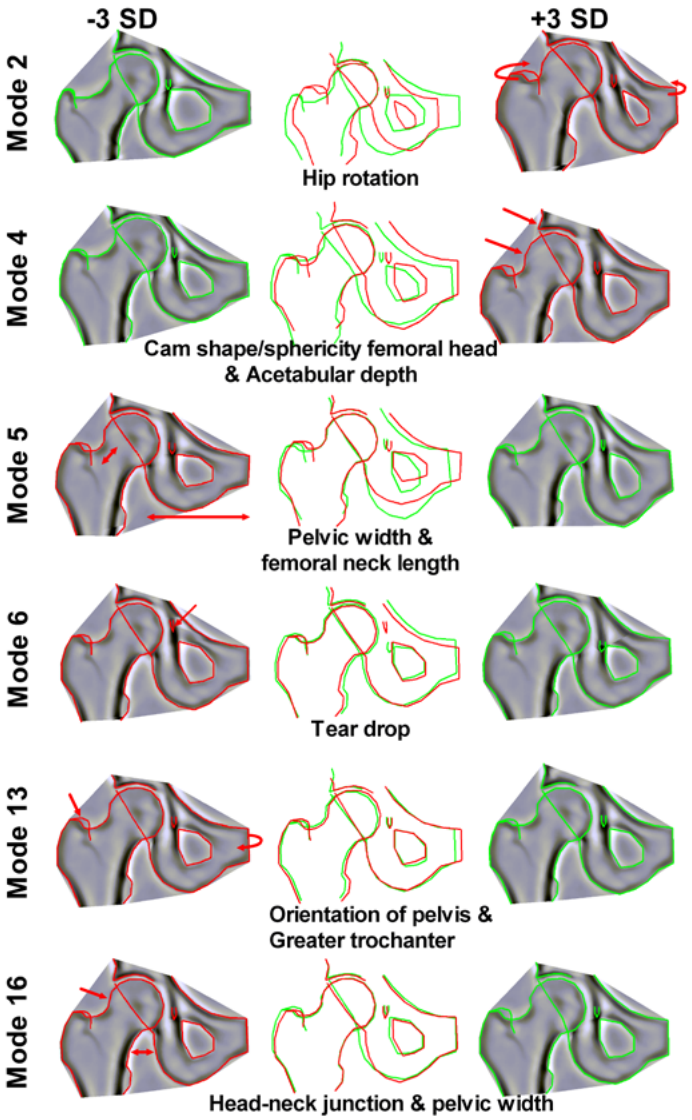


Figure 3. Modes which predicted THR at a p-value level <0.05, but >0.002 are shown. The shapes corresponding with the -3 and +3 standard deviations of the mean are illustrated on the left and right side respectively. The middle column shows the overlapping shapes of the -3 and +3 standard deviations; the extremes which are predictive for THR are shown in red.

DISCUSSION

In this prospective study we showed that the shape of the hip at baseline, as quantified using SSM, can predict THR after 5 years but not clinical OA after 5 years as defined by the ACR criteria. By using SSM in individuals that consulted their GP for the first time with knee or hip pain, it was possible to identify shape variants that increased the risk of requiring THR, before the actual radiographic onset of OA. At baseline, especially a broad and short femoral neck, and a retroverted acetabulum together with a non-spherical femoral head were predictive of fast progressing OA. In addition, hip shape at baseline might predict hip pain and decreased internal rotation at 5-year follow-up.

This study confirmed the important role of hip shape on development of OA. In previous cross-sectional and case control studies, the importance of hip morphology as a risk factor of radiographic hip OA was already shown.[63,208] In these studies, shape variants of the femoral head and femoral neck appeared to pose the highest risk for end-stage OA. Recently, Barr et al. retrospectively studied hip morphology of individuals, which presented with hip pain 5 years before, also using THR as an outcome measure[213]. Consistent with their findings, we found a predictive mode which represented femoral head flattening and superior neck broadening (mode 15, figure 2). The predictive role of bone shape on clinical OA remains poorly studied, as most other studies defined the presence of OA by radiographic criteria. Only one study by Waarsing et al., using dual-energy X-ray absorptiometry (DXA) images, indicated that subtle shape aspects of the proximal femur not captured by common radiological measures contain information about clinical status.[209] However, in the present study, we found that baseline hip shape could not predict development of clinical OA as determined by the ACR criteria. This might be explained by the fact that in this study, the ACR clinical criteria were not stable in participants with early symptomatic OA. For instance, 103 out of 116 (89%) individuals which fulfilled the ACR criteria at baseline did not have OA anymore at 5-year follow-up when determined by the same criteria. An explanation of the discrepancy between hips fulfilling the ACR criteria at baseline and at follow-up might be the presence or absence of pain at both time points. For example, if an individual met the ACR criteria at baseline, he or she might not necessarily experience hip pain during the follow-up visit because the presence and severity of pain in hip OA is highly variable, especially in the early stage.[214] When analyzing those hips that fulfilled the ACR criteria either at baseline or at follow-up as an outcome measure, no predictive modes were found either. Another explanation of this discrepancy might be the variability in the measured internal hip rotation.[215]

Although hip shape was not predictive for OA as determined by the combination of the ACR criteria, it could predict two clinical criteria independently; hip pain and decreased internal rotation. For pain, higher values of mode 9 at baseline associated with more pain at 5-year follow-up. The thicker and shorter femoral neck as represented by higher values of mode 9 shows striking similarities with mode 3 of the study by Waarsing et al., who also found a broad and short femoral neck to be the most significant predictor for VAS pain score.[209] For internal rotation, a higher value of mode 7, which correspond with a straight and longer femoral neck (figure 2), was predictive for internal rotation <15° at 5 year follow-up. Remarkable in this respect is that the opposite of mode 7 (lower values), representing a short femoral neck, was predictive for THR.

As decreased internal rotation is a clinical sign for cam impingement, we assumed a mode describing a non-spherical femoral head to be predictive for decreased internal rotation.[216] However, we did not find such a mode when applying a threshold value of 15°, but for limited internal rotation of 20° or less, mode 4, describing a non-spherical femoral head together with a shallow acetabulum, became highly significant (figure 3). Interestingly, this mode was a predictor for THR as well (p-value of 0.003), but did not remain significant when corrected for multiple testing (p-value threshold of 0.002).

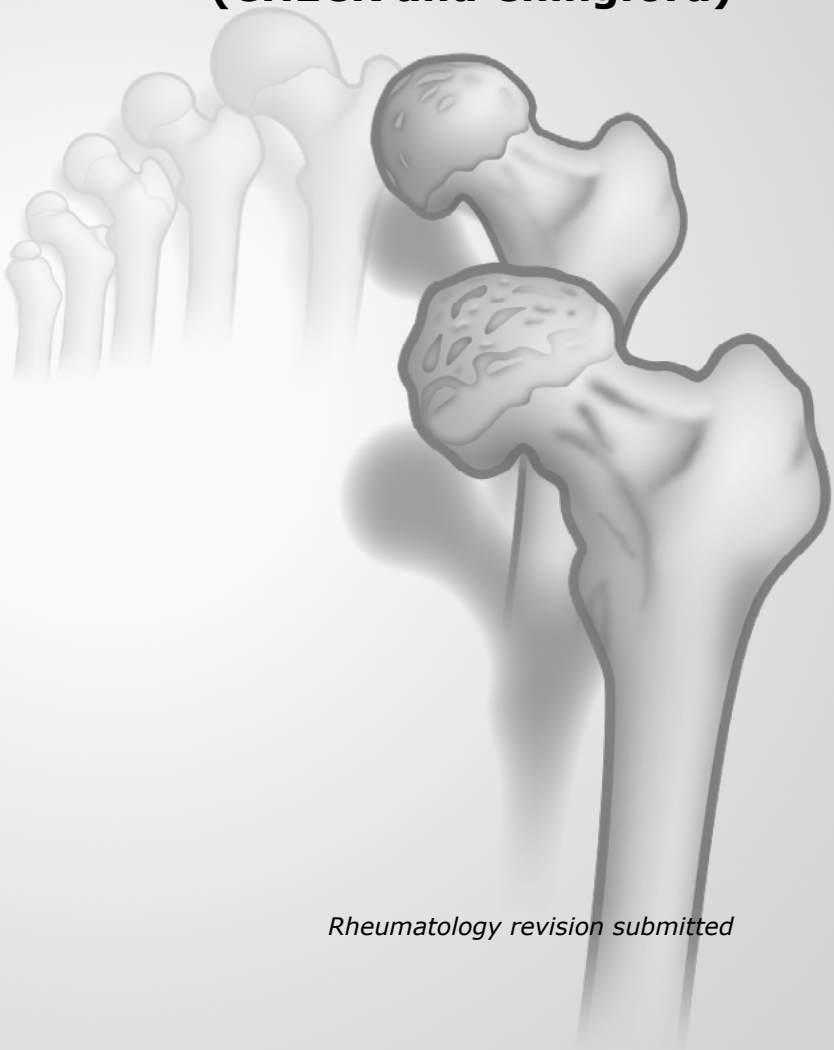
A larger statistical shape model might be more powerful for predicting OA.[213] Previous studies using SSM mostly included the proximal femur only, and despite the importance of the interaction between the proximal femur and acetabulum, only two studies additionally included the acetabular roof or a portion of the pelvis.[206,209,213,217] In order to quantify this interaction, we created a shape model of the complete hip joint by including both the proximal femur and the pelvis. The advantage of this model is that it can describe both the position of the proximal femur relative to the pelvis, and it can describe morphological variation of the femur, which is correlated with morphological variation of the pelvis. The importance of the interaction between proximal femur and pelvis for predicting OA was reflected in the significant modes. For example, higher values of mode 11 describe a flat head-neck junction, resulting in a broad femoral neck. Interestingly, the same mode also described a retroverted acetabulum as seen by a posterior wall located medially with respect to the centre of the femoral head (see figure 2). Acetabular retroversion has previously been described as a risk factor for hip OA, but the evidence is conflicting.[61,218,219] Our results from the SSM indicate that acetabular retroversion only when combined with a flattened head poses a higher risk for THR.

Strengths of this study are the large number of hips assuring a robust statistical shape model, the prospective design, and the large statistical shape model. Also, the shape of the hips at baseline was not influenced by the arthritic process, as no hips showed definite radiographic OA at baseline. This was confirmed when the analysis were corrected for K&L grade at baseline. The same modes became significant without change in OR, assuring that the found shapes were true OA predisposing shapes. There are however some limitations. The hip joint is a complex three-dimensional structure and variants of shape might not be visible on the AP radiographs. Still, SSM is able to quantify variation in orientation of bone structures from the projection of the radiographs. Another issue concerns variation in orientation of the bones, which will influence the projected shape. Variation in position was minimized by using a standardized protocol. Since remaining positional variation is often dictated by variation in anatomy, the effect on the projected shape cannot be separated from true anatomical shape variants. Still, both effects might contain valuable information with regards to OA development. We aimed to use clinical outcomes of OA, although THR could be considered not to be a pure clinical outcome, but is rather a combination between radiographic signs of OA and symptoms. The significant modes for THR might therefore also be predictive for radiographic OA. However, when analyzing the five predictive THR modes for those hips with radiographic OA as defined by a K&L grade of 2, 3, or 4 at follow-up (n=64), only mode 15 (a broader femoral neck) could predict radiographic OA. Further, THR is a validated and clinically relevant outcome measure.[220]

In conclusion, the morphology of the hip at baseline could not predict which hips fulfilled the ACR criteria at 5-year follow-up, probably due to the instability of those criteria in these participants, likely related to variability in pain. However, receiving a THR within 5 years was predicted well by the shape of the hip. In particular, before the presence of definite radiographic OA as defined by the K&L score, shape variants can be identified that pose a higher risk for THR during the 5-year follow-up. Hip morphology might therefore be used as a radiographic biomarker to predict the future risk of THR.

Chapter 4

Validation of Statistical Shape Modeling to predict hip osteoarthritis in females: data from two prospective cohort studies (CHECK and Chingford)



Rheumatology revision submitted

ABSTRACT

Objectives: To prospectively investigate whether hip shape variants at baseline are associated with the need for future total hip replacement (THR) in women and to validate the resulting associated shape variants of the CHECK cohort in the Chingford cohort.

Methods: Female participants from the CHECK cohort without radiographic OA (K&L<2) at baseline were included (1100 hips); 22 hips had a THR within 5 years follow-up. For the Chingford cohort, with only female participants, hips without radiographic OA at baseline were selected and a nested case-control design was used, with 19 THR cases within 19 years follow-up and 95 controls matched 5 to 1 for age and BMI. Hip shape on baseline anteroposterior pelvic radiographs was assessed by statistical shape modeling (SSM) using the same model for both cohorts.

Results: In the CHECK and Chingford cohorts, the respective mean(SD) age was 55.8(±5.1) and 53.6(±5.4), and BMI 26.14(±4.3) and 25.7(±3.3). Multiple shape variants of the hip were significantly ($p<0.05$) associated with future THR in both the CHECK (modes 4,11,15,17, and 22) and Chingford (modes 2 and 17) cohorts. Mode 17, representing a flattened head-neck junction and flat greater trochanter, could be validated in the Chingford cohort. Mode 4 and 15 of the CHECK cohort also showed non-significant trends in the Chingford cohort.

Conclusion: Several baseline shape variants are associated with the future need for THR within a cohort. Despite differences in participant characteristics, radiographic protocol, and follow-up time, we could validate at least one shape variant, suggesting that SSM is reasonably transferable between cohorts.

INTRODUCTION

Osteoarthritis (OA) is a common disease which accounts for a detrimental impact on quality of life and a considerable economic burden.[27,68] Due to the aging population, the need for total hip replacement (THR) is expected to grow 174% to more than half a million primary THRs per year by 2030 in the United States only.[28]

An increasing amount of evidence suggests that the shape of the hip plays a causative role in the development of hip OA and the subsequent need for THR.[63,74,203,206,221] A cam deformity, characterised by extra bone formation at the anterolateral head neck junction, and acetabular dysplasia are consistently found to be associated with hip OA in prospective cohort studies.[53,63,74,203,222] Interestingly, because these shape abnormalities are present before the actual onset of OA, relatively simple measurements (alpha angle[223,224], centre-edge angle[225]) can strongly predict the future risk of THR.[63,203,226,227]

Many other non-optimal shape variants might predict the development of hip OA as well, but these are difficult to capture by linear measurements (i.e. lengths and angles) because of the complex overall hip shape. Statistical shape modeling (SSM) is a technique which recognises all independent shape variants in a given population, and describes them quantitatively. Using this technique, it is possible to identify shape variants at risk for developing OA without any predefined hypothesis. SSM has therefore considerably increased in popularity as a tool to study the association between hip shape and the risk of OA. As a result, multiple subtle shape variants of the proximal femur and/or pelvis have been reported to be associated with OA.[206,209,213,217,221,228-231] SSM might therefore be a potential radiographic biomarker which can be used in research and clinical practice. However, all published studies on SSM and OA used different shape models (point sets of femoral head-neck junction or entire proximal femur with or without acetabulum), which makes the results difficult to compare and interpret. Certain shape variants have been associated with hip OA within a single cohort, but their generalisability remains unknown. To this end we have used one identical shape model for anteroposterior (AP) pelvis radiographs in two cohorts.

The aim of this study was to investigate which shape variants at baseline in OA free female hips are associated with the need for THR at follow-up in two prospective cohorts (CHECK and Chingford). Since both cohorts now have an identical model in our study, a comparison can be made between the findings of the shape variants in the two cohorts that are associated with THR at a later time point. Thereby we can test how consistent the associated shape variants for development of OA are in various populations.

METHODS

Study population

Subjects were selected from two prospective cohorts, the Dutch CHECK cohort and the UK Chingford cohort. CHECK is a nationwide multicenter prospective cohort study of 1002 individuals aged 45-65 years (mean 55.9) at baseline with early symptoms of OA (pain) of the hip and/or knee. They had not yet consulted their general practitioner for these symptoms, or the first consultation was within 6 months before entry. An extensive description of the CHECK cohort can be found elsewhere.[210] For the current study, only females of the CHECK cohort were included to allow comparison with the Chingford cohort. Of the 1002 individuals of the CHECK cohort, 791 (79%) were women and of these, 682 had radiographs available on both baseline and 5 years follow-up. Of these 682 women, the first 93 women that had entered the cohort had AP hip radiographs instead of AP pelvis radiographs obtained and were therefore excluded as a different radiographic view might influence the morphological appearance of the hip joint on the radiographs. Of the remaining 589 individuals who had AP pelvis radiographs at both timepoints, 39 women had radiographs of insufficient quality to apply the shape model, most often because the edge of the greater trochanter was missing on the radiographs. Ultimately, 550 women (1100 hips) were included. The 241 excluded women did not differ on baseline age (p=0.75) or BMI (p=0.69) from the 550 included individuals.

The Chingford cohort is a population-based cohort of 1003 women aged 44-67 years (mean 54.2 years) at baseline. These women were registered at a single general practice in London and were invited to participate in a study assessing musculoskeletal disease in the population. Yearly clinic visits included morphometric, clinical, biological, and radiographic measurements. Subjects who had radiographs obtained both at baseline and at 19-year follow-up were included using a nested case control design. To allow comparison with the CHECK cohort, only women without definite signs of radiographic OA (Kellgren&Lawrence [K&L] score <2) at baseline were included.[211] This selection resulted in 19 cases who received THR within 19 years follow-up. For each case, 5 control hips were matched based on age and BMI resulting in a total of 95 controls. Only one hip per person was included. When a woman had received bilateral THR, the left side was selected.

Radiographs

In the CHECK study, weight-bearing AP pelvis radiographs were obtained from the 11 participating research centers according to a standardized protocol, taken at baseline and at 2 and 5 years follow-up. Feet were positioned such that the medial side of the distal part of the first phalanx touched and a wedge was used to assure 15° internal rotation. In the Chingford cohort, each woman had a standardized supine AP pelvis radiograph, taken at years 2, 8 and 20. A small sand bag under the knees was used to minimize hip rotation so that the hips were in neutral position.

In both the CHECK and Chingford cohorts, baseline AP pelvis radiographs were graded using an atlas-based scoring method (K&L), with investigators blinded to all clinical and demographic information.[211,232] The K&L scores were independent of the positioning of the SSM point set.

Statistical Shape Modeling (SSM)

From the baseline radiographs of the CHECK cohort and Chingford cohort, the shape of the proximal femur and pelvis was outlined using SSM software (ASM tool kit, Manchester University, Manchester, UK).[233] The shape model was created by a set of 75 landmark points that were manually positioned along the surface of the bone in the image (figure 1). This was done by three investigators in the CHECK cohort, one of whom also did the point set in the Chingford cohort. The placement of the points has previously shown good reproducibility.[221] Each of the 75 points is always positioned on the same anatomical landmark using a standardized manual, allowing for comparison between shapes. CHECK and Chingford data were combined, with principal component analysis (PCA) used to transform the point sets into a statistical shape model (SSM). The SSM consists of a number of modes that together describe the total variation in shape in the study population. Shape aspects which are correlated are captured in one mode such that each single mode represents an independent shape variant. The mean shape of each mode is quantitatively described as 0, and the positive or negative deviation from the mean is expressed in the number of standard deviations (SD). The modes of variation are ordered in descending order of the percentage of shape variation explained by that mode of variation, so that the resulting first few modes contribute most to the total variation in shape.[234] We retained enough modes to explain 90% of the total variation in hip morphology of the included females.

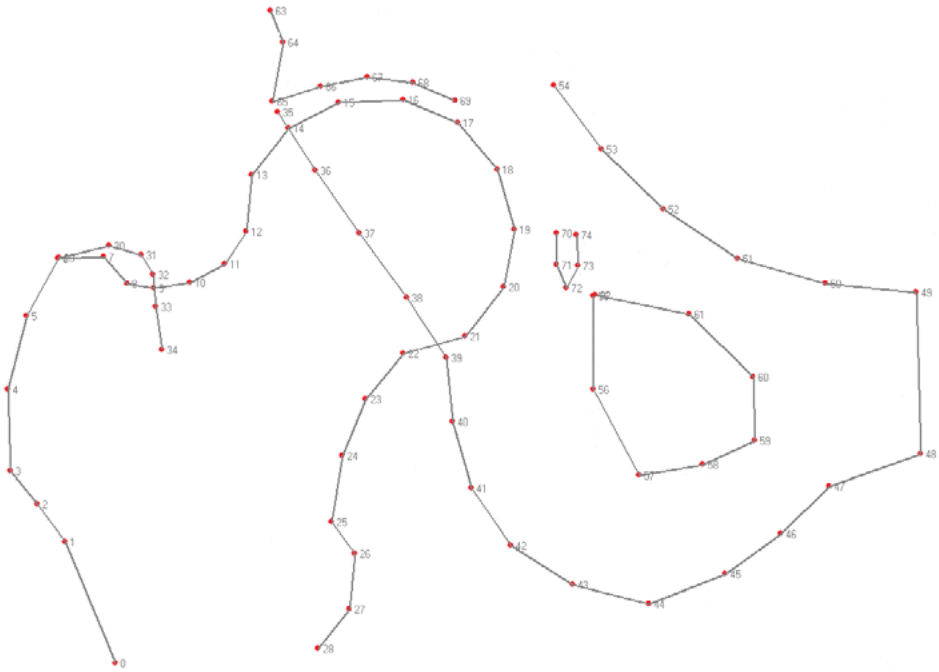


Figure 1. The point set of the statistical shape model which consisted of 75 points

Outcome measure

Total hip replacement due to OA at follow-up (5 years follow-up in the CHECK cohort and 19 years follow-up in the Chingford cohort) was used as an outcome measure. THR was confirmed for all cases on the follow-up radiographs.

Statistical analysis

Differences between baseline characteristics within a cohort and between the cohorts were calculated by independent samples T-test for normally distributed continuous variables, by Chi squared test for sex and K&L score in the Chingford cohort, and by generalized estimating equation model (GEE) for K&L score in the CHECK cohort, to account for the correlation between the left and right hips within an individual. To analyze whether a mode of shape variation was associated with THR in the CHECK cohort, logistic regression with GEE was used. The model was adjusted for age, BMI, and baseline K&L score. In the Chingford cohort, these associations were calculated by conditional logistic regression due to the matched nature of the data. From these models, odds ratios (ORs), 95% confidence intervals (95% CI) and p-values were calculated to describe the strength of association for each independent mode within each cohort. To

analyze the validity of the modes of shape variation for THR as an outcome, a comparison was made between the findings of the shape variants in the two cohorts that are associated with THR. An effect was considered significant at a p-value <0.05. All statistical analysis were performed in SPSS version20.0.

RESULTS

Participants

The baseline characteristics of the CHECK and Chingford cohort are presented in table 1. At baseline, the 550 females (1100 hips) of the CHECK cohort had a mean age of 55.8 years (range 44-66) and a mean BMI of 26.1 (range 17.5-48.9). Of the 1100 hips, 80% had a K&L score of 0, and 20% had a K&L score of 1. Of these hips, 22 hips had received THR within the 5 years follow-up period. In the Chingford cohort, the included 114 females (114 hips) had a mean age of 53.6 years (range 46-64) and a mean BMI of 25.7 (range 20.0-37.8) at baseline. The K&L score was 0 in 95% of the hips and 1 in 5% of the hips. Between the two cohorts, there were significant differences in baseline age (55.8 in CHECK vs 53.6 in Chingford, p<0.001) and baseline K&L=1 score (20% in CHECK vs 5% in Chingford, p<0.001), but no difference in mean BMI was found (26.1 in CHECK vs 25.7 in Chingford, p=0.26).

Table 1. Baseline characteristics of the individuals of the CHECK and Chingford cohorts

	CHECK				Chingford				
	All	Cases	Controls	p-value*	All	Cases	Controls	p-value*	p-value**
Number (hips)	1100	22	1078		114	19	95		
Age in years: mean (±SD)	55.8 (5.1)	57.9 (4.3)	55.8 (5.1)	0.06	53.6 (5.4)	53.6 (5.6)	53.6 (5.4)	1.00	<0.001
BMI kg/m²: mean (±SD)	26.1 (4.3)	25.3 (3.5)	26.2 (4.3)	0.36	25.7 (3.3)	25.8 (3.6)	25.7 (3.2)	0.90	0.26
K&L grade 0: %	80	27	81	<0.001	95	100	94	NA	<0.001
K&L grade 1: %	20	73	19	<0.001	5	0	6	NA	<0.001

*Difference between cases and controls **differences between all individuals of the CHECK and Chingford cohorts. BMI, body mass index; K&L, Kellgren & Lawrence; NA, not applicable.

Baseline modes associated with THR at follow-up

A total of 24 modes were extracted from the SSM, which together explained 90% of the total variation in shape that exists in the CHECK and Chingford cohorts together. The association between all baseline modes and THR at follow-up is given in table 2, including the ORs, 95% CI and corresponding p-values. Five

modes of shape variation had a significant positive (+) or negative (-) association with THR at follow up in the CHECK cohort [mode 4 (-), 11 (+), 15 (+), 17 (-), and 22 (+)] and two modes of shape variation in the Chingford cohort [mode 2 (+) and 17 (-)](figure 2). Negative values of mode 17, representing a flattened head-neck junction, a flat major trochanter, and a prominent acetabular posterior wall, was associated with future THR in both the CHECK and Chingford cohorts (figure 2). Moreover, negative values of mode 4 and positive values of mode 15, which were significantly associated with future THR in the CHECK cohort, had the same effect in the prediction of THR in the Chingford cohort, though not statistically significant (p=0.27 and p=0.16 respectively).

Table 2. the strength of association between all modes at baseline and THR at follow-up (5 years in the CHECK cohort and 19 years in the Chingford cohort).

	Check				Chingford		
Modes	**aOR**	**95% CI**	**p-value**	**Modes**	**OR**	**95% CI**	**p-value**
M0	0.799	0.519-1.232	0.310	M0	0.909	0.554-1.492	0.705
M1	1.181	0.671-2.077	0.564	M1	0.890	0.494-1.603	0.697
M2	0.823	0.530-1.279	0.388	**M2**	**1.607**	**1.017-2.539**	**0.042**
M3	1.029	0.732-1.445	0.871	M3	1.088	0.651-1.816	0.748
M4	**0.375**	**0.204-0.690**	**0.002**	M4	0.710	0.387-1.304	0.270
M5	0.893	0.567-1.406	0.624	M5	1.013	0.619-1.658	0.959
M6	1.311	0.888-1.935	0.174	M6	1.298	0.784-2.151	0.311
M7	0.937	0.578-1.520	0.793	M7	1.026	0.623-1.690	0.921
M8	1.441	0.935-2.220	0.098	M8	1.688	0.999-2.853	0.051
M9	1.139	0.724-1.793	0.573	M9	0.739	0.449-1.216	0.234
M10	1.280	0.899-1.822	0.170	M10	1.347	0.823-2.206	0.236
M11	**2.179**	**1.229-3.863**	**0.008**	M11	1.062	0.632-1.786	0.820
M12	0.769	0.484-1.222	0.266	M12	1.060	0.618-1.819	0.832
M13	1.439	0.874-2.371	0.153	M13	1.257	0.679-2.328	0.467
M14	0.783	0.534-1.148	0.211	M14	0.768	0.481-1.226	0.268
M15	**1.657**	**1.024-2.681**	**0.040**	M15	1.368	0.884-2.118	0.160
M16	0.808	0.500-1.307	0.386	M16	0.875	0.538-1.422	0.590
M17	**0.513**	**0.330-0.797**	**0.003**	**M17**	**0.413**	**0.228-0.816**	**0.010**
M18	1.153	0.705-1.885	0.571	M18	0.950	0.566-1.597	0.847
M19	1.095	0.662-1.810	0.723	M19	0.987	0.548-1.775	0.964
M20	1.275	0.823-1.976	0.277	M20	0.703	0.420-1.176	0.180
M21	1.172	0.805-1.707	0.408	M21	0.818	0.472-1.417	0.473
M22	**1.897**	**1.294-2.783**	**0.001**	M22	0.902	0.562-1.448	0.670
M23	0.928	0.557-1.546	0.775	M23	1.043	0.649-1.675	0.862

The statistically significant modes ($p<0.05$) are highlighted in bold. aOR=adjusted OR; corrected for age, BMI, and K&L grade at baseline. The presented ORs represent every increase in one SD of that specific mode. CI=confidence interval.

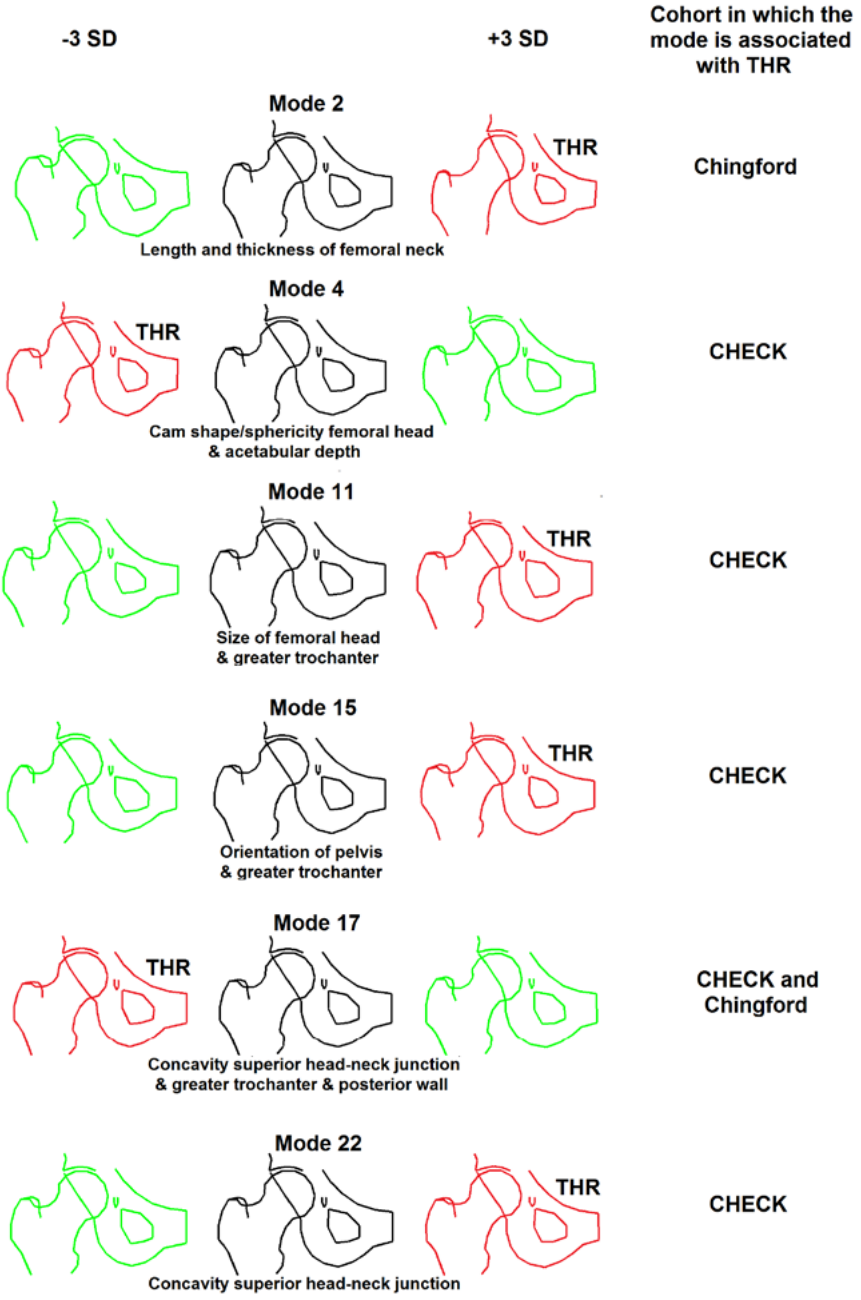


Figure 2. Modes significantly predictive for THR are shown. The odds ratios presented in table 2 represent every increase in SD, but for clarity the -3SD (left column) and +3 SD (right column) from the mean (middle column) are presented. The extremes which are associated with THR are indicated in red.

DISCUSSION

Multiple shape aspects of the hip as quantified by SSM have previously been shown to be associated with, or even predictive for radiographic OA[206,209,228,229], clinical criteria of OA[209,221], and THR[206,213,221]. However, due to the application of different shape models (different point sets) the results between studies are difficult to compare. Consequently, the generalisability of the resulting modes of shape variation is limited to the characteristics of each specific cohort and therefore, the validity in the prediction of OA is unknown. In this study we showed in two prospective cohorts that several shape aspects in female hips without definite features of radiographic OA at baseline was significantly associated with the need for THR at follow-up within each cohort. One shape aspect was associated with THR in both the CHECK and Chingford cohorts. This specific shape variant –describing a flattened head-neck junction together with a flat major trochanter and a prominent acetabular posterior wall- might be a generalisable shape aspect in the prediction of THR in women, even regardless of other factors including cohort characteristics, follow-up time, or radiographic protocol. In contrast, some other shape variants found to be associated with THR might be co-dependent on those or other factors.

Gregory et al. were the first to quantify hip shape by SSM in order to study its relationship with OA in a case-control design.[206] Their point set of the shape model involved the femoral head and neck (but excluded the acetabulum) and was applied to 110 subjects (without radiographic OA) from the Rotterdam study at baseline and 6 years follow-up. One shape variant that they identified that could significantly predict OA at follow-up represented a less pronounced curve from the upper femoral neck into the head, indicated by negative values of this variant. This association was even more pronounced in the OA cases who had received a THR. The variant values also decreased significantly over time in the OA group, highlighting the importance to study predictive shape aspects before the actual onset of radiographic OA. Furthermore, another variant they identified could predict the need for THR but not the development of radiographic OA, suggesting that baseline shape aspects may predict disease severity.[206]

The finding that hip shape was associated with the future risk of THR was further supported by other studies. Previous research in the CHECK cohort for both men and women showed five modes predictive of future THR in baseline radiographic-free hips (K&L <2).[221] The predictive modes primarily described a broad and short femoral neck, and a retroverted acetabulum together with a non-spherical femoral head. In the Rotterdam study, especially shape variants related to the superior head-neck junction and the shape of the acetabular

socket were significantly associated with development of OA.[235] Waarsing et al. also found various shape aspects associated with OA that were in line with our findings, such as a smaller greater trochanter and a cam-shaped femoral head.[209] In a retrospective study of patients that presented with hip pain, Barr et al. found one mode of shape variation being significantly associated with THR 5 years later when adjusted for baseline K&L score.[213] Subtle shape variations as quantified by SSM have therefore been suggested as a potential radiographic biomarker to predict the future risk of OA. But again, all studies on SSM and OA used different shape models so that the resulting predictive modes of shape variation cannot be directly compared.

Our results are in line with previously published articles showing that certain shape variants of the hip can predict the risk of a THR within a cohort. More importantly however, we found that one shape variant was predictive for a THR in both the CHECK and Chingford cohorts. There are several explanations for the fact that not all predictive shape variants of the CHECK cohort could be validated in the Chingford cohort, which include differences in follow-up time, radiographic protocol and participant characteristics. First, there was a difference in follow-up time between both cohorts and the pathophysiology of fast progressing OA (THR within 5 years in CHECK) might be different from slow progressing OA (THR within 19 years in Chingford). This is supported by a study showing that the predictive value of hip shape and other risk factors at baseline decreased when using a longer follow-up time.[235] An example is a cam deformity that results in fast progressing hip OA[203] which will be detected at 5 years but it is less likely to be detected at 19 years of follow-up as other factors may dilute the predictability of a cam deformity. Lower values of mode 4, representing a non-spherical femoral head (together with a shallow acetabulum), and higher values of mode 15 might be modes that are stronger associated with fast progressing OA (figure 2). Though not as strong as in CHECK, the predictive effect of these modes were still present in the Chingford cohort, though not statistically significant ($p=0.27$ for mode 4 and $p=0.16$ for mode 15). Secondly, the radiographic protocol was different between both cohorts. in the CHECK cohort, AP pelvic weight-bearing radiographic views with 15° internal hip rotation were obtained while in the Chingford cohort AP pelvic supine radiographs were obtained in neutral position. Consequently, there will be differences in how the outline of the bone, and thus hip shape, appears on the radiograph. Thirdly, although no difference in BMI between the cohorts was found and the significant difference of 2.2 years in baseline mean age is probably negligible, differences in other participants characteristics might play a role. In the CHECK cohort there is a larger proportion

of females presenting with hip and/or knee pain (as first onset of knee and/or hip pain was an inclusion criterion) whereas Chingford women were recruited from the general population. This difference might influence the association between hip shape and OA. Furthermore, there might be other (unknown) differences between the two cohorts, for example genetics, which is known to affect both hip shape and the relationship between hip shape and OA.[217,230]

It is unknown whether the shape variants found to be associated with OA are causative factors for OA, or whether they represent early changes in bone morphology as a result of OA. As the shape variants of our model describe the overall hip shape, it is unlikely a result of the OA process. Furthermore, most modes associated with THR show some variation in the head-neck junction, which might reflect different subtypes of cam deformities, which result in OA by a motion dependent process of cam impingement.[75] Interestingly, a cam deformity is known to be highly associated with OA, and develops during growth, probably as a bone adaptation to high impact athletic activities.[226,227,236] It is unknown whether other predictive shape variants are also present before the onset of OA.

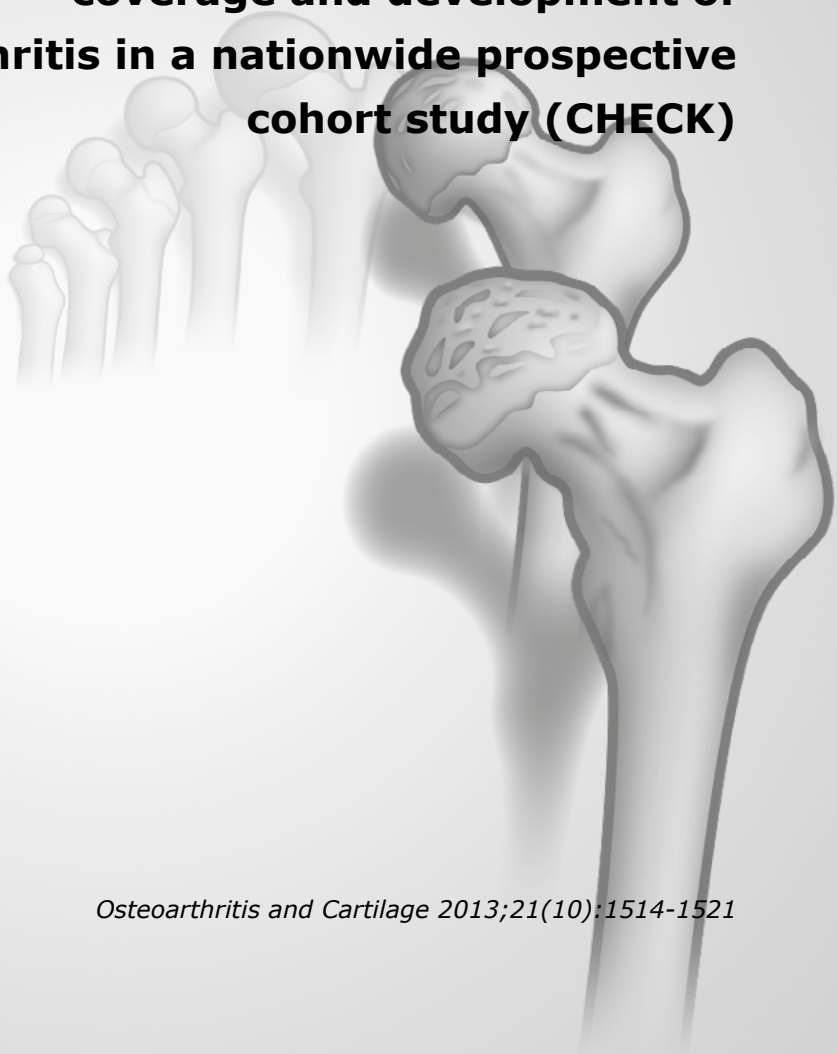
Several potential limitations of this study need to be acknowledged. First, we only included females and hence the results of this study might be different for males, as there might be a gender difference in how much hip shape contributes to the prediction of OA and also, the predictive shape variants might be different between males and females.[229] Second, rotation of bones might influence the projected radiographic shape, which was however minimized by the use of a standardized radiographic protocol. Thirdly, THR is a surrogate measure for OA and as it is a surgical endpoint, questions might arise on the accessibility to health care and THR. In this study, all THRs were a result of OA, a THR was confirmed on follow-up radiographs, and it is a validated and clinically relevant outcome measure.[220] Also, both the Netherlands and the United Kingdom have a public health system in which all people have equal access to THR, independent of for example social status. Moreover, the definitions of radiographic OA and clinical OA have their limitations as well.[221]

Predictive shape variants might be dependent on many factors including follow-up time, inclusion criteria of the cohort, and radiographic protocol. Despite the differences in these factors between the two cohorts, we could validate one mode (mode 17), while two modes (modes 4 and 15) that were significantly associated with THR in the CHECK cohort showed trends in the same direction in the Chingford cohort, though not statistically significant. Therefore, SSM might be a useful tool as a radiographic biomarker. For this purpose, the manual

positioning of landmark points is labor intensive but a recently developed fully automatic shape modelling software might provide future opportunities.[237]
In conclusion, we found several shape variants that were associated with the future need for THR within a cohort and one shape variant in the CHECK cohort that could be validated in the Chingford cohort. Despite differences in participant characteristics, radiographic protocol, and follow-up time, SSM as a predictive radiographic biomarker was reasonably transferable between cohorts.

Chapter 5

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)



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ABSTRACT

Objective Determining the relation between acetabular coverage, especially overcoverage which may lead to pincer impingement, and development of osteoarthritis (OA) of the hip.

Design From a prospective cohort study of 1002 individuals with symptoms of early OA (Cohort Hip and Cohort Knee, CHECK), 720 participants were included. Standardized anteroposterior pelvic radiographs and false profile lateral radiographs were obtained at baseline and 5 years follow-up. Acetabular undercoverage (mild dysplasia) and overcoverage (pincer deformity) were measured by a centre edge angle of <25° and >40° respectively in both radiographic views. The strength of association between those parameters at baseline and development of incident OA (Kellgren and Lawrence (K&L) grade >2 or total hip replacement), or joint space narrowing within 5 years was expressed in odds ratio (OR) adjusted for K&L grade, age, body mass index (BMI), and sex using generalized estimating equations.

Results At baseline, 76% of the included hips had no signs of radiographic OA (K&L=0) whereas 24% had doubtful osteoarthritis (K&L=1). Within 5 years, 7.0% developed incident OA. Acetabular dysplasia was significantly associated with development of incident OA with ORs between 2.62 (95% confidence interval (CI) 1.44 - 4.77) and 5.45 (95% CI 2.40 - 12.34), dependent on the radiographic view. A pincer deformity was not associated with any outcome measure, except for a significantly protective effect on incident OA when a pincer deformity was present in both radiographic views OR 0.34 (95% CI 0.13 - 0.87).

Conclusion Acetabular dysplasia was significantly associated with development of OA. However, a pincer deformity was not associated with OA, and might even have a protective effect on its development, which questions the supposed detrimental effect of pincer impingement.

INTRODUCTION

The aetiology of osteoarthritis (OA) is mainly unclear, though both systemic factors and local biomechanical factors are known to play a role.[238] OA of the hip often occurs without the presence of OA in other susceptible joints, indicating that local biomechanical factors may predominate.[202]

Growing evidence supports the theory that these local factors are mainly explained by bone shape variants of the hip, causing OA by an altered biomechanical loading pattern.[55,101,209,239] These bone shape variants can be located at the femoral side, acetabular side, or both. An example of a femoral sided morphological abnormality is a non-spherical femoral head (cam deformity) which may lead to a motion dependent abnormal contact between the femoral head and the acetabulum, also known as cam-type FemoroAcetabular Impingement (FAI).[55] A cam deformity is thought to develop during growth and is an important risk factor for OA.[203,226,240] An abnormal shape of the acetabulum may also lead to OA by either acetabular undercoverage, also known as (mild) dysplasia, or acetabular overcoverage, known as a pincer deformity.

In hips with mild acetabular dysplasia, a decreased contact area between femur and acetabulum results in higher static loads on the anterosuperior acetabular cartilage. In hips with a pincer deformity, the mechanism leading to OA is much less understood. The proposed mechanism is that of a dynamic abnormal linear contact between the overcovered acetabular rim and the femoral neck during terminal motion of the hip, which is known as pincer-type FAI.[55] When vigorous hip motion causes repetitive impingement events, the soft tissue structures within the hip joint might gradually damage, leading to hip OA.

This hypothesis is supported by intra-operative findings in symptomatic patients with a pincer deformity, where acetabular cartilage damage was found throughout the acetabulum in a small thin strip around the labrum.[57] Also, cartilage damage at the posterior-inferior site has been described as a result of a 'countrecoup lesion' by the femoral head, due to the leverage effect of the neck when it abuts against the anterior acetabular rim (Figure 1).

Evidence for the relation between mild dysplasia and development of OA provided by cross-sectional or retrospective studies is inconsistent, but prospectively designed studies generally show a moderate increased risk for hip OA.[53,222,241-243] In contrast, the relation between pincer deformities and development of OA is conflicting.[59-61,63-66,244] However, these studies are often limited by a retrospective or cross-sectional design, making it difficult to draw conclusions on causality. As in mild dysplasia, prospective studies might identify an association, but no such studies are available for pincer deformities.

The aim of this study was to examine the relation between baseline anterior and lateral acetabular coverage, specifically pincer deformities, and the risk of developing OA after 5 years follow-up. We further investigated whether acetabular coverage was associated with pain and decreased hip function.

METHODS

Study design and participants

Individuals were extracted from Cohort Hip and Cohort Knee (CHECK). CHECK is a nationwide prospective cohort study of 1002 individuals with symptoms of early OA of knee or hip. On entry, all participants had pain with or without stiffness of knee or hip and were aged 45-65 years; they had not yet consulted their general practitioner (GP) for these symptoms, or the first consultation was within six months before entry. Participants with another pathological condition that could explain the symptoms were excluded.[210]

Radiographs and clinical examination were obtained from eleven (general and university) hospitals at baseline, and at 5-year follow-up. The mean (SD) follow-up was 5.06 (0.17) years. Individuals were recruited either by GPs who were invited to refer eligible persons to one of the participating centres and by advertisements in local newspapers. The 720 individuals (1391 hips) of the 1002 participants who had both anteroposterior (AP) pelvic radiographs and False Profile (FP) radiographs of sufficient quality obtained both at baseline and at five year follow-up were included in the current study (figure 2). The study was approved by the medical ethics committees of all participating centres, and written informed consent was obtained from all participants.

Radiographs

Weight bearing AP pelvic radiographs and FP oblique view radiographs were obtained according to a standardized protocol at baseline and five years follow-up.[203] For AP radiographs, feet were positioned in 15° internal rotation. For FP radiographs, individuals stood sidewise with the hip of interest against the radiographic table and with the second metatarsal phalanx of the same leg parallel to the radiographic table. Then, the pelvis was rotated 25° backwards, confirmed by a 65° wedge between the back and radiographic table, to profile the anterosuperomedial edge of the acetabulum.[245]

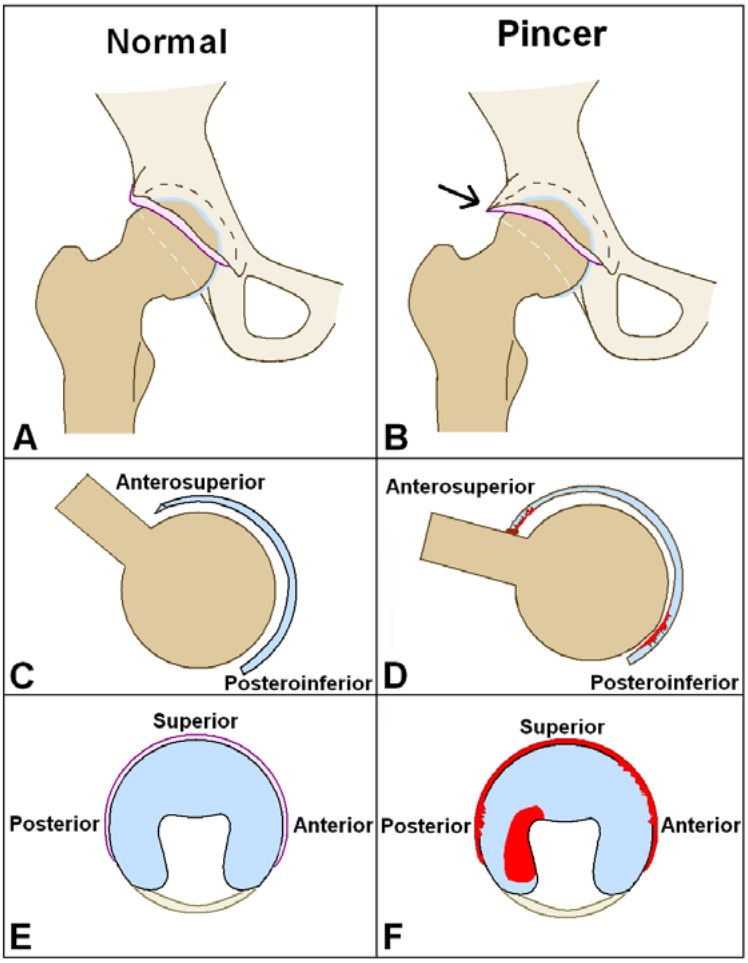


Figure 1. The mechanism of pincer impingement

A normal hip (A) and a hip with a pincer deformity (B) are shown. The anatomy of the normal hip provides the hip a physiological ROM (C) whereas a pincer deformity (arrow) is proposed to lead to an abnormal linear contact between the overcovered acetabular rim and the femoral neck during terminal motion of the hip, which is known as pincer impingement (D). When vigorous hip motion causes repetitive impingement events, the acetabular cartilage might gradually damage throughout the acetabulum in a small thin strip around the labrum. Also, the leverage of the femoral head in the acetabulum might lead to a contrecoup lesion posteroinferiorely (F).

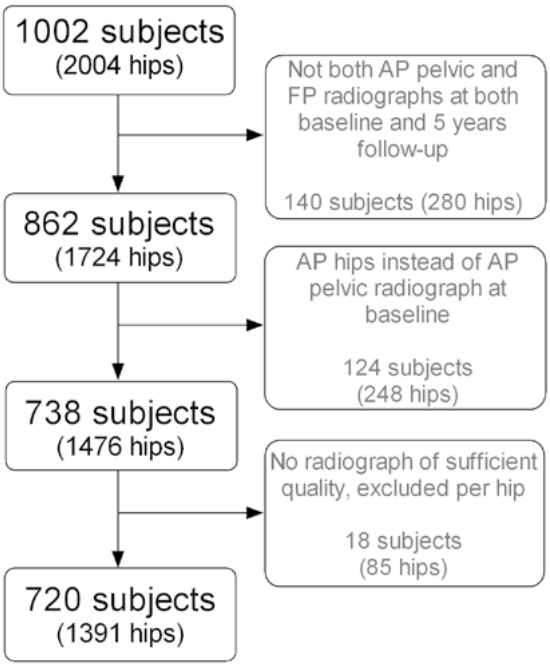


Figure 2. Flow of subjects from cohort inclusion to the final study population

Radiographic measurements

The shape of the hip on the AP and FP radiographs was outlined using the ASM tool kit (Manchester University, Manchester, UK). The shape is given by a set of landmark points that are positioned along the surface of the bone in the radiograph.[206,221] The lateral centre edge angle (LCEA) and anterior centre edge angle (ACEA) were automatically calculated from the points outlined on the AP and FP radiographs respectively, using Matlab (version 7.1.0, MathWorks Inc, Natick, Massachusetts, USA).

The centre edge angle measures the amount of acetabular coverage with respect to the centre of the femoral head. The centre of the femoral head is found by drawing a best-fitted circle around the femoral head. From the centre of the femoral head, a first line is drawn vertical and a second line is drawn to the edge of the sourcil (the dense subchondral bone) of the acetabulum. The angle between those lines is the centre edge angle (Figure 3).[225,246] The vertical line was drawn perpendicular to the horizontal line connecting both femoral heads In the AP view, and perpendicular to the horizontal line of the radiographic film in the FP view. We defined the presence of a pincer deformity by an LCEA or

ACEA >40° and the presence of mild acetabular dysplasia by an LCEA or ACEA <25°.[247,248]

At baseline and 5 years follow-up, all AP pelvic radiographs were scored for OA according to the Kellgren and Lawrence (K&L) classification (grade 0-4).[211] In addition, superior and inferior joint space was determined on FP radiographs (grade 0-3).

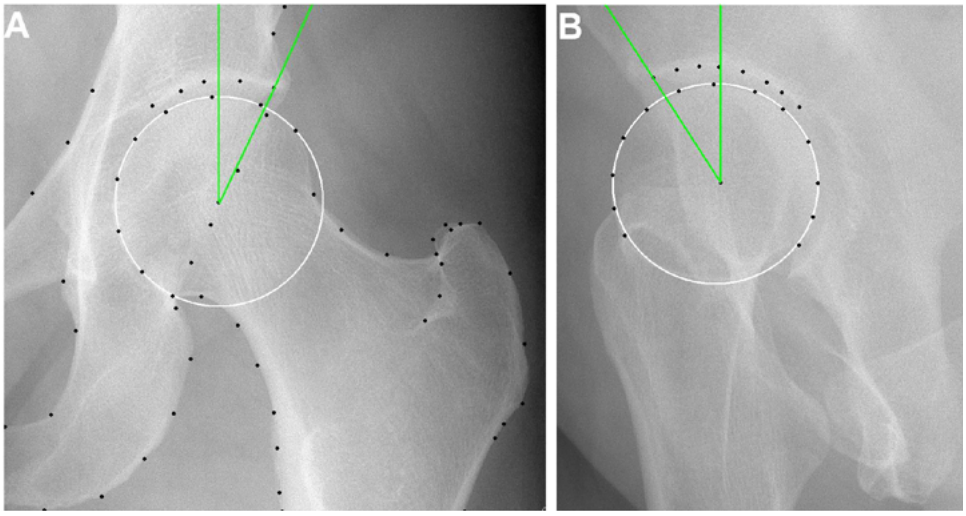


Figure 3. The LCEA and ACEA **A.** The lateral centre edge angle (LCEA) as measured on an anteroposterior pelvic radiograph. **B.** The anterior centre edge angle (ACEA) as measured on a false profile radiograph.

Clinical measurements

At baseline, all individuals were clinically examined by measuring the range of motion (ROM) of the hip. Active ROM was measured by a goniometer in flexion, internal rotation, external rotation, abduction, and adduction. Further, the presence and severity of hip and knee pain was assessed using the Visual Analog Scale (VAS) at baseline and follow-up. This scale runs from 0 (no pain) to 10 (very intense pain) .[249]

Reliability of the LCEA and ACEA

The points were positioned in the baseline AP radiographs by three investigators and in the FP radiographs by two investigators who were unaware of any follow-up data. To examine inter and intra-observer reliability, the point set was positioned twice by each investigator in 25 randomly selected radiographs with

an interval of two months.

Outcome measures

Development of incident OA was defined by K&L grade 2, 3, 4, or a total hip replacement (THR) at 5-year follow-up. This outcome measure was further subdivided in mild OA (K&L=2) and end-stage OA (K&L=3, 4, or THR). As it has been described that pincer impingement may result in specific acetabular cartilage damage anterosuperiorely, adjacent to the point where the abnormal contact occurs, and posteroinferiorely, as a result of the contrecoup lesion, both superior and inferior joint space narrowing (JSN) (grade ≥1) on the FP view was used as an outcome measure.[250] Grade 1 JSN is indicative for mild, but definite disease.

Statistical analysis

Reliability of the LCEA and ACEA was assessed using intra-class correlation coefficient (ICC). Univariate differences in baseline characteristics between included and excluded hips, and between hips that developed OA and normal hips, were evaluated by the Mann-Whitney test for continuous variables, by chi-square test for sex, and by generalized estimating equations (GEE) for K&L score. The strength of the independent relationship between acetabular coverage at baseline and development of OA was calculated using GEE, adjusted for baseline K&L classification, age, sex, and body mass index (BMI), and expressed in terms of odds ratios (ORs). Using GEE allowed to model the correlation between the left and the right hip. Hips with either a pincer deformity or mild dysplasia were compared with a
reference group of hips with a centre edge angle ≥25° and ≤40° in the corresponding radiographic view, representing normal acetabular coverage. When mild OA or JSN was used as an outcome measure, baseline hips that had developed end-stage OA at 5-year follow-up were excluded from analysis. When end-stage OA was used as an outcome measure, hips that had developed mild OA were excluded. Differences in pain scores at follow-up and ROM at baseline between hips with and without mild acetabular dysplasia or a pincer deformity were calculated using GEE, adjusted for K&L grade at baseline. All statistical analyses were performed in SPSS version 20.0.

RESULTS

Participants

Baseline demographic data is summarized in table 1. The 720 included individuals did not differ on any baseline characteristic from the 282 individuals who were excluded. At baseline, the 720 individuals (1391 hips) were included in the CHECK cohort because they consulted the GP for the first time with mild pain in their hip (n=127, mean ± SD VAS hip pain 2.73 ± 2.07), pain in their knee (n=292, mean ± SD VAS knee pain 2.71 ± 2.04), or pain in both hip and knee (n=301, mean ± SD highest VAS pain 3.29 ± 2.12).

Table 1. Baseline characteristics of the participants, stratified by the absence or presence of incident OA.

	Total n=720 (1391 hips)	Absence of incident OA at follow-up n=657 (1294 hips)	Presence of incident OA at follow-up n=80 (97 hips)	p-value Absence vs presence of incident OA at follow-up
Age in years: mean (±SD)	55.9 (5.21)	55.8 (5.2)	58.0 (4.7)	<0.001
Women, No. (%)	572 (79)	540 (81)	54 (68)	0.001
BMI, kg/m²: mean (±SD)	26.1 (4.1)	26.2 (4.2)	25.8 (3.7)	0.67
Length in cm: mean (±SD)	169.9 (8.2)	169.7 (8.1)	172.6 (8.8)	0.003
Weight in kg: mean (±SD)	75.3 (13.7)	75.2 (13.7)	76.9 (12.8)	0.116
K&L grade 0, No (%)	1045 (76)	1029 (81)	16 (17)	<0.001
K&L grade 1, No (%)	324 (24)	248 (19)	76 (83)	<0.001

BMI: body mass index, K&L: Kellgren and Lawrence.

Osteoarthritis classification

At five years follow-up, 97 (7.0%) hips developed incident OA, of which 39 hips (2.8%) end-stage OA and 58 hips (4.2%) mild OA. On the FP view, JSN was present superiorly in 107 hips (7.7%) and inferiorly in 107 hips (7.7%).
At baseline, the K&L grade could be scored reliably in 1369 hips. Of these hips, 76% did not show radiographic evidence of OA (K&L grade 0) whereas 24% had doubtful OA (K&L grade 1). On the FP view, superior joint space was scored as grade 0 in 94%, grade 1 in 5%, and grade 2 in 1%, and inferior joint space as grade 0 in 95% and grade 1 in 5%.

Association between acetabular coverage and OA

The association between a pincer deformity or mild dysplasia and OA is summarized in table 2. In hips with a pincer deformity on both the AP and

FP view, a significant protective effect for OA was found with an adjusted OR (aOR) of 0.34 (95% confidence interval (CI) 0.13 - 0.87, p = 0.025). There was no significant association between a pincer deformity in other radiographic views and the outcome measures, though a nearly significant association with posteroinferior joint space narrowing was found aOR=1.48 (95%CI 0.93-2.34, p = 0.10).
For both anterior and lateral acetabular dysplasia, a significant association was found for incident OA, with respective aORs of 2.62 (95% CI 1.44 - 4.77, p = 0.002) and 2.83 (95% CI 1.54 - 5.20, p = 0.001). The strength of association between mild dysplasia and incident OA increased when deficient coverage was present both at the lateral and anterior side in one hip aOR=5.45 (95%CI 2.40-12.34, p<0.001). For end-stage OA, slightly stronger associations were found.

Acetabular coverage and pain and function

Neither a pincer deformity nor mild dysplasia in any view was significantly predictive for higher VAS hip pain scores at 5 years follow-up. Similar results were found for VAS pain scores at baseline (Table 3).
Significant, though clinically irrelevant, decreased ROM was found. A lateral pincer deformity resulted in decreased internal rotation (29.87° vs 30.82°, p = 0.035). Further, external rotation tended to be increased (maximum difference 2.1°, p = 0.05) in hips with pincer deformity but no differences in flexion were found (maximum difference 1.5°, p = 0.36). Hips with anterior dysplasia and hips with dysplasia both anteriorely and laterally showed decreased adduction of respectively 20.42° vs 21.79°, p = 0.02 and 19.33° vs 21.75°, p = 0.015. In those hips, external rotation tended to be decreased (maximum difference 2.8°, p = 0.06).

Table 2. Association (n=1391 hips) between both pincer deformity and mild acetabular dysplasia at baseline and both osteoarthritis and JSN at 5-year follow-up

		Incident OA (n=97 hips)		Mild OA (n=58 hips)		End-stage OA (n=39 hips)		Inferior JSN (n=107 hips)		Superior JSN (n=107 hips)	
	Radiographic View	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
	AP LCEA>40° (n=201 hips)	0.78 (0.38-1.57) p=0.48	0.53 (0.25-1.10) p=0.090	0.96 (0.41-2.24) p=0.92	0.62 (0.26-1.46) p=0.27	0.33 (0.08-1.37) p=0.13	0.28 (0.07-1.21) p=0.09	1.44 (0.85-2.43) p=0.17	1.40 (0.81-2.43) p=0.23	0.88 (0.48-1.59) p=0.67	0.76 (0.41-1.41) p=0.38
PINCER	**FP** ACEA>40° (n=418 hips)	0.96 (0.58-1.59) p=0.96	0.77 (0.43-1.37) p=0.77	0.78 (0.41-1.48) p=0.45	0.68 (0.33-1.41) p=0.30	0.83 (0.40-1.72) p=0.62	0.69 (0.32-1.50) p=0.35	1.50 (0.97-2.31) p=0.07	1.48 (0.93-2.34) p=0.10	1.11 (0.73-1.70) p=0.63	1.00 (0.62-1.59) p=0.99
	AP+FP LCEA+ACEA>40° (n=141 hips)	0.52 (0.19-1.43) p=0.21	**0.34 (0.13-0.87) p=0.025**	0.81 (0.26-2.49) p=0.71	0.53 (0.19-1.45) p=0.22	X	X	1.10 (0.56-2.17) p=0.78	1.04 (0.50-2.16) p=0.93	1.10 (0.59-2.07) p=0.77	0.89 (0.47-1.66) p=0.70
	AP LCEA<25° (n=176 hips)	**2.50 (1.53-4.09) p=0.000**	**2.83 (1.54-5.20) p=0.001**	**1.98 (1.03-3.78) p=0.040**	**2.33 (1.03-5.27) p=0.042**	**3.42 (1.74-6.72) p=0.000**	**3.80 (1.84 - 7.84) p=0.000**	0.97 (0.54-1.73) p=0.90	0.95 (0.51-1.80) p=0.88	1.15 (0.65-2.01) p=0.63	1.13 (0.58-2.20) p=0.73
MILD DYSPLASIA	**FP** ACEA<25° (n=144 hips)	**2.61 (1.55-4.41) p=0.000**	**2.62 (1.44-4.77) p=0.002**	1.78 (0.83-3.80) p=0.14	2.02 (0.85-4.76) p=0.11	**4.51 (2.12-9.62) p=0.000**	**4.34 (1.99-9.47) p=0.000**	1.49 (0.83-2.67) p=0.18	1.59 (0.86-2.94) p=0.14	0.98 (0.47-2.08) p=0.97	0.91 (0.38-2.18) p=0.83
	AP+FP LCEA+ACEA<25° (n=62 hips)	**3.64 (1.91-6.99) p=0.000**	**5.45 (2.40-12.34) p=0.000**	2.59 (0.99-6.81) p=0.053	**4.88 (1.38-17.26) p=0.014**	**4.98 (2.17-11.42) p=0.000**	**6.48 (2.69-15.59) p=0.000**	0.92 (0.36-2.31) p=0.85	1.04 (0.39-2.78) p=0.94	1.28 (0.45-3.64) p=0.64	1.49 (0.41-5.43) p=0.54

Odds ratios were adjusted for K&L grade, age, BMI, and sex at baseline. X= no cases of end-stage OA.
Hips with pincer or dysplasia were compared with a reference group with a centre edge angle ≥25° and ≤40° in the corresponding radiographic view. Hips with pincer or dysplasia in both radiographic views were compared with a reference group with a centre edge angle ≥25° and ≤40 in both radiographic views. Significant associations ($p < 0.05$) are indicated in bold.

Table 3. Difference (n=1391 hips) in amount of internal rotation at baseline and VAS pain score at follow-up between either hips with a pincer deformity or mild acetabular dysplasia and normal hips.

		IR (SD)			VAS pain (SD)		
		at baseline			at follow-up		
	Radiographic view	No pincer	Pincer	p-value	No Pincer	Pincer	p-value
PINCER	AP LCEA>40°	**30.82 (8.68)**	**29.87 (8.45)**	**0.035**	1.77 (2.39)	1.96 (2.19)	0.79
	FP ACEA>40°	30.85 (8.62)	30.29 (8.73)	0.10	1.76 (2.34)	1.87 (2.40)	0.74
	AP+FP	30.76 (8.70)	30.02 (8.19)	0.27	1.77 (2.37)	2.00 (2.29)	0.77
		No dysplasia	Dysplasia	p-value	No dysplasia	Dysplasia	p-value
Dysplasia	AP LCEA<25°	30.57 (8.57)	31.43 (9.21)	0.96	1.76 (2.34)	2.03 (2.50)	0.05
	FP LCEA<25°	30.68 (8.58)	30.67 (9.25)	0.87	1.82 (2.35)	1.60 (2.40)	0.22
	AP+FP	30.65 (8.61)	31.27 (9.48)	0.10	1.80 (2.36)	1.61 (2.37)	0.78

IR: internal rotation in degrees

Reliability and reproducibility of the LCEA and ACEA

The ICC for inter-observer reliability was 0.97 (95% CI 0.94 - 0.99) for the LCEA and 0.99 (95% CI 0.97 - 0.99) for the ACEA. ICC scores for intra-observer reliability ranged from 0.91 to 0.96 for the LCEA and from 0.97 to 0.99 for the ACEA.

Table 4. Association between pincer deformity as defined by a CEA >45° and OA

Radiographic view	Incident OA (n=97 hips)		Mild OA (n=58 hips)		End-stage OA (n=39)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
AP LCEA >45°	1.25	0.76	1.86	1.17	**X**	**X**
Lateral pincer	(0.45 - 3.51)	(0.25 - 2.34)	(0.63-5.48)	(0.37 - 3.70)		
n=63 hips	p=0.67	p=0.64	p=0.26	p=0.79		
FP ACEA >45°	1.12	0.81	0.78	0.62	1.14	1.73
Anterior pincer	(0.61 - 2.06)	(0.40 - 1.63)	(0.35 - 1.71)	(0.26 - 1.52)	(0.45 - 2.90)	(0.72 - 4.17)
n=211 hips	p=0.71	p=0.55	p=0.53	p=0.30	p=0.79	p=0.22
AP+FP	0.92	0.57	1.26	0.77	**X**	**X**
LCEA and ACEA >45°	(0.20 - 4.38)	(0.13-2.55)	(0.22 - 7.38)	(0.16 - 3.71)		
n=35 hips	p=0.92	p=0.46	p=0.80	p=0.75		

Odds ratios were adjusted for K&L grade, age, BMI, and sex at baseline. X= no cases of end-stage OA. Hips with pincer or dysplasia were compared with a reference group with a centre edge angle ≥25° and ≤40° in the corresponding radiographic view. Hips with pincer or dysplasia in both radiographic views were compared with a reference group with a centre edge angle ≥25° and ≤40 in both radiographic views.

DISCUSSION

This prospective study of individuals with first onset of mild pain complaints without radiographic evidence of definite OA at baseline shows that a pincer deformity does not increase the risk for development of OA whereas mild acetabular dysplasia is associated with development of OA. The latter is in agreement with previously reported prospective studies.

In retrospective or case control studies on pincer impingement, some authors showed a moderately increased risk for OA in the presence of a pincer deformity,[60,61,66,244] where others did not find an association or even suggested a potential protective effect of a pincer deformity for development of OA.[59,63-65] Our data supports the latter studies and found surprisingly a protective effect of a pincer deformity when present both anterior and lateral in one hip. This was supported by the fact that none of the hips with a pincer deformity on both radiographic views (n=141 hips) developed end-stage OA.

Interestingly, a nearly significant association was found between a pincer deformity on the FP view and JSN posteroinferiorely, in the specific region where the so called 'contrecoup lesions' may occur (figure 1).[57,250] Most hips with posteroinferior JSN at follow-up already showed JSN at baseline, indicating that this indirect measure of cartilage loss is not progressive in hips with pincer deformity. This could suggest that these cases do impinge and suffer from a limited ROM. However, we did not find a limited flexion, neither in hips with anterior and/or lateral overcoverage nor in those hips with overcoverage and JSN posteroinferiorely at follow-up.

We did not find a positive association between a pincer deformity and OA, but regarding its slow progression the 5-year follow-up might have been too short.[240] However, Nicholls et al. could neither identify an association between a higher LCEA and THR after 19 years follow-up.[63] Moreover, the first structure that fails in pincer impingement is the labrum, which is associated with pain.[240,251,252] However, a pincer deformity was neither associated with higher pain scores at follow-up. Second, pincer impingement might lead to OA rapidly, before the age

of 45 years, so that those subjects were not included in this cohort. However, this is unlikely as it has been described that complaints as a result of pincer impingement starts from the age of 30-40 years.[240]

A pincer deformity is a description of a variety of acetabular morphological or orientation abnormalities causing excessive coverage of the femoral head. The overcoverage may result from either a generally overcovered acetabulum, i.e., when the femoral head is positioned deep inside the acetabulum or when there is an overgrowth of the acetabular rim, or it may result from focalized overcoverage, as seen in acetabular retroversion.[248] General overcoverage can be quantified by the LCEA as seen on an AP radiograph. Coxa profunda has also been used to define general overcoverage, but two recent studies showed that coxa profunda should not be used to define a pincer deformity.[253,254] Acetabular retroversion, resulting in anterior overcoverage, can be quantified on AP radiographs by the cross-over sign or posterior wall sign, though both measures have their limitations.[255] We measured anterior coverage on the FP radiograph by the ACEA, by which we assume that hips with anterior overcoverage due to retroversion are accurately identified.[256]

Although an LCEA and ACEA threshold for a pincer deformity of >40° is subjective, it is most often used to quantify overcoverage. Gosvig et al. found cross-sectionally a mild association between a deep acetabular socket (LCEA >45°) and a joint space width of ≤2 mm, but we neither found a significant or increased risk of OA when using a threshold of 45° (see Table 4).[57].

FAI is a motion dependent abnormal contact between the proximal femur and acetabular rim due to a non-optimal morphology of either the proximal femur (cam-type) or the acetabulum (pincer-type). Both types of FAI are being treated with increasing frequency by restoring the normal anatomy to prevent the abnormal contact to occur. This appears to be justified for cam impingement regarding its relation with OA and the promising short-term to mid-term surgical outcomes.[203] However, for surgical treatment (acetabular rim trimming) of pincer impingement caution is necessary. Based on our results, a pincer deformity might even have a protective effect. Obviously, some symptomatic pincer impingement patients might benefit from a surgical procedure, but proper patient selection is critical.

For mild dysplasia, prospective studies generally showed an association with OA, though cross-sectional and retrospective studies have confused this issue. Two well designed studies showed a moderate increased risk for development of OA.[53,222] Lane et al. conducted a prospective nested case-control study with 8 years follow up in 176 women (mean age 70 years) and showed an aOR of 3.3

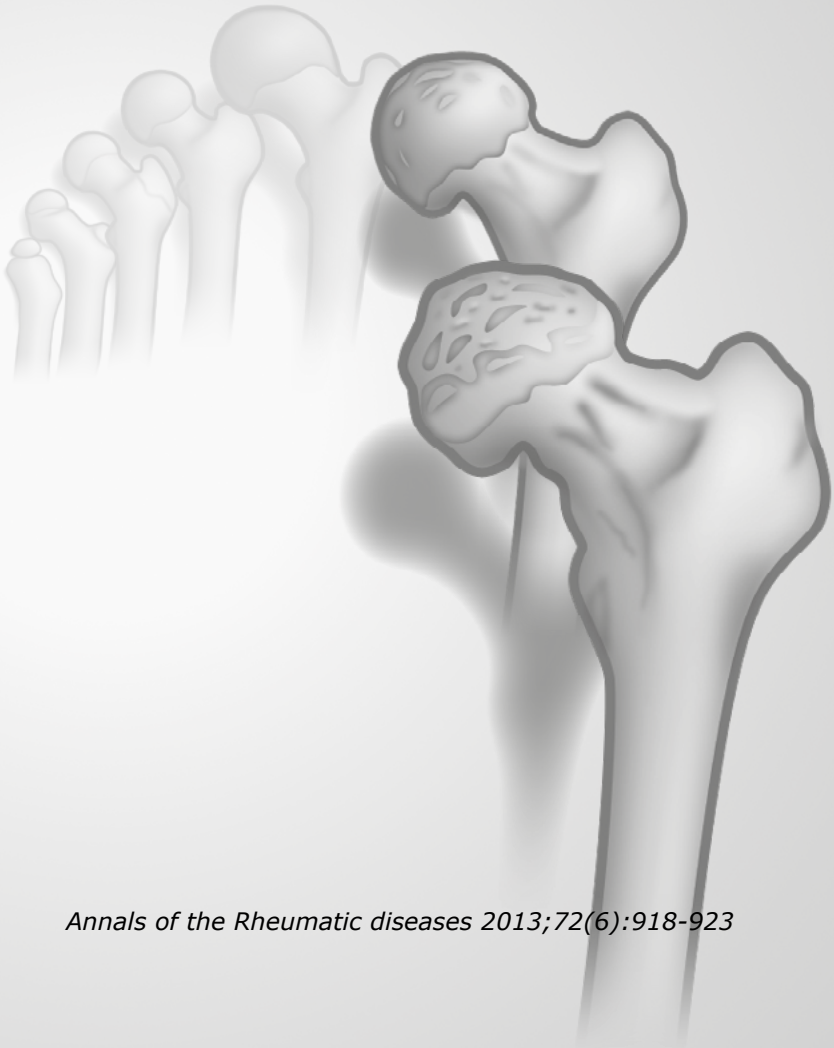
(95% CI 1.1-10.1) for acetabular dysplasia (LCEA<30°) and OA. Reijman et al. defined acetabular dysplasia in 835 subjects (mean age 65 years) by an LCEA <25° and found an aOR of 2.4 (95% CI 1.2-4.7) for OA as defined by a K&L grade ≥2 and an aOR of 4.3 (95% CI 1.8-4.5) for JSN ≥1mm. It was suggested that the association between acetabular dysplasia and OA might be higher in a younger population. In the current study of 720 individuals with a mean age of 55 years, we confirmed above mentioned associations between dysplasia and OA and showed aORs of roughly 3 to 4 for OA. Other studies did not use an additional FP view, and we showed a clearly increased aOR when acetabular dysplasia was present both anteriorely and laterally in one hip.

There are some limitations that need to be acknowledged. Although both an anteroposterior and lateral radiographic view per hip was obtained, acetabular retroversion might have been missed in some cases. Secondly, as opposed to the LCEA, we were not able to draw a horizontal reference line for calculating the ACEA. Still, a FP view might be more sensitive for the diagnosis of dysplasia and showed additional predictive value as compared with an AP view alone.[246,257] Thirdly, a pincer deformity is a risk factor for pincer impingement, but the occurrence and frequency of impingement depends on patient activity, which is unknown in this cohort. However, the same holds true for cam deformities, which were highly predictive for OA in this cohort.[203] Moreover, the occurrence of pincer impingement might also depend on femoral version and the presence of a cam deformity. We could not correct for femoral version, but the prevalence of cam deformities was similar in hips with and without pincer deformities, implying that this risk factor did not influence the association between pincer deformities and OA. Individuals with a known diagnosis of acetabular dysplasia were excluded from the CHECK cohort, implicating that the study subjects only represent a mild, subclinical subset of acetabular dysplasia. Finally, the reader should bear in mind that all participants had mild pain in their hips, knees, or both at baseline, which might represent a very early stage of symptomatic OA, although no definite radiographic OA was present at baseline.

In conclusion, a significant association between both lateral and anterior acetabular dysplasia and development of OA within 5 years was found. The strength of association increased when dysplasia was present both anteriorly and laterally in one hip. In contrast, when a pincer deformity was present both anteriorely and laterally in one hip, a protective effect for development of OA was found. No association between a pincer deformity and joint space narrowing at the specific anatomical locations of pincer impingement was identified. These results questions the hypothesis that pincer impingement leads to OA.

Chapter 6

Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK)



Annals of the Rheumatic diseases 2013;72(6):918-923

ABSTRACT

Objective To determine the association between cam impingement, which is hip incongruity by a non-spherical femoral head and development of osteoarthritis.

Methods A nationwide prospective cohort study of 1002 early symptomatic osteoarthritis patients (CHECK), of which standardised anteroposterior pelvic radiographs were obtained at baseline and at 2 and 5 years follow-up. Asphericity of the femoral head was measured by the alpha angle. Clinically, decreased internal hip rotation (≤20°) is suggestive of cam impingement. The strength of association between those parameters at baseline and development of incident osteoarthritis (K&L grade 2) or end-stage osteoarthritis (K&L grades 3, 4, or total hip replacement) within 5 years was expressed in OR using generalised estimating equations.

Results At baseline, 76% of the included hips had no radiographic signs of osteoarthritis and 24% doubtful osteoarthritis. Within five years, 2.76% developed end-stage osteoarthritis. A moderate (alpha angle >60°) and severe (alpha angle >83°) cam-type deformity resulted in adjusted OR of 3.67 (95% CI 1.68 - 8.01) and 9.66 (95% CI 4.72 - 19.78), respectively, for end-stage osteoarthritis. The combination of severe cam-type deformity and decreased internal rotation at baseline resulted in an even more pronounced adjusted OR, and in a positive predictive value of 52.6% for end-stage osteoarthritis. For incident osteoarthritis, only a moderate cam-type deformity was predictive OR=2.42 (95% CI 1.15 – 5.06).

Conclusions Individuals with both severe cam-type deformity and reduced internal rotation are strongly predisposed to fast progression to end-stage osteoarthritis. As cam impingement might be a modifiable risk factor, early recognition of this condition is important.

INTRODUCTION

Osteoarthritis is the most frequently occurring chronic joint disease and its main characteristics are pain and dysfunction.[26] Symptomatic OA affects 9.6% of men and 18% of women aged 60 years or older and, with an ageing population, the prevalence of OA will increase substantially.[68] Although osteoarthritis implies an increasing economic burden and detrimental impact on quality of life,[27] no methods are available to prevent the disease or delay its progression. If modifiable risk factors can be identified at an early stage of the disease, preventive measures might be implemented.[72]

Many cases of idiopathic hip osteoarthritis may be secondary to minor variations in the morphology of the proximal femur.[24] These minor variations in shape were described by Ganz et al., who introduced the concept of femoroacetabular impingement (FAI).[55] FAI is a condition of abnormal contact between the femoral head-neck junction and the acetabulum, due to a bone shape abnormality on either the femoral or acetabular side. Two types of FAI can be distuingished,[55] cam impingement and pincer impingement. Pincer impingement is caused by overcoverage of the acetabulum relative to the femoral head, and cam impingement is caused by extra bone formation (a cam-type deformity) in the anterolateral head neck junction.[67,258] Such a deformity can develop in response to sporting activities during adolescence.[226,227] These cam-type deformities may cause impingement against the acetabular rim, especially during flexion and internal rotation of the hip (figure 1). Subsequently, a cascade of structural damage (including labral tears and cartilage delamination) may occur, which might gradually lead to osteoarthritis of the hip.[32] Therefore, cam impingement has been proposed as a biomechanical risk factor for the development of hip osteoarthritis.[208,240]

However, there are no cohorts combining radiographic and clinical parameters of cam impingement to study the risk of the development of osteoarthritis. Furthermore, due to the lack of prospective studies on this topic, no causal relationship between cam impingement and the development of osteoarthritis has been established.[241] Interestingly, cam impingement is a potentially modifiable risk factor of osteoarthritis, as a cam-type deformity can be treated surgically and diagnosed before the onset of severe hip damage

Assuming an association between cam impingement and the development of osteoarthritis, we examined the association between clinical and radiographic parameters suggestive of cam impingement at baseline and the risk of developing osteoarthritis within 5 years.

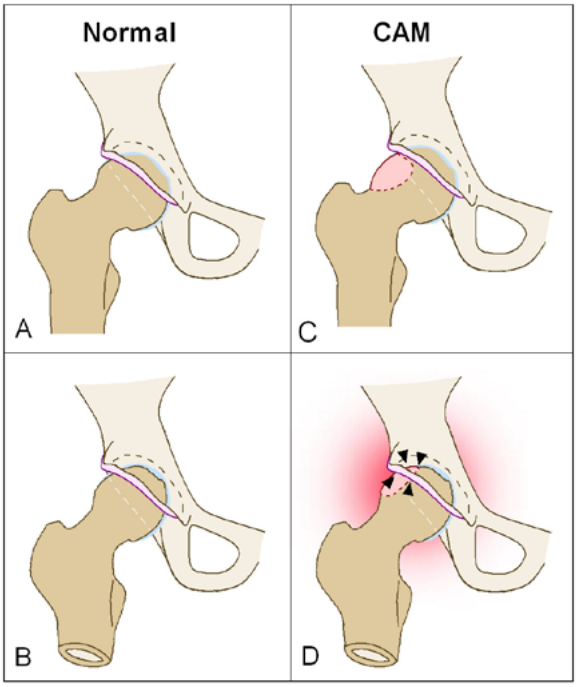


Figure 1. Mechanism of cam impingement. A normal spherical-shaped femoral head (**A**) provides the hip with a physiological range of motion without impingement (**B**). A cam-type deformity as seen on an anteroposterior view (**C**) may cause impingement against the acetabular rim causing cartilage damage (arrowheads) (**D**).

METHODS

Study design and participants

All subjects were extracted from the Cohort Hip and Cohort Knee (CHECK) cohort. CHECK is a nationwide prospective cohort study of 1002 individuals with early symptomatic osteoarthritis of knee or hip. On entry, all participants had pain or stiffness of knee or hip and were aged 45-65 years; they had not yet consulted their general practitioner for these symptoms, or the first consultation was within 6 months before entry. Participants with a pathological condition that could explain the symptoms were excluded (for hip: trauma, rheumatoid arthritis, dysplasia, Perthes disease, subluxation, osteochondritis dissecans, fracture, septic arthritis, Kellgren & Lawrence (K&L) grade 4 or total hip replacement, previous hip surgery, and individuals having only symptoms of bursitis or tendinitis).[210]

Radiographs and clinical examination were obtained from 10 (general and university) hospitals. General practitioners were invited to refer eligible persons to one of those centres; advertisements in local newspapers were also used. Of the 1002 individuals, 865 individuals (1730 hips) were included in the present study because they had anteroposterior radiographs obtained at baseline (from October 2002 to December 2005) and at 5 year follow-up (from November 2007 to December 2010); the mean (SD) follow-up was 5.06 (0.17) years. The study was approved by the medical ethics committees of all participating centres, and written informed consent was obtained from all participants.

Radiographs

Weight-bearing anteroposterior pelvic radiographs and faux profil oblique view radiographs were obtained according to a standardised protocol at baseline, and at 2 and 5 years follow-up.[245] For anteroposterior radiographs, feet were positioned such that the medial side of the distal part of the first phalanx touched and a wedge was used to assure 15° internal rotation. The tube to film distance was 100 cm and the beam was centred at the top of the pubic symphysis.

Radiographic measurements

The shape of the proximal femur and acetabulum on the anteroposterior radiographs was outlined using statistical shape modelling (SSM) software (ASM tool kit, Manchester University, Manchester, UK). The shape on the anteroposterior radiographs is given by a set of landmark points that are positioned along the surface of the bone in the image. Each point is always placed on the same landmark of the outline, to allow comparison between the shapes. The alpha angle was automatically calculated from the points set of the SSM software (figure 2), using Matlab (V.7.1.0)

The alpha angle measures the extent to which the femoral head deviates from spherical and is a measure mostly applied to quantify a cam-type deformity. It is measured by first drawing the best fitting circle around the femoral head, then a line through the centre of the neck and the centre of the head. From the centre of the femoral head a second line is drawn to the point where the superior surface of the head-neck junction first departs from the circle. The angle between these two lines is the alpha angle.[224] We defined the radiographic presence of a cam-type deformity by an alpha angle greater than 60° and greater than 83°.[259,260]

At baseline, and at 2 and 5 years follow-up, all anteroposterior pelvic radiographs were scored for osteoarthritis according to the K&L classification (grade 0-4).[211] In addition, superior and inferior joint space was determined on faux profil

radiographs (grade 0-3).[245] The development of incident osteoarthritis was defined by K&L grade 2 at 5-year follow-up, and the development of end-stage osteoarthritis was defined by K&L grades 3, 4, or a total hip replacement (THR) within 5 years.

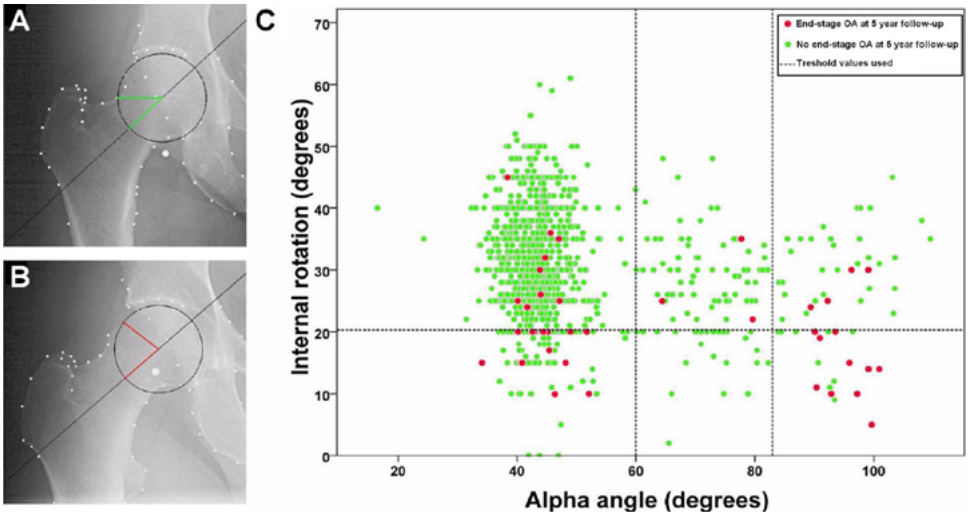


Figure 2. Cam impingement associates with end-stage osteoarthritis of the hip. (**A**) A spherical femoral head with an alpha angle of 43°; (**B**) a cam-type deformity resulting in an alpha angle of 78°; and (**C**) scatterplot of baseline measurements of the alpha angle and internal hip rotation in 90° of flexion (the red dots indicate hips that developed end-stage osteoarthritis within 5 years).

Clinical measurements

All individuals were clinically examined by measuring the range of motion (ROM) of the hip. The ROM was measured in flexion, internal rotation, external rotation, abduction, and adduction. The presence of reduced internal rotation (in 90° of flexion) is suggestive of impingement. We used a threshold value of 20° or less.[216] Furthermore, the presence and severity of hip pain were assessed using validated self-report questionnaires, including the Western Ontario and McMaster University Osteoarthritis Index (WOMAC, pain subscale) and the Visual Analog Scale.[249,261]

Reliability of the alpha angle

The points of the SSM software were positioned in all radiographs by three investigators who were unaware of any follow-up data. To examine interobserver

reliability, the point set was positioned twice by each investigator in 25 randomly selected radiographs with an interval of 2 months. Intra-observer reliability was tested for each investigator in 10 randomly selected radiographs.

Statistical analysis

Reliability of the alpha angle was assessed using intraclass correlation coefficient (ICC) (two-way random, absolute agreement). Univariable differences in baseline characteristics between included and excluded hips, and between hips that developed osteoarthritis and normal hips, were evaluated by the Mann-Whitney test for continuous variables, by the chi-square test for sex and by generalised estimating equations (GEE) for K&L score. The strength of the independent relationship between cam impingement parameters at baseline and the development of osteoarthritis was calculated using GEE and expressed in terms of OR. Using GEE allowed to model the correlation between the left and the right hip. To adjust for confounders, in the GEE model, K&L classification and sex were entered as a factor, and body mass index and age as a covariate. Hips with end-stage osteoarthritis at 5-year follow-up were excluded from analysis when incident osteoarthritis was used as an outcome measure. The positive predictive value of cam impingement parameters for osteoarthritis was also calculated. Differences in pain scores and ROM between individuals with and without radiographic cam-type deformity were calculated using the Mann-Whitney test and GEE, respectively, the latter adjusted for K&L grade at baseline. All statistical analyses were performed in SPSS V.15.0.

RESULTS

Participants

Of the 1002 individuals in the CHECK cohort, 89 were lost to follow-up, 16 were not able to visit the hospital during the 5-year follow-up, and 32 refused to undergo radiographs or had missing radiographs. For this study, 865 individuals (682 women, 183 men; aged 45-65 years) were included. At baseline, these 865 individuals (1730 hips) were included in the CHECK cohort because of the first onset of pain in their hip (n=148), knee (n=354), or both (n=363). Anteroposterior hip radiographs (instead of anteroposterior pelvic radiographs) were obtained in the first 124 individuals of the CHECK cohort. These individuals were excluded from baseline measurements because an anteroposterior hip view is known to influence the alpha angle.[248] Radiographs of insufficient quality were also excluded (figure 3). To calculate the OR, all hips with an anteroposterior

pelvic radiograph of sufficient quality were included (n=1411 hips). Excluded individuals did not differ on any baseline characteristic from the included individuals. Table 1 presents baseline demographic data of the participants stratified for the absence or presence of OA at follow-up.

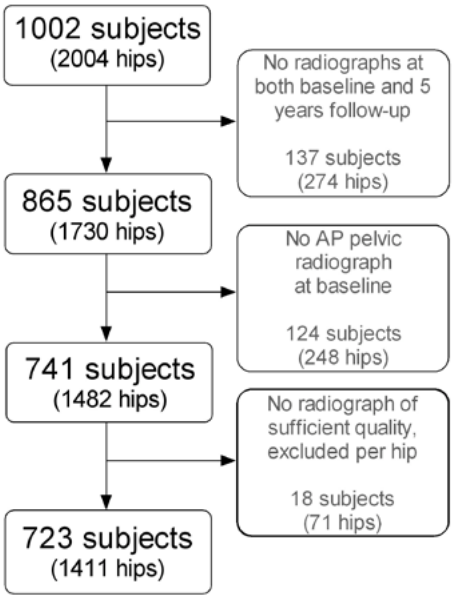


Figure 3. Flow of subjects from the start of the cohort to the final study population.

Osteoarthritis classification

Of the 1411 included hips, 4.25% (n=60) developed incident osteoarthritis and 2.76% (n=39) end-stage osteoarthritis within 5 years follow-up. THR patients did not have other hip pathology than osteoarthritis nor other hip surgery during follow-up.

At baseline, the K&L grade could be scored reliably in 1389 hips. Of these hips, 76% had no signs of radiographic hip osteoarthritis (K&L grade 0) and 24% had doubtful radiographic hip osteoarthritis (K&L grade 1). On the faux profil view, superior joint space narrowing was scored as grade 0 in 94%, grade 1 in 5%, and grade 2 in 1% (n=1379), and inferior joint space narrowing as grade 0 in 95% and grade 1 in 5% (n=1378). Of those hips having K&L grade 0 on the anteroposterior view, 2% had a superior and 5% an inferior joint space narrowing grade 1 on the faux profil view.

Table 1. Baseline characteristics of the participants, stratified by the absence or presence of end-stage osteoarthritis and incident osteoarthritis.

	Total n=723 (1411 hips)	Absence of end-stage osteoarthritis at follow-up n=686 (1372 hips)	Presence of end-stage osteoarthritis at follow-up n=37 (39 hips)	p-value Absence vs presence of end-stage osteoarthritis at follow-up	Absence of incident osteoarthritis at follow-up n=669 (1312 hips)	Presence of incident osteoarthritis at follow-up n=52 (60 hips)	p-value Absence vs presence of incident osteoarthritis at follow-up
Age in years: mean (±SD)	55.9 (5.20)	55.9 (5.2)	57.7 (4.2)	0.032	55.8 (5.2)	58.2 (4.9)	0.001
Women, No. (%)	575 (80)	552 (80)	23 (62)	0.004	538 (80)	36 (69)	0.017
BMI, kg/m²: mean (±SD)	26.1 (4.1)	26.1 (4.2)	25.4 (4.0)	0.25	26.2 (4.2)	26.0 (3.5)	0.78
Length in cm: mean (±SD)	169.9 (8.2)	169.8 (8.2)	171.3 (9.3)	0.44	169.7 (8.1)	173.1 (8.5)	0.003
Weight in kg: mean (±SD)	75.3 (13.6)	75.3 (13.7)	74.6 (13.0)	0.97	75.2 (13.7)	78.0 (12.7)	0.064
K&L grade 0, No (%)	1058 (76)	1048 (78)	10 (26)	<0.001	1042 (80)	6 (11)	<0.001
K&L grade 1, No (%)	331 (24)	302 (22)	29 (74)	<0.001	253 (20)	49 (89)	<0.001

For the comparison between absence and presence of incident OA, hips which developed end-stage OA were excluded.
BMI, body mass index; K&L, Kellgren and Lawrence.

Osteoarthritis classification

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Association between cam-type deformity and osteoarthritis

When adjusted for confounders, only hips with a moderate cam-type deformity (alpha angle >60°) were significantly associated with development of incident osteoarthritis OR=2.42 (95% CI 1.15 - 5.06, p=0.020, see table 2). The positive predictive value was 12.2%.

A cam-type deformity at baseline was strongly associated with end-stage osteoarthritis (Table 3 and Figure 2). In particular, the OR for a severe cam-type deformity (alpha angle >83°) was high (9.66, 95% CI 4.72 – 19.78, p<0.00001). Furthermore, the positive predictive value for end-stage osteoarthritis when having a cam-type deformity as determined by an alpha angle greater than 83° and greater than 60° was 25.0% and 10.9%, respectively.

Table 2 Association (n=1372 hips) between cam impingement parameters and incident osteoarthritis (n=60) at 5-year follow-up

Cam impingement parameter		Incident	No Incident	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Radiographic	**Alpha angle >60º** Referent group ≤60º	n = 19/139 n=41/1233	n = 120/139 n=1192/1233	4.43 (2.36-8.32) **p<0.0001**	2.42 (1.15-5.06) **p=0.020**
	Alpha angle >83º Referent group ≤83º	n = 4/42 n=56/1330	n = 38/42 1274/1330	2.25 (0.78-6.44) p=0.13	1.09 (0.35-3.38) p=0.88
Clinical	**Hip internal rotation ≤20º** Referent group >20º	n =15/200 n=45/1172	n = 185/200 n=1127/1172	2.27 (1.19-4.33) **p=0.013**	1.47 (0.74-2.90) p=0.27
Combined	**Alpha angle>83º and hip internal rotation ≤20º** Referent group: hips not having both conditions	n = 1/9 n=59/1363	n = 8/9 n=1304/1363	2.97 (0.49-18.17) p=0.24	0.75 (0.10-5.68) p=0.78

† Adjusted OR was corrected for K&L grade, age, body mass index, and sex at baseline.

Reduced internal rotation of 20° or less at baseline was significantly associated with the development of end-stage osteoarthritis, expressed by an adjusted OR of 7.13 (95% CI 3.38-15.04, p<0.00001). The positive predictive value for end-stage osteoarthritis was 10.3%. Data on ROM and pain scores in hips with cam-type deformity compared with normal hips are presented in Table 4.

There was a strong association between the combination of clinical and radiographic parameters suggestive of cam impingement and end-stage osteoarthritis. Individuals with both an alpha angle greater than 83° and internal rotation of 20° or less at baseline were at high risk of end-stage osteoarthritis within five years (Table 3 and Figure 2). The strength of this association by means of an adjusted OR was 25.21 (95% CI 7.89-80.58, p<0.00001) and the positive predictive value was 52.6%.

Reliability and reproducibility of the alpha angle

The ICC score for interobserver reliability was 0.73 for the alpha angle. ICC scores for intra-observer reliability ranged from 0.85-0.99.

Table 3 Association (n=1411 hips) between cam impingement parameters and end-stage osteoarthritis (n=39) at 5-year follow-up

Cam impingement parameter		No end-stage osteoarthritis at follow-up	=End-stage osteoarthritis At follow-up	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Radiographic	**Alpha angle >60º** Referent group ≤60º	n = 139/156 n=1233/1255	n = 17/156 n=22/1255	6.82 (3.55-13.10)	3.67 (1.68-8.01)
	Alpha angle >83º Referent group ≤83º	n = 42/56 1330/1355	n = 14/56 n=25/1355	17.71 (8.71-36.02)	9.66 (4.72-19.78)
Clinical	**Hip internal rotation ≤20º** Referent group >20º	n = 200/223 n=1172/1188	n =23/223 n=16/1188	9.34 (4.66-18.71)	7.13 (3.38-15.04)
Combined	**Alpha angle>83º and hip internal rotation ≤20º** Referent group: hips not having both conditions	n = 9/19 n=1363/1392	n = 10/19 n=29/1392	53.79 (20.96-138.08)	25.21 (7.89-80.58)

All p-values for OR are <0.0001
† Adjusted OR are corrected for K&L grade, age, body mass index, and sex at baseline.

Table 4 Range of motion and pain scores in all hips and in hips with a cam-type deformity.

	Clinical Parameter	Total (n=1411*)	Alpha angle >60° (n=156) p-value†	Alpha angle >83° (n=56) p-value‡
Range of motion mean (±SD)	Internal rotation	30.64 (8.67)	26.31 (8.61) <0.001	25.76 (9.59) <0.001
	External rotation	29.27 (9.88)	27.00 (8.62) 0.002	25.08 (7.53) 0.01
	Flexion	118.64 (11.21)	117.10 (12.47) 0.18	117.27 (12.99) 0.31
	Adduction	21.73 (8.40)	20.19 (8.61) 0.23	19.74 (9.24) 0.02
	Abduction	33.81 (10.95)	31.56 (10.03) 0.72	30.56 (10.42) 0.30
Pain scores mean (±SD)	WOMAC pain subscale	24.43 (16.93)	23.56 (16.75) 0.45	23.39 (19.07) 0.33
	VAS current pain	2.96 (2.10)	3.23 (2.14) 0.10	3.23 (2.23) 0.41
	VAS pain during previous week	3.50 (2.14)	3.48 (2.17) 0.88	3.36 (2.14) 0.43

Abbreviations: VAS, visual analog scale; WOMAC, Western Ontario and McMaster University Osteoarthritis Index
* n=1410 for internal rotation and flexion, n=920 for external rotation, adduction, and abduction
† Compared with hips with alpha angle ≤60°
‡Compared with hips with alpha angle ≤83°

DISCUSSION

This first prospective study on cam impingement shows a strong association between cam impingement in radiographically non-arthritic individuals presenting with the first onset of pain complaints at baseline, and the development of osteoarthritis within five years. The results indicate that hip incongruity by a cam-type deformity is highly predictive of especially fast progression to end-stage osteoarthritis.

The data suggest that the risk for end-stage osteoarthritis is higher when the cam-type deformity is more pronounced. This is in line with a study reporting a correlation between the magnitude of the alpha angle and the severity of acetabular cartilage damage as measured with delayed gadolinium-enhanced contrast MRI of cartilage.[262] Another group examining the relationship between morphological parameters and the risk of receiving THR within 19 years, concluded that the alpha angle was significantly associated with THR in women, independent of the presence of radiographic hip osteoarthritis at baseline; they reported an adjusted OR for receiving a THR of 1.052 for every degree increase in the alpha angle.[63]

Cross-sectional studies have shown a positive association between cam morphology and osteoarthritis. One study showed an estimated OR of 2.2 for having a non-spherical femoral head and osteoarthritis as defined by a minimum joint space width of 2 mm or less.[60] Another group found an estimated OR (adjusted for confounders) of 6.95 (95% CI 4.64-10.41) for the association of a visually scored non-spherical femoral head with osteoarthritis in a case-control study.[208] This latter value lies within the range of our findings for a radiographic cam-type deformity.

In those studies it was noticed that a non-spherical head could also partly be a consequence of rather than a cause of osteoarthritis. However, in the present study, as all hips had only doubtful or no signs of radiographic osteoarthritis at baseline, we could exclude a cam-type deformity from being a consequence of osteoarthritis. In addition, we found no increase in cam-type deformity over time, as the alpha angle at 5 years follow-up did not differ from that at baseline in either normal hips or hips that developed osteoarthritis. This indicates that cam-type deformity is probably not a consequence of a dynamic remodelling process in this adult cohort, but is a more or less static phenomenon. There is some evidence that this deformity develops during puberty by (over)active participation in certain sports.[226,227]

As only four hips had a K&L score of 3 or greater, most of the hips were judged to be end-stage osteoarthritis based on having received a THR. Although THR

is a validated and clinically relevant osteoarthritis outcome measure,[220] some concern might rise as to whether end-stage osteoarthritis was truly the reason for surgery and not pain caused by the cam-type deformity itself. At baseline, subjects with a cam-type deformity did not have more pain (see table 4). Nor did we find any difference in pain scores between the subjects with a cam-type deformity and a normal hip within the group that underwent THR. Furthermore, of all the hips that underwent THR within 5 years, the hips with a cam-type deformity demonstrated a more severe osteoarthritis score than normal hips already after 2 years of follow-up. Together, this suggests that the reason for a THR in individuals with a cam-type deformity was most likely the fast progression of osteoarthritis, and not pain due to impingement. This is further supported by the fact that two of the four hips with a K&L score of 3 or greater also had a cam-type deformity at baseline.

Because there is no consensus on how to quantify a cam-type deformity, we used two threshold values. Osseous abnormalities below the threshold value of 60° are suggested to pose less of a risk for developing hip pain.[259] A value of 83° was defined as a pathological threshold value based on anteroposterior radiographs in a large cross-sectional cohort of 2803 asymptomatic individuals.[260] Interestingly, in our cohort, when studying the distribution of the alpha angle at baseline, hips with a cam-type deformity (alpha angle >60°) appear to be a clearly different cluster from hips with a normal alpha angle (figure 2).

The main limitation of the present study is the use of anteroposterior radiographs only. Because cam-type deformities are located in the anterolateral head-neck junction and might be missed on an anteroposterior radiograph, the prevalence of cam-type deformities might have been underestimated.[67,263] Of the hips that developed end-stage osteoarthritis, at baseline 12 hips had clinical signs suggestive of impingement but no radiographic cam-type deformity; three of these hips were non-clinical forms of hip dysplasia as seen by a dysplastic appearance on the osteoarthritis radiograph (centre-edge angle <25°). The remaining nine hips might have had a cam-type deformity not visible on the anteroposterior view. Cohorts using MRI might elucidate this uncertainty.[264] Nevertheless, anteroposterior radiographs are extensively used in clinical practice; on these radiographs, a simple measure to predict the risk of end-stage osteoarthritis in individuals with hip complaints would be of considerable value. Moreover, anteroposterior radiographs are a simple and inexpensive tool for use in large cohorts and are the only validated imaging modality for the assessment of osteoarthritis progression in the hip.[265]

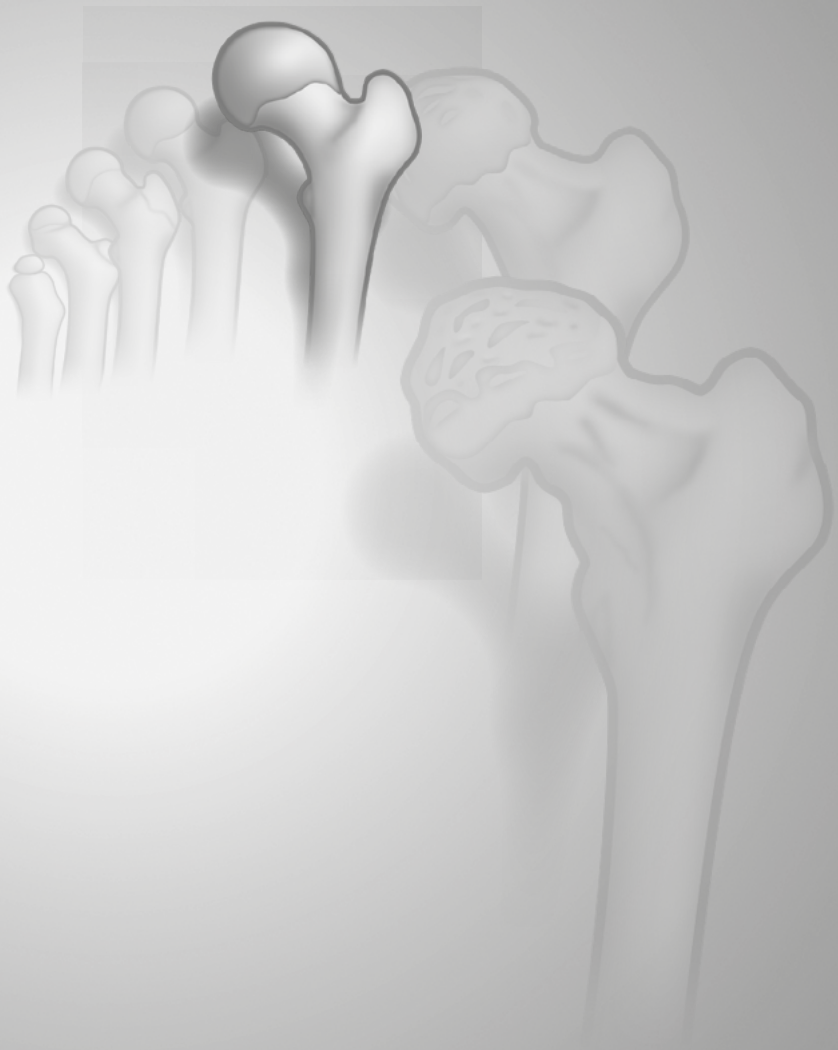
It is important to note that having a radiographic cam-type deformity will not always cause impingement. To distinguish between those who have cam impingement and those who do not, the presence of decreased internal rotation is a useful clinical tool. The combination of clinical and radiographic measures, which can be simply obtained in an outpatient setting, results in an extremely positive prediction for end-stage osteoarthritis. Although the lower CI limit is still 7.89, one should be aware of the wide CI. Furthermore, decreased internal rotation might also be a sign of clinical osteoarthritis, because it is part of the American College of Rheumatology criteria for clinical osteoarthritis.[32] However, decreased internal rotation due to clinical osteoarthritis would be more likely in a more advanced stage of the disease than in our cohort at baseline. In addition, it has been shown that internal rotation of the hip is largely determined by the osseous structures of the hip, which makes impingement a plausible explanation for decreased internal rotation.[216]

Individuals with symptomatic cam impingement are eligible for treatment of the deformity in an open or arthroscopic surgical procedure in which the femoral head is shaved to its normal congruity.[266] Such a treatment is currently performed with increasing frequency in an attempt to relieve complaints and to halt the destructive cascade. The short-term and mid-term results of this treatment show a relief in pain and an increase in hip function; however, no randomised (placebo) controlled trial is available and the long-term results on the prevention of osteoarthritis are unknown.[267] The findings of the present study justify further study on the treatment of cam impingement, and indicate that follow-up periods of a few years seem sufficient to show a potential effect of treatment.

In conclusion, cam impingement is strongly related to the development of hip osteoarthritis. Our results indicate that individuals who present with the first onset of pain complaints, and have both a radiographic cam-type deformity and reduced internal hip rotation, are at high risk of fast progression to end-stage osteoarthritis. A cam-type deformity might be a modifiable risk factor that can be diagnosed before severe hip damage is present, providing an opportunity to prevent hip osteoarthritis.

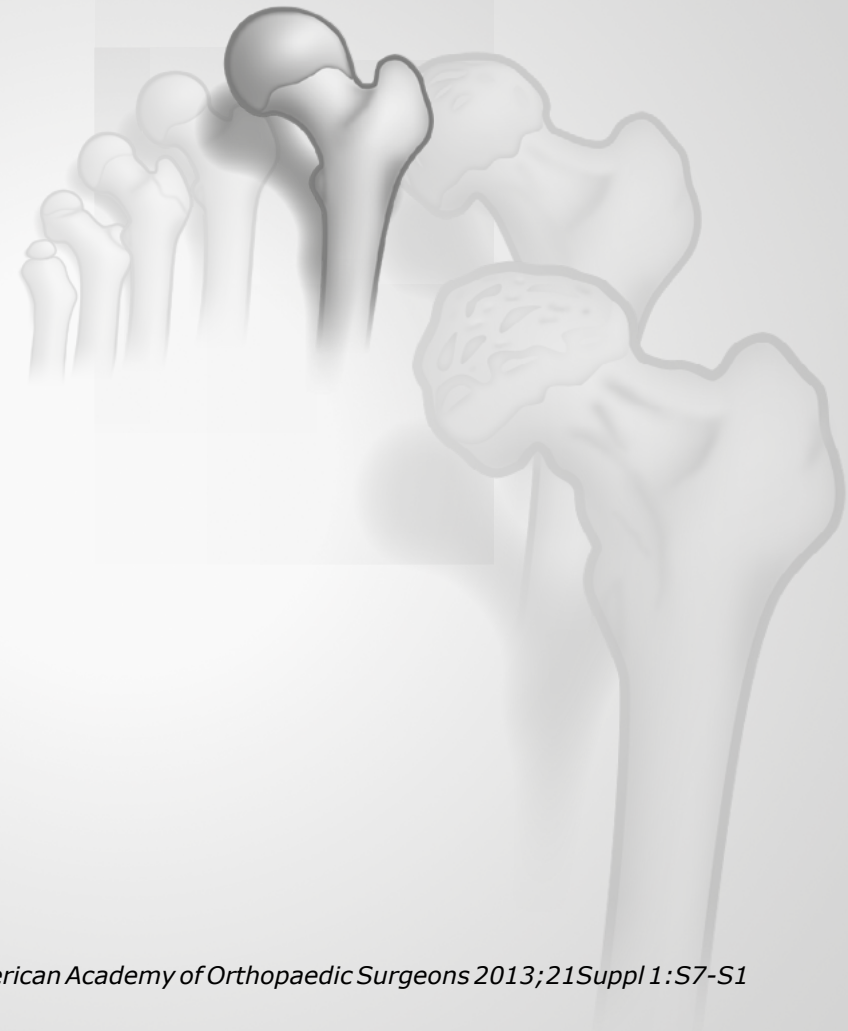
PART 2

Definition of femoroacetabular impingement



Chapter 7

Femoroacetabular impingement: Defining the condition and its role in the pathofysiology of osteoarthritis



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ABSTRACT

Femoroacetabular impingement (FAI) is an increasingly recognized cause of hip pain. It is best defined as a pathological mechanical process by which morphologic abnormalities of the acetabulum and/or femur combined with vigorous hip motion lead to repetitive collisions that damage the soft-tissue structures within the joint itself. Based on cross-sectional studies in which FAI morphology was studied before the presence of radiographic osteoarthritis (OA), and on prevalence studies in younger, asymptomatic persons, it is clear that FAI and its morphologic risk factors are common in young adult hips and predispose to the later development of OA in certain patients. Longitudinal studies also support the assertion that, in middle-aged adults, the presence of cam deformities at baseline substantially increases the risk of developing OA and the need for total hip arthroplasty. More long-term data are needed to better define the natural history of pincer deformities as well as FAI in younger cohorts.

INTRODUCTION

Femoroacetabular impingement (FAI) is an increasingly recognized and treated condition in patients presenting with pain about the hip, particularly active young adults. In spite of the increased interest in this condition, the nature of this clinical entity remains ill defined. Furthermore, the idea that FAI may be a risk factor for the development of early hip osteoarthritis (OA) is viewed by many as unproven. The primary purpose of this article is to define FAI, with the goal of developing an operational definition for the purpose of clinical trial planning. Secondary goals are to summarize the current knowledge about the possible relationship between FAI and the later development of hip OA and to define areas for future research.

Defining the condition

the Medical Subject Headings thesaurus of the US National Library of Medicine defines femoroacetabular impingement as a clinical entity in which a pathologic mechanical process causes hip pain when morphologic abnormalities of the acetabulum and/or femur, combined with vigorous hip motion (especially at the extremes), lead to repetitive collisions that damage the soft-tissue structures within the joint itself. This definition contains five essential elements: (1) abnormal morphology of the femur and/or acetabulum, (2) abnormal contact between these two structures, (3) especially vigorous supraphysiologic motion that results in such abnormal contact and collision, (4) repetitive motion resulting in the continuous insult, and (5) the presence of soft-tissue damage. Although FAI can be further divided into subcategories based on whether the primary deformity is situated in the femur, acetabulum, or both, these five elements are both necessary and sufficient for diagnosis.[55]

Although hip symptoms are not among the five essential elements of FAI required for an operational definition to determine eligibility for clinical trials investigating the management of FAI, individuals should be symptomatic in the affected hip. Their clinical presentations, based on the history and physical examination, should be consistent with the diagnosis of FAI.[268,269] This generally includes the gradual onset of hip pain, which occasionally may radiate laterally toward the trochanteric region, medially into the adductor region, and rarely into the buttocks or even down to the knee. In most patients, symptoms are exacerbated by periods of hip flexion, such as prolonged sitting. Typical findings include loss of motion, particularly with hip flexion and internal rotation, and a positive impingement test (ie, pain with hip flexion to 90°, adduction, and internal rotation).[269]

Imaging of the affected hip should demonstrate morphologic characteristics consistent with FAI. Examples of imaging findings consistent with FAI include an increased alpha angle, impingement cysts (eg, herniation pits) at the head-neck junction, crossover and/or posterior wall signs, and an increased lateral center-edge angle.[224,269,270] All three elements (ie, symptoms, clinical presentation, imaging findings) should be present in any patient who is being considered for inclusion into a prospective study or clinical trial investigating the treatment of FAI. Studies investigating the diagnosis or natural history of FAI may not require the presence of symptoms. From a clinical practice perspective—and potentially for OA prevention trials—hips with fewer than all three elements present still might suffer from FAI. For example, hips with radiographically normal morphology may impinge during activities that involve extreme hip motion.

FAI and osteoarthritis: Cause and effect

Evolving concepts regarding the etiology of hip OA suggest that in most cases, an underlying cause can be identified. In 1976, Solomon[50] suggested that <10% of OA was primary, with no other known factor implicated in the pathogenesis. In >90% of cases, however, a causative factor could be identified, including mechanical, inflammatory, metabolic, or biologic conditions. After introducing the modern concept of FAI, Ganz et al.[240] also argued that ≥90% of hip OA could be attributed to an underlying condition, with mechanical factors such as acetabular dysplasia and impingement playing the largest roles.

The contemporary theory of FAI as a causative factor in the development of OA has been championed by Ganz et al.[55] and holds that the morphologic abnormalities of the femoral head and/or acetabulum result in abnormal contact between the femoral neck and head and the acetabular margin. This leads to supraphysiologic stress that causes tearing of the labrum and avulsion of the underlying cartilage region.[240,269] The continued abnormal contact results in further deterioration and wear of the articular cartilage, with the eventual onset of arthritis. Questions remain, however, about whether FAI is a cause or a result of OA, and whether the joint deformities in FAI are congenital or developmental or are the reaction to the arthritic process, as in the case of osteophytes. For example, osteophyte formation at the femoral head-neck junction resulting from OA can restrict joint motion, leading to secondary FAI.

Recent epidemiologic studies have attempted to clarify the role of FAI in the pathogenesis of OA. Previous cross-sectional, population-based studies in elderly patients with existing OA have confused this issue because it is difficult to differentiate premorbid impingement-related morphology from advanced bony

changes secondary to OA (eg, osteophyte formation, femoral remodeling).[271] More recent cross-sectional studies with younger subjects have demonstrated that a relatively high prevalence of morphologic abnormalities associated with FAI exists in patients with minimal or no symptoms (table 1). Reichenbach et al.[272] reported on 1,080 asymptomatic military recruits in Sumiswald, Switzerland, of whom 430 were selected randomly; 244 underwent radial MRI to evaluate for abnormal morphology at the head-neck junction. In this asymptomatic cohort with a mean age of 19.9 years, the adjusted overall prevalence of cam-type deformity was 24% (95% confidence interval [CI], 19 – 30).

In a follow-up study, the presence of cam deformity in asymptomatic hips was associated with MRI evidence of labral lesions (adjusted odds ratio [OR], 2.77 [95% CI, 1.31–5.87]) and impingement pits (adjusted OR, 2.9 [95% CI, 1.43–5.93]).[264] The adjusted mean difference in combined anterosuperior femoral and acetabular cartilage thickness was -0.19 mm (95% CI, -0.41 to 0.02) lower in those with cam-type deformities than in those without. Recent evidence also suggests that cam deformities are more common in adolescents who participate in high-impact sports and, thus, may be acquired during skeletal maturation.[227,278]

Jung et al.[277] evaluated 838 asymptomatic hips in 419 randomly selected patients aged 25 to 92 years who underwent abdominal or pelvic CT for other medical diseases unrelated to the hip. AP scout views of CT scans, which provide information similar to that of AP pelvic radiographs, were used to measure asphericity of the femoral head-neck junction using the alpha angle as described by Nötzli et al.[224] Study participants were classified according to criteria defined by Gosvig et al.[260] based on the Copenhagen Osteoarthritis Study. For men, three ranges of values were defined for the alpha angle: pathologic (≥83°), borderline (69° to 82°), and normal (≤68°). For women, these values were pathologic (≥57°), borderline (51° to 56°) and normal (≤50°).[277] In 49 men aged ≤50 years, the mean alpha angle was 57.2°, with 14% demonstrating pathologic alpha angles. A similar magnitude and distribution of alpha angles were found in men older than 50 years. In 107 women younger than 50 years, the mean alpha angle was 45.3°, with 7% demonstrating pathologic alpha angles. The authors reported similar findings in 433 women older than 50 years.

Table 1. Prevalence of FAI findings in asymptomatic persons

Study	Sample Characteristics	Mean Age in Years (Range)	Sex (M/F [%])	No. of Patients (No. of Hips)	Imaging Modality
Kang et al.[273]	Abdominal pain or trauma	— (15–40)	54/46	50 (100)	CT
Pollard et al.[274]	General population with no evidence of OA	46 (22–69)	47/53	83 (166)	Cross-table lateral radiography
Reichenbach et al.[272]	General population	19.9 (18–24)	All male	244 (244)	MRI
Hack et al.[275]	General population	29.4 (21–50.6)	44/56	200 (400)	MRI
Gosvig et al.[60]	General population	60.5 (21–90)	37/63	3,620 (7,240)	AP radiography
Laborie et al.[276]	General population (young adults)	18.6 (17.2–20.1)	42/58	2,060 (4,120)	AP and frog-leg lateral radiography
Jung et al.[277]	Persons undergoing CT for disease unrelated to the hip	60.4 (25–92)	28/72	380 (755)	AP scout CT
Kapron et al.[278]	Collegiate football players	21 ± 1.9	All male	67 (134)	AP and frog-leg lateral radiography

[a] Multiplanar imaging was used in three studies [b]Prevalence per joint [c] Visually scored (semiquantitatively). AA = alpha angle, AI = acetabular index, AOR = anterior offset ratio, AVA = acetabular version angle, FAI = femoroacetabular impingement, FHNO = femoral head-neck offset, FP = focal prominence, IR = internal rotation, IS = impingement sign, LCEA = lateral center-edge angle, OA = osteoarthritis, PGD = pistol grip deformity, PWS = posterior wall sign, TI = triangular index

Table 1. Prevalence of FAI findings in asymptomatic persons *(Continued)*

Clinical Exam for FAI?	Pattern of Deformity	Measurement and Threshold Value	Prevalence	Prevalence Notes
No	Pincer	AVA <15°	14%[b]	Overall: 52% of males and 33% of females had ≥1 sign of FAI. ≥66% of findings were bilateral.
		Crossover sign	20%[b]	
		LCEA >40°	16%[b]	
	Cam	FHNO <8 mm	12%[b]	
		AA >55°	10%[b]	
No	Cam	AA >62°	All: 10%	Males, 13%; females, 7%
		AOR <0.14 (left and right hip averaged)	All: 5%	Males, 8%; females, 2%
IR	Cam	Definite or severe deformity[c]	24%	48% in those with IR < 30° 13% in those with IR > 40°
IR, IS	Cam	AA >50.5° in 3:00 (anterior) position	14% in ≥1 hip (3.5% bilateral)	Males, 24.7%; females, 5.4%
		AA >50.5° in the 1:30 (anterosuperior) position	53% in ≥1 hip (27% bilateral)	Males, 75.3%; females, 35.1%
		AA >55° in the 1:30 (anterosuperior) position	33.5% in ≥1 hip (13% bilateral)	Males, 51.7%; females, 18.9%
No	Cam	TI ≥0 mm	All: 10.5%	Males, 19.6%; females, 5.2%
	Pincer	LCEA ≥45°	All: 17.8%	Males, 15.2%; females, 19.4%
	Combined		All: 1.6%	Males, 2.9%; females, 0.9%
No	Cam	PGD, FP of femoral neck, flattening of femoral head	All: ≥1 finding[c] in 20.6%	Males, 35%; females, 10.2%
	Pincer	Crossover sign, PWS, excessive acetabular overcoverage	All: ≥1 finding[c] in 24.1%	Males, 34.3%; females, 16.6%
No	Cam	Pathologic (males): AA ≥83°	14%[b]	
		Borderline (males): AA 69°–82°	14.9%[b]	
		Pathologic (females): AA ≥57°	5.6%[b]	
		Borderline (females): AA 51°–56°	6.1%[b]	
No	Cam	AA >50°	72%[b]	78%[b] had ≥1 sign of cam deformity
		FHNO <8 mm	64%[b]	
	Pincer	LCEA >40°	7%[b]	66%[b] had ≥1 sign of pincer deformity
		AI <0°	16%[b]	
		Crossover sign	61%[b]	
	Combined	Mixed impingement	50%[b]	95%[b] had ≥1 sign of cam or pincer deformity

[a] Multiplanar imaging was used in three studies [b]Prevalence per joint [c] Visually scored (semiquantitatively). AA = alpha angle, AI = acetabular index, AOR = anterior offset ratio, AVA = acetabular version angle, FAI = femoroacetabular impingement, FHNO = femoral head-neck offset, FP = focal prominence, IR = internal rotation, IS = impingement sign, LCEA = lateral center-edge angle, OA = osteoarthritis, PGD = pistol grip deformity, PWS = posterior wall sign, TI = triangular index

The Genetics of Osteoarthritis and Lifestyle (GOAL) study recruited subjects from Nottingham, United Kingdom, and compared hip morphology in 566 persons with unilateral hip OA with the contralateral asymptomatic hip as well as with nonosteoarthritic control hips in 1,100 patients who had undergone intravenous urography.[208] The assumption was that hip morphology was symmetric and that the contralateral hip represented the premorbid state. All patients were aged ≥45 years (mean, 66 years), and 48% of the subjects were women. Cam morphology was defined as a ratio of head-to-neck diameter <1.27. Based on this criterion, the investigators reported a 5.5% risk of developing OA in the contralateral nonosteoarthritic hip, compared with a 3% risk in the control group. Similarly, pistol grip deformity conferred an 8.3% risk of developing OA in the contralateral nonosteoarthritic hip, compared with a 3.6% risk in the control group. Both measures were associated strongly and significantly with an increased risk of developing hip OA, after adjusting for age, body mass index (BMI), and sex.

Longitudinal studies of FAI are also critical to establish the temporal relationship of cause to effect. By their nature, they ensure that the exposure to the risk factor occurs before development of the disease by measuring proximal femoral morphology before it is altered by OA. A prospective study of FAI in the Cohort Hip and Cohort Knee (CHECK) study reported on a Dutch national sample of 723 patients presenting for the first time with recent onset of hip or knee pain, thereby representing a sample of early potential OA.[203] Of the cohort, 80% were female, ranging in age from 45 to 65 years. Subjects had doubtful or no OA at baseline, with a Kellgren-Lawrence osteoarthritic grade of 0 or 1 (76% and 24%, respectively). Initial AP pelvic radiographs were measured to determine the alpha angle, and subjects were followed for 5 years to determine the risk of developing end-stage OA. Hips with a baseline AP alpha angle >83° had a 25% risk of developing end-stage OA within 5 years, compared with a <2% risk of end-stage OA in hips with an alpha angle of <83° (OR, 9.7 [adjusted for age, sex, BMI, and baseline Kellgren-Lawrence grade]). Interestingly, hips with both an alpha angle >83° and decreased internal rotation ≤20° had a 53% risk of developing end-stage OA within 5 years.

Gregory et al.[206] performed a longitudinal study of hip OA in a population-based sample drawn from residents of Rotterdam, the Netherlands. In the study, 835 subjects aged 55 to 80 years underwent an initial AP pelvic radiograph, with a follow-up radiograph 6 years later. Of these, 57% had no definite evidence of OA at baseline (Kellgren-Lawrence grade 0 or 1). Progression to significant OA at the 6-year follow-up was defined by the need for total hip arthroplasty (THA) or the presence of Kellgren-Lawrence grade 3 or 4 OA. Statistical shape modeling was used to characterize the main variants in shape of the proximal femur at baseline

and in changes over time. Baseline shape variants were compared between 55 patients with minimal arthritis (Kellgren-Lawrence grade 0 or 1) who developed advanced arthritis or needed THA compared with 55 control subjects with no arthritic progression. Statistical shape mode scores that were consistent with flatter baseline femoral heads and reduced femoral head-neck offset in patients without OA at baseline were associated significantly with an increased risk of developing OA and requiring THA. For each standard deviation difference in this femoral head shape mode score, the risk of developing advanced radiographic OA of the hip increased 62% and the risk of THA increased 135%.

The Chingford cohort is another recent longitudinal study of the relationship between hip morphology and the development of OA.[63] The study enrolled 1,003 healthy women aged 44 to 67 years after they underwent baseline AP radiography of the pelvis, which was measured for several morphologic characteristics, including the presence of cam and pincer deformity. At 19-year follow-up, these radiographs were repeated. The baseline hip morphology of the 25 hips that went on to require THA was compared with a random sample of 243 hips that did not require THA. The median AP alpha angle in those who required THA was 62.4° at baseline, compared with 45.8° in the control group (P = 0.001). The odds ratio of needing a THA increased 1.05 for each 1° increase in initial alpha angle. Additional results from the Chingford cohort were presented at the 2012 Osteoarthritis Research Society International meeting in Barcelona, Spain. In women, hips with an AP alpha angle ≥65° at baseline had a higher risk of incident radiographic hip OA than did those with an alpha angle of <65°. The odds ratio was 2.7, adjusted for age, BMI, and baseline hip joint space width (P <0.001). Although this and other longitudinal studies show strong associations between cam deformities and later OA (table 2), it should be noted that, in this study, as in the others, the overwhelming majority of hips with cam deformities did not reach end points of THA or radiographic OA even up to approximately a 19-year follow-up.[63]

Table 2. Association of femoroacetabular impingement with osteoarthritis

Study	Study Design (Follow-up [y])	Sample Characteristics	Mean Age in Years (Range)	Sex (M/F [%])	No. of Patients (No. of Hips)
Agricola et al.[203]	Prospective cohort (5)	Dutch subjects from CHECK cohort. Baseline K&L grade 0 or 1.	55.9 (46–65)	20/80	723 (1,411)
Nicholls et al.[63]	Longitudinal nested case-control (19)	Chingford cohort. C: THA at 19 y. Con: 243 randomly selected people from UK.	55 (50–60) (IQR)	All female	135 (268 [C:25/ Con: 243])
Gregory et al.[206]	Longitudinal case-control (6)	Dutch subjects (Rotterdam study). Baseline K&L grade 0 or 1. C: OA at FU; Con: no OA at FU.	C: 69 (55–80) Con: 68 (55–78)	C: 25/75 Con: 24/76	C: 55 (110); Con: 55 (110)
Doherty et al.[208]	Case-control	Subjects from GOAL cohort. C: clinically severe OA; Con: persons from UK without OA.	C: 67.7±7.1 Con: 64.3±8.4	C: 50/50 Con: 54/46	2,076 (4,152 [C:965/ Con:1,111])
Reichenbach et al.[264]	Cross-sectional	Subjects from Sumiswald cohort, general population of young adults	19.9 (18–24)	All male	244 (244)
Gosvig et al.[60]	Cross-sectional	Subjects from Copenhagen Heart Study	60.5 (22–90)	37/63	3,620 (7,240)
Chung et al.[66]	Cross-sectional	Subjects from Korean study on health and aging	71.7 (all ≥65 y)	43/57	674 (1,378)
Hartofilakidis et al.[279]	Retrospective analysis (18.5)	Greek subjects with asymptomatic contralateral hips treated for unilateral disease	49.3 (16–65)	32/68	96 (96)
Bardakos and Villar[64]	Retrospective analysis (≥10)	Subjects with PGD and mild or moderate OA at baseline (Tönnis grade 1 or 2)	54 (28–55)	81/19	43 (43)
Clohisy et al.[65]	Retrospective analysis (8.8)	Contralateral hip of subjects ≤50 who underwent THA	44 (23–50)	71/29	70 (70)
Ecker et al.[244]	Retrospective case-control	Contralateral hips of subjects who underwent THA. C: Tönnis grade 2; Con: Tönnis grade 0 or 1	C: 57.5 (36-85) Con: 5.8 (60–82)	C:73/26 Con: 52/48	119 (119) C: 94 Con:25

Table 2. Association of femoroacetabular impingement with osteoarthritis *(Continued)*

Imaging Modality	Clinical Exam for FAI	Definition of OA	Pattern of Deformity	Measurement and Threshold Value	Relation to OA[b]
AP radiography	IR ≤20°	THA or K&L grade ≥3	Cam deformity	AA >60° AA >83°	OR, 3.7 (95% CI, 1.7–8.0) OR, 9.7 (95% CI, 4.7–19.8)
			Cam impingement	AA >83° and IR ≤20°	OR, 25.2 (95% CI, 7.9–80.6)
AP radiography	No	THA	Cam	AA (LM)	OR, 1.052 for every 1° increase in AA
				Modified TI (mm)	OR, 1.296 for every 1-mm increase
			Pincer	LCEA (LM)	NS
AP radiography	No	THA or K&L grade ≥3	Hypothesis-free description of hip shape	Mode 6 (flatter femoral head and reduced head-neck offset)	OR, 1.62 (95% CI, 1.1–2.45) for every 1 SD decrease in mode score
C: AP radiography; Con: IV urography	No	JSW ≥2.5 mm	Cam	PGD[c] FHR <1.27	OR, 7.0 (95% CI, 4.6–10.4) OR, 12.1 (95% CI, 8.1–18.2)
MRI	IR ≤30°	Labral lesions Cartilage	Cam	Definite or severe deformity[c]	OR, 2.77 (95% CI, 1.3–5.9) Cam hips: ~0.2 mm decreased
		thickness			cartilage thickness
AP radiography	No	JSW <2 mm	Cam Pincer	TI ≥0mm LCEA ≥45°	RR, 2.2 (95% CI, 1.7–2.8) RR, 2.4 (95% CI, 2.0–2.9)
AP radiography	No	Minimum JSW ≤2.0mm	Pincer	LCEA ≥40°	NS
		Minimum JSW ≤2.5mm			OR, 2.3 (95% CI, 1.5–3.4)
AP radiography	No	Any subtle indication of decreased JSW and/or osteophyte	Cam	PGD[c] or AA>68 (men), AA >50° (women), or NSA <125°	1/17 hips developed OA
		Formation	Pincer	LCEA ≥35°, IA ≤45°, crossover sign, or PWS	7/34 hips developed OA
			Mixed	Any combination of cam and pincer	9/45 hips developed OA
AP radiography	No	Tönnis grade 3 or THA	Cam	MPFA <84	OR, 20.6 (95% CI, 3.4–34.8) (AA, NSA, LCEA: NS)
			Pincer	PWS	OR, 10.2 (95% CI, 1.0–99.8) (crossover sign, coxa profunda, protrusio acetabuli: NS)
AP, cross-table, and false-profile radiography	No	THA	Cam	AA (LM) FHR (LM)	OR, 1.98 (95% CI, 1.33–2.95) for every 10° increase OR, 0.23 (95% CI, 0.07–0.82) for every 0.1 increase
			Pincer	LCEA (LM)	OR, 0.87 (95% CI, 0.79–0.95)
CT, AP radiography	No	Tönnis grade 2	Cam Pincer	AA (LM) LCEA (LM)	OR, 1.09 (95% CI, 1.03–1.15) OR, 1.14 (95% CI, 1.02–1.27)

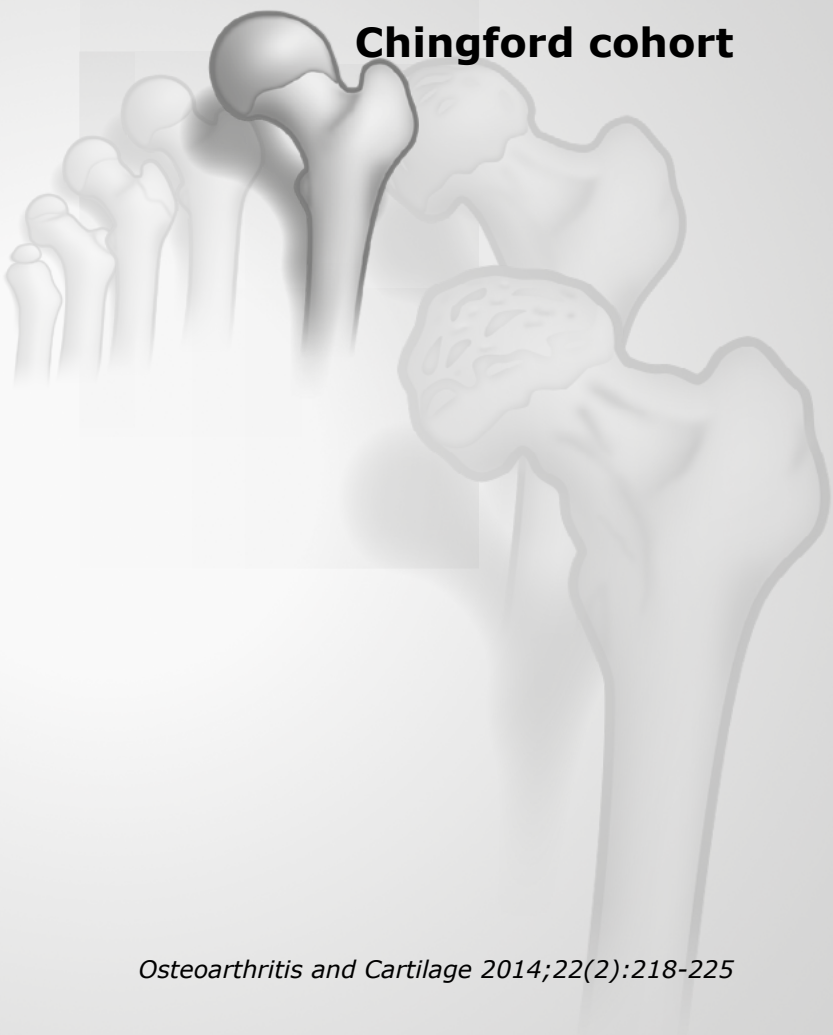
Based on the previously mentioned studies, in which FAI morphology was studied before the presence of radiographic OA, and the prevalence studies in younger, asymptomatic persons, it is clear that FAI and its morphologic risk factors are common in young adult hips and predispose to the later development of OA in certain patients. Longitudinal studies also support the assertion that, in both men and women aged 45 to 65 years, the presence of cam deformities at baseline substantially increases the risk of developing OA and the need for THA. In most hips, however, the presence of a cam lesion is not sufficient in itself to lead to the development of clinically significant and symptomatic OA. Currently, insufficient evidence from longitudinal population studies exists to confirm a similar association between the presence of a pincer deformity and the development of clinical or radiographic OA. It also should be pointed out that many of the longitudinal epidemiologic studies of FAI and hip OA are based on data from AP pelvic radiographs, which are insensitive to milder cam deformities and those located more anteriorly[280] and may not assess pincer deformities accurately.[281] Thus, these epidemiologic studies may underestimate the true association of FAI-related deformities with the risk of developing hip OA. Evidence also is insufficient to demonstrate a causal link between the presence of radiographic FAI morphology, clinical findings of FAI, and FAI-associated tissue damage in younger persons and the long-term risk of developing OA of the hip in mid to late life.

FUTURE DIRECTIONS

Using existing longitudinal population studies, it will be important in the future to determine which persons with FAI-related morphologic abnormalities are at greatest risk of developing hip OA at a relatively young age and which are at increased risk of hip OA in mid to late life. It also will be important to identify the subject- and limb-specific risk factors of OA. We hypothesize that these risk factors are likely to include the type, severity and combinations of the anatomic abnormalities, genetic influences, activity levels, and clinical findings at baseline. In addition, long-term follow-up of younger cohorts is needed to fully describe the natural history of FAI and hip OA and to determine the relationship between the type and severity of intra-articular damage and the longer-term risk of developing clinically significant hip OA. Longitudinal data on the progression of morphologic abnormalities in hips with FAI that are in the process of developing osteoarthritic changes should be used to investigate whether the deformities progress in a way that could increase the risk of hip impingement and worsen the prognosis.

Chapter 8

Cam impingement: defining the presence of a cam deformity by the alpha angle: Data from the CHECK cohort and Chingford cohort



Osteoarthritis and Cartilage 2014;22(2):218-225

ABSTRACT

Introduction Cam impingement is characterized by abnormal contact between the proximal femur and acetabulum caused by a non-spherical femoral head, known as a cam deformity. A cam deformity is usually quantified by the alpha angle; greater alpha angles substantially increase the risk for osteoarthritis (OA). However, there is no consensus on which alpha angle threshold to use to define the presence of a cam deformity.

Aim To determine alpha angle thresholds that define the presence of a cam deformity and a pathological cam deformity based on development of OA.

Methods Data from both the prospective CHECK cohort of 1002 individuals (45-65 years) and the prospective population-based Chingford cohort of 1003 women (45-64 years) with respective follow-up times of 5 and 19 years were combined. The alpha angle was measured at baseline on anteroposterior radiographs, from which a threshold for the presence of a cam deformity was determined based on its distribution. Further, a pathological alpha angle threshold was determined based on the highest discriminative ability for development of end-stage OA at follow-up.

Results A definite bimodal distribution of the alpha angle was found in both cohorts with a normal distribution up to 60°, indicating a clear distinction between normal and abnormal alpha angles. A pathological threshold of 78° resulted in the maximum area under the ROC curve.

Conclusion: Epidemiological data of two large cohorts shows a bimodal distribution of the alpha angle. Alpha angle thresholds of 60° to define the presence of a cam deformity and 78° for a pathological cam deformity are proposed.

INTRODUCTION

Historically, the cause of most hip osteoarthritis (OA) has been defined as 'idiopathic', but recent evidence suggests that development of hip OA is largely influenced by the presence of a cam deformity.[55,203,208] A cam deformity is characterized by extra bone formation at the anterolateral head-neck junction resulting in a non-spherical cam-shaped deformity.[67] It is forced into the acetabulum during flexion and internal rotation of the hip, a process referred to as cam impingement.[75,240] In time and with repeated movement, the cam deformity might damage the soft tissue structures of the hip, leading to pain, decreased function, and subsequently OA of the hip.[63,203,264] In the prospective CHECK cohort, an odds ratio (OR) of 9.7 (95% CI 4.7-19.8) was found for a large cam deformity (alpha angle >83°) at baseline and subsequent development of end-stage OA after 5 years. Moreover, in a case control study within the prospective Chingford cohort, an OR of 1.05 (95% CI 1.02-1.09) was found for every degree increase in alpha angle at baseline and receiving total hip replacement (THR) within 19 years follow-up.[63,203]

The presence of a radiographic cam deformity is a common finding with prevalence numbers of roughly 15-25% in males and 5-15% in females.[60,272,275] The wide range of prevalence reported is mainly due to the inconsistency in the definition of what is a cam deformity. A cam deformity is commonly assessed by the alpha angle, which measures the extent to which the femoral head deviates from spherical.[224] Greater alpha angles increase the risk for development of OA substantially.[63,203,262,282,283] However, there is neither a validated alpha angle threshold value to define the presence of a cam deformity, nor a pathological threshold that indicates an increased risk for development of OA. As a consequence, threshold values ranging from 50° to 83° have been used in literature, which makes prevalence numbers and associations with subsequent pathology difficult to compare and interpret.[75,224,260]

In order to determine alpha angle thresholds, large cohort studies are needed. For that reason, we combined data of the CHECK cohort and Chingford cohort, both with prospective follow-up. Using these data, the aim of this article is to determine an alpha angle threshold for defining the presence of a cam-type deformity, and to determine a pathological alpha angle threshold based on development of OA at follow-up.

METHODS

Study population

The alpha angle threshold values were determined in the CHECK cohort with a current follow-up of 5 years, and in the Chingford study with a follow-up of 19 years.

CHECK is a nationwide multicenter prospective cohort study of 1002 individuals aged 45-65 years (mean 55.9 years) at baseline with symptoms of early OA (pain) of the hip or knee. They had not yet consulted their general practitioner for these symptoms, or the first consultation was within 6 months before entry. Participants with any other pathologic condition that could explain the symptoms were excluded (for hip: other rheumatic disease, previous THR or K&L grade 4, trauma, dysplasia, Perthes disease, subluxation, osteochondritis dissecans, fracture, septic arthritis, bursitis, tendinitis, or previous hip surgery).[210]
The Chingford cohort is a population-based cohort of 1003 asymptomatic women aged 44-67 years (mean 54.2 years) at baseline. These women were registered at a general practice in London and were invited to participate in a study assessing musculoskeletal disease in the population. Yearly clinic visits were performed, which included; morphometric, clinical, biologic, and radiographic measurements.

Radiographs

In the CHECK study, weight-bearing Anterio-Posterior (AP) pelvis radiographs were obtained from the 11 participating research centers according to a standardised protocol, taken at baseline and at 2 and 5 years follow-up. Feet were positioned such that the medial side of the distal part of the first phalanx touched and a wedge was used to assure 15° internal rotation. In the Chingford cohort, each woman had a standardised supine AP pelvis radiograph, taken at years 2, 8 and 20. A small sand bag under the knees was used to minimize hip rotation.
In both the CHECK and Chingford cohorts, AP pelvis radiographs were scored atlas based and 'blind' to clinical details according to the method of Kellgren and Lawrence (K&L) at baseline, and at 5 year follow-up in the CHECK cohort and at year 20 in the Chingford cohort.[211,232]. End-stage OA was defined by K&L grade 3, 4, or total hip arthroplasty (THA) at follow-up.

Alpha angle

The alpha angle measures the extent to which the femoral head deviates from spherical. It is measured by first drawing the best fitting circle around the femoral head, then a line through the centre of the neck and the centre of the head. From the centre of the femoral head, a second line is drawn to the point where the superior surface of the head-neck junction first departs from the circle. The angle between these two lines is the alpha angle (Figure 1).[224]
In both cohorts, the alpha angle was semi-automatically calculated. In the CHECK study, the shape of the proximal femur was outlined by a set of points that were positioned on anatomical landmarks using statistical shape modeling

(SSM) software (ASM tool kit, Manchester University, Manchester, UK). From this points set, the alpha angle was calculated using Matlab (V.7.1.0).[203,221] In the Chingford cohort, the alpha angle was also measured using a validated Matlab based (Matlab R2009b; MathWorks) software package called Hip Morf 2.0.

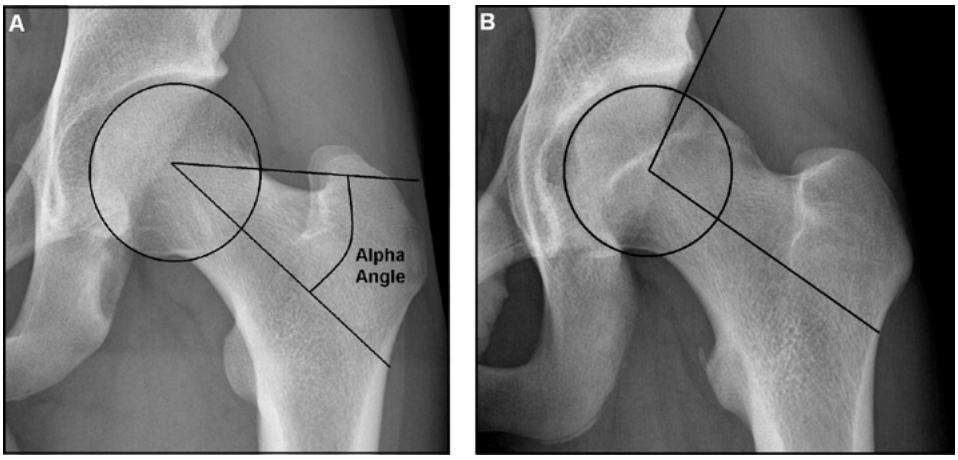


Figure 1. The alpha angle quantifies the asphericity of the femoral head. **A.** a normal alpha angle of 41° is shown representing a spherical femoral head **B.** an abnormal alpha angle of 98° is shown representing a cam deformity.

Reliability of the alpha angle was examined in both cohorts and between both techniques. In the CHECK cohort, interobserver reproducibility was examined by positioning the point set twice in 25 randomly selected hips by three investigators. Intra-observer repeatability was tested for each investigator in 10 randomly selected radiographs. In the Chingford cohort, intra-observer repeatability was assessed by 1 investigator reading 10 randomly selected blinded radiographs on 3 occasions. Interobserver reproducibility was assessed by 2 further observers reading the same 10 radiographs.[63] Finally, in order to examine interobserver reliability between both techniques, the alpha angle was calculated in 30 randomly selected hips using SSM software and Hipmorf 2.0 (14 hips of the CHECK cohort and 16 hips of the Chingford cohort).

Statistics

Reliability of the alpha angle as a continuous measure was assessed using intraclass correlation coefficient (ICC) and Cohen's kappa indicating agreement for whether a hip was classified as having or not having a cam deformity. A Bland-Altman plot was used to visualize agreement in the alpha angle measurements between the two techniques (SSM and Hipmorf).[284]

Explorative analysis showed a bimodal distribution of the alpha angle in both cohorts, indicating two different populations, one without cam deformity and one with cam deformity. To determine the presence of a cam deformity, the optimal threshold that distinguishes between both distributions was assessed. The alpha angle data of all hips in both cohorts were combined and an optimal fit through the data was determined based on a mixture of normal distributions using matlab (V7.1.0). The alpha angle corresponding with the minimum of the fit was used as a threshold to define the presence of a cam deformity. The confidence interval was obtained through bootstrapping using 2000 bootstrap samples. Difference in alpha angle between men and women below the found threshold was calculated using generalized estimating equations.
To define a pathological threshold, end-stage OA at follow-up was used as an outcome. The maximum area under the receiver operating characteristic (ROC) curve was calculated for each possible alpha angle threshold. The maximum area under the ROC curve corresponds with the threshold having the highest sum of sensitivity and specificity for development of OA, which indicates the optimal alpha angle threshold to distinguish between hips with and without end-stage OA at follow-up.
As bilateral hips might not be statistically independent, a sensitivity analysis using one randomly selected hip per person was performed for both the alpha angle threshold that defines the presence of a cam deformity and for the pathological threshold.

RESULTS

Participants CHECK and Chingford

Of the 1002 individuals in the CHECK cohort, 89 were lost to follow-up, 16 were not able to visit the hospital during the five year follow-up, 32 refused to undergo radiographs or had missing radiographs, and 124 were excluded because this first cluster of participants had AP hip radiographs (instead of AP pelvic radiographs) obtained at baseline. Of the remaining 741 individuals (1482 hips), another 71 hips (with a total of 18 subjects because of bilateral involvement) were excluded because the radiographs were of insufficient quality to reliably position the SSM points, leaving 1411 hips in 723 individuals for inclusion with 80% (n=575) being women. Of the included hips, 76% had no signs of radiographic hip OA (K&L=0) and 24% had doubtful radiographic hip OA (K&L=1).
From the initial Chingford cohort of 1,003 individuals at baseline, 795 individuals had AP pelvis radiographs obtained at year 2. Of those, 20 individuals were excluded due to poor radiograph quality. Five hip joints were excluded because they had a metalwork in situ, indicating previous femoral neck fracture. Seventy-

two hip joints were excluded due to excessive tilt. A total of 119 hips in 61 individuals were excluded, leaving 1468 hips in 734 individuals for inclusion at baseline. At baseline, 80% had a K&L score of 0, 6% had a K&L score of 1 and 14% had a K&L score of ≥2.

Reliability and reproducibility of the alpha angle

In the CHECK cohort, the ICC score for interobserver reliability was 0.73 (95% CI 0.56-0.86) and the ICC score ranged from 0.85 (95% CI 0.49-0.96) to 0.99 (95% CI 0.93-1.0) for intra-observer reliability. In the Chingford cohort, the ICC score for interobserver reliability were 0.89 (95% CI 0.80-0.95) and the ICC score ranged from 0.79 (95% CI 0.54-0.91) to 0.95 (95% CI 0.91-0.98) for intra-observer reliability ICC scores.

The ICC score for interobserver reliability using both techniques was 0.66 (95% CI 0.40-0.83). When the alpha angle was analyzed as a dichotomous measure based on the presence or absence of a cam deformity, a Cohen's kappa of 0.85 was found when both techniques were compared. The Bland-Altman plot is shown in figure 2 and illustrates two outliers; no systematic differences between the measurements were identified.

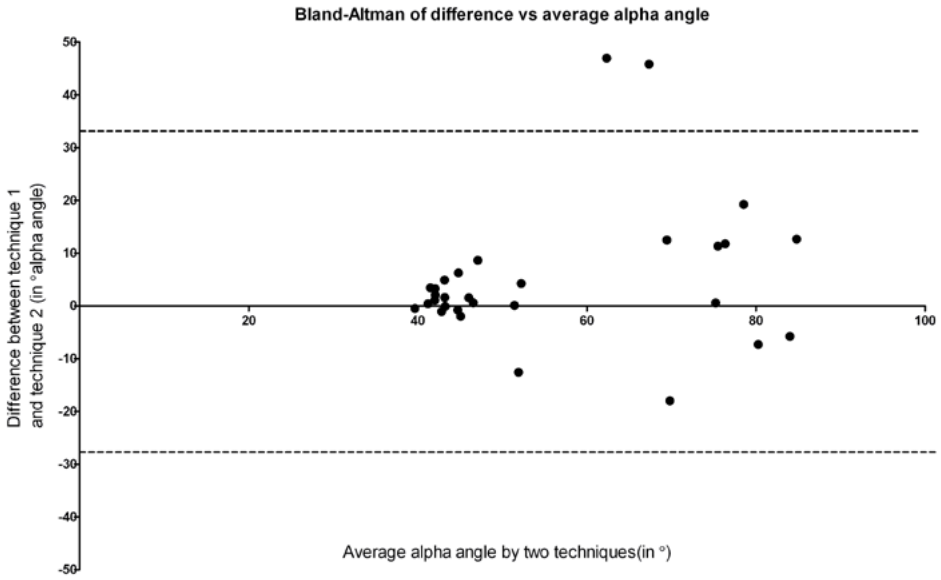


Figure 2. Bland Altman plot. The difference vs average alpha angle showing the agreement in alpha angle measurement of 30 hips between the SSM point set and Hipmorf technique.

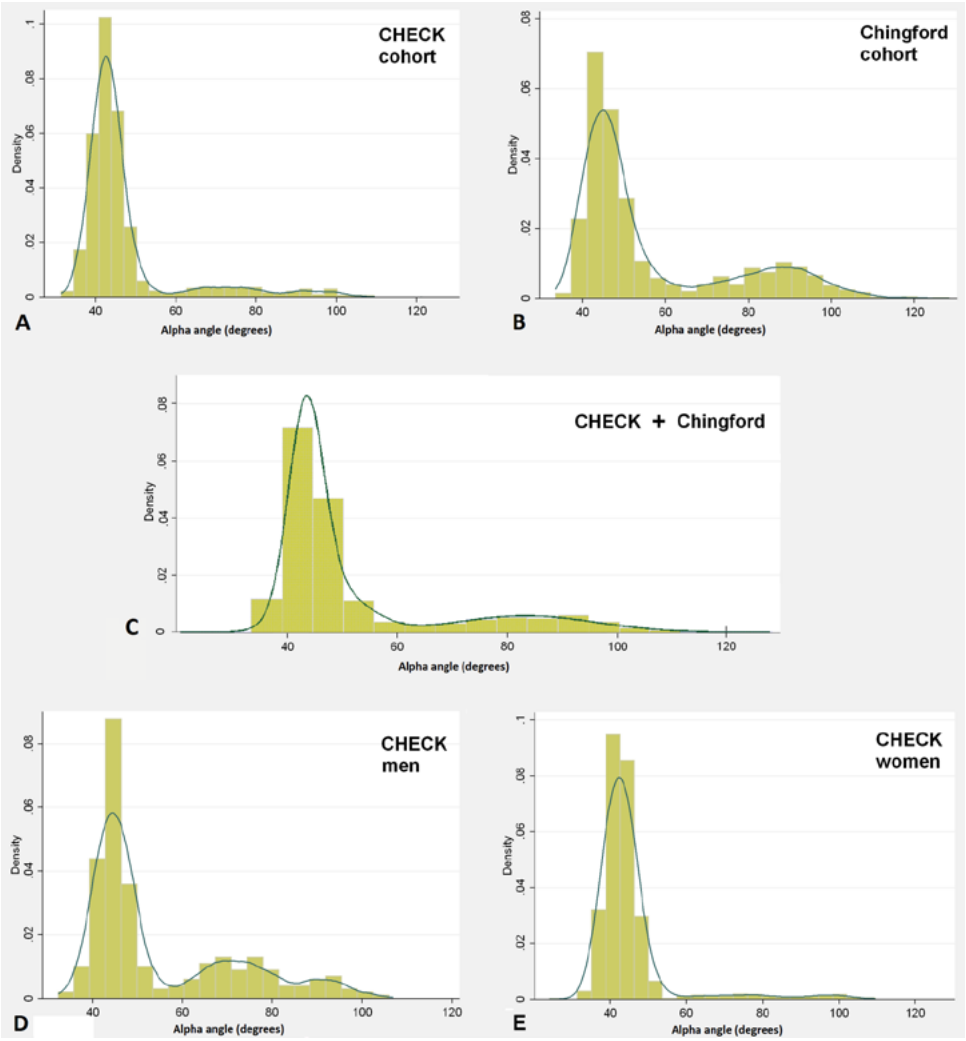


Figure 3. Presence of cam deformity: 60°. Histograms of the alpha angle as measured on anteroposterior radiographs with kernel density plot show a clear bimodal distribution in the CHECK cohort (**A**), the Chingford cohort (**B**), and the combined data of both cohorts (**C**). A corresponding normal distribution of the alpha angle until a value of 60° is shown in both men (**D**) and women (**E**) in the CHECK cohort. These histograms also illustrate the higher prevalence of cam deformity in men than in women.

Threshold for defining the presence of a cam deformity

In both the CHECK cohort and the Chingford cohort, a definite bimodal distribution of the alpha angle was found (figure 3a-b). The optimal fit through the combined data showed a minimum at an alpha angle of 62.7° (95% CI 57.1

– 69.7, figure 3c). The sensitivity analysis comprising one randomly selected hip per person (n=1440 hips) yielded a similar value of 61.5°. Figure 3d-e depicts the distribution of the alpha angle in men and women separately in the CHECK cohort. A corresponding bimodal distribution of the alpha angle was found in both men and women and the higher prevalence of cam deformities in men than in women is clearly illustrated. When analyzing the hips with an alpha angle less than 62.7° in the CHECK cohort, the mean (SD) alpha angle in men 45.0 (± 4.15) was significantly higher than in women 42.7 (± 3.9), p<0.001.

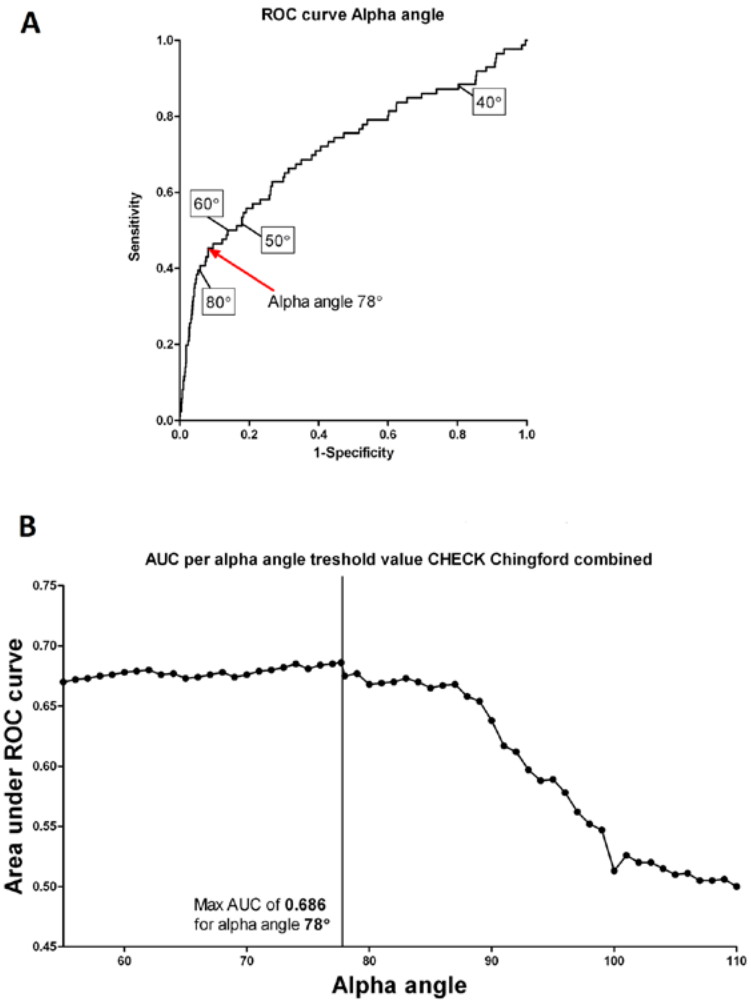


Figure 4. ROC curve. A. the ROC curve of the alpha angle as a continuous measure for end-stage OA is shown, with the pathological threshold of 78° indicated. B The area under the ROC curve for each alpha angle threshold is shown.

Pathological threshold

In the CHECK cohort, 2.76% (39 hips) developed end-stage OA within five years follow up. THA patients did not have other hip pathology than OA nor other hip surgery during follow-up. In the Chingford cohort, 7.05% (66 hips) had developed end-stage OA at year 20.

A pathological threshold was determined based on the hips with cam deformity that developed end-stage OA at follow-up. An alpha angle threshold of 78° (95% CI 62° - 87°) resulted in the maximum area under the ROC curve, which was 0.69 (95% CI 0.62-0.75) for end-stage OA (figure 4). It is illustrated by figure 5 that the majority of hips with a cam deformity that developed OA had an alpha angle greater than 78°. The sensitivity analysis based on the random selection of one hip per person which contained 50 hips with end-stage OA at follow-up, resulted in a maximum area under the ROC curve of 0.66 at an alpha angle of 82°.

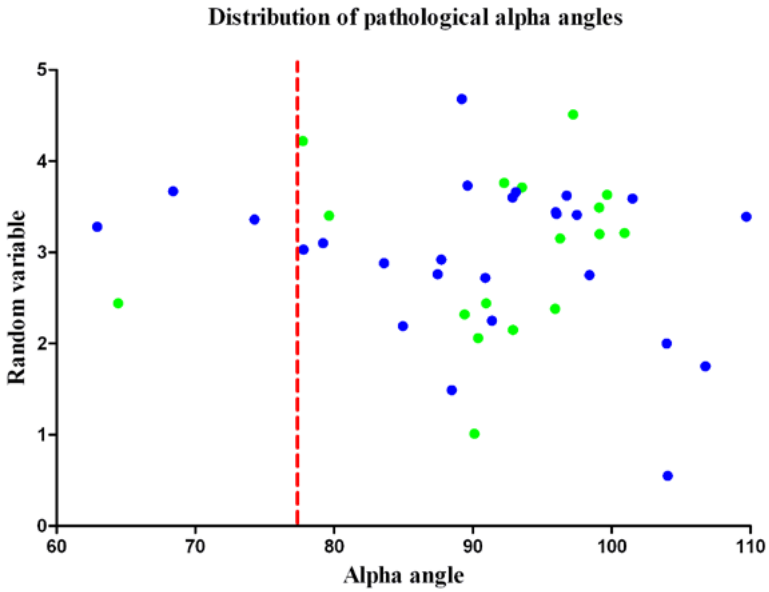


Figure 5. Pathological alpha angle threshold: 78°. Scatterplot showing the alpha angle on the X-axis and a random variable on the Y-axis. The dots represent the combined hips of the CHECK cohort (green) and Chingford cohort (blue) at baseline with a cam-deformity that developed end-stage OA (K&L 3, 4, or THA). The pathological threshold of 78° is indicated.

DISCUSSION

In the present study that combined data of two large prospective cohorts, comprising almost 3000 hips, an alpha angle threshold for defining the presence of a cam deformity was determined based on the finding of a bimodal distribution of the alpha angle. Also, a pathological threshold value was determined based on development of end-stage OA at follow-up.

Previously, threshold values based on the distribution of the alpha angle in a certain population have been proposed, and ranged from 50° to 83°.[224,260,262,285] These studies defined the presence of a cam-type deformity either by the upper limit of the 95% reference interval, or by the +1 standard deviation of the mean. Although these values might give an indication, the reference interval or standard deviation might for several reasons not be optimal to define an alpha angle threshold. First, the assumption that only the upper 5% of a given population has an abnormal alpha angle is incorrect. Many studies showed a prevalence higher than 5% in asymptomatic individuals with various threshold values for the alpha angle.[226,258,273,275,276] Secondly, reference intervals assume a normal distribution of the alpha angle, which was clearly not the case in both cohorts. Also, different threshold values for men and women have been proposed based on significant differences in mean alpha angle between men and women.[260,285] However, as the prevalence of cam deformities is higher in men than in women, a greater mean alpha angle in men can be expected, but this does not imply that the alpha angle cut-off in women should be lower. Figure 3 d-e clearly illustrates that the higher mean alpha angle in men is actually influenced by outliers, which are in fact the hips with a cam deformity.

To define the presence of a cam deformity, we propose a threshold of 60°. The threshold of 62.7° was based on the minimum of the optimal fit through the combined alpha angle data. However, the optimal fit actually consisted of three distributions, as the distribution of the alpha angles <60° was slightly skewed to the right. When we forced a fit of two distributions through the data, the minimum was found at an alpha angle of 56.7°, which was clearly too low. The benefit of a bimodal distribution is that there are only a few cases in between those alpha angle thresholds, assuring that separation in cam versus non cam cases is not too sensitive to small differences in threshold value (Figure 3). We therefore regard a non gender specific threshold of 60° to be optimal to distinguish between normal hips and hips with cam deformity.

When comparing the distribution of the alpha angle in the CHECK cohort with the distribution in the Chingford cohort, a higher prevalence of cam deformities in the Chingford cohort was found. As no systematic differences in measurement between both techniques were found, this might be due to the differences of inclusion or differences in radiographic protocol. The Chingford cohort is a

population based cohort, where individuals might have had hip complaints for a longer time. In contrast, an inclusion criterion of the CHECK cohort was that individuals consulted the GP for the first time because of hip or knee pain. Individuals suffering from pain because of cam impingement are likely to present with complaints at a younger age than 45 years, which means that they were not included in the CHECK cohort but those individuals might have been included in the Chingford cohort. Secondly, radiographs in the CHECK cohort were obtained in standing position, whereas in the Chingford cohort radiographs were taken in supine position, which might have influenced alpha angles and thereby partly explain the discrepancy in prevalence. Finally, radiographs in the Chingford cohort were controlled for hip rotation in a lesser degree than in the CHECK cohort, which might also have influenced alpha angles, as it is known that alpha angles might become higher when the hip is more externally rotated hips.[260]

As higher alpha angles are associated with more severe cartilage damage and OA, Gosvig et al. proposed a pathological threshold based on the +2 standard deviations of the mean which resulted in pathological thresholds of 83° for men and 57° for women.[260] However, in our opinion a pathological threshold value should rather be based on 'true' pathology. Still, as opposed to the threshold based on the bimodal distribution of the alpha angle, the definition of a pathological threshold value might be more subjective. We determined a pathological threshold value based on the highest discriminative ability for development of end-stage OA during the follow-up period, using the maximum area under the receiver operating characteristic (ROC) curve. Using this method, we propose a non gender specific threshold of 78°. It can also be visualized in figure 5 that most hips with cam deformity that developed end-stage OA had an alpha angle higher than 78°.

The proposed threshold value for defining the presence of a cam deformity is based on all hips (n=2879) and corresponds with the value obtained by the sensitivity analysis in which only one hip per person was randomly selected (n=1440). For the pathological threshold a slight discrepancy of 4° was found. As the majority of the end-stage OA cases were unilateral, we regard the analysis using all hips for the pathological threshold the most appropriate.

For upcoming clinical trials it is important to avoid misclassification of the radiographic presence of a cam deformity. An alpha angle below 60° is often used to quantify a cam deformity, but below this value we could not discriminate between hips with and without a cam deformity. This might also explain why a value of 60° has previously been shown to be optimal to discriminate between symptomatic and asymptomatic cam deformities.[259,286] However, a cam deformity is highly prevalent in the general population and is only a prerequisite for cam impingement. Whether someone with a cam deformity will become

symptomatic and develops cartilage damage depends on many other factors such as the orientation of the acetabulum, the frequency of impingement events represented by for example sporting activities, genetics, and the vulnerability of the soft tissue structures within the hip joint. The presence of a radiographic cam deformity alone is therefore not suitable for the diagnosis of cam impingement. Although the alpha angle has been shown to be associated with decreased function and to be highly predictive for development of OA, concern might rise about the reported wide range of reliability.[287,288] In our cohorts, bias in measuring the alpha angle was limited by two factors. First, observers were blinded for clinical status and did not know which hips were going to develop OA at follow-up. Second, the alpha angle was semi-automatically calculated from a point set which was positioned on the contour of the bone. When the alpha angle is drawn manually, the observer might be influenced by the visual appearance of the head-neck junction. ICC scores as examined in our cohorts were in between previously reported values and showed strong agreement. The greatest differences in alpha angle occurred when both methods were compared, as illustrated by an ICC of 0.66. This was caused by two outliers (figure 2). Using the SSM-technique, an alpha angle of 39° and 44° for these outliers was measured. However, using Hipmorf a very small part of the femoral head was outside the best fitting circle, which is why an alpha angle of 86° and 90° was measured. This might also partly explain the differences in prevalence between both cohorts. Excluding these two hips increased the ICC between the two techniques from 0.66 to 0.89. Except for these outliers, there was agreement in categorizing hips with or without cam deformity in all hips. It appears that drawing a best fitting circle is crucial for reliably determining the alpha angle. In the CHECK cohort, 8 points on the femoral head were used to determine a best fitting circle around the femoral head whereas 3 points were used in the Chingford cohort. Those differences might explain the slight differences in best fitting circle.

Several measures to quantify the cam deformity besides the alpha angle have been proposed, such as the head-neck ratio, anterior offset ratio, and triangular index.[260] All those measures quantify the loss of concavity of the head-neck junction and show good reproducibility. However, a nonspherical, flattened femoral head might have a normal concavity of the head-neck junction. Such an abnormal morphology might lead to impingement but is not captured by above mentioned measures, except for the alpha angle. Further, in both the CHECK and Chingford cohort, the alpha angle was most predictive for OA.[63,203]

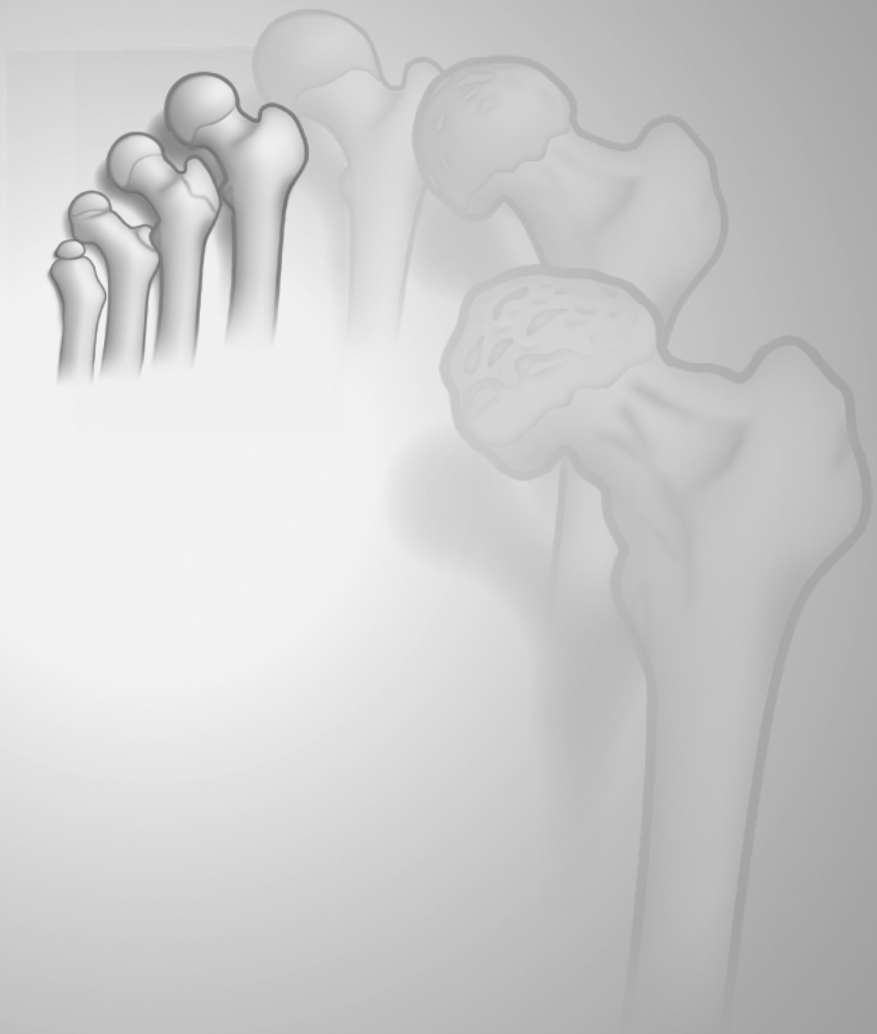
This study has some limitations. First, the use of AP radiographs might not be optimal for quantifying a cam deformity. Although the exact amount of cam deformities missed on AP radiographs varies in different reports, we acknowledge that the prevalence of cam deformities is underestimated.[260,280,289] Though, when

only AP radiographs are used, the alpha angle is still highly predictive for OA. Second, it is unknown whether the proposed thresholds are applicable for other radiographic views, or in other planes when 3D imaging techniques are used. The proposed thresholds should therefore be validated in large cohorts using CT or MRI.

In conclusion, the alpha angle in this study of combined epidemiological data showed a bimodal distribution, indicating a clear distinction between hips with and without cam deformity. An alpha angle threshold of 60° is proposed for defining the presence of a cam deformity. In addition, a pathological threshold of 78° is proposed based on development of OA at follow-up.

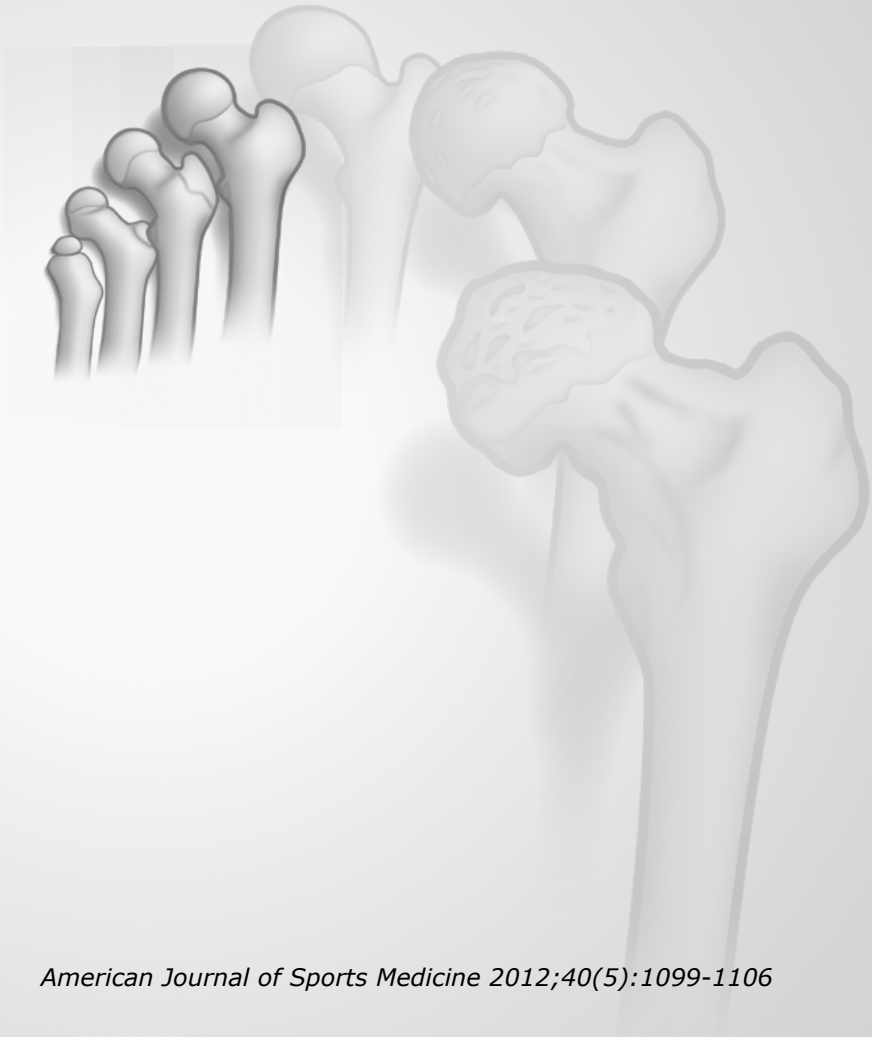
PART 3

Development of a cam deformity



Chapter 9

The development of cam-type deformity in adolescent and young male soccer players



American Journal of Sports Medicine 2012;40(5):1099-1106

ABSTRACT

Background Cam impingement is a well-recognized cause of hip pain and might cause osteoarthritis of the hip. Clinically, cam impingement is mostly observed in young, active males patients, but only few studies have focused on the manifestation of cam-type deformities during skeletal development.

Purpose To determine the age of onset and prevalence of cam-type deformities in young male soccer players versus controls.

Methods In this study, 89 elite preprofessional soccer players and 92 controls aged 12-19 years were included. In the soccer players, range of motion and impingement tests were performed. Both an anteroposterior (AP) pelvic radiograph and a frog-leg lateral radiograph of the hip were obtained according to a standardized protocol. Controls with both an AP pelvic and a frog-leg lateral radiograph and no hip pathology were obtained from radiology databases. The alpha angle was automatically determined in all radiographs, using a threshold value of 60° to define a cam-type deformity. Further, all radiographs were scored using a 3-point scoring system. The anterosuperior head-neck junction was classified as (1) normal, (2) flattened, or (3) having a prominence. Differences in prevalence were tested using logistic regression. Differences in range of motion were calculated using generalized estimating equations.

Results An alpha angle >60° was already found at the age of 12 years in some soccer players and controls. A cam-type deformity defined by alpha angle tended to be more prevalent in soccer players (26%) than in controls (17%, $p=0.31$). In 13% of soccer players, a prominence was visible on radiographs and was first seen at the age of 13 years. The anterosuperior flattening (56% vs 18%, $p=0.0001$) and prominence (13% vs 0%, $p<0.03$) were more prevalent in soccer players than in controls.

Conclusion Cam-type deformities were recognizable and present from the age of 13 years and were more prevalent in soccer players than in their non-athletic peers. Cam-type deformity develops during adolescence and is likely to be influenced by high-impact sports practice.

INTRODUCTION

Some sporting activities have been associated with a higher incidence of hip osteoarthritis (OA).[47,290] This applies for soccer, especially in elite soccer players.[291] A possible explanation for the higher risk for hip OA in elite soccer players is the existence of shape deformities of the femoral head.

From the 1960s until the 1980s, it was suggested that many cases of 'primary' or 'idiopathic' hip OA are actually secondary to shape deformities and thus do not have a systemic origin.[24,50,292,293] From the 1990s, research has indicated that subsets of hip OA are indeed secondary to minor, previously unrecognized, or subclinical shape deformities.[55,64,206,244,294,295] The path from these minor shape deformities to OA might follow the mechanism of femoroacetabular impingement (FAI) proposed by Ganz et al.[55]

FAI is an abnormal contact between the femoral neck and the acetabulum. There are two classic types.[55] The first one, pincer impingement, is an overcoverage of the femoral head by the acetabulum and is mostly seen in middle-aged women. The second one, the subject of this article, is cam impingement, mostly seen in young active males.[240] It is caused by an abnormal morphology of the proximal femur: a non-spherical head that is due to a flattening or prominence on the anterosuperior part of the femoral head-neck junction.[67] As a result of this anatomical anomaly, the head-neck offset is smaller and squeezed in the acetabulum. It has been suggested that this causes repetitive minor trauma to the anterior acetabular margins, and thus causing labral tears and cartilage damage.[296,297] These injuries may eventually lead to hip OA.

Although the exact etiology of a cam-type deformity is not well understood, suggested causes are bone remodelling,[298-301] a growth abnormality of the epiphysis,[25] or subclinical slipped capital femoral epiphysis (SCFE).[294,302] The general hypothesis based on research on young, active adult men is that the deformity develops during adolescence after a long period of excessive sports practice during growth.[23] Recently, Siebenrock et al. showed that young basketball players are at higher risk for having a cam-type deformity, which developed especially around the time of physeal closure.[227] Thus, high impact sports, such as basketball, ice hockey, and soccer, might predispose to developing a cam-type deformity because of the high shear stress applied to the femoral head.[303]

For this study, we investigated at what age a cam-type deformity develops and tested the hypothesis that cam-type deformities are more prevalent in adolescent preprofessional elite soccer players than in their nonathletic peers.

METHODS

Participants

We included boys (12-19 years) who played in selection teams of Feyenoord soccer club in Rotterdam, the Netherlands. They follow a particular school program to train at the optimal intensity. An information letter was sent to 141 boys who met the inclusion criteria; 101 boys gave informed consent, of whom 89 finally joined this study, while 12 boys did not come for clinical and radiological evaluations. Exclusion criteria for soccer players were any hip disorder. The study was approved by the Medical Ethical Committee of Erasmus Medical Center (Rotterdam, the Netherlands).

All soccer players had anteroposterior (AP) pelvic and frog-leg lateral hip (commonly known as the Lauenstein view) radiographs and a clinical investigation. For controls, boys aged 12-19 years in whom both an AP and a frog leg lateral radiograph of both hips were available were selected from the radiology databases of Erasmus Medical Center and Reinier de Graaf Groep Hospital. The exclusion criteria were any hip disorder as diagnosed clinically by a pediatric orthopedic surgeon or radiographically by a musculoskeletal radiologist. Further, 19 subjects were excluded because sports practice was reported by the orthopaedic surgeon in their medical records. Subjects were not excluded when a cam-type deformity without any other hip disease was diagnosed (n=2). The selected controls have had radiographs of both hips in the diagnostic course of complaints of hip (84%), knee (4%), back (5%), or other (7%). None of the controls visited the hospital again because of their complaints within a minimum of two years after the radiographs were obtained. There were 92 subjects in the control group.

The soccer players were clinically examined to measure the range of motion (ROM) of the hip, and an anterior impingement test was performed. The ROM was measured by a goniometer in flexion, extension, abduction, adduction, internal rotation and external rotation of the hip. A positive impingement test was defined as a sharp pain in 90° of flexion with adduction and internal rotation. The boys were asked to complete a questionnaire including items related to groin pain, medical history and demographic data.

Radiology

Most cam-type deformities are located anterosuperior in the femoral head-neck junction. To detect a cam-type deformity in this region, an AP view as well as a lateral view of the hip is needed.[248] Both radiographs were obtained, namely an AP pelvic view and a frog-leg lateral view.[304] The radiographs were made according to a standardized protocol.

For the AP radiograph the subject was positioned supine with his feet in a frame to assure 15° internal rotation. This provides the best view of the head-neck junction. The tube to film distance was 130 cm and the beam was centered 5 centimeters above the pubic symphysis.
The frog-leg lateral radiograph was performed in supine position with the leg of interest abducted using a 45° wedge under the knees. The heel rested against the medial aspect of the contralateral knee to position the leg in 90° of external rotation. The tube to film distance was 115 cm, and the beam was centered in the middle of the groin on the femoral head. Gonadal shields were worn to reduce the radiation load.

Measures

We used the alpha angle as a quantitative outcome measure and a visual scoring system as a semi-quantitative outcome measure for a cam-type deformity.
The shape of the proximal femur in the AP and frog leg lateral radiographs was assessed using statistical shape modelling (SSM) software (ASM tool kit, Manchester University, Manchester, UK). The shape is defined by a set of landmark points that are positioned along the contour of the bone in the image. Each point is always placed on the same landmark of the contour, to allow comparison between the shapes. All radiographs of the left hip were mirrored to appear as right hips in order to be able to use the same set of landmarks.
The alpha angle was automatically calculated in all radiographs from the point sets of the SSM software using matlab (version 7.1.0, MathWorks Inc, Natick, Massachusetts, USA) (figure 1). The alpha angle is measured by first drawing the best fitting circle around the femoral head, then a line through the center of the neck and the center of the head. From the center of the head a second line is drawn to the point where the superior surface of the head neck junction first departs from the circle. The angle between these two lines is the alpha angle.[224]
We defined the presence of a cam-type deformity as an alpha angle >60°, as osseous abnormalities below this threshold value have been suggested to pose less of a risk for developing hip pain.[259] In addition, radiographs were scored semi-quantitatively by an experienced orthopedic surgeon and a musculoskeletal radiologist based on consensus, using a three-point scoring system[305] (figure 2). The anterior head-neck junction was classified as

1. Normal: slight symmetric concavities of the anterior head-neck junction with respect to the posterior head-neck junction.
2. Flattening of the head-neck junction: moderate decrease in the anterior head-neck offset with respect to the posterior head-neck junction..
3. Presence of a prominence: a convexity in the anterior head-neck junction, as opposed to a concavity.

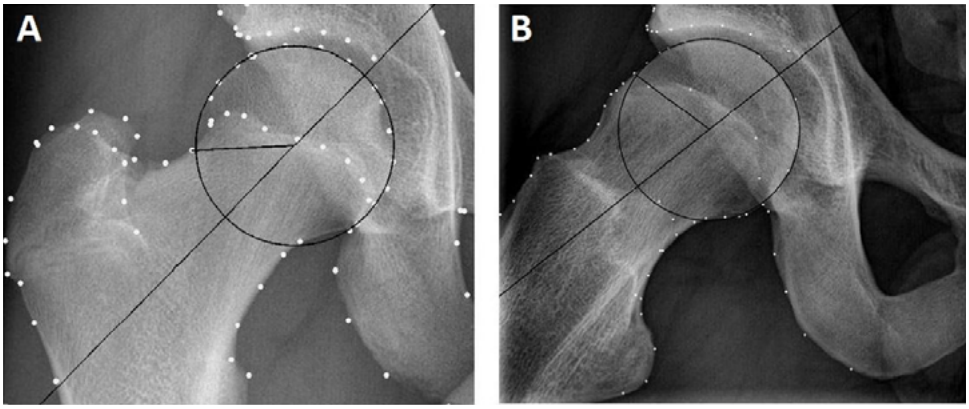


Figure 1. To measure the alpha angle we fitted a circle to the femoral head and placed a line through the center of the head and the middle of the neck. The alpha angle is the angle between the line through the neck and the point where the head-neck junction deviates from the circle. (**A**) Normal alpha angle of 42° is shown in a 16-year-old soccer player. (**B**) An abnormal alpha angle of 76° is shown in a 19-year-old soccer player.

Radiographs were presented in a randomized order to the orthopedic surgeon and the musculoskeletal radiologist, who were blinded for and unaware whether the hip radiographs were of a soccer player or of a control subject. Repeating this procedure in a random sample of 52 hips showed an ICC of 0.82 for intra observer reliability.
Finally, the skeletal maturity was determined in all radiographs using the Oxford score, because the chronological age can be different from the skeletal age. The Oxford score ranges from 0 to 45 and is determined by maturity indicators in the pelvic region.[306]

Statistical analysis

A subject was classified as having a cam-type deformity when an alpha angle > 60º was measured in at least one hip in either the AP or frog-leg lateral view. A subject was classified as having a flattening or prominence when such was visually scored in at least one hip in either the AP or frog-leg lateral view. When a subject had both a flattening and a prominence, he was classified as having a prominence. Differences in prevalence numbers between groups were calculated using logistic regression, corrected for age. By correcting for age, differences in prevalence between the groups were not influenced by the slight difference in age between the groups. Differences in the ROM between cam-type deformity cases and normal soccer players were calculated using generalized estimating equations (GEE), corrected for age. By using a GEE regression model, we could model the correlation between left and right hips. Differences

between the Oxford score in soccer players and controls were calculated using a univariate general linear model, corrected for age. Chi-squared test was used to study groin pain, leg dominance, and impingement test results in relation to the existence of a cam-type deformity.

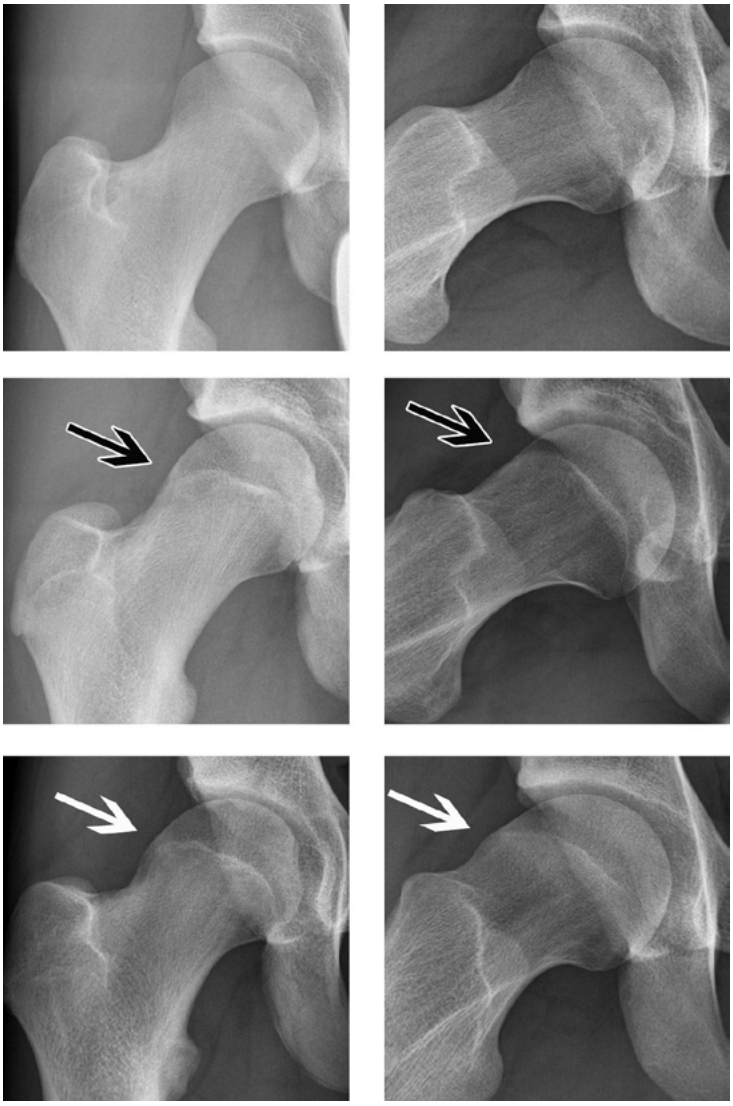


Figure 2. anteroposterior pelvic (left) and frog-leg lateral (right) radiographs showing typical examples illustrating the three categories of the used visual scoring system. Normal (top), flattening (middle, black arrow), and a prominence (bottom, white arrow) were scored.

RESULTS

The mean age of the 89 soccer players (178 hip joints) was 14.8 years (range, 12 – 19 years), and the mean body-mass index was 20.13 kg/m² with a standard deviation (SD) of 2.25. The intensity of soccer practice had a mean ±SD of 7.96 ± 1.77 h/wk and the years playing soccer ranged from 4 to 15 years, with a mean of 8.97 years. None of the participants had a history of hip disease. The mean age of the 92 (184 hip joints) controls was 13.8 years (range, 12 – 19 years), which was significantly lower than the soccer players ($p<0.001$). From the age of 14 years, the Oxford score tended to be slightly higher in the soccer players, although no statistically significant differences were measured in skeletal maturity ($p=0.07$). Table 1 illustrates the mean per age.

Table 1. Numbers, Oxford scores, and Demographic data per age

Controls			Soccer players				
Age, y	n	Oxford score[a]	N	Oxford score[a]	Body Mass Index[a]	Training intensity[a], h	Soccer experience[a],y
12	30	27.0 (1.7)	12	27.6 (1.8)	17.7 (2.1)	6.1 (1.6)	6.0 (1.3)
13	13	28.8 (3.8)	13	28.8 (2.9)	18.4 (1.3)	7.6 (2.2)	6.9 (1.5)
14	23	31.7 (4.2)	20	33.1 (4.7)	19.5 (1.5)	8.7 (1.8)	8.1 (1.5)
15	13	35.2 (5.6)	12	36.1 (3.9)	21.4 (1.9)	7.5 (1.1)	9.6 (1.5)
16	5	37.0 (4.6)	11	39.5 (2.5)	21.5 (1.9)	8.5 (1.3)	10.1 (0.9)
17	4	39.3 (4.7)	11	41.2 (1.6)	21.4 (0.8)	8.7 (1.2)	11.3 (1.5)
18	1	43.0 (0.0)	9	41.7 (0.87)	22.1 (1.3)	8.6 (0.89)	12.4 (2.2)
19	3	41.0 (2.8)	1	43.0 (0.0)	23.9 (0.0)	8.0 (0.0)	12 (0.0)
Total	92	31.1 (5.5)	89	34.95 (6.0)	20.1 (2.3)	8.0 (1.8)	9.0 (2.5)

[a]Values are shown as mean ± standard deviation

In the soccer players, an alpha angle >60° was first found at the age of 12 years on the frog-leg lateral view and at the age of 14 years on the AP view. In the control group, an alpha angle >60° was found at the age of 12 years in both the frog-leg lateral as well as the AP views. Hips having a visual prominence were found only in the soccer players and were present from the age of 13 years. Hips having a flattening were found both in soccer players and controls from the age of 12 years.

In 26% of the soccer players and in 17% of the controls, an alpha angle >60° was measured in at least one hip in either the AP view or the frog-leg lateral view, although this difference was not significant when corrected for age ($p=0.31$). Significantly more prominences in the head-neck junction were visually scored in soccer players than in controls (13% vs 0%, $p<0.033$), with prevalence increasing with age ($p=0.003$). A flattening of the head-neck junction was significantly more frequently found in the soccer players as well (53% vs 19%, $p<0.001$). Prevalence numbers per age are given in table 2 and figure 3.

Table 2. Prevalence of a cam-type deformity per age

	Soccer players			Controls		
Age,y	**α-angle >60°**	**prominence**	**flattening**	**α-angle >60°**	**prominence**	**flattening**
12	25% (n=3/12)	0% (n=0/12)	33% (n=4/12)	16.7% (n=5/30)	0% (n=0/30)	10% (3/30)
13	7.7% (n=1/13)	7.7% (n=1/13)	23% (n=3/13)	15.4% (n=2/13)	0% (n=0/13)	0% (0/13)
14	30% (n=6/20)	5% (n=1/20)	65% (n=13/20)	17.4% (n=4/23)	0% (n=0/23)	17% (4/23)
15	25% (n=3/12)	8.3% (n=1/12)	83% (n=10/12)	15.4% (n=2/13)	0% (n=0/13)	38% (5/13)
16	27.3% (n=3/11)	18.2% (n=2/11)	45% (n=5/11)	20% (n=1/5)	0% (n=0/5)	40% (n=2/5)
17	27.3% (n=3/11)	27.3% (n=3/11)	73% (n=8/11)	25% (n=1/4)	0% (n=0/4)	50% (n=2/4)
≥18	40% (n=4/10)	40% (n=4/10)	40% (n=4/10)	25% (n=1/4)	0% (n=0/4)	25% (n=1/4)
total	26% (n=23/89)	13% (n=12/89)	53% (n=47/89)	17% (n=16/92)	0% (n=0/92)	18% (n=17/92)

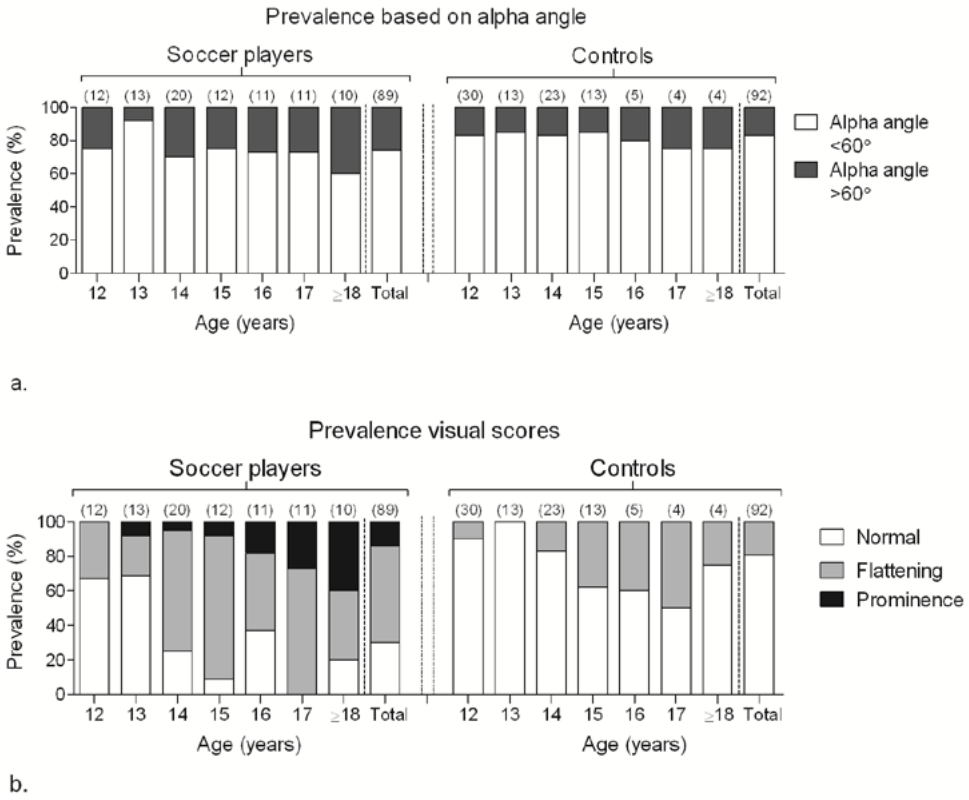


Figure 3. Prevalence of a cam-type deformity based on the alpha angle (A) and the visual scores (B) stratified per age in years for soccer players and controls. The number of participants in each group is given above the bars. note that cam-type deformities started with a flattening, and with increasing age, more prominences were found in the young soccer players.

Of all cam-type deformity cases in the soccer players determined by an abnormal alpha angle, 44% of the cam-type deformities were located only in the right femur, 26% were located only in the left femur, and 30% were bilateral. In addition, the visual prominences were located in the right femur in 33%, in the left femur in 17%, and were bilateral in 50% of the cases. The side affected was independent of leg dominance. In the controls, 31% of the cam-type deformities defined by an abnormal alpha angle were located only in the right femur, 63% were located only in the left femur, and 6% of these deformities were bilateral. In the soccer players, internal rotation was significantly reduced in hips with cam-type deformities determined by alpha angle >60° compared with hips without cam deformities (19.7° vs 26.2°, p=0.002); This was also true for hips with a flattening or prominence on the frog-leg lateral view compared with those

without (20.4 vs 29.8 p<0.001). No such differences in ROM were found when having a flattening or prominence on the AP view. No significant association was found between a positive impingement test result and the existence of a cam-type deformity or between groin pain and the existence of a cam-type deformity.

DISCUSSION

Cam impingement has been defined as a cause of hip pain in young adults and a potential cause for OA.[268,307] Young, active males are thought to have a higher risk for developing cam impingement. Some evidence exists that young active males indeed have a higher prevalence and that a cam-type deformity develops during closure of the growth plate.[227] Our study supports this line of thinking.
The two main results of our study were that a cam-type deformity is present early in adolescence, and seems to be more prevalent in soccer players. Furthermore, prevalence of cam-type deformities based on visual scores increases with age. The higher prevalence of cam-type deformities in soccer players has also be shown by Murray et al., who reported more tilt deformities on AP radiographs from males exposed to a more active regime in school.[23] Recently, Siebenrock et al.[227] showed that high intensity basketball playing during adolescence was associated with a higher risk of cam impingement. They reported a prevalence of 89% cam-type deformities in basketball players after closure of the capital growth plate, which is comparable with the visual scores for flattening and prominence from the age of 14 years in our study. Other studies have shown that the prevalence of such deformities in asymptomatic men ranges from 9% to 25%.[227,260,272,275] However, these percentages are difficult to compare, since different measures were used to quantify a cam-type deformity. Nowadays, the alpha angle is the measure generally applied to quantify a cam-type deformity, although a validated threshold value for an abnormal alpha angle remains to be determined. Osseous abnormalities below the threshold value of 60° have been suggested to pose less of a risk for developing hip pain,[259] which is why we applied this cut-off value as a quantitative outcome measure.
A remarkable finding was an alpha angle >60° in some 12-year-old boys. However, in 12-year-old boys, the alpha angle might be a less accurate measure for cam-type deformities. When the growth plate is not fused anterosuperiorally, the contour of the femoral head appears more oval, resulting in large alpha angles (Figure 4). In addition, we could not define a cam-type deformity purely visually when the growth plate was incompletely closed. Once the growth plate has almost closed, the typical shape of a cam-type deformity is more pronounced and recognizable. An interesting observation was that in some 12 years old the proximal femoral growth plate was more extended into the neck, which gave the head-neck junction a flat appearance. A follow-up study is needed to find out

whether the large alpha angles and an extended growth plate in the youngest boys are precursors to the development of a classic cam-type deformity.

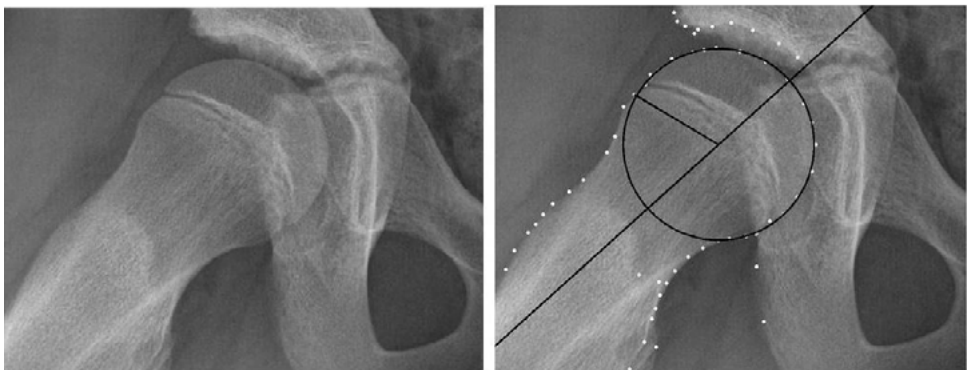


Figure 4. A high alpha angle in a frog-leg lateral radiograph of a 12-year-old boy when the growth plate was not completely fused. On the left, the original radiograph which was visually scored as normal and on the right, an alpha angle of 72° is shown.

Soccer players did not only have cam-type deformities more often, but these deformities were also more pronounced at this age. In soccer players, most hips with cam-type deformities that were identified with an abnormal alpha angle were visually scored as having a flattening or as having a prominence. In contrast, in the hips of controls with cam-type deformities identified by an abnormal alpha angle, most hips were visually scored as normal and some as having a flattening. In addition, in soccer players, 35% of the cam cases had an alpha angle >60° in both the AP and frog-leg lateral radiographs, whereas none of the controls had an alpha angle >60° in both radiographs. Dudda et al. showed that those cases with an aspherical head-neck junction in both an AP and a lateral radiograph had the most prominent asphericity on magnetic resonance arthrography.[280] Thus, obvious 'bumps' were not seen in the controls, whereas these were present in soccer players and significantly increased in prevalence with age, reaching a prevalence of 40% in soccer players older than 17. The prevalence of a flattening did not increase with age in the soccer players, though figure 3b suggests that a flattened head-neck junction can evolve towards a prominence over time.

Our study showed some discordance between the presence of a cam-type deformity defined by alpha angle >60° and the visual scores. In soccer players, six of the 18 hips visually scored as having a prominence did not have an alpha angle >60°. This was caused either by a convexity anterior in the head-neck junction, which is visually detectable as a sclerotic region on the frog leg lateral view, or by a convexity in the femoral neck instead of the head-neck junction.

In both situations the alpha angle was normal because these abnormalities do not affect the contour of the head-neck junction. Vice versa, in controls, 13 of the 17 hips with an alpha angle >60° were visually scored as normal. Because all the radiographs of the controls were taken during normal clinical routine, these were not as standardized as in the soccer players. As a result, the alpha angles might have been influenced by the rotational position of the femur.[260] For instance, we observed that hips with an alpha angle >60° that were visually scored as normal, often had more externally rotated legs in the radiographs, which led to the higher alpha angle. In these cases, the head-neck junction could still be visually assessed and a prominence or a flattened head-neck junction would have been recognised. Finally, in both soccer players and controls, the alpha angle might be less accurate when the growth plate is not completely fused anterosuperiorely. Taken together, the alpha angle is important as a quantitative outcome measure, but in this population we observed that the alpha angle might have underestimated the prevalence in soccer players and might have overestimated the prevalence in controls. Therefore, we applied a visual scoring system which better represented the differences between soccer players and controls.

In addition to an AP pelvic view, a lateral view is necessary to visualize cam-type deformities.[248] Meyer et al. showed both the Dunn view in 45° or 90° flexion, and the cross-table projection to be optimal for identifying femoral head-neck asphericity.[263] However, they did not study the frog-leg lateral view. Clohisy et al. concluded the frog-leg lateral view to be the most distinctive and reliable view for detecting cam-type deformities.[304] In our study as well, most prominences were visually detectable in the frog leg lateral view.

The anterior impingement test is most commonly used when FAI is suspected. In our study, the outcome of the impingement test was not associated with the existence of a cam-type deformity, for which we have two possible explanations. The first is that the anterior impingement test was not sufficiently sensitive. The second is that in these young soccer players, labral pathology, which causes pain, was not yet present. The second explanation is more likely, since studies with arthroscopically proven labral tears have reported high numbers of positive impingement tests.[308] In hip joints with a cam-type deformity defined either by an alpha angle >60° or by a flattening and prominence, internal rotation in 90° of flexion was significantly reduced. Thus, in young adolescents without any significant labral or cartilage damage, reduced internal rotation might be a more clinically relevant sign for a cam-type deformity than a positive anterior impingement test. This point needs further study.

Cam-type deformities were more often bilateral in soccer players than in controls. In the soccer players, prominences were bilateral in half of the cases, and cam-type deformities defined by alpha angle were bilateral in 30% of the cases. On

the other hand, cam-type deformities defined by alpha angle in the controls were bilateral in only 6% of the cases. In addition, the higher prevalence and the more pronounced cam-type deformities in soccer players, combined with the fact that such deformities were already present when the growth plate had closed, suggests that a cam-type deformity develops during skeletal maturation and high impact sports practice. The longer lateral extension of the epiphysis into the neck as described by Siebenrock et al. that we frequently noticed, indicates that a growth abnormality of the epiphysis, due to the high shear stresses applied on the proximal femoral epiphysis, might be a cause of a cam-type deformity.[25] This growth abnormality might be caused by a delayed separation of the common physis between the femoral head and the greater trochanter,[309] or by a structural adaptation of the epiphysis in order to resist the higher demands of the proximal femur. A subclinical SCFE has been hypothesized to cause a cam-type deformity as well.[294,302] However, all soccer players were without complaints during weight-bearing, so a subclinical SCFE was not very likely. The controls in our study did have complaints but because none of them had follow-up radiographs within the first two years after the initial radiographs, (subclinical) SCFE is unlikely. Radiographs of both soccer players and controls had no signs of a preslip i.e. widening and irregularity of the physis.[310] We therefore have no indication that most cam-type deformities are caused by a subclinical SCFE.

This study had some limitations. First, the prevalence of cam-type deformities might have been underestimated because conventional radiographs were used. Although radiographs are important for the initial diagnosis of cam impingement, several studies have shown that 3-dimensional imaging such as computed tomography or magnetic resonance imaging is slightly more sensitive for diagnosing a cam-type deformity.[280,289,311] Using 3-dimensional imaging, the complete anterosuperior portion can be evaluated and maximum alpha angles can be calculated.[275] In contrast, when using AP and frog leg lateral radiographs, the alpha angle only can be measured in the superior and anterior portion respectively, which may therefore be lower and prevalences might be underestimated. Secondly, we were unable to include a healthy control group, due to ethical considerations related to radiation in the pelvic area. As an alternative, we selected a control group of comparable age from the radiology databases of two hospitals. Since these radiographs were mainly made in response to complaints related to the hip, the control group might not completely represent a healthy adolescent population. However, because none of the controls visited the hospital again with a minimum of two years after the radiographs were obtained, we consider the control group as a relatively normal adolescent population. Still, the prevalence of complaints related with cam-type deformity might have been overestimated in our controls relative

to healthy controls.[312] Subjects of whom sports activity was reported in their medical records were excluded from the control group. Though activity level is well documented, especially when participating at a high level, it is possible that some of the included controls did participate in sport. Taken together, this may explain why Siebenrock et al. found a slightly lower prevalence in their healthy, non-athletic adolescent control group than we did (9% vs 17%). We could not compare the outcomes of the clinical examination between soccer players and controls because no ROM and impingement tests were performed in the controls. Finally, controls aged over 15 years were less available, and thus the age distributions of the two groups did not match completely.

This study showed that a cam-type deformity in young male soccer players and in the control group was visually recognizable and present as soon as the growth plate had closed. Cam-type deformities were more prevalent among young male soccer players than among the control group. This might suggest that intense high impact sporting activities at young age, especially during the closure of the proximal femoral growth plate, could be an important factor in the development of a cam-type deformity.

Chapter 10

Cam deformity is gradually and exclusively acquired during skeletal maturation: a prospective study with a minimum of 2 years follow-up

American Journal of Sports Medicine 2014;42(4):798-806

ABSTRACT

Background: A cam deformity is a major risk factor for hip osteoarthritis, and its formation is thought to be influenced by high impact sporting activities during growth.

Purpose: To (1) prospectively study whether a cam deformity can evolve over time in adolescents and whether its formation only occurs during skeletal maturation and (2) examine whether clinical or radiographic features can predict the formation of a cam deformity.

Methods: Preprofessional soccer players (n=63; mean age, 14.43 years; range 12-19 years) participated both at baseline and follow-up (mean follow-up, 2.4 ± 0.06 years). At both time points, standardised anteroposterior and frog-leg lateral radiographs were obtained. For each hip, the alpha angle was measured, and the anterosuperior head-neck junction was classified by a 3-point visual system as normal, flattened, or having a prominence. Differences between baseline and follow-up values for the alpha angle and the prevalence of each visual hip classification were calculated. Additionally, the amount of internal hip rotation, growth plate extension into the neck, and neck shaft angle were determined.

Results: Overall, there was a significant increase in the prevalence of a cam deformity during follow-up. In boys aged 12 and 13 years at baseline, the prevalence of a flattened head-neck junction increased significantly during follow-up (13.6% to 50%, p=0.002). In all hips with an open growth plate at baseline, the prevalence of a prominence increased from 2.1% to 17.7% (p=0.002). After closure of the proximal femoral growth plate, there was no significant increase in the prevalence or increase in severity of a cam deformity. The alpha angle increased significantly from 59.4° at baseline to 61.3° at follow-up (p=0.018). The amount of growth plate extension was significantly associated with the alpha angle and hip classification (p=0.001). A small neck shaft angle and limited internal rotation were associated with cam deformities and could also significantly predict the formation of cam deformities (alpha angle >60°) at follow-up.

Conclusion: In youth soccer players, cam deformities gradually develop during skeletal maturation and are probably stable from the time of growth plate closure. The formation of a cam deformity might be prevented by adjusting athletic activities during a small period of skeletal growth, which will have a major effect on the prevalence of hip osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) of the hip is a highly prevalent and disabling disease, especially among former athletes.[30,48] The role of femoral morphological characteristics, in particular a cam deformity, has become increasingly recognized in the pathophysiology of OA.[75,101,203,221,313] A cam deformity is a nonspherical extension of the femoral head anterosuperiorly that may lead to intra-articular damage by a motion dependent inclusion of the cam deformity into the acetabulum, known as cam impingement.[55,313,314] It consistently shows an association with hip pain, limited internal rotation, labral tears, chondral lesions, and ultimately hip OA.[57,63,203,208,216]

The cause of a cam deformity is largely unknown, although several reports suggest that participating in high impact sports during growth plays an important role.[23,226,227] Two recent studies reported a markedly higher prevalence of cam deformity in asymptomatic adolescents participating in soccer and basketball, respectively, as compared with their non athlete controls.[226,227] These findings are supported by other studies that reported a high prevalence of cam deformities in both symptomatic and asymptomatic athletic adults.[278,315-317]

It was shown in a cross-sectional study that a cam deformity is radiographically visible from the age of 13 years and may evolve in time.[226] However, to the best of our knowledge, no prospective data are available on how a cam deformity evolves during skeletal maturation and whether it can evolve after skeletal maturation. Furthermore, it is unknown whether the formation of a cam deformity can be predicted from other radiological or clinical features before a cam deformity appears radiographically. As high impact sport activities may influence the formation of a cam deformity, a better insight into the time of onset and development of a cam deformity might provide clues for prevention.

The primary aim of this study was to examine whether a cam deformity can evolve over time in adolescents and whether such evolution continues after skeletal maturation. A secondary aim was to study whether other clinical or radiographic features are associated with or are predictive for the formation of a cam deformity.

METHODS

Participants

For this study, all 141 elite preprofessional soccer players aged 12 to 19 years who practiced in the selection teams of the Feyenoord Soccer Club (Rotterdam, the Netherlands), performing at the highest national level, were invited to participate at baseline. Exclusion criteria were any hip disorders, but none of the eligible participants were excluded because of these criteria. Of 141 eligible

asymptomatic subjects, 89 agreed to participate at baseline, of whom 63 (126 hips) also participated at 2-year follow-up (follow-up rate, 71%). At baseline, the 26 soccer players lost to follow-up were older than those who participated at follow-up (15.7 years vs 14.4 years, p=0.002). The reasons for not participating at follow-up were two-fold; about 40% of the drop outs continued their professional careers abroad or in other parts of the Netherlands not in the surrounding areas of the research centre. The other 60% of the dropouts were not motivated to participate in the study anymore, which is inherent to their pubertal behaviour. In this study, we only used the data of the athletes who participated both at baseline and follow-up. The study was approved by the Medical Ethical Committee of Erasmus Medical Center (Rotterdam, the Netherlands).

Radiographs

Most cam deformities are located in the anterosuperior head-neck junction.[67] Therefore, both an anteroposterior (AP) pelvic view and a frog-leg lateral view were obtained at both time points according to a standardized protocol, which has been described in the baseline study.[226]

Quantification of morphology

Both the commonly used alpha angle and a semiquantitative visual classification system were used to define the presence of a cam deformity.[224,305] The latter was used because the alpha angle might be less accurate for cam deformities in skeletally immature individuals, as the contour of the femoral head appears more oval when the growth plate is open, resulting in large alpha angles.[226]
Using Matlab (version 7.1.0, MathWorks Inc, Natick, Massachusetts, USA), the alpha angle was automatically calculated in all AP and frog-leg lateral radiographs from a point set that was manually positioned along the contour of the bone (figure 1).
The alpha angle is measured by first fitting a circle to the femoral head. A line is then drawn through the center of the neck and the center of the head, and a second line is drawn from the center of the head to the point where the head neck junction first departs from the circle. The angle between these two lines is the alpha angle.[224] We defined the presence of a cam deformity using a recently validated alpha angle threshold of >60° and the presence of a pathological cam deformity using an alpha angle >78°.[318]
All radiographs were also classified semiquantitatively by an experienced orthopaedic surgeon and musculoskeletal radiologist based on consensus, using a 3-point visual system (figure 2).[226,305] The anterior head-neck junction was graded as the following:

1. normal: slight symmetric concavities of the anterior head-neck junction with respect to the posterior head-neck junction;
2. flattening of the head-neck junction: a moderate decrease in the anterior head-neck offset with respect to the posterior head-neck junction; or
3. presence of a prominence: a convexity in the anterior head-neck junction, as opposed to a concavity.

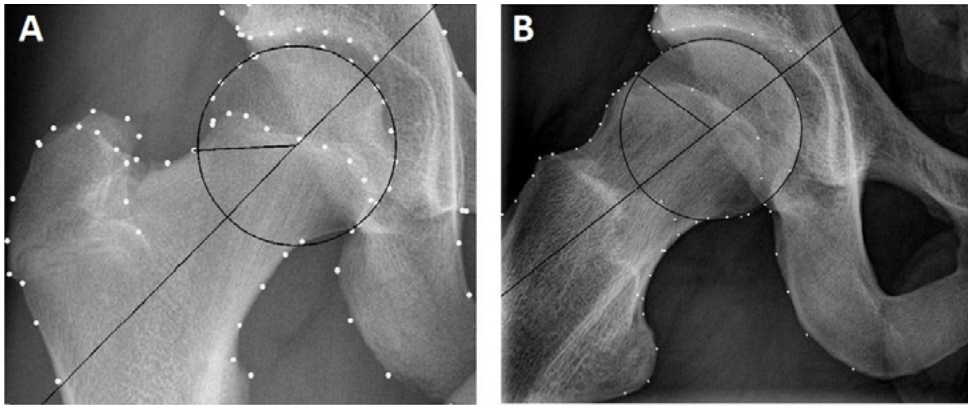


Figure 1. To measure the alpha angle, Matlab was used to calculate the best fitting circle around the femoral head, the center of the head, and the middle of the neck, from a point set along the contour of the bone. The alpha angle is the angle between the line through the neck and the point where the head-neck junction deviates from the circle, with the latter also calculated by Matlab. (A) A normal alpha angle of 42° is shown in a 16-year-old soccer players at baseline. (B) An abnormal alpha angle of 76° is shown in a 19-year-old soccer player at baseline. (From Agricola R. et al. The development of cam-type deformity in adolescent and young male soccer players. *Am J Sports Med.* 2012;40(5):1099-1106. Reprinted with permission)

Baseline radiographs were already classified at baseline and the follow-up radiographs were presented in a randomized order to the observers, who were blinded to any baseline data of the soccer player. This method showed an intraclass correlation coefficient (ICC) of 0.82 for intra observer reliability in the baseline study.[226]

Radiographic and clinical parameters that might be predictive for, or are associated with, a cam deformity were assessed at baseline and included the anterosuperior growth plate extension as described by Siebenrock et al.[25], the neck shaft angle (NSA) as measured on the AP radiographs (figure 3), and the amount of internal hip rotation. The passive amount of internal hip rotation was measured by a goniometer in a supine position in 90° of hip flexion and 90° of knee flexion. To determine whether those parameters can predict the formation of a cam deformity, we studied all hips without a cam deformity at baseline and

compared the parameters between hips that had developed a cam deformity with those that had not at follow-up.

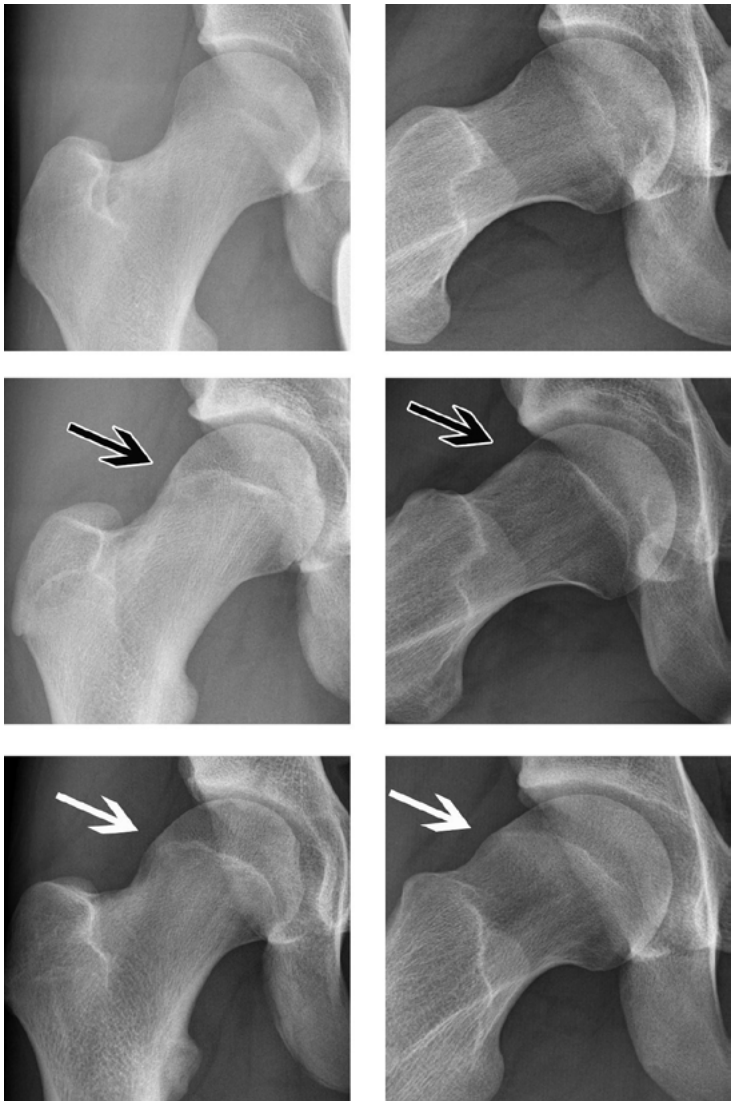


Figure 2. The AP pelvic (left) and frog-leg lateral (right) radiographs showing typical examples illustrating the 3 categories of the visual classification system used. Hips were graded as normal (top), flattened (middle, black arrow), or having a prominence (bottom, white arrow). (From Agricola R. et al. The development of cam-type deformity in adolescent and young male soccer players. *Am J Sports Med.* 2012;40(5):1099-1106. Reprinted with permission)

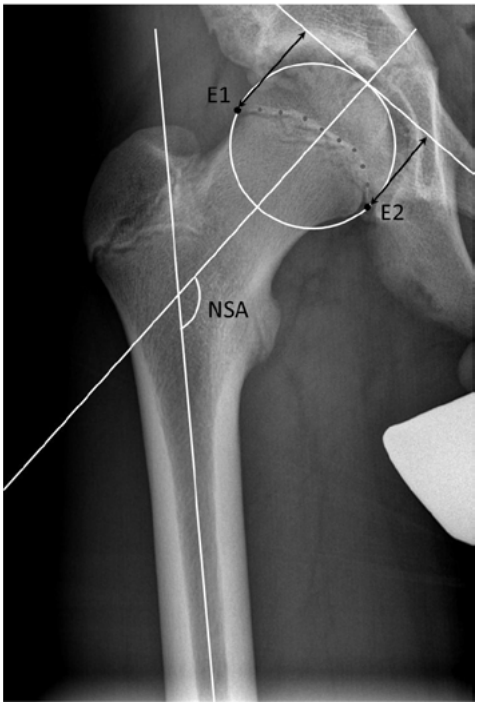


Figure 3. Neck-shaft angle (NSA) and growth plate extension. The NSA was calculated by the line through the center of the neck and the center of the head, and the line parallel to the femoral shaft, as determined by the direction of the shaft below the minor trochanter. The amount of growth plate extension (E1) into the neck was calculated by first drawing a line perpendicular to the line through the center of the neck and the center of the head at the intersection with the medial femoral head. The distance from this line to the end point of the growth plate was measured and divided by the diameter of the femoral head.

The reliability of the growth plate extension and NSA measurements has not been described previously in this cohort. Therefore, intraobserver repeatability was assessed by a single investigator reading 10 randomly selected blinded radiographs on 2 occasions. Interobserver reproducibility was assessed by another observer reading the same 10 radiographs.

Statistical analysis

The reliability of the growth plate extension and NSA measurements were assessed using ICC (2-way random, absolute agreement). A hip was classified as having a cam deformity when an alpha angle >60º was measured in at least one radiographic view, and it was classified as being flattened or having a prominence when such was visually graded in at least 1 radiographic view. The difference in prevalence numbers and difference in alpha angle between baseline and follow-up were tested using Generalized Estimating Equations (GEEs). By

using a GEE logistic regression model, we could model the correlation between left and right hips. The prevalence at both time points is presented for the entire group, by age category (12-13 years, 14-15 years, and >16 years at baseline), and by growth plate status at baseline (open vs closed). The Pearson correlation coefficient was used to describe the correlation between the amount of growth plate extension and the alpha angle. The association of the amount of growth plate extension, NSA, and internal rotation with the presence of a cam deformity was tested using GEEs, all adjusted for age. Finally, in hips without a cam deformity at baseline (either hips with an alpha angle <60° or hips graded as normal), they were tested using GEEs on whether the above-mentioned parameters could predict the formation of a cam deformity at follow-up. Each parameter was tested separately and corrected for age. Differences in baseline characteristics between included participants and drop-outs were tested using an independent-samples *t* test.

RESULTS

Participant characteristics

Demographic data of the participants are summarized in Table 1. The mean follow-up time was 2.4 years (range, 2.3-2.6). All included participants continued to play soccer at a high level during follow-up.

Table 1. Demographic data at baseline and follow-up (n = 63 soccer players)

	Baseline	Follow-up
Age, y	14.43 ± 1.94	16.63 ± 2.07
Weight, kg	56.87 ± 14.29	68.36 ± 11.11
Height, cm	168.16 ± 12.52	177.44 ± 7.96
Body mass index, kg/m²	19.73 ± 2.37	21.58 ± 2.21
Soccer experience, y	8.61 ± 2.61	11.10 ± 2.49
Training intensity, h/wk	7.79 ± 1.79	8.68 ± 1.91

Values are expressed as mean ± standard deviation.

Prevalence of cam deformities at baseline and follow-up

Differences between baseline and follow-up in the prevalence of each visual classification are summarized in Figure 4 and Table 2. A cam deformity developed and continued to evolve over time in adolescent hips with an open growth plate at baseline. In those hips, the anterosuperior head-neck junction gradually changed from being concave at the age of 12 years to being flattened around the age of 14 years (figure 5) and finally to a convexity around the age of 16 years (figure 6).

Table 2. Prevalence of cam deformities at baseline and follow-up based on visual hip classification and alpha angle.

		Total	Age 12-13 years	Age 14-15 years	Age ≥ 16 years	Open growth plate	Closed growth plate
Prevalence % (CI)		**n=126**	**n=44**	**n=48**	**n=34**	**n=96**	**n=30**
	baseline	7,1% (2.6-11.7)	2.3% (0.0-6.9)	6.2% (0.0-13.4)	14.7% (2.2-27.3)	2.1% (0.0-5.0)	23.3% (7.3-39.4)
Prominence	Follow-up	22.2% (14.9-29.6)	6.8% (0.0-14.6)	27.1% (14.0-40.1)	35.3% (18.4-52.2)	17.7% (9.9-25.5)	36.7% (18.4-55.0)
	p-value	**<0,001**	0.33	0.19	0.074	**0,002**	0.19
	Baseline	42.1% (33.3-50.8)	13.6% (3.1-24.2)	62.5% (48.3-76.7)	50% (32.3-67.7)	40.6% (30.6-50.6)	46.7% (27.7-65.6)
Flattening	Follow-up	46.8% (38.0-55.7)	50.0% (34.6-65.4)	56.2% (41.7-70.8)	29.4% (13.3-45.6)	51.0% (40.9-61.2)	33.3% (15.4-51.2)
	p-value	0.46	**0.002**	0.53	0.085	0,24	0.27
	Baseline	50.8% (41.9-59.6)	84.1% (72.8-95.3)	31.3% (17.7-44.9)	35.3% (18.4-52.2)	57.3% (47.2-67.4)	30.0% (12.6-47.4)
Normal	Follow-up	31.0% (22.8-39.1)	43.2% (28.0-58.4)	16.7% (5.7-27.6)	35.3% (18.4-52.2)	31.3% (21.8-40.7)	30.0% (12.6-47.4)
	p-value	**0,001**	**<0,001**	0.15	0.94	**0,001**	0.95
	baseline	36.5% (28.0-45.0)	25.0% (11.7-38.3)	45,8% (31.2-60.5)	38.2% (21.0-55.5)	34.4% (24.7-44.1)	43.3% (24.5-62.2)
Alpha angle >60°	Follow-up	38.9% (30.3-47.5)	31.8% (17.5-46.1)	45,8% (31.2-60.5)	38.2% (21.0-55.5)	37.5% (27.6-47.4)	43.3% (24.5-62.2)
	p-value	0.51	0.78	0.49	0.34	0.36	0.37
	baseline	7.9% (3.2-12.7)	0% (0.0-0.0)	10.4% (1.5-19.4)	14.7% (2.2-27.3)	3.1% (0.0-6.7)	23.3% (7.3-39.4)
Alpha angle >78°	Follow-up	13.5% (7.4-19.5)	2.3% (0.0-6.9)	16.7% (5.7-27.6)	23.5% (8.5-38.6)	9.4% (3.4-15.3)	26.7% (9.9-43.5)
	p-value	0.09	X	0.88	0.35	0.07	0.34

Bolded p-values indicate a statistically significant difference between baseline and follow-up ($p<0.05$). X indicates that no statistical analysis was possible.

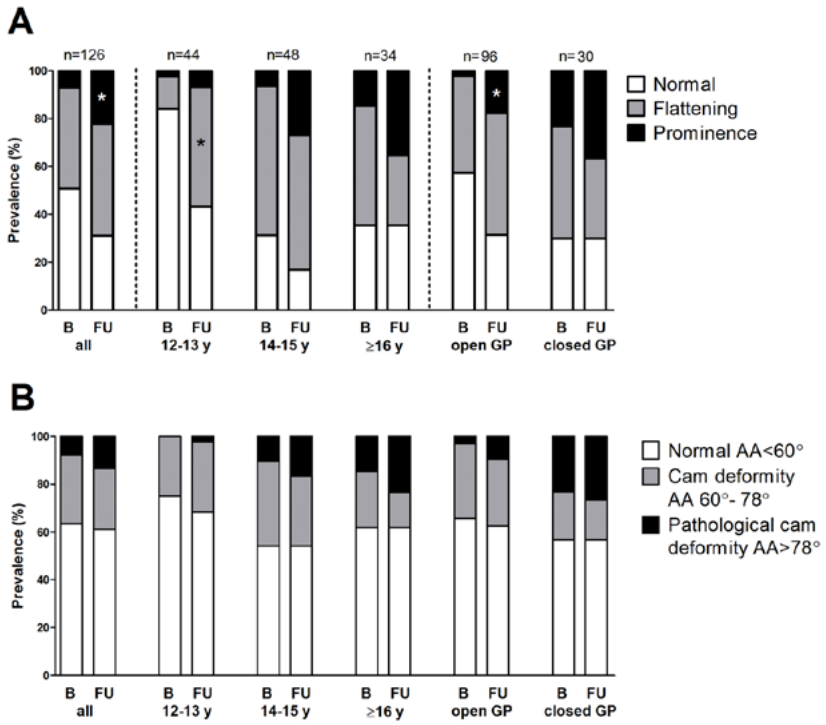


Figure 4. The prevalence of cam deformities at baseline and follow-up based on (A) hip classification and (B) alpha angle is presented for all hips (left column), by age category (middle columns), and by growth plate status at baseline (right columns). The number of hips in each category is indicated on top of each column. AA, alpha angle; B, baseline; FU, follow-up; GP, growth plate; y, years, *Statistically significant difference ($p<0.05$) between baseline and follow-up.

Based on the visual grades, the prevalence of a prominence per hip in the entire group increased from 7.1% at baseline to 22.2% at follow-up ($p<0.001$) (Figure 6). Of the soccer players aged 12 or 13 at baseline, 84.1% had a normal appearance of the head-neck junction, which decreased significantly to only 43.2% at follow-up ($p<0.001$). These soccer players predominantly acquired a flattened head-neck junction ($p=0.002$) (Figure 5). Among players aged ≥14 years at baseline, 15 of the 47 hips (32%) with a flattened head-neck junction evolved into a prominence, although the difference in prevalence was not statistically significant in the subgroup of soccer players aged 14 to 15 years at baseline (6.2% to 27.1%; $p=0.19$), while it showed a strong trend towards a significant difference for those aged >16 years at baseline (14.7% to 35.3%; $p=0.07$) (Figure 4 and 6). Of the hips with an open growth plate at baseline, the prevalence of normal hips decreased significantly (57.3% to 31.3%; $p=0.001$), and the prevalence of a prominence increased significantly

(2.1% to 17.7%; p=0.002). There was no difference in the prevalence of the visual hip classifications between baseline and follow-up for hips with a closed growth plate at baseline (Figure 7).

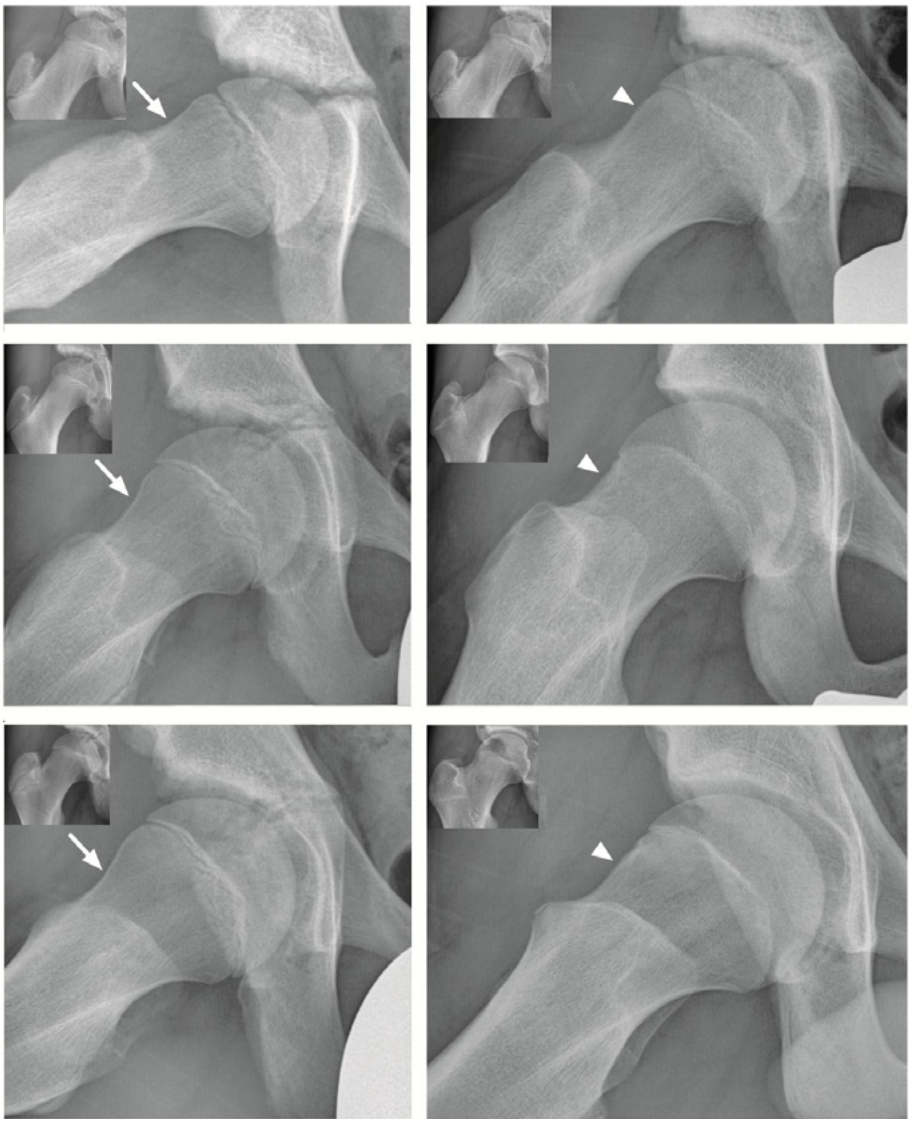


Figure 5. Typical examples of hips with a normal, concave head-neck junction at baseline (left, arrows) that developed into a flattened head-neck junction at follow-up (right, arrow heads). This was typically seen in soccer players aged 12 to 13 years at baseline. The corresponding AP view is shown in the upper left corner of each frog-leg lateral radiograph.

The alpha angle increased significantly from 59.4° at baseline to 61.3° at follow-up for the entire group (p=0.018). The prevalence of a pathological cam deformity (alpha angle >78°) tended to increase (7.9% at baseline to 13.5% at follow-up; p=0.09). No significant differences in prevalence were seen when stratified by age group, although the pattern was similar to that of the hip classifications, albeit with lower prevalence numbers. Of the hips with an open growth plate, the prevalence of a pathological cam deformity tended to increase (p=0.07), whereas no differences were found in hips with a closed growth plate at baseline (Figure 4).
Of all hips with a prominence at follow-up, 17.6% were located only in the left femur, 17.6% were only in the right femur, and 64.8% were bilateral. A flattening was observed in 13.9% located in the left femur, in 22.2% in the right femur, and in 63.9% bilateral. Of all cam deformities determined by an alpha angle >60°, 19.4% were located in the right femur, 22.6% were in the left femur, and 58.0% were bilateral. The side affected by a cam deformity was independent of leg dominance.

Associated parameters

Considering all hips at baseline, a decreased NSA (mean 129.1° vs 133.6°; p=0.001) and an increased epiphyseal extension (mean 1.54 vs 1.43; p=0.001) were associated with the presence of a cam deformity based on an alpha angle >60°. The correlation coefficient between amount of epiphyseal extension and the alpha angle in the AP view was r=0.62 (p<0.001) for all hips at baseline, and r=0.81 (p<0.001) for hips with a cam deformity. Limited internal rotation was only associated with an alpha angle >60° from the age of 13 years (mean, 20.6° in hips with a cam deformity vs 26.1° in those without; p=0.009).
Regarding the visual grading, no association was found with the NSA, but the epiphyseal extension was significantly associated (p=0.002) with mean values of 1.39 ±0.16 for normal hips, 1.53 ±0.16 for hips with a flattened head-neck junction, and 1.69 ±0.18 for hips with a prominence. In all hips, internal rotation was associated with prevalence of the hip classifications (p=0.001), with mean values of 29.5° ±7.0° for normal hips, 22.6° ±8.8° for hips with a flattened head-neck junction, and 16.4° ±7.3° for hips with a prominence.
The ICC of the growth plate extension was 0.97 for intra-observer and 0.97 for inter-observer reliability. For the NSA, the ICC score was 0.89 for intra-observer and 0.92 for inter-observer reliability.

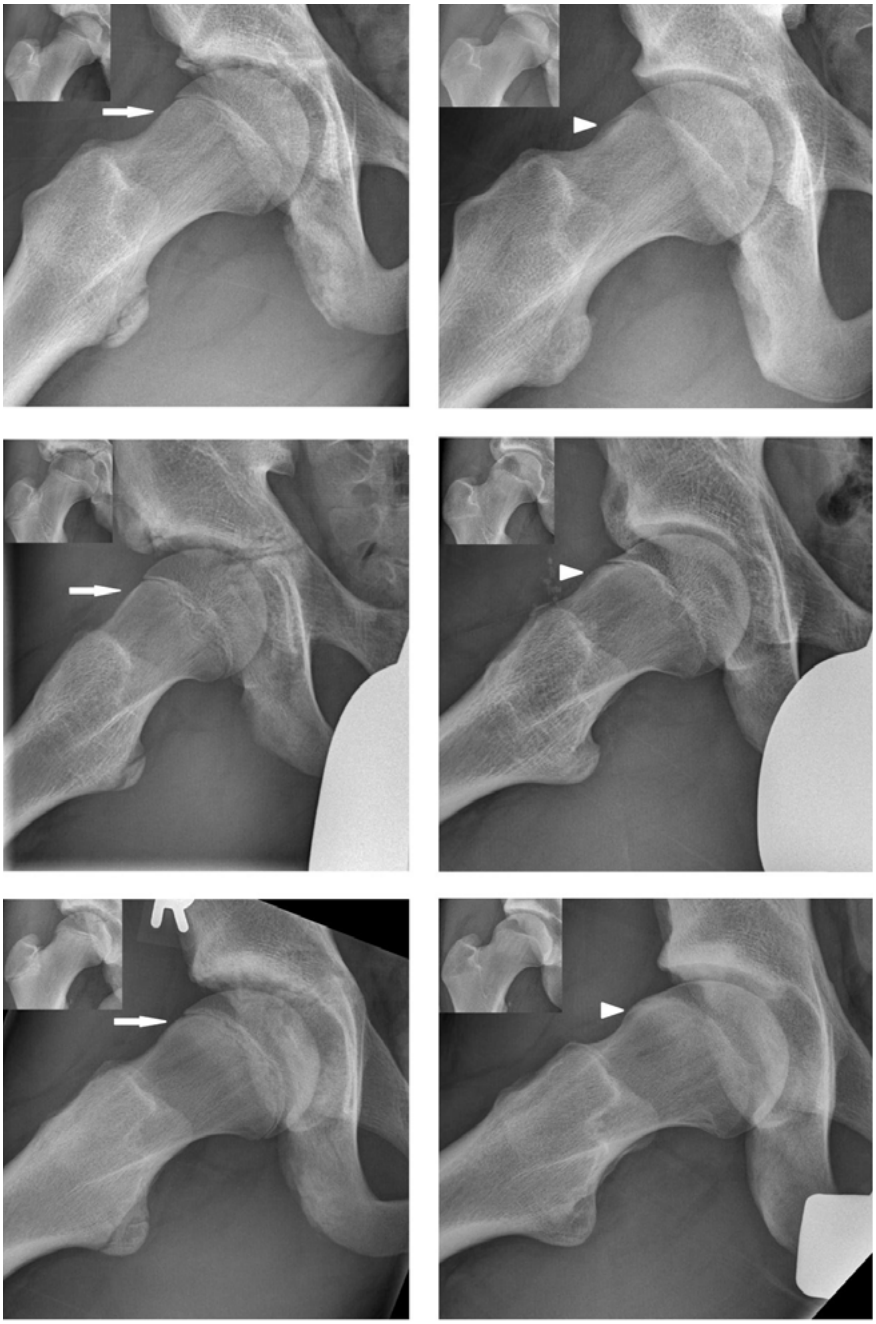


Figure 6. Typical examples of hips with a flattened head-neck junction at baseline (left, arrows) that evolved into a prominence at follow-up (right, arrow heads). This was typically seen in soccer players aged 14 to 16 years at baseline. The corresponding AP view is shown in the upper left corner of each frog-leg lateral radiograph.

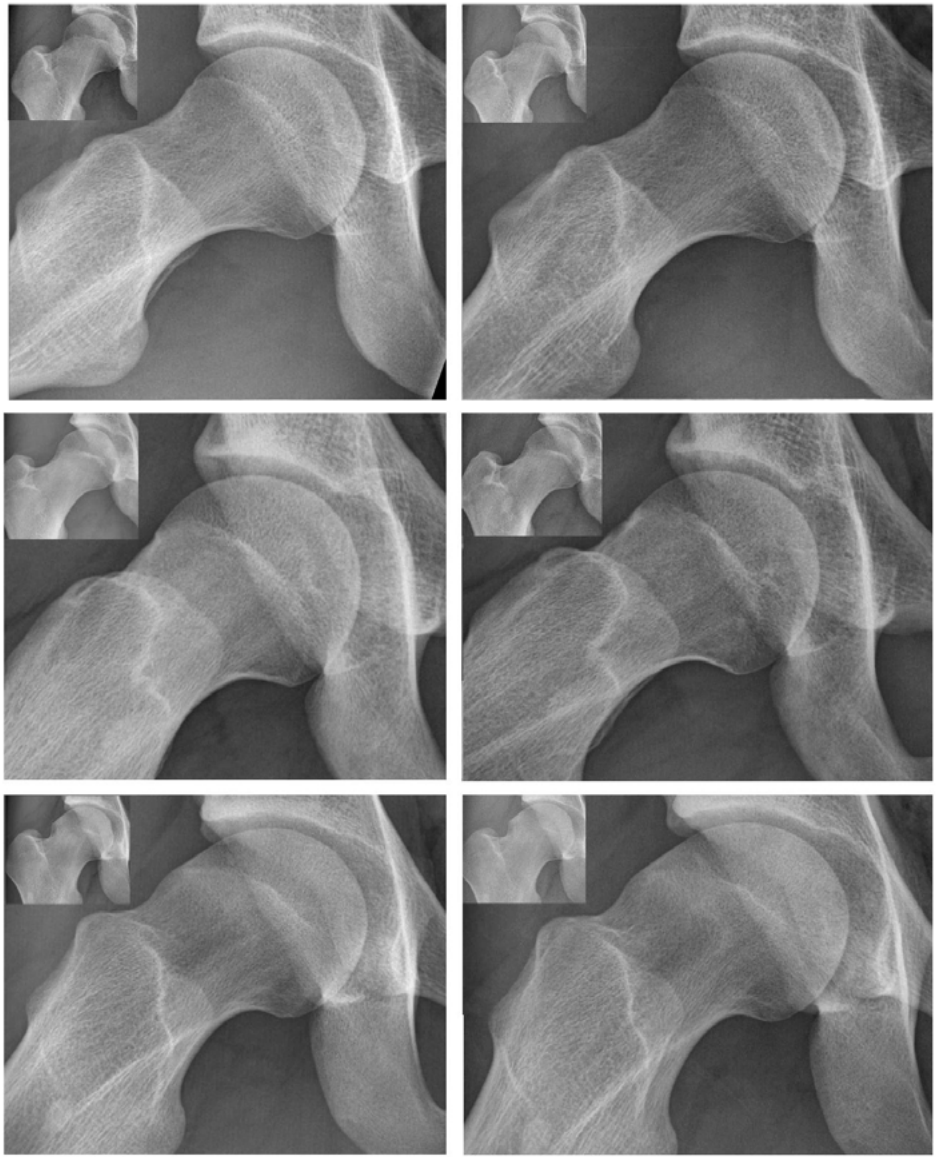


Figure 7. The morphology of hips with a closed growth plate at baseline (left) did not change during follow-up (right). Hips with a normal head-neck junction (top), flattened head-neck junction (middle), or prominence (bottom) appeared equal. The corresponding AP view is shown in the upper left corner of each frog-leg lateral radiograph.

Predictive parameters

At baseline, 64 hips had a visually normal appearance of the anterosuperior head-neck junction, of which 35 developed either a flattening or prominence at

follow-up. Regarding the visual grading system, none of the tested parameters could significantly predict which hips were going to develop a flattening or prominence at follow-up. Regarding the alpha angle, 80 hips did not have a cam deformity (alpha angle <60°) at baseline, but 15 of those hips had an alpha angle >60° at follow-up. Of those hips, both limited internal rotation (odds ratio [OR], 0.90; 95% confidence interval [CI], 0.84-0.98; p=0.009) for every increase in the degree of internal rotation and a small NSA (OR, 0.82; 95% CI, 0.70-0.96; p=0.015) for every increase in the degree of NSA were significantly predictive for the formation of a cam deformity, also after correction for the baseline alpha angle. The amount of epiphyseal extension was not predictive for the formation of a cam deformity (p=0.73).

DISCUSSION

A cam deformity has been recognized as a cause of hip pain and limited function in young adults and is a major risk factor for development of hip OA.[75,203,216,319] Recent studies reported a high prevalence of cam deformities in young adults participating in high-impact sporting activities.[226,227,278,315,317] This is the first prospective study on the development of a cam deformity in which we showed that a cam deformity is gradually acquired and probably only during skeletal maturation. The formation of a cam deformity may therefore be a result of structural adaptation to high-impact sporting activities during growth, when the skeleton is highly sensitive to mechanical loading.[320]

The formation of a cam deformity occurred during skeletal maturation, as was shown by both the visual grading system and the alpha angle. Especially from the age of 12 to 14 years, half of the normal hips acquired a flattened head-neck junction (Figure 4 and 5). From the age of 14 years until growth plate closure, the flattening continued to evolve into a prominence in a substantial number of hips (figure 6). After closure of the proximal femoral growth plate, we did not observe a significant increase in the prevalence or severity of a cam deformity, either based on the visual hip classifications or the alpha angle. The slight nonsignificant increase in the prevalence of a prominence after skeletal maturation was within the range of measurement error and caused by the fact that follow-up radiographs were graded blinded, without information on the baseline radiographs, as a comparison between the baseline and follow-up radiographs revealed that these were exact copies of each other (figure 7). These results are supported by 2 large cohort studies of adults >45 years that did not show an increase in the prevalence of cam deformities at a follow-up of 5 and 19 years, which favor the theory that a cam deformity is a growth-related acquired phenomenon.[63,203]

The correlation coefficient between the amount of internal rotation and the alpha angle in the frog-leg view of the 30 hips with a closed growth plate at baseline (*r*= -0.58 at baseline and -0.52 at follow-up) was similar to the correlation found by Siebenrock et al. in young basketball players with a closed growth plate (32 hips) and the alpha angle as measured at the 1 o'clock position (r= -0.55).[227] These correlations were also in agreement with those of other reports.[216,272,275,321,322] Interestingly, limited internal rotation was also a significant predictor for a cam deformity in those hips with an alpha angle <60° at baseline. A possible explanation is that a cartilage-like structure not visible on radiographs, which will ossify into a cam deformity later, might already be present and limit internal rotation.

The prevalence per person of a visually detected flattening or prominence in the group with a closed growth plate was 86.7% at baseline and 80% at follow-up. Based on the alpha angle, we found a prevalence of 60% at both time points. These high prevalence numbers of a cam deformity correspond with the reported prevalence among (a)symptomatic athletes participating in high-impact sports such as soccer (60%-68%)[315,316], football (72%)[278], basketball (89%)[227], and ice hockey (75%)[317]. However, the prevalence of cam deformity depends on the definition used and threshold value of the alpha angle.

The correlation between a cam deformity and the extension of the growth plate was first reported by Siebenrock et al.[25] Moreover, in a 1-year follow-up study, it was shown that there is a physiological increase in epiphyseal extension during growth until closure of the physis, which was supported by our data.[323] An extension beyond a certain physiological value is probably associated with the formation of a cam deformity. The correlation in our study between the epiphyseal extension and the alpha angle (*r*=0.62) in all 126 hips was mainly explained by the correlation coefficient (*r*=0.81) in hips with a cam deformity (alpha angle >60°), implicating that the larger the epiphyseal extension toward the neck, the greater the cam deformity. Siebenrock et al. showed in a cross-sectional study that hips of young adolescent basketball players with an open growth plate that had not yet developed a cam deformity already had a greater epiphyseal extension than their non-athletic peers.[324] Because of their cross-sectional design, it was unknown if these hips with a greater epiphyseal extension toward the femoral neck would develop a cam deformity, but it was suggested that this alteration in growth plate precedes a cam deformity as basketball players are more likely to develop a cam deformity. However, in our prospective study, we did not find the epiphyseal extension to be predictive. Regarding its strong association with the presence of a cam deformity and correlation with the alpha angle, our data show that the epiphyseal extension does not precede the cam deformity but rather suggest that the altered epiphyseal extension toward the femoral neck runs analogous with the gradual formation of the cam deformity.

Therefore, the growth plate might play an important role in the development of a cam deformity.

A smaller NSA was significantly predictive for the formation of a cam deformity. Of all hips without a cam deformity (alpha angle <60°) at baseline, those that developed a cam deformity (alpha angle >60°) at follow-up had a significantly smaller NSA, independent of age and baseline alpha angle. Moreover, the NSA was strongly associated with the presence of a cam deformity at baseline, but only in the age categories from 12 to 15 years and in those with an open growth plate. In contrast, NSA was similar between hips with and without a cam deformity in the older soccer players and in those with a closed growth plate. Because the NSA decreases with age during growth[325], this suggests that hips have a greater risk for developing a cam deformity when the NSA reaches adult values (more varus position) already in early adolescence. However, as the NSA was not predictive with regard to visual grading, this point needs further study.

The exact cause of a cam deformity is still unknown, but the current study provides some important indications toward a better understanding of its development. Several hypotheses have been proposed, of which some are and some are not supported by our results. First, it has been suggested that a cam deformity is a result of secondary remodelling due to OA, which is unlikely for the majority of cam deformities considering the age of onset. Second, it is probably not caused by remodelling after a subclinical slipped capital femoral epiphysis (SCFE) because none of the subjects who developed a cam deformity during follow-up showed any clinical or radiographic signs of a (subclinical) SCFE at baseline.[23,294] Another proposed hypothesis on the formation of a cam deformity is a delayed separation of the initially common physis of the greater trochanter and the femoral head.[309] We could not confirm this hypothesis, as all of the 12-year-old boys in this study had a wide distance between the growth plate of the femoral head and greater trochanter. We instead observed that after separation, the distance between the physis of the greater trochanter and the femoral head decreased again during adolescence (figure 8). It is possible that subtle stresses in the proximal femoral growth plate and its connection via the neck isthmus with the growth plate of the greater trochanter might play an important role. As the femoral head classically slips toward a posteroinferior direction with an SCFE, the anterosuperiorly located cam deformity might very well be a preventive mechanism for a slip, like a 'clamp'. Another explanation is that the remnant of the formerly common epiphysis, the femoral neck isthmus, might continue to have a potential for bone apposition, leading to a broader neck and aspherical femoral head. This is supported by a study that reports a bone-bridge formation between the greater trochanter and the femoral head as a variation in ossification pattern during adolescence.[326] The formation of a cam deformity probably results from an interplay between the proximal femoral growth plate, the femoral neck isthmus, and the growth plate of the greater

trochanter as a structural adaptation to higher loads, as suggested by studies showing a significantly lower prevalence of cam deformity in nonathletes.[226,227] The exact loading pattern that triggers the formation of a cam deformity is unknown, although it is unlikely explained by the kicking movement, as there was no association between the dominant leg and a cam deformity. Furthermore, regarding the trend toward bilateral involvement, a more general loading pattern as experienced by both legs might trigger its formation. The hypothesis that the shape of the proximal femur adapts to the loads applied on the hip is also supported by a study reporting significantly smaller alpha angles at the anterior and superior locations in ballet dancers, who might functionally benefit from a spherical femoral head to allow broader ranges of motion.[327]

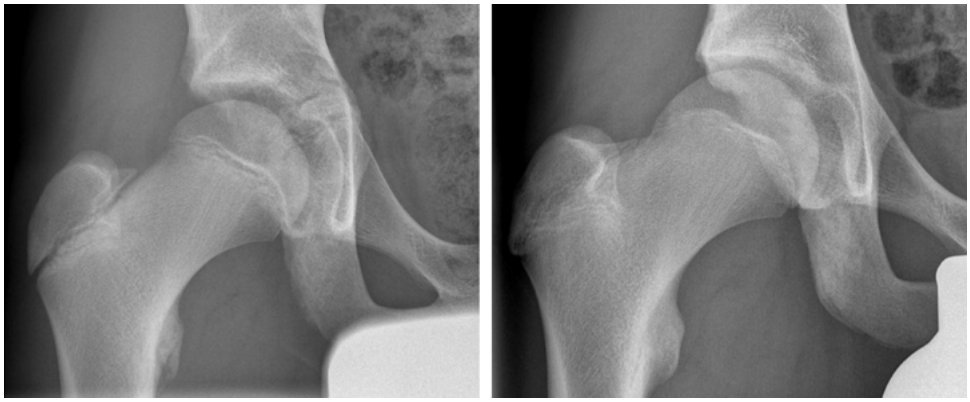


Figure 8. The distance between the lateral part of the proximal femoral growth plate and the growth plate of the major trochanter is shown (left). During adolescence, this distance becomes smaller and the head and trochanter might eventually almost connect (right).

Several limitations of this study need to be acknowledged. Because of ethical reasons, we did not include a nonathlete control group. However, the aim of the 2 years' follow-up was to study the formation of a cam deformity in a population in which a high prevalence of cam deformities is expected. Second, the NSA is optimally measured on long-leg views based on the position of the femoral condyles. As we used the midpoint of the femoral shaft about 10 cm below the minor trochanter on the AP radiographs, the NSA, although highly reproducible, might differ from its true value. Third, although an AP view together with a frog-leg view can accurately identify cam deformities, the prevalence might have been slightly underestimated as compared with magnetic resonance imaging. Finally, because some soccer players moved far from the research center for their soccer careers and because adolescents are difficult to stimulate to participate in a study during puberty, there was a 29% drop-out rate.

In conclusion, the formation of a cam deformity is probably a result of frequent high-impact sports activities that biomechanically trigger extra bone formation at the anterolateral head-neck junction. A cam deformity develops gradually in adolescents and probably only during skeletal growth, when the skeleton is highly responsive to mechanical loading. The formation or further development probably stops after closure of the growth plate. A better understanding of the timeframe in which a cam deformity develops may lead to development of preventive measures, which might have a potential effect on the prevalence of OA.

Chapter 11

Mechanical factors explain development of cam-type deformity

Osteoarthritis and Cartilage accepted for publication

ABSTRACT

Objective A cam-type deformity drastically increases the risk of hip osteoarthritis. Since this type of skeletal anomaly is more prevalent among young active adults, it is hypothesized that the loading conditions experienced during certain types of vigorous physical activities stimulates formation of cam-type deformity. We further hypothesize that the growth plate shape modulates the influence of mechanical factors on the development of cam-type deformity.

Design We used finite element (FE) models of the proximal femur with an open growth plate to study whether mechanical factors could explain the development of cam-type deformity in adolescents. Four different loading conditions (representing gait, internal rotation, external rotation, and flexion) and three different levels of growth plate extension towards the femoral neck were considered. Mechanical stimuli at the tissue level were calculated by means of the osteogenic index for all loading conditions and growth plate shape variations.

Results It was found that loading conditions and growth plate shape influence the distribution of osteogenic index in hips with an open growth plate, thereby driving the development of cam-type deformity. In particular, external rotation and flexion and a larger growth plate extension towards the femoral neck increases the chance of cam-type deformity.

Conclusions Specific/typical loading patterns seem to stimulate the development of cam-type deformity by modifying the distribution of the mechanical stimulus. This is in line with recent clinical studies and reveal mechanobiological mechanisms that trigger the development of cam-type deformity. Avoiding these loading patterns during a certain period of skeletal growth might be a potential preventative strategy for future hip osteoarthritis.

INTRODUCTION

In cam femoroacetabular impingement (FAI), an osseous bump at the femoral head neck junction results in an abnormal contact between the acetabulum and femoral head during hip movements. The impingement causes higher compression and shear forces in the joint that might damage the articular cartilage and labrum.[55] Therefore, cam impingement is thought to be an important factor in the development of osteoarthritis (OA) of the hip especially in young and active adults.[203] A recent prospective cohort study showed that the presence of a cam deformity at baseline in hips without OA confers a 10-fold increased risk for development of end-stage OA within 5 years.[203] Previous studies have focused on improving the diagnosis options,[67,263,328] characterizing the related symptoms,[308] and identifying the best treatments possibilities for cam FAI.[329-332] Nevertheless, the etiology of cam impingement is not yet well understood.

The formation of the osseous bump that causes the impingement might be due to childhood hip diseases such as slipped capital femoral epiphysis (SCFE)[333-335] or Legg-Calve-Perthes disease.[336] Additionally, incorrect healing after a femoral neck fracture can result in a bump at the anterosuperior region.[337,338] However, cam-type deformity is in most cases observed without signs of any pediatric disease or a former fracture. As cams are generally diagnosed in young and active adults,[23,226,227,285,339] it has been suggested that excessive femoral loading due to a high level of physical activity during skeletal development might trigger the abnormal morphology.[340] Agricola et al.[226] studied adolescent soccer players and compared them with a control group of the same age (12 to 18 years). They observed that cam-type deformities are more prevalent within the athletes group. Furthermore, a cam-type deformity was already present from the age of 13, before complete closure of the growth plate. After 2,5 years follow-up, it was observed that a cam-type deformity in the soccer players only developed during skeletal maturation, when the growth plate is open. Similar trends were observed in adolescent basketball players as studied by Siebenrock et al.[227] who reported a prevalence of 89% in basketball players with a closed growth plate as compared with only 9% in non-athletic peers. These results indicate that a cam-type deformity is a risk factor of hip osteoarthritis that is acquired during adolescence and initiated or triggered by physical activity. In addition, both Agricola et al.[236] and Siebenrock et al.[324] observed that a cam-type deformity is associated with greater extension of the growth plate into the femoral neck.[25] Sports that require extreme ranges of motion (ROM) combined with high repetitive impact loading could increase the contact of the femoral head

and acetabulum leading to higher mechanical stresses in the femur. Chronic mechanical stress has a great impact on the structure and tissue properties of bone during skeletal development.[341] Immature skeletons are especially more responsive to mechanical loading, because their tissue is more elastic and the remodeling process is more active.[342] It is therefore hypothesized that both loading conditions and the shape of the epiphyseal growth plate might influence the development of cam-type deformity.

In this study, we use finite element (FE) models to study the effects of loading conditions and the shape of the epiphyseal growth plate on the development of cam-type deformity. We hypothesize that i. certain types of physical activity increase the chance of formation of cam-type deformity, and ii. the shape of the growth plate modulates the effects of mechanical loading. To address these hypotheses, we have created a finite element model of the adolescent growing hip and studied the load distribution in the bone and growth plate in terms of the osteogenic index[341,343-346] under various loading situations and growth plate shapes. We consider four different loading conditions associated with four different types of hip joint movements. The movements include gait, internal rotation, external rotation, and flexion. As for the growth plate shape, we consider three different levels of growth plate extension towards the femoral neck.

METHODS

Geometry and mesh generation

The geometry of the proximal femur was extracted from a CT dataset of a young and healthy individual (male, 12 years old, left leg) using the image processing software Mimics 14.0 (Materialise, Belgium). The CT-scans were obtained for other unrelated medical reasons and came from a database of the Erasmus Medical Centre Rotterdam, The Netherlands. The images were acquired using Siemens SOMATOM Emotion 6 with an in-plane isotropic voxel size of 0.545 mm and a slice thickness of 1.3 mm. That is thin enough to account for the complex innominate structure.[347]

A convergence study was conducted using both 10-node quadratic tetrahedral elements (C3D10) and 4-node linear elements (C3D4). The elements of a selected region of the femoral head were chosen for the convergence study. It was found that when 500,000 degrees-of-freedom are used, the calculated field variables such as strain energy and displacement of the elements converge within 1% both for linear and quadratic elements. Therefore, the mesh generated using

4-node linear tetrahedron elements with a maximum edge length of 1.5 mm (resulting in 1,064066 elements or ≈500,000 degrees-of-freedom) was used in the remainder of the study.

Growth plate shapes

The results of our prospective follow-up study of young soccer players[236] were used for defining the different growth plate shapes considered in this study. In order to create the growth plate shapes, the FE model was positioned such that it corresponded to the anterior-posterior pelvic radiographic view. A cross-section was created to draw the neck axis and the tangent line to the femoral head (fitted) circle to determine superior and inferior extensions, points A and B (Figure 1a). The definitions of epiphyseal extension (Q_1 and Q_2) used in this study are the same as the one described in[25]: the distances between the superior and inferior endpoints of the growth plate and the tangent line (E_1 and E_2 in Figure 1a) are divided by the femoral head radius to calculate Q_1 and Q_2. Analysis of the collected data during the prospective follow-up study[236] showed that there is no significant difference between Q_2 values of the healthy and cam impingement groups. The mean Q_2 value (= 0.9)[236] was therefore used for all considered growth plate shapes. Since Q_1 values are found to be different between hips with and without cam-type deformity, three Q_1 values (= 1.2 [CGP1], 1.4 [CGP2], and 1.6 [CGP3]) in the range of values measured in the prospective study were used in this study to define the shapes of the growth plates. A third point, namely point *C* (Figure 1b) is needed for defining the convexity of the growth plate shapes. The convexity of the growth plate was determined based on visual analysis of multiple CT scans. An average growth plate length to height ratio of 6:1 resulted in a height of around 6.7 mm (Point *C*). Points *A*, *B*, and *C* were used to determine the coordinates of the center of the sphere (*D*) that was used for generating the growth plate shapes. The outer and inner radii of the spheres (r_1 and r_2) had a difference of 3 mm, corresponding to the growth plate thickness of a 12 year old person. The intersection of the spherical shape with the 3D femoral geometry was considered to represent the convex growth plate shapes (CGP1-CGP3). The parameters of the growth plate shapes are presented in Table 1.

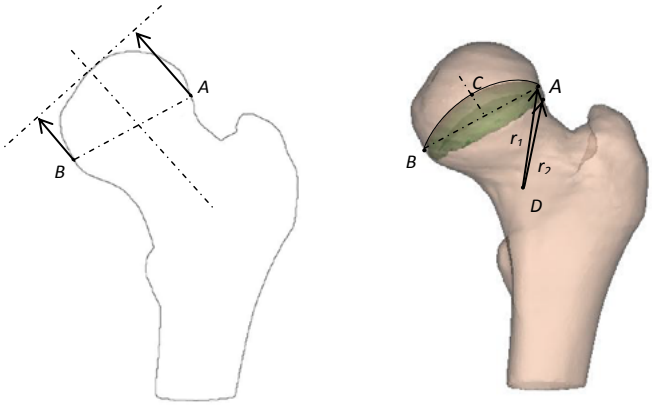


Figure 1. Determination of growth plate orientation. (a) Cross-section of the femur to determine the superior and inferior extension of the growth plate. (b) Point *C* determines the convexity of the growth plate.

Table 1

Name	*t*[1] *(mm)*	r_1 *(mm)*	r_2 *(mm)*	*C-ratio*[2]
CGP1	3	33	30	1:6
CGP2	3	32	29	1:6
CGP3	3	32	29	1:6

[1]*t*: thickness of the growth plate, [2]*C*-ratio: height to length ration of the growth plate

Material properties

The material properties of the model are based on the x-ray attenuation values measured in Hounsfield Unit's (HU) derived from CT images. The average HU value for each element was computed and 200 bone density values were assigned according to the following linear relation:

$$\rho(\mathrm{g/cm^3}) = \alpha + \beta \mathrm{HU} \quad (1)$$

Since there was no calibration phantom included in the scans, the α and β values were determined based on the average value of the cortical bone density and air density. The air density was set to 1.225×10^{-3} g/cm³. For the cortical bone, an average density of 0.9 g/cm³ was chosen.[348] Using the HU values corresponding to average cortical bone density and to air, the parameters of Equation (1) were determined as $\alpha = 0.45$, $\beta = 0.44\times10^{-3}$.

The relationship between apparent bone density and elastic modulus was based on the experiment by Öhman *et al.* [348] on the cortical bone tissue of children:

$$E(\mathrm{MPa}) = 12900\rho^2 \quad (2)$$

The Poisson's ratio was fixed at 0.3 similar to other studies that have used Öhman's relationship.[349] The growth plate was modeled with a constant Young's modulus of 6 MPa and a Poisson's ratio of υ=0.49 to account for almost incompressible material.[350] FE models were solved using an implicit nonlinear FE solver, namely Abaqus Standard (Dassault Systems Simulia).

Loading Conditions

Various loading conditions were considered to study the effects of loading conditions on the formation of cam-type deformity. The literature was consulted to find the appropriate range of load magnitudes and inclination angles. The first 'control' loading scenario was based on the resultant hip contact force of the normal walking cycle of the study of study by Bergmann et al.[351]. Although the measurements were carried out for arthroplasty patients and may not represent the loading conditions of healthy individuals, they were considered to be accurate enough for the purpose of the current study. The peak force was 1200 N, i.e. 250% body weight (BW) with inclination angles of 15º and 35º in the coronal and transverse planes, respectively. Since the angle in the sagittal plane was not specified, a value of 20º was used based on the normal gait in the study by Carriero et al.[352]

It is hypothesized that specific types of movements trigger the formation of cam-type deformity. For example, 90 degrees of flexion together with internal rotation causes the impingement of the cam-type deformity into the acetabulum. Therefore, it has been suggested that these motions might also trigger the formation of the cam-type deformity itself. Carriero et al. studied the gait cycle of children with cerebral palsy who have muscle spasticity that results in excessive internal hip rotation. The peak inclination values of this study were used in establishing loading case 2 that represents internal rotation. In loading case 3 that represented external rotation, the load was placed close to the position where the cam-type deformity normally develops, i.e. more laterally in the lateral anterosuperior region. For loading case 4, different motions were analysed from the range of motions available in Orthoload database (http://www.orthoload.com) that correspond to an extreme hip flexion [353].

Table 2

	Forces on the Femoral Head				Muscle Force	
Model	Coronal Medial (°)	Transverse Ventral (°)	Sagittal Anterior (°)	Magnitude (N)	Coronal Medial (°)	Magnitude (N)
Normal gait						
Case 1	15	35	20	1200	-	-
Internal rotation						
Case 2	40	15	10	1200	35	364
External rotation						
Case 3	-15	90	10	1200	-8	364
Hip flexion						
Case 4	15	80	70	1200	-	-

The inclination angles are positive in lateral or posterior direction.

The movement analysis of getting out of a car indicates an anterior angle of almost 90º in the transverse view, which corresponds to pronounced hip flexion. All joint reaction forces were applied as pressures and were distributed over a circular patch with a diameter of 15 mm. An overview of the four loading cases is presented in table 2 and figure 2. The force magnitude of 250% BW was used in all loading scenarios for objective comparison between the angles of inclination.

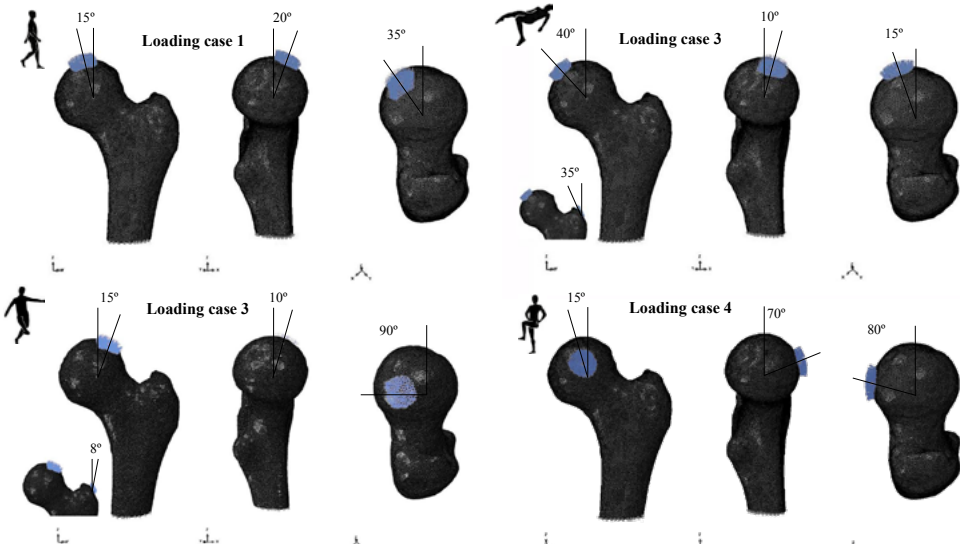


Figure 2. Four loading cases depicted in the coronal, sagittal, and transverse views

Analysis of growth

According to Hueter-Volkmann's law, pressure on the epiphyseal plate retards bone growth, while tension accelerates it.[354,355] This principle can be simulated using mechanobiological models such as those proposed by Stokes[356] and Carter[346]. In this study, we used Carter's model to predict bone growth. In Carter's model, the rate of bone growth is dependent on both biological and mechanical components.[345] The biological factors include intrinsic genetic factors, hormonal regulation, and nutrients. The biological component is usually set as a constant when studying the effects of mechanical loads on growth. The mechanical component can be described by the osteogenic index (OI):[346]

$$OI = a\sigma_S + b\sigma_H \quad (3)$$

where σ_S is the peak octahedral shear stress and σ_H is the peak hydrostatic stress. It is assumed that cyclic hydrostatic stress inhibits bone growth while cyclic octahedral shear stress stimulates growth [343]. The constants *a* and *b* regulate the contributions of both components on the growth rate. Since bone grows between 40 and 80% of the normal size without mechanical loading, the ratio of *b* to *a* should be set between 0.3 and 1 to ensure the contribution of mechanical loading is about 50% of the contribution of biological factors. In this study, the biological component was not included and *b* was set to 0.5.[357,358]

RESULTS

As the epiphyseal extension, Q_1, increases from 1.2 (CGP1) to 1.6 (CGP3), the values of the osteogenic index (OI, a measure of the relevant mechanical loading of the tissue) calculated for the proximal and distal sides of the growth plate deviate from each other (Figure 3). The difference between proximal and distal sides is the largest close to the region where cam-type deformity normally develops (Figure 3). The same trend holds for all loading cases (Figure 3). However, there is a major difference between the various loading conditions in terms of the side that experiences the highest values of OI. For loading cases 1 (normal gait) and 2 (internal rotation), the level of osteogenic index is higher on the proximal side of the growth plate, whereas the reverse holds for loading cases 3 (external rotation) and 4 (flexion).

For CGP1 (Q_1= 1.2), loading case 3 results in a compression peak at the lateral-anterior region that is reflected in the low OI values in that same region (Figure 4). In loading case 2, the peak is located at the medial-anterior region (Figure 4). Higher growth rates appear when the load is directed more parallel to the growth plate axis on the opposite site of the contact force, as in the extreme

loading cases 3 and 4. In CGP3 (Q_1= 1.6) under loading case 3, a lateral edge occurs under tension resulting in high OI values laterally (Figure 4). A clear increase in OI can be observed when comparing loading cases 3 and 4 with 1 and 2 (Figure 4).

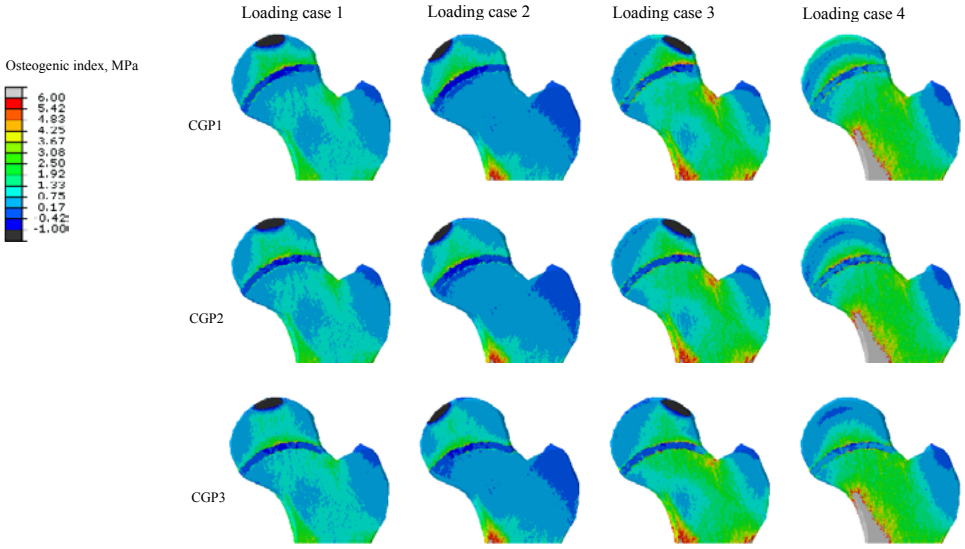


Figure 3. The distribution of OI for different loading cases and convex growth plate shapes.

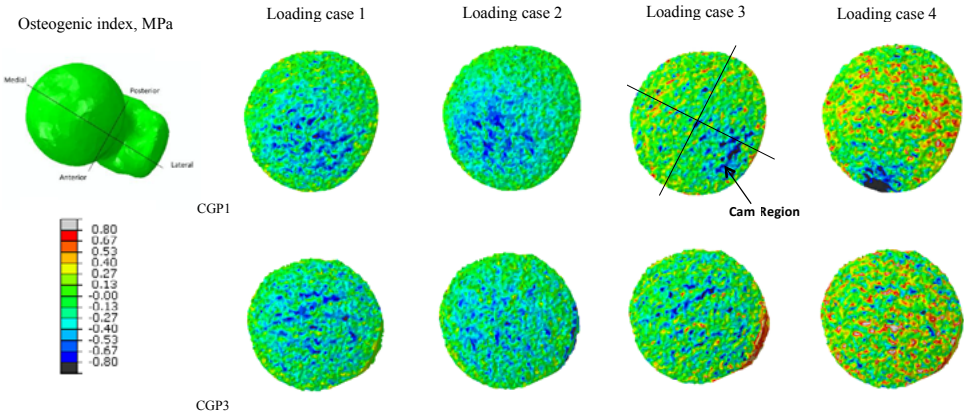


Figure 4. The distribution of OI in the growth plate for different loading cases and two different growth plate shapes.

From the clinical follow-up study,[236] a femur of an adolescent soccer player with an epiphyseal extension, Q_1, of 1.6 at baseline who appeared to have developed

a cam-type deformity at two years follow-up (Figure 5a-b) was selected for comparison with simulation results. Formation of cam-type deformity was found anterosuperiorly while bone resorption was observed inferiorly (Figure 5b). The formation of cam-type deformity was found for most femurs that had an open growth plate at baseline. After epiphyseal closure, the morphology did not change substantially (see e.g. Figure 5a-b). The FE model could explain these clinical findings where the distribution of OI of the proximal femur with CGP3 (corresponding to Q_1=1.6) under loading case 3 shows high OI values in the epiphysis distributed along the top of the growth plate towards the lateral side (Figure 5c). Low OI values were found in the area under the medial side of the growth plate (Figure 5c). The scaled plot and contour plot of the growth plate indicate high growth rates at the lateral edge of the growth plate (Figure 5d).

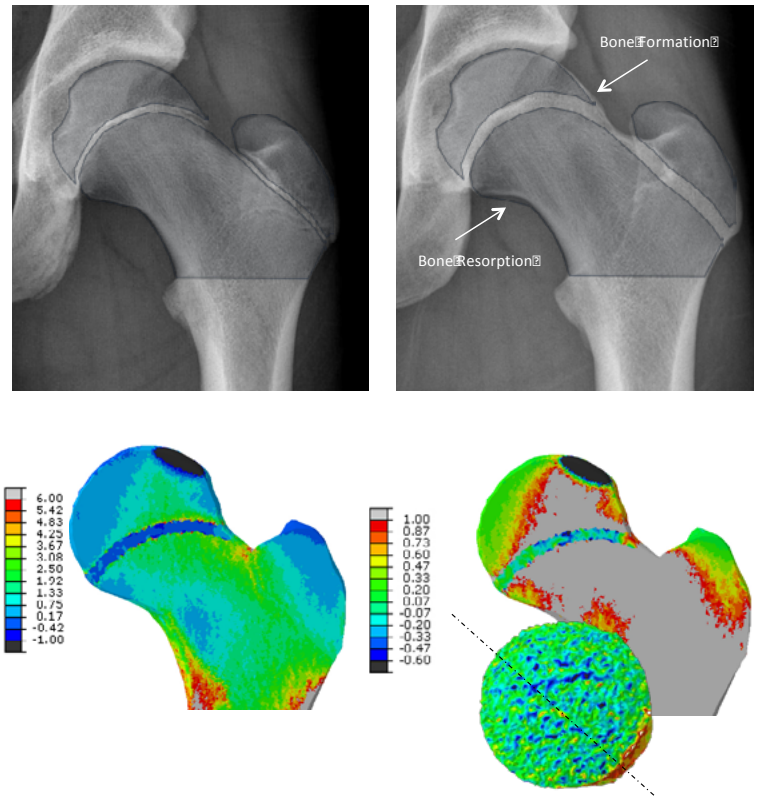


Figure 5. (a) Radiograph of a femur with an epiphyseal extension of Q_1>1.6 at the baseline and (b) The same femur at 2 year follow-up with an alpha angle > 60°. The blue contour indicates the shape and illustrates the growth region. (c) The distribution of OI in the proximal femur for CGP3 under loading case 3. (d) The distribution of OI in the proximal femur and growth plate.

Another representative femur with a low extension at the baseline (Q_1=1.2) was also selected from the prospective study (Figure 6). The femoral head was found to deflect minimally at the anterosuperior side (Figure 6a). Under the superior side of the growth plate, low OI values were observed (Figure 6c-d). The high values were distributed along the growth plate (Figure 6c-d).

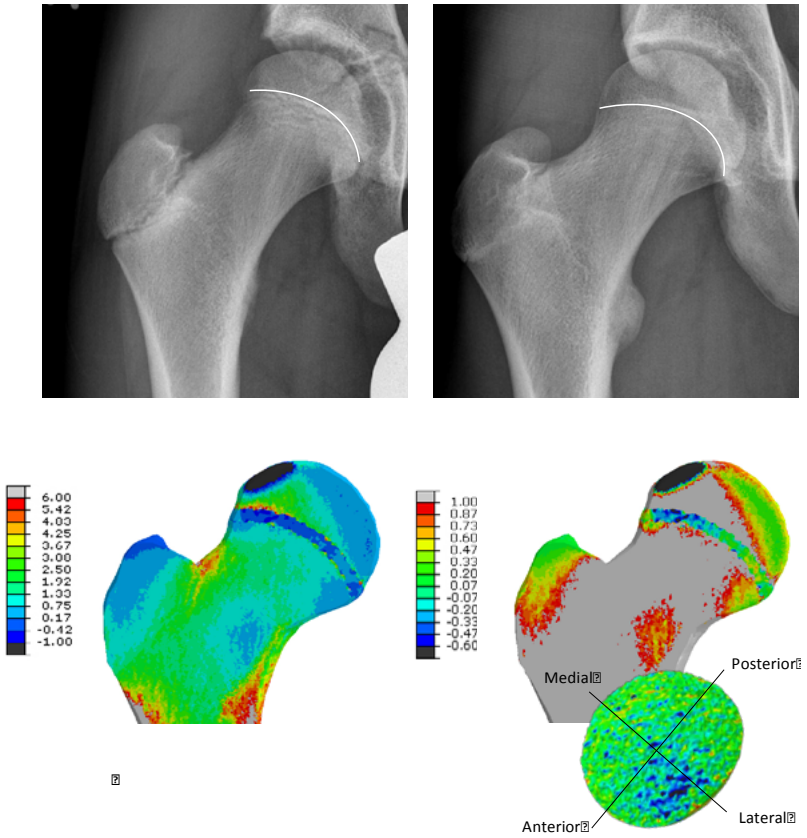


Figure 6. (a) Radiograph of a femur with an epiphyseal extension of Q_1>1.2 at the baseline and (b) 2 year follow-up. (c) The distribution of OI in the proximal femur for CGP2 under loading case 3 (d) Scaling indicates a region of low OI that could cause deflection of the growth plate.

DISCUSSION

A larger epiphyseal extension results in large differences between the OI values on the proximal and distal sides of the growth plate particularly for loading cases 3 and 4 (external rotation and flexion, Figure 3). For the largest epiphyseal extension (Q_1=1.6), some of the highest OI values are found on the lateral side

of the femur in the area where cam-type deformity normally develops (Figure 3). On the other hand, OI values are relatively low on the medial side of the femur (Figure 3). As a result of this imbalance and concentration of high OI values close to the site of cam-type deformity, the anomalistic bone growth occurs. These observations match the results of our prospective follow-up study[236] where cam-type deformity is found to be associated with a large epiphyseal extension. Detailed analysis of a representative radiograph from the cam-type deformity group (Figure 5) shows that both bone apposition and bone resorption occur during the development of cam-type deformity (Figure 5b). The location of the bone apposition is coincident with the location where high OI values are found in the FE analysis (Figure 5b-c) whereas bone resorption occurs on the medial side of the femur where low OI values are found (Figure 5b-c).

The results of this study clearly show that the development of cam-type deformity is directly related to the physical activities undertaken by the individual before growth plate closure. Both the level of OI values and the distribution of OI within the epiphysis are significantly different between gait (loading case 1) and external rotation and flexion (loading cases 3 and 4) (Figure 3). As for the level of OI, higher OI values are calculated for loading cases 3 and 4 (Figure 3) as compared to loading case 1. In addition, the areas with high osteogenic index values are located closer to the cam-type deformity in loading cases 3 and 4 as compared to loading case 1 (Figure 3). It is therefore expected that people who are exposed to loading cases 3 and 4 (such as soccer players and basketball players) are more likely to develop cam-type deformity as compared to the control group whose loading is predominantly described by patterns similar to loading case 1. These phenomena combined with the fact that the loading conditions are more dynamic in sports (impact-like forces) increase the chance of cam-type deformity in young individuals practicing in (pre-professional) sports requiring external rotation and flexion of the hip while weight-bearing such as young soccer players. These observations are in agreement with the results of clinical studies that have shown young active adults participating in those sports have significantly higher prevalence of cam-type deformity.[226,303]

Interestingly, the effects of loading scenarios are modulated with the effects of growth plate shape, meaning that certain growth plate shapes give rise to anomalistic distribution of OI in presence of loading cases 3 and 4, while they may not cause cam-type deformity if subjected to normal loading conditions (i.e. loading case 1). In addition, it is important to note that the shape of the growth plate could be even a result of certain loading conditions. An important example is the deflection of the growth plate due to excessive external rotation (loading case 3). If the epiphyseal extension is assumed to be relatively small (e.g.

Q_1=1.2) before starting vigorous physical activity, the distribution of hydrostatic stress (Figure 7) shows that relatively large compressive stresses can be found within the growth plate at the lateral side of the femur.

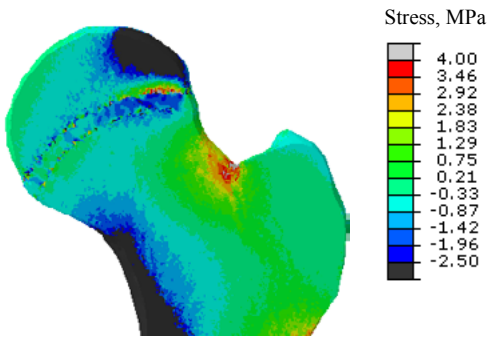


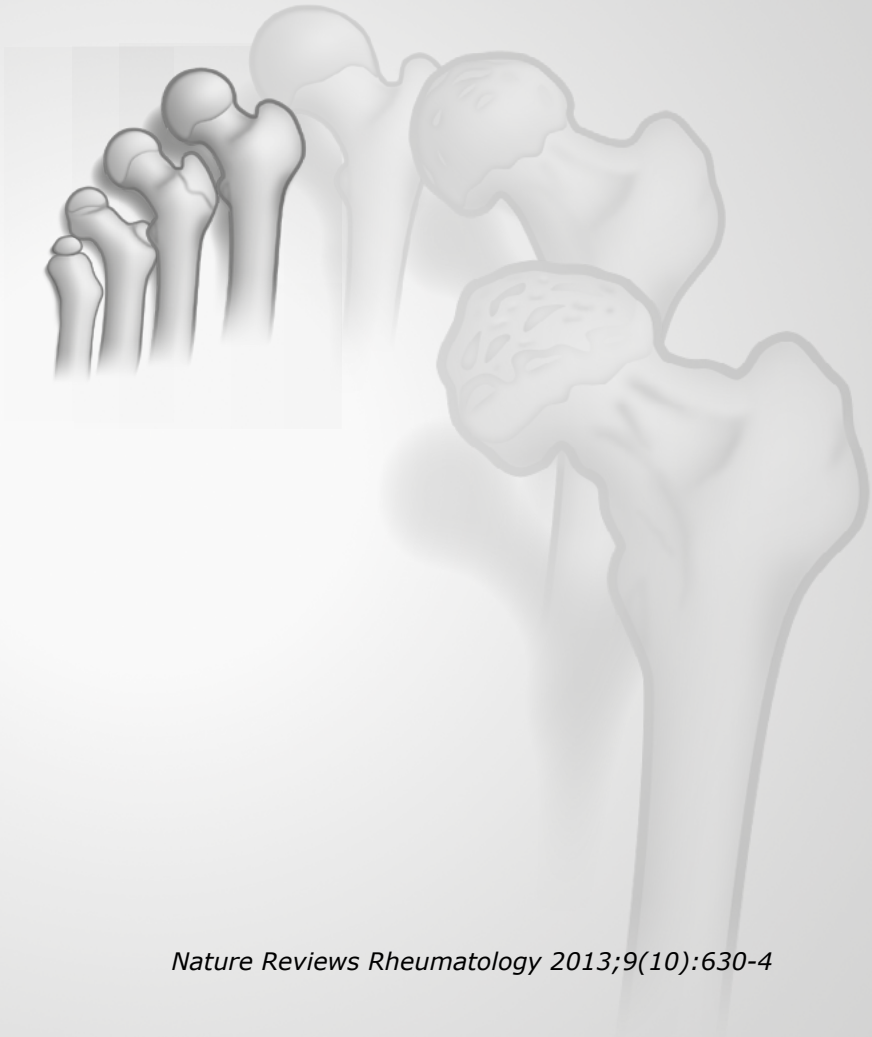
Figure 7. Hydrostatic stress contour plots for loading case 3 with CGP1 (see methods for description).

Those relatively large compressive stresses tend to inhibit bone growth while tensile stresses can be found on the medial side of the growth plate that stimulate bone growth. As a result of this mismatch between the growth of the lateral and medial sides, the growth plate may start to deflect and the epiphyseal extension may increase. It could therefore be postulated that the loading patterns experienced by soccer players may be partially responsible for the large epiphyseal extension seen in the cam-type deformity groups.[236] Once the epiphyseal extension increases due to excessive external rotation, the distribution of the OI caused by large epiphyseal extension further increases the chance of cam-type deformity, as described above.

In summary, the results presented here support both hypotheses of the study and show that both growth plate shape and loading conditions contribute to increased mechanical stimuli that initiate the development of cam-type deformity. Moreover, there is a modulation between the shape of growth plate and the loading conditions experienced during vigorous sport activities. As far the shape of the growth plate is concerned, a large epiphyseal extension increases the chance of formation of cam-type deformity. The presented results are in agreement with the observations reported in a our recent prospective follow-up study of young soccer players[236] and reveal the role of mechanical factors in the etiology of FAI. These findings might be useful when considering implementation of preventive strategies on the formation of cam-type deformity, which might have a considerable impact on the incidence of osteoarthritis.

Chapter 12

Cam impingement of the hip: a risk factor for hip osteoarthritis



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ABSTRACT

Femoroacetabular impingement (FAI) is characterized by abnormal contact between the proximal femur and the acetabulum. Two subtypes have been described: pincer impingement, caused by an overcovered acetabulum; and cam impingement, which occurs as a result of an aspherical femoral head (cam abnormality). A strong correlation exists between cam impingement and the subsequent development of hip osteoarthritis (OA). Major cam deformities confer a high risk of OA. However, the association between cam abnormalities and the pathology of OA has been difficult to compare between studies, as different methods have been used to define the abnormality. Cam abnormalities are acquired during skeletal growth and could be influenced by high impact sporting activities. Preventative treatments aiming to reduce the incidence of cam abnormalities and subsequent OA could, therefore, be developed. In this Perspective, we discuss the current understanding of FAI, focusing on cam abnormalities and their association with OA.

INTRODUCTION

Historically, most hip osteoarthritis (OA) has been defined as idiopathic, as the cause is often unknown. Over the past decade, subtle morphological abnormalities have been increasingly recognised as potential risk factors for OA. The observation that a nonspherical femoral head might lead to OA of the hip was first made at the beginning of the last century, but was only sporadically reported thereafter.[24,50,359]

Morphological abnormalities in the hip joint can cause femoroacetabular impingement (FAI), which can, in turn, cause motion-dependent soft-tissue damage.[55] Two types of FAI exist, one caused by an abnormality in acetabular shape or orientation (pincer type), the other caused by a shape abnormality in the proximal femur (cam type). In pincer impingement, the abnormal contact between the femoral neck and the overcovered acetabular rim is thought to cause an impaction type of impingement which compresses the labrum, and may subsequently lead to circumferential cartilage damage. The cam type of FAI is caused by extra bone formation at the anterolateral head–neck junction, which results in a nonspherical, cam-shaped abnormality (figure 1). The cam is forced into the acetabulum during flexion and internal rotation of the hip, a process referred to as cam impingement (Figure 1). Cam impingement can cause an inclusion type of damage to the acetabular labrum and articular cartilage, which is typically accompanied by detachment of the acetabular cartilage from the subchondral bone. This biomechanically based hypothesis of how damage is caused by cam impingement is supported by intra-operative findings in symptomatic patients with cam abnormalities—acetabular cartilage delamination has been found in the anterosuperior quadrant of the joint, corresponding to the site where the cam abnormality is forced into the acetabulum.[57] These observations suggest a relationship between cam impingement and OA, but the epidemiological evidence for this link is scarce.

The presence of a cam abnormality can be found radiographically in 15–25% of males and 0–15% in females in the general population.[60,275] Treating the cam abnormality surgically has become increasingly common, but the underlying etiology is unknown. Cam abnormalities might be acquired during skeletal maturation and influenced by certain loading patterns of the hip.[226,227] In this Perspectives article, we discuss the current knowledge within the field of FAI, focusing on cam impingement, and especially on the aetiology of cam abnormalities, the definition of abnormal in this context, and how these abnormalities are related to the subsequent development of OA.

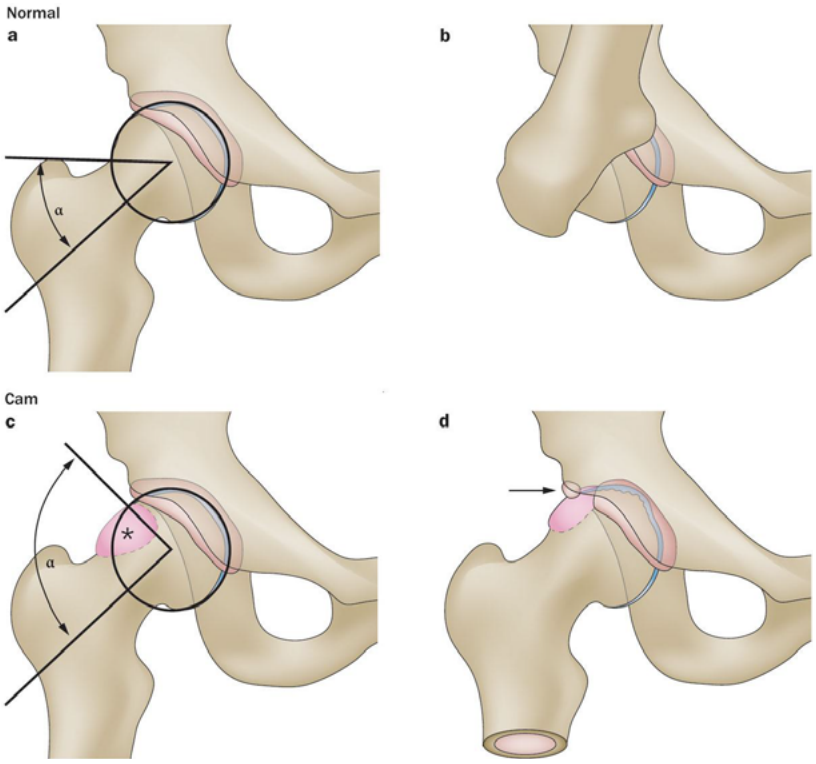


Figure 1. Mechanism of cam impingement. a, b | A spherical femoral head provides the hip with a wide range of motion. c, d | A cam abnormality (asterisk) can cause impingement (arrow) against the acetabular rim, especially during flexion and internal rotation of the hip.

Defining a cam abnormality

several measures to quantify the presence of a cam abnormality have been proposed, which quantify the amount of head-neck offset (such as the head:neck ratio and anterior offset ratio) or the extent to which the femoral head deviates from spherical (such as the triangular index and the alpha angle).[224,260] The alpha angle is the most commonly used method and was first described on axial plane MRI images. If a circle is inscribed with the circumference following the edge of the femoral head, alpha is defined as the angle between the neck axis and the line that connects the centre of the femoral head with the first point along the inscribed circle where the head-neck junction enters that circle (Figure 1). The alpha angle is a simple measure for quantifying the extent to which the femoral head deviates from spherical, and has been adapted to other MRI planes, CT images and radiographs. In all imaging modalities, the alpha angle predicts pain, function, and the development of hip OA.[63,203,259] Of note,

the cam is a three-dimensional abnormality centred anterosuperiorly, and the alpha angle can therefore depend on which view is used to measure it (table 1). To date, diverging threshold values to define the presence of a cam abnormality have been used (alpha angle values of 50–83°), thereby limiting the ability to correlate the prevalence of cam abnormalities with subsequent pathology or the development of OA. Furthermore, for upcoming surgical and clinical trials a validated cut-off value is needed to avoid misclassification. Numerous studies have proposed alpha angle threshold values or reported on the mean and deviation of the alpha angle in different radiographic projections (table 1).

Cam abnormalities and oa

Cam impingement is strongly associated with OA, but few well designed studies assessing this link exist; this association was first demonstrated in retrospective, cross-sectional, and case–control studies. In retrospective and cross-sectional studies,[60,64,208] the association between cam impingement and OA had an odds ratio (OR) varying between 2.2 (95% CI 1.7–2.8) and 20.6 (95% CI 3.4–34.8). Only one study[64] has failed to identify an association between a retrospectively identified cam abnormality and OA after a mean of 18.5 years, although the asymptomatic hips in this study were contralateral to hips treated for other diseases.

Radiographs of 965 patients with clinically severe OA (joint space width ≤2.5 mm) were compared with radiographs obtained using intravenous urography from patients without OA in a large case–control study.[208] The presence of a cam abnormality was quantified using a visually scored rating of the sphericalness of the femoral head, also known as the 'pistol grip deformity' (what a cam abnormality on anteroposterior radiographs was formerly called), and by calculating the femoral head:neck ratio (<1.27 was considered abnormal). Both the pistol grip deformity and a small femoral head:neck ratio were found more frequently in patients with OA (OR 7.0 [95% CI 4.6-10.4] and 12.1 [95% CI 8.1-18.2], respectively).[208]

Prospective data from the Chingford cohort were used in a nested case–control study,[63] with a follow-up time of 19 years after the initial hip X-ray. End-stage OA was defined by the requirement for total hip arthroplasty during follow-up. Radiographs from patients with end-stage OA were compared with radiographs from 243 randomly selected control hips. A significant association between baseline cam abnormality, as quantified on anterioposterior radiographs using the alpha angle, and total hip arthroplasty was found with an adjusted OR of 1.05 for every one degree increase in alpha angle (P = 0.001).[63]

Table 1. Studies presenting descriptive data of the alpha angle

Study	Sympt/ Asympt	Age mean (sd, range)	Hips (n)	Men (%)	Imaging modality view/location	Alpha angle threshold	Alpha angle mean (sd, range)
Gosvig et al.	Asympt	62 (men) (3) (NA, 23-93)	2110	37.6%	X-ray: AP	69°, 83° (1)	Right hip 51.7° (13.5, 34.0-100.0) Left hip 53.1° (13.9, 30.0-94.0)
		65 (women) (NA, 22-92)	3496		X-ray: AP	51°, 57° (1)	Right hip 44.4° (5.5, 34.0-90.0) Left hip 45.5° (5.1, 32.0-108.0)
Pollard et al.	Asympt	48 (men) (12, 28-69)	78	47.0%	X-ray: cross-table	62° (2)	Men: 48° (8, 95% CI 45-50)
		44 (women) (11, 22-67)	88		X-ray: cross-table	62° (2)	Women: 47° (8, 95% CI 45-49)
Fraitzl et al.	Asympt	47 (men) (17, NA)	170	50.1%	X-ray: AP Frog leg	70° (2) 70° (2)	Men: 49.4° (10.5, 34.5-88.3) Women: 49.1° (10.6, 27.0-87.9)
		55 (women) (17, NA)	169		X-ray: AP Frog leg	61° (2) 66° (2)	Men: 45.0° (8.0, 29.5-77.6) Women: 46.1° (9.9, 23.0 - 82.5)
Notzli et al.	Sympt	35 (9, 18-57)	39	66.7%	MRA obl. ax/ant	NA	All sympt:74° (5.4, 55-95)
	Asympt	30 (5, 20-46)	35	48.6%	MRI obl. ax/ant	NA	All asympt: 42° (2.2, 33-48)
Kassarjian et al.	Sympt	37 (NA, 17-67)	42	55.0%	MRA obl. sag/ant	55°	All: 69.7° (NA, 41 - 91)
Beaule et al.	Sympt	41 (NA, 25-54)	36	56.7%	CT sag. ax/ant	50.5°	All sympt: 66.4° (17.2, 39-94) Men 73.3° (NA, NA) women 58.7° (NA, NA)
	Asympt	37 (NA, 18-70)	20	58.3%	CT sag. ax/ant	50.5°	All asympt: 43.8° (4.46, 39-48) Men 43.7° (NA, NA) women 43.8° (NA, NA)
Pfirrmann et al.	Sympt	29 (NA, 19-48)	50	60.0%	MRA	NA	Cam hips (4): 68° (19, NA), 81° (15, NA), 53° (20, NA)
					rad/ant, ant-sup, sup		Pincer hips (4): 54° (11, NA), 66° (19, NA), 42° (5, NA)
Clohisy et al.	Sympt	32 (NA, 14-53)	61	74.0%	X-ray: AP cross-table, frog leg	NA	All sympt: 71.5° (sd 19.4, 38-132) 58.8° (sd 15.7, 31-101), 65.2° (15.0, 38-114)
	Asympt	35 (NA, 18-49)	24	54.0%	X-ray: AP cross-table, frog leg	NA	All asympt: 51.2° (sd 15.7, 36-94) 47.2° (15.4, 30-92), 43.7° (12.1, 31-76)
Toogood et al.	Asympt	44 (NA, 18-89)	400	50.0%	Photographed anterior, lateral	NA	All: 53.5° (12.68, 31-112), 45.6° (10.5, 17-79)

Table 1. Studies presenting descriptive data of the alpha angle *(Continued)*

Study	Sympt/ Asympt	Age mean (sd, range)	Hips (n)	Men (%)	Imaging modality view/location	Alpha angle threshold	Alpha angle mean (sd, range)
Rakhra et al.	Sympt	39 (11, 17-60)	41	43.9%	MRA obl. ax/ant	55°	All: 53.4° (sd 11.1 range 39.9-84.2),
					rad/12, 1, 2, 3 o'clock (5)		56.3° (14.1, 39-96), 64.7° (16.1, 44-98) 65.9° (13.4, 44-99), 54.5° (11.9, 40-89)
Allen et al.	Sympt	38 (NA, 16-55)	226	72.6%	X-ray: cross-table or Dunn view	55.5°	All: 67.1° (10.6, 39-92) Men: 69.1° (10.4, NA) women: 62.1° (9.6, NA)
Hack et al.	Asympt	29 (NA, 21-50)	400	55.5%	MRI obl. ax/ant, rad/ant-sup	50.5° & 55°	All: 40.8° (7.1, 27-70), 50.2° (8.1, 33-76)
							Men: 44.0° (7.8, 30-70), 54.1 (8.5, 37-76) Women: 38.2° (5.1, 27-57), 47.0 (6.2, 33-70)
Jung et al.	Asympt	60 (NA, 25-90)	755	28.5%	CT: AP scouts	69° & 83° (men) 51° & 57° (women)	All: 49.3° (12.8, NA) Men: 59.1° (17.61, NA) women: 45.5° (7.4, NA)

Data from the CHECK cohort,[203] a large nationwide Dutch prospective cohort study, confirmed the association between a cam abnormality and an elevated risk of OA in 723 subjects who had no radiographic evidence of OA upon entry into the cohort but developed OA after 5 years. The presence of a moderate (alpha angle >60°) or severe (alpha angle >83°) cam abnormality at baseline was significantly associated with the development of end-stage OA, defined by Kellgren & Lawrence grade 3 or 4, or total hip arthroplasty within 5 years (OR = 3.7, 95% CI 1.7–8.0 and OR = 9.7, 95% CI 4.7–19.8 for moderate and severe cam abnormalities, respectively).[203] Notably, if a severe cam abnormality was accompanied by limited internal hip rotation (≤20°), the OR was further increased. Moreover, larger alpha angles, which often imply more severe cam abnormalities, are associated with a substantially increased risk of cartilage damage and OA.[63,203,262]

The prevalence of cam abnormalities in these epidemiological studies might be underestimated, as only anterioposterior radiographs were used for assessment. Ideally, a potential cam abnormality is assessed using 3-dimensional radial images, which are better than standard radiography for visualizing cam abnormalities located anterolaterally.[67] In addition, almost all published longitudinal cohorts consisted of only middle-aged individuals, despite the relationship between cam impingement and OA being poorly defined in individuals 20–45 years of age. Although cam impingement is strongly correlated with the development of OA in patients ≥45 years of age, there are indications that cartilage damage caused by a cam abnormality might already exist from the age of 20 years. In a study of symptomatic patients with a mean age of 28 years, cam abnormalities were often found in hips with the types of intra-articular damage, such as cartilage delamination, that are associated with OA of the hip.[59] In only one study[264] has the relationship between cam abnormality and intra-articular hip damage been examined in asymptomatic younger individuals. In this study, MRI was used to assess hip morphology in this cross-sectional study of 244 young males (mean age 19.9 years). A decreased combined femoral and acetabular cartilage thickness was found in individuals with a visually scored definite or severe cam abnormality.[264] The OR for labral lesions was 2.77 (95% CI 4.6–10.4) when comparing those with and without cam abnormalities. The association between labral tears and cam abnormalities, however, should be interpreted with caution, as labral tears are highly prevalent in the asymptomatic population.[264]

Aetiology of cam abnormalities

Research in the past 10 years has improved our understanding of how to surgically manage cam abnormalities and how they contribute to intra-articular pathology, but the aetiology of the osteochondral extension has not been elucidated. Distinguishing between primary and secondary impingement is

important. Femoral morphologies that predispose the hip to cam impingement could be secondary to hip diseases such as Perthes disease, slipped capital femoral epiphysis (SCFE), healed proximal femoral fractures, or an outgrowth of osteophytes. These secondary shape variants can mimic cam abnormalities, but primary cam abnormalities, which are more frequent than these secondary changes, are of unknown origin.

Initially, researchers proposed that a cam abnormality might be a sequelae of a subclinical SCFE.[23] This hypothesis was questioned in a study in which none of the 15 symptomatic patients with FAI, who had substantially less offset between the femoral head and neck than the 15 controls, had a posterior tilt by lateral radiography (a sign of SCFE).[25] Furthermore, in a 2012 study of asymptomatic adolescents with cam abnormalities, no evidence of a subclinical slip (such as complaints during weight bearing), or a widening or irregularity of the physis, all of which suggest SCFE, was found.[226] Rejecting the SCFE hypothesis, the main etiological question remains whether a cam abnormality is a developmental or acquired phenomenon. If a cam deformity is developmental, genetics or other factors present before birth are likely to determine its presence. Acquired phenomena result from interactions with the environment.

Developmental causes

The prevalence of cam abnormalities has geographical variability. The prevalence in Chinese people is substantially lower than in white people.[38] Although cultural differences in activities that involve hip loading and subsequent adaptation during growth could exist, genetic differences between Chinese and white people could also contribute to the difference in the prevalence of cam abnormalities. Siblings of patients with cam abnormalities had a relative risk of 2.8 of having a cam abnormality compared with the patients' spouses.[360] However, siblings might participate in similar sporting activities during growth, and so far only indirect associations between genetics and cam abnormalities have been documented. Although some genetic involvement is likely, current evidence is scarce.

Environmental causes

Indications exist to support the hypothesis that a substantial proportion of cam abnormalities are acquired during skeletal maturation. First, a cam abnormality is not present, or at least not radiographically visible, in boys <13 years of age.[226] Second, the formation of a cam abnormality in individuals 13–14 years of age, during skeletal maturation, is highly influenced by athletic activities (figure 2).[23,226,227] The prevalence of cam abnormalities in skeletally mature, nonathletic males is 9%, but is as high as 89% in skeletally mature, male elite basketball players who practiced their sport from childhood.[227] This hypothesis was further supported by a study[315] in which a higher prevalence of cam abnormalities was

found in symptomatic female soccer players (50%) than would be expected in the general population (<15%). Furthermore, in longitudinal data from epidemiological studies, cam abnormalities (as measured on anterioposterior radiographs) neither develop during mid-adulthood, nor evolve over time, indicating that cam abnormalities are static after skeletal maturation.[63,203] A substantial proportion of cam abnormalities are, therefore, likely to result from physeal damage or as an adaptation to high impact loading during growth. The proximal femoral growth plate might have a crucial role in this process, as cam abnormalities are associated with an unusual extension of the epiphyseal scar onto the femoral neck (Figure 2).[25] Further, this unusual extension of the growth plate was already present before epiphyseal closure and before a cam abnormality was detectable in adolescent basketball players, who are at risk of cam abnormalities.[324] These results suggest that cam abnormalities are primarily an adaptation to the environment and not a purely reactive phenomenon (in which extra bone formation results from an abnormal contact between the proximal femur and acetabulum, without an initial cam deformity or environmental trigger), although no longitudinal data are available.

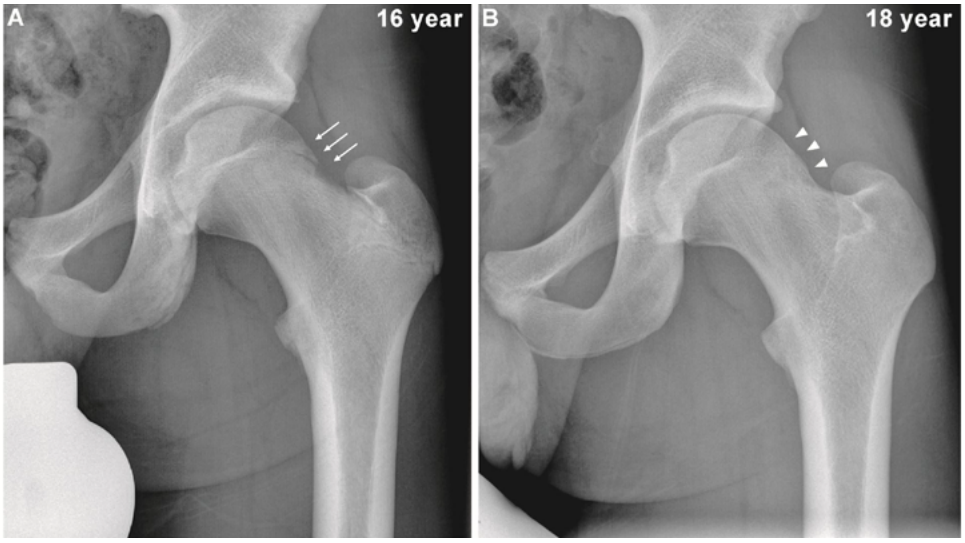


Figure 2 Formation of a cam abnormality. **A.** Radiography of the hip joint of a 16-year-old asymptomatic male elite soccer player. An extension of the growth plate into the femoral neck can be seen (arrows). **B.** After 2 years of follow-up, a cam abnormality is clearly visible where the femoral head deviates from spherical (arrowheads).

Most cam abnormalities are probably acquired during growth and are heavily influenced by high impact and high intensity athletic activities. Interestingly, this theory implies that the formation of a cam abnormality could be prevented

by adjusting loading patterns during adolescence. If this theory holds true, opportunities to modify the progression towards OA could be found. However, more research is needed to elucidate questions such as which activities or loading types and training intensity are associated with the greatest risks of the formation of a cam abnormality, and whether loading history can explain the difference in prevalence of cam abnormalities between males and females.

Cam abnormality vs impingement

Despite the strong association between a cam abnormality and the subsequent development of OA, most individuals with radiographic evidence of a cam abnormality will not develop OA. Depending on the characteristics of the cohort and how the cam abnormality was defined, with a follow-up of either 5[203] or 19[63] years, the positive predictive value of a cam abnormality to determine subsequent development of OA was 6–25%, and the negative predictive value was 98–99%.[63,203] This observation suggests that although radiographic evidence of a cam abnormality is almost a prerequisite for cam impingement (a risk factor for OA), other risk factors, including repetitive impinging activities such as flexion and internal rotation, injury, or actabular morphology, can also influence the probability of developing OA in patients with cam abnormalities.

In the absence of repetitive dynamic impingement events, a cam abnormality probably does not cause OA. The quantification of dynamic impingement might therefore, be important to identify and treat patients with cam abnormalities who are at risk of OA. However, assessing whether somebody with a cam abnormality truly has cam impingement is not straightforward. Factors other than the presence of a cam abnormality are involved, including variations in femoral or acetabular orientation. Femoral retroversion or retrotorsion can place the anterolateral head–neck junction closer to the acetabular rim than normal, thereby increasing the risk of impingement. Correspondingly, the spatial orientation of the acetabulum can affect cam impingement. Furthermore, even if cam impingement is present based on the osseous morphology, an individual might only become symptomatic if repetitive impingement episodes, such as those caused by sporting activities, are also present.

Clinical signs of impingement, such as groin pain, limited internal hip rotation, and a positive impingement test, together with a history of participation in work or sports that require repetitive flexion and/or internal rotation, can also determine whether an individual with a cam abnormality also has cam impingement.[328] Combining radiographic and clinical signs of cam impingement in those without radiographic OA at baseline has been shown to improve the positive predictive value of cam impingement to identify patients who will subsequently develop OA.[203]

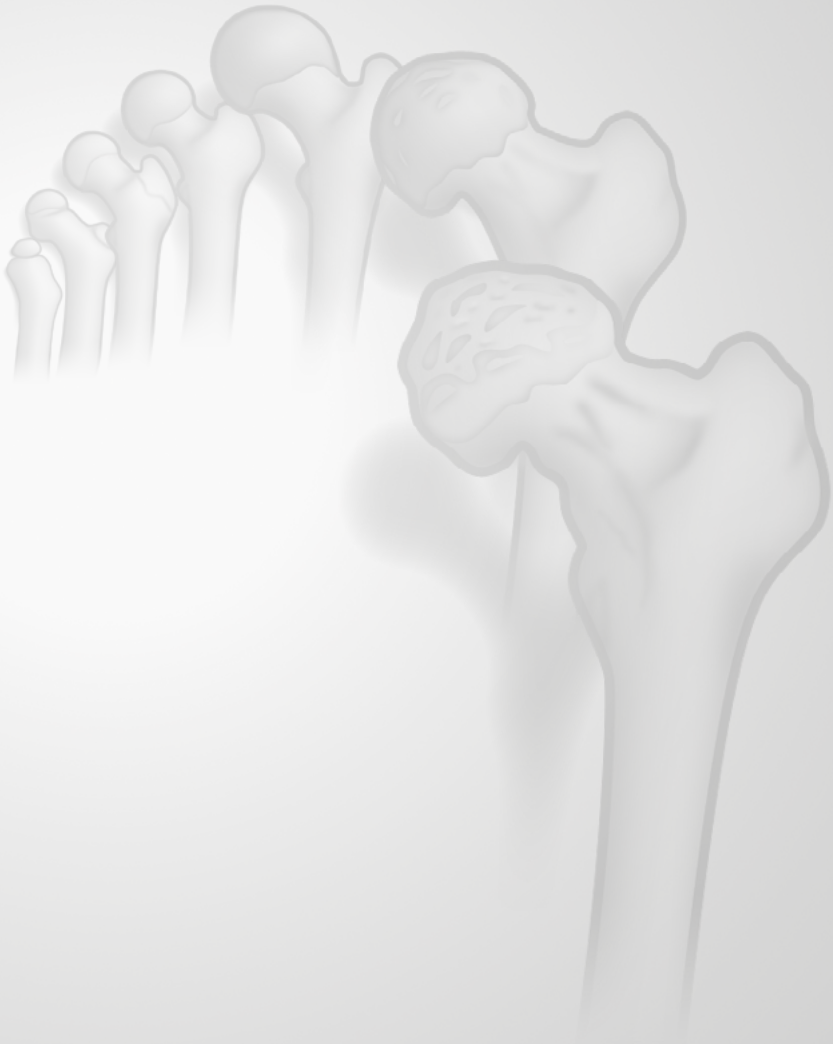
Advanced imaging modalities are also being developed to predict the presence of dynamic impingement. Acetabular chondrolabral damage at the typical anterosuperior location in an individual with a cam abnormality could support the diagnosis of cam impingement. Quantitative analysis of biochemical cartilage composition using techniques such as delayed gadolinium-enhanced MRI of cartilage, T1 rho, and T2 mapping, could provide such evidence in the very early stages of cartilage damage.[262] Motion simulations of the hip, based on MRI or CT, provide further insight into the range of motion, and the location of bone impingement.[361,362] Logically, other causes that might lead to groin pain should be ruled out.

CONCLUSIONS

Cam abnormalities are prevalent in the general population and probably result from high impact activities during bone maturation. The diagnosis of cam impingement should be based on both radiographic and clinical findings. Cam impingement is strongly associated with the development of OA and future studies should therefore focus on the pathophysiology of cam abnormalities. Altering activity levels during adolescence could then be used as strategies to prevent cam abnormalities from developing, thereby eliminating a major risk factor for hip OA.

Chapter 13

Summary



Osteoarthritis (OA) is a common disease and accounts for a detrimental impact on the quality of life.[27] In the coming years, the prevalence of hip OA will continue to grow with an estimated 23% increase in the need for total hip replacement (THR) by 2030.[28,363] In addition, patients requiring primary total hip replacement tend to be younger and more demanding. To date, there are no disease modifying osteoarthritis drugs (DMOADS) or preventive surgical procedures available so treatment for early stage disease is limited to pain management. For end-stage OA, THR is an effective treatment, but there can be adverse functional outcomes and the lifespan of prostheses is limited. Consequently, the focus of the battle on OA should shift towards early treatment or even prevention of OA. Overcoming these challenges is inevitably related to understanding the etiology of the disease.

If modifiable risk factors can be identified at an early stage of the disease, preventive measures could be implemented.[72] It has been suggested that many cases of idiopathic hip OA might be secondary to minor and possibly modifiable variations in the morphology of the proximal femur and acetabulum. These minor shape variations were described by Ganz et al., who introduced the concept of femoroacetabular impingement (FAI).[55] Here we provide a summary of the chapters covering the three aims of this thesis. The first aim was to study the relationship between baseline hip morphology and the development of hip OA five years on. We studied general hip morphology and subsequently focused on FAI morphology. Our second aim was to provide a clinical and radiographic definition of FAI. Our third aim was to investigate if and how a cam deformity develops during skeletal maturation. Following on from this summary, I will continue to discuss several topics including the mechanism of FAI, the CHECK cohort, statistical shape modelling, and I will provide a hypothesis on the formation of a cam deformity. Finally, I will come to the conclusions of this thesis and will speculate on some potential areas for future research.

PART 1. ASSOCIATION BETWEEN HIP MORPHOLOGY AND DEVELOPMENT OF OSTEOARTHRITIS

In **chapter 2** we provided a general overview of OA including its epidemiology, pathogenesis, diagnosis, and treatment, in which we also speculated on potential targets for prevention of OA development or progression. With regard to hip OA, surgical correction of a cam deformity to prevent cam impingement has shown symptomatic benefit beyond 5 years and may modify the long-term risk of developing OA. However, randomised controlled trials are required to determine whether any such disease prevention truly exists. Another approach to lower the incidence of hip OA might be the prevention of the development of a cam deformity itself during adolescence, which will be extensively debated in the

general discussion. In **chapter 3** we used the CHECK cohort (a Dutch nationwide cohort of people that visited the general practitioner for the first time with knee and/or hip pain or stiffness) to study the relationship between overall hip shape and development of clinical OA as defined by both THR and the American College of Rheumatology (ACR) criteria for symptomatic OA. Baseline general hip shapes were quantified by Statistical Shape Modelling (SSM), which describes the total variation in shape in the study population. Shape variants which are correlated are captured in one mode such that each single mode represents independent shape variants. It is therefore possible to study the association between all shape variants that exist in a population with any potential outcome of interest. We showed that several independent shape variants (modes) of the hip at baseline could predict THR after five years, but not symptomatic OA as defined by the ACR criteria. In particular, a broad and short femoral neck and a retroverted acetabulum together with a cam-shaped femoral head were predictive of fast progressing OA. Although hip shape was not predictive for the combination of symptoms in the ACR definition, it could borderline significantly predict two ACR criteria independently at follow-up; decreased internal rotation and pain. Based on the findings of this study, the generalisability of the resulting shape variants were studied in **chapter 4.** We used an identical shape model in the CHECK cohort and Chingford cohort (an open population cohort of females from the United Kingdom) in order to test how consistent the associated shape variants (modes) for development of hip OA are in different female populations. In accordance with chapter 3 and other literature, we showed that several shape aspect of the hip were significantly associated with THR within each cohort. Interestingly, we found one shape aspect that was significantly associated with THR in both cohorts. Furthermore, two shape aspects that were significantly associated with THR in the CHECK cohort also showed non-significant trends in the Chingford cohort. This indicates that these shape aspects can be generalised to other female populations in the prediction of THR, even regardless of other factors such as cohort characteristics, follow-up time, or radiographic protocol. In contrast, some other shape variants only found to be associated with THR in the CHECK cohort might be co-dependent on those or other factors. Based on the findings of chapters 3 and 4, more specific shape variants such as acetabular dysplasia and FAI-related shape patterns were further investigated. In **chapter 5** we showed that a pincer deformity does not increase the risk for development of OA whereas mild acetabular dysplasia was associated with the development of OA. In agreement with previously published prospective studies we found that acetabular dysplasia -as quantified on an AP radiographic view by a lateral centre edge angle <25°- was moderately associated with development of hip OA (odds ratios between 2.3 and 3.8 depending on the definition of OA). Interestingly, in contrast to previous studies an additional lateral radiographic

view of the hip was included and it was demonstrated that the risk of hip OA significantly increased when acetabular dysplasia was present both laterally and anteriorly in one hip (odds ratios between 4.9 and 6.5). Current evidence for the relationship between a pincer deformity and OA is conflicting and limited by retrospective or cross-sectional study designs. We found a protective effect of a pincer deformity when present both anteriorly and laterally in one hip, with a corresponding odds ratio of 0.34 (95% CI 0.1-0.9) for incident hip OA (K&L ≥2). This finding was supported by the fact that none of these hips developed end-stage OA (K&L 3,4, or THR) within 5 years' follow-up. The currently available literature suggests that pincer impingement is a mechanism which might lead to pain and hip damage as shown by studies of symptomatic patients. However, our data suggests that pincer impingement is not associated with hip OA on an epidemiological scale but might even be protective. In **chapter 6**, we looked to see whether cam impingement at baseline was associated with the development of hip OA over a period of 5 years. We showed that a cam deformity was strongly associated with the development of end-stage OA. A moderate cam deformity (alpha angle >60°) and a severe cam deformity (alpha angle >83°) resulted in respective odds ratios of 3.7 (95% CI 1.7-8.0) and 9.7 (95% CI 4.7-19.8) for end-stage OA. The combination of a severe cam deformity and decreased internal rotation –a clinical sign of cam impingement– at baseline resulted in an even more pronounced odds ratio of 25.2 (95% CI 7.9-80.6) and in a positive predictive value of 52.6%. The data suggest that the risk of OA is higher when the cam deformity is more pronounced.

PART 2. DEFINITION OF FEMOROACETABULAR IMPINGEMENT (FAI)

From the moment that the mechanism of FAI has been described, the literature on this topic has increased exponentially. This has resulted in a better understanding of the role of FAI in the development of hip OA as described above, but also the prevalence and association with hip pain and limited functionality of the hip. Consequently, clinical practice has significantly changed over recent years regarding the acceptance and treatment of FAI. Despite the increased interest in this condition, the nature of this clinical entity has remained ill-defined. The aim of **Chapter 7** was to define FAI, with the goal of developing an operational definition for the purpose of clinical trial planning. Together with a team of clinical and scientific experts in the field of FAI, we proposed the following definition of FAI: 'a clinical entity in which a pathological mechanical process causes hip pain when morphological abnormalities of the acetbaulum and/or femur, combined with vigorous hip motion (especially at the extremes), lead to repetitive collisions that damage the soft-tissue structures within the joint

itself'. This definition contains five essential elements: (1) abnormal morphology of the femur (cam) and/or acetabulum (pincer), (2) abnormal contact between these two structures, (3) especially vigorous supraphysiological motion that results in such abnormal contact and collision, (4) repetitive motion resulting in the continuous insult, and (5) the presence of soft tissue damage. The most investigated subcategory of FAI is cam impingement, in which a cam-shaped femoral head causes impingement. However, there is no consensus on how to define and quantify the presence of a cam deformity. It is usually quantified by the alpha angle, which measures the extent to which the femoral head deviates from being spherical, but there is no consensus on which alpha angle threshold to use to define the presence of a cam deformity. In **Chapter 8**, we proposed alpha angle threshold values to define the presence of a cam deformity and a pathological cam deformity. By combining alpha angles of two large prospective cohort studies (CHECK cohort and Chingford cohort), comprising almost 3000 hips, an alpha angle threshold for defining the presence of a cam deformity was determined based on the finding of a bimodal distribution of the alpha angle. Interestingly, a bimodal distribution indicates two different populations, one without cam deformity and one with cam deformity. The optimal threshold that distinguishes between both distributions was assessed and resulted in an alpha angle threshold of 60°. As greater alpha angles substantially increase the risk for OA, we also determined a pathological alpha angle threshold based on developing end-stage OA at follow-up. A pathological threshold of 78° was proposed, as this value resulted in the maximum area under the ROC curve (highest sum of sensitivity and specificity), which was 0.69 (95% CI 0.62-0.75) for end-stage OA.

PART 3. DEVELOPMENT OF A CAM DEFORMITY

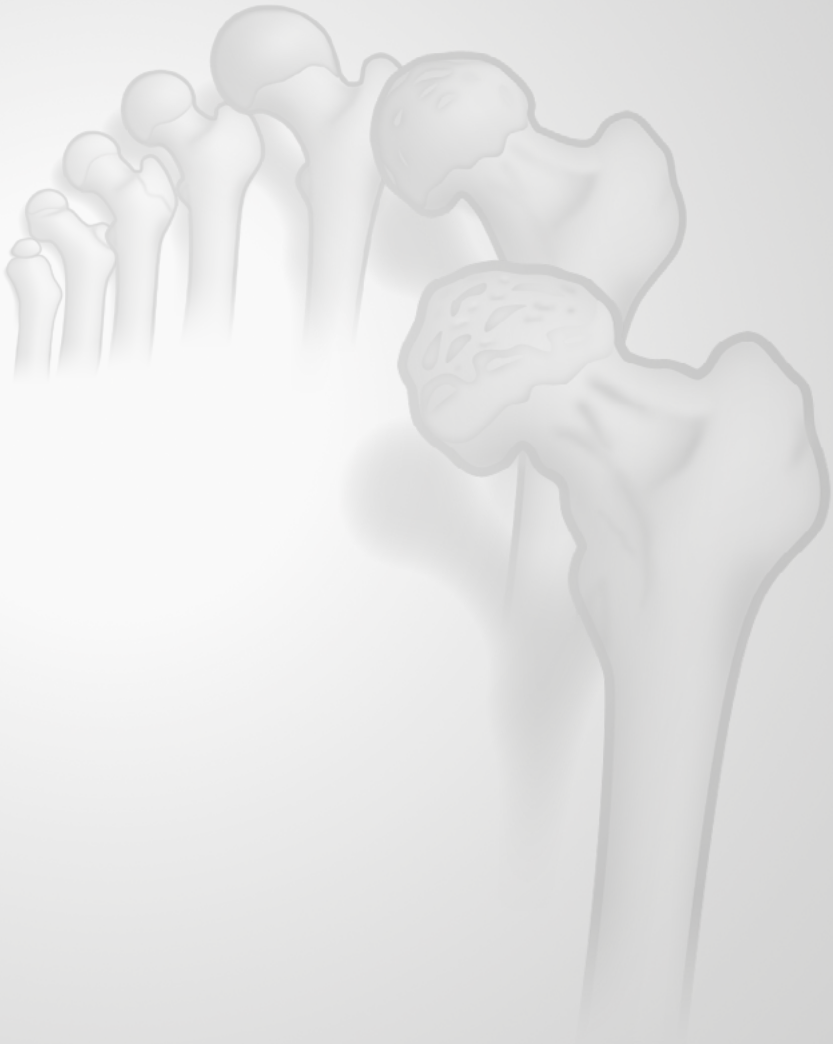
Research in the past 10 years has improved our understanding of how to surgically manage cam deformities and how they contribute to intra-articular pathology, but the etiology of a cam deformity has not yet been clarified. Regarding its strong association with the development of hip OA, hip pain, and decreased functionality, a better understanding of its etiology is necessary. In **chapter 9**, we aimed to determine the age of onset and prevalence of cam deformities in young male soccer players versus non-athletic controls. We obtained AP pelvic and frog-leg lateral radiographs and performed a clinical examination on 89 pre-professional soccer players aged 12-19 years. Controls (n=92) without hip disorders and with both radiographic views available in radiology databases were selected. We showed that a cam deformity is radiographically present early in adolescence, from the age of 13 years. Furthermore, the prevalence of cam deformities was higher and the cam deformities were more pronounced

in soccer players than in their non-athletic peers. The prevalence of cam deformities seemed to increase with age. In **chapter 10** we described the 2.5 years follow-up results of this cohort of adolescent soccer players, in which we aimed to study whether a cam deformity can evolve in time in adolescents and whether or not its formation only occurs during skeletal maturation. The second aim was to examine whether other clinical or radiographic features are associated with or predictive of the formation of a cam deformity. In this follow-up study, 63 of the 89 soccer players were still able and willing to participate, and the same radiographs and clinical examination were obtained. It was found that a cam deformity is gradually acquired over time and only during skeletal maturation. Generally, the femoral head is spherical at the age of 12 years, then until the age of 14 years the head-neck junction becomes flat and from the age of 14 years towards the end of skeletal growth the flattening continues to evolve into a prominence in a substantial number of hips. After closure of the growth plate, the morphology of the hip does not change anymore during follow-up. The formation of a cam deformity might therefore be a result of a structural adaptation to high impact athletic activities during growth, when the skeleton is highly sensitive to mechanical loading. A greater extension of the growth plate towards the neck, a small neck-shaft angle (more varus position), and limited internal rotation at baseline were all associated with the presence of a cam deformity at baseline. A small neck shaft angle and limited internal rotation might even predict the formation of a cam deformity at follow-up in hips without a cam deformity at baseline. Following the results of chapter 10, we aimed to determine if mechanical factors could explain the development of a cam deformity in **chapter 11**. We used finite element (FE) models to study which specific loading condition (gait, internal rotation, external rotation, and flexion) could explain the formation of a cam deformity, and also considered three different levels of growth plate extension towards the femoral neck. Mechanical stimuli at the tissue level were calculated for the combination of all loading conditions and the three growth plate shape variants by means of the osteogenic index, which is the resultant of the peak octahedral shear stress (stimulates bone growth) and the peak hydrostatic stress (inhibits bone growth). It was found that external rotation and flexion could stimulate the formation of a cam deformity in hips with an open growth plate by modifying the distribution of the mechanical stimulus. The effects of the different loading scenarios are modulated with the effects of growth plate shape, meaning that certain growth plate shapes (larger extension towards femoral neck) can result in anomalistic bone growth during flexion and external rotation while weight bearing. These findings can explain the high prevalence of cam deformity in athletes practising high impact sports. These results also support the findings in chapter 10 that the amount of growth plate extension towards the femoral neck is strongly

associated with the presence of a cam deformity. In **chaper 12**, we discussed the current understanding of FAI, focusing on the etiology of cam deformities and their relationship with hip OA. By putting these concepts in perspective, we speculate on possible preventive treatments aiming to reduce the incidence of cam deformities and subsequent OA. Furthermore, differences between the radiological entity of a cam deformity and the clinical entity of cam impingement, and how both entities influence development of OA were discussed.

Chapter 14

General discussion



GENERAL DISCUSSION

In this thesis, the rise (skeletal development) and fall (OA) of the hip was studied. In the first part, the role of hip morphology in the development of hip OA was investigated. In the second part, we defined FAI and the presence of a cam deformity. In the third part, we studied if and how a cam deformity developed during skeletal maturation and how this was influenced by athletic activities.

Hip shape and other risk factors of hip osteoarthritis: a mechanical explanation

Regardless of the joint of interest, OA is characterised by cartilage degradation, subchondral bone sclerosis, and osteophyte formation. These characteristics of end-stage joint degradation probably result from different etiologies or subtypes of OA. As described in chapter 2, a combination of systemic risk factors (age, gender, obesity, genetics), environmental risk factors (physical/sports activity, occupation, injury), and biomechanical risk factors (joint morphology, limb alignment, leg length) are involved in the development and progression of OA. However, the contribution of each risk factor to the development of OA is joint specific.

OA of the hip might primarily be caused by local biomechanical factors rather than systemic factors. This is supported by the observation that OA is often present in multiple joints (i.e. both in knees and hands),[364,365] but hip OA frequently occurs in isolation.[202] In contrast to knee OA, systemic factors such as obesity and female gender are not risk factors for the development of hip OA.[42,44,366] I hypothesise that a biomechanically non-optimal shape of the hip joint is the main trigger of hip OA. This hypothesis is not new, since it has been suggested that up to 90% of all hip OA cases might result from an abnormal hip shape.[55] However, an abnormal hip shape alone will not always cause OA. My second hypothesis is that the relationship between an abnormal hip shape and development of OA is influenced by genetics and environmental factors; both during childhood when the hip shape is determined, and during mid adulthood when OA starts to develop (figure 1).

Genetics, high impact athletic activities, and heavy physical workload (farmers) are associated with hip OA, but they might actually act via an abnormal shape of the hip. The GDF5[217,367-369], FRZB[370-373], and DIO2[374] single nucleotide polymorphisms (SNPs) have been independently associated with hip OA. Interestingly, these SNPs are also involved in joint development and might influence hip shape, although data on the association between SNPs and hip shape are conflicting.[217,230,375,376] The same holds for high impact athletic activities, which is an independent risk factor of OA,[45] but is also known to influence hip

shape during skeletal maturation as has been shown in chapter 9 and 10 of this thesis. Finally, there is a relationship between heavy physical workload and OA; farmers have an up to 10-fold increased risk to develop OA.[45] Like high impact athletic activities, heavy physical workload during skeletal growth might also lead to an abnormal hip shape, although no studies are available on this topic. Besides the fact that these factors are important in establishing the shape of the hip during skeletal growth, they are also important during mid adulthood because they might determine whether or not an abnormal hip shape will lead to development of OA. For example, OA susceptible SNPs might affect cartilage structure or metabolism such that it becomes more vulnerable to biomechanical stresses of an abnormal hip shape. Also, certain athletic activities and occupations reported to be at risk of OA might modify the association between a cam deformity and hip OA as they require impingement movements (flexion + internal rotation). These movements might cause damage in the presence of a cam deformity, while somebody with a cam deformity not experiencing these movements repetitively will probably not develop OA. Thus, the main risk factor for hip OA is probably an abnormal shape of the hip joint, while this relationship is modified by genetics and environmental factors. The different types of hip shape which are considered 'abnormal' will be discussed below.

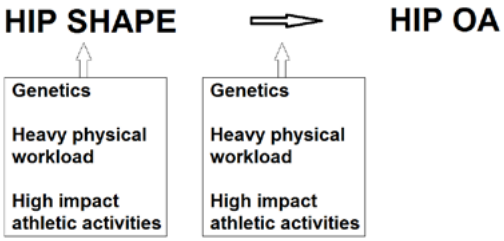


Figure 1. A non-optimal hip shape might be the main trigger for hip OA. This pathway might be influenced by genetics and environmental factors twice in life: during skeletal maturation, since these factors co-determine the final hip shape and during adulthood, when these factors might modify the association between an abnormal hip shape and hip OA.

Acetabular dysplasia

Acetabular dysplasia is characterised by acetabular undercoverage of the femoral head, leading to a decreased contact area which might result in higher static loads on the anterosuperior acetabular labrum and cartilage. Mild acetabular dysplasia has previously been associated with hip OA in prospective studies,[53,222] but the results from cross-sectional and retrospective studies are conflicting.[241,242] Also, the prospective studies included primarily older people (mean ages between 65 and 70 years) and evidence for the relationship between acetabular dysplasia and OA at the age of 50-60 years is limited. It has been suggested that the

relationship between acetabular dysplasia and hip OA in younger people might be much higher. In chapter 5, we showed an association between acetabular dysplasia and OA, which was in line with the previous prospective studies; the strength of association in these younger individuals (mean age 55 years) was not higher. When comparing with the study of Reijman et al.,[53] who included subjects from the same country (the Netherlands) and quantified dysplasia (CE angle <25°) and OA (K&L ≥2) in the same manner, the strength of association was comparable (OR 2.4 [95% CI 1.2-4.7] in the study by Reijman et al. vs 2.5 [95% CI 1.5-4.1] in our study). However, in contrast to all previously published studies, we also included a lateral radiograph (false profile view) which increased our prediction of future hip OA. On the often used AP pelvic view, acetabular dysplasia is only quantified at the lateral side, whereas a lateral view provides quantification of acetabular dysplasia at the anterior side as well. The combination of lateral and anterior acetabular dysplasia increased the strength of association up to an OR of 6.5 (95% CI 2.7-15.6) for end-stage OA.

Femoroacetabular impingement (FAI)

As stated in the introduction, the concept of FAI has been introduced only a decade ago and hence, no prospective studies on the relationship between FAI and development of hip OA are available. More importantly, there is no proper definition of what FAI exactly is. In chapter 7, we defined FAI as a clinical entity in which a pathological mechanical process causes hip pain when morphologic abnormalities of the acetabulum and/or femur, combined with vigorous hip motion (especially at the extremes), lead to repetitive collisions that damage the soft-tissue structures within the joint itself. The operational definition of FAI contains five key elements but in epidemiological studies, FAI is usually quantified by only one element: the presence of an abnormal morphology of the femur and/or acetabulum. FAI is a dynamic, motion dependent process and in our studies we quantified FAI morphology in a static way. To date, there are no validated techniques to quantify the dynamic process of FAI. Range of motion simulations from three-dimensional imaging techniques might be a solution, although no definition for what range of motion we accept is available and/or validated, and this can vary between individuals. The additional value above a static radiographic measurement together with details from clinical examination in the prediction of OA are unknown.

Based on whether there is an abnormal femoral or acetabular morphology, FAI is divided into two subtypes: pincer impingement and cam impingement. These two types of FAI have an essentially different pathophysiology by which it causes OA, which has been explained extensively in the introduction (figure 2).

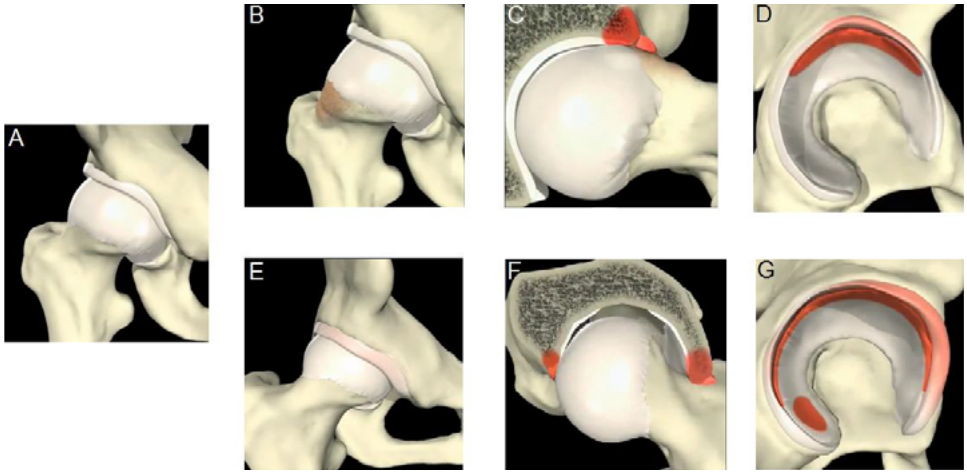


Figure 2. A schematic representation of the hypothesised mechanism of FAI.[58] **a.** A spherical femoral head and acetabulum which is congruent with the femoral head provides the hip a wide range of motion. **b, c, d.** A cam deformity (b) can cause cam impingement against the acetabular rim, especially during flexion and internal rotation of the hip (c) leading to a typical pattern of acetabular chondrolabral damage antero-superiorly (d). **e, f, g.** A pincer deformity (e) can cause pincer impingement against the femoral neck, especially during terminal flexion of the hip (f) leading to a typical pattern of circumferential acetabular cartilage damage.

Pincer impingement

The presence of a pincer deformity is thought to result in labral damage by the linear impaction of the femoral neck against the acetabular rim. During abutment, the femoral neck might create a leverage effect, so that the femoral head is forced in the posteroinferior portion of the acetabulum, leading to a so-called *contre-coup* lesion (figure 2 E-G). Although this pattern of labral and cartilage damage damage has been demonstrated intra-operatively in symptomatic hips with a pincer deformity,[57] scarce epidemiological data on the risk of development of hip OA is available. In chapter 5, we could not identify such an association between a pincer deformity at baseline and development of hip OA five years on. In contrast to our expectations, a pincer deformity might even have a protective effect on the risk of developing OA when acetabular overcoverage is present both anteriorly and laterally in one hip. Regarding the results of the properly designed studies, the question arises whether such as pincer impingement truly exists. Based on clinical observations and case series, a pincer deformity is likely to be a cause of hip pain and subsequent OA in some patients, but on an epidemiological scale a pincer deformity is probably not associated with hip OA. One explanation might be that there is a mismatch between individuals with a radiographic pincer deformity and individuals who

truly suffer repetitive episodes of pincer impingement. A pincer deformity is a description of a variety of acetabular morphological or orientation abnormalities causing excessive coverage of the femoral head including coxa profunda, protrusio acetabuli, acetabular retroversion, or overgrowth of the acetabular rim. Besides its broad definition, another explanation might be that a pincer deformity only rarely causes impingement because extreme supraphysiological hip motion might be necessary to cause the bony impingement. Finally, in contrast to a cam deformity it is unknown from which age a pincer deformity is present. When a pincer deformity also develops during skeletal maturation it can place a life-long unnecessary stress on structures within the hip joint, ultimately leading to hip OA in some cases. However, when it develops later in life individuals might remain asymptomatic.

Cam impingement

A cam deformity is an extra bone formation in the anterolateral head-neck junction, resulting in a nonspherical femoral head which can be forced into the acetabulum during flexion and internal rotation of the hip (figure 2 B-D). Using the definition for the presence of a cam deformity from chapter 8, we showed in chapter 6 a strong association between cam impingement and development of especially fast progression to end-stage OA. The presence of a radiographic cam deformity resulted in a grossly fourfold increased risk for development of hip OA, and a severe cam deformity (alpha angle >83°) resulted in a tenfold increased risk. These results are in agreement with other studies showing an association between a cam deformity and hip OA and with studies showing a correlation between the magnitude of the alpha angle and the severity of acetabular cartilage damage at the side where the cam deformity is forced into the acetabulum.[57,59,60,63-65,208,244,283,377]

Despite its strong association with hip OA, there are still more people with a cam deformity that will not develop OA. As a cam deformity is a potential modifiable risk factor, it is important to recognise which individuals will eventually develop OA. Distinguishing these people who might benefit from surgery should be done before too much intra-articular damage has occurred, as post operative results become worse with more advanced cartilage damage.[166] Our proposed clinical definition of FAI which comprises five essential elements can help to distinguish between people that will or will not develop OA. In most cohort studies only the first element, the presence of abnormal morphology (the radiographic presence of a cam deformity), is taken into account. Therefore, we attempted to include the second element, abnormal contact between the cam deformity and the acetabulum, as well. We defined abnormal contact by a decreased internal hip rotation (<20°) in 90° of flexion, which is a typical clinical sign of cam impingement.[216] By combining the presence of a radiographic cam deformity

together with decreased internal rotation, we assumed to exclude individuals with a cam deformity that is less likely to cause impingement, because they for example have an anteverted acetabulum. Combing these two elements of FAI, we could make a substantially better prediction of which people were going to develop hip OA. The strength of association increased to an adjusted OR of 25.2 (95% CI 7.9 - 80.6) and more than half of the non-arthritic hips at baseline meeting these two elements developed end-stage OA within five years (positive predictive value 53%). Although the relatively low number of hips meeting these criteria should be taken into account, the addition of clinical signs of cam impingement is of considerable importance. Including the other three elements: (3) vigorous supraphysiological motion that results in impingement, (4) repetitive motion resulting in the continuous insult, and (5) the presence of soft tissue damage, will probably optimize the prediction. Element 3 and 4 are explained by the type, frequency and intensity of activities that an individual undertakes. Sports activities requiring repetitive forceful flexion and internal rotation of the hips such as soccer, ice hockey or basketball are hence often asscociated with symptomatic OA. Element 5 might be quantified by sensitive imaging techniques.

We studied pincer impingement and cam impingement separately. However, FAI is a motion dependent process and the proximal femur and acetabulum should therefore not be regarded as two separate entities. The intuitive feeling was that a mixed type of FAI, that is a cam deformity together with a pincer deformity, results in the highest risk of hip OA. However, the results of chapter 3 indicate that a cam deformity with a more dyplastic acetabulum results in the highest risk of hip OA. Preliminary results indeed indicate that a hip with a cam deformity together with a more overcovered acetabulum (higher LCE angle) is less likely to progress towards OA when compared with normal acetabular coverage. In addition, a hip with a cam deformity and a lower LCE angle (more dysplastic acetabulum) has a higher chance to develop hip OA when compared with normal acetabular coverage. The explanation for this phenomenon is not clear and further studies are required. The combination of static stresses (acetabular dysplasia) together with dynamic stresses (cam impingement) on the acetabular cartilage might continuously place the hip into a biomechanically deleterious environment leading to fast progressing hip OA.

CHECK cohort

CHECK is a nationwide prospective cohort study of 1002 individuals between 45 and 65 years who visited their general practitioner (GP) for the first time with pain and/or stiffness in their hip and/or knee. These inclusion criteria were set to study the factors related to development and progression of hip and knee OA. Of the included individuals, 80% were women. Using these criteria, it happened

that none of the individuals had radiographic signs of definite hip OA at baseline with a K&L score of 0 in 76% of the hips and a K&L score of 1 in 24%.
These inclusion criteria should be kept in mind by interpreting the results of chapter 3, 4, 5 and 6. The results found in our studies might be different in open population cohorts, where a relatively smaller proportion of people will have hip pain. Still, the results can be generalised to a relevant group of individuals, namely those who visit their GP for the first time. We showed that besides clinical examination, a simple and inexpensive pelvic radiograph can provide considerably more information on the prediction of future hip OA. Furthermore, the minimum age to enter the cohort study was 45 years, which might have influenced the strength of association between hip shape and development of OA. Individuals with a cam deformity are at high risk of fast progression to end-stage OA and preliminary results indicate that the strength of association becomes weaker when the follow-up time is longer. When somebody with a cam deformity has not developed OA at a certain age, he or she will be less likely to develop OA as a result of the cam deformity. Therefore, in cohorts including older people, the strength of association between a cam deformity and hip OA is probably lower than in the CHECK cohort, because people will develop OA for other reasons than a cam deformity. On the other hand, a large number of people that developed OA as a result of a cam deformity might have been excluded from the CHECK cohort because they probably had hip complaints before the age of 45 years. Conversely, the predictive value of a cam deformity might be higher in younger people than the individuals included in the CHECK cohort, but no such studies are available yet. This is an interesting point considering the fact that a cam deformity is present immediately after skeletal growth. It is unknown from which age someone with a cam deformity will show the first signs of hip OA and this should be subject of future studies.
In the CHECK cohort, anteroposterior (AP) pelvic and False Profile lateral (FP) radiographs were obtained both at baseline and 5 years follow-up according to a standardized protocol. There are no other large cohorts available that obtained both radiographic views and the addition of lateral radiographs considerably increased the predictive value of future hip OA, especially by a more precise quantification of acetabular coverage. Moreover, at follow-up we were able to quantify the joint space at the locations where impingement occurs. In addition, an FP view is advocated to be more sensitive in the quantification of joint space narrowing than an AP view.[246] Despite the advantages of two radiographic views, three-dimensional imaging techniques like MRI or CT might capture more morphological aspects of the hip joint.[67] As a result, we might have slightly underestimated the prevalence of FAI morphology. The effect of this underestimation on the prediction of hip OA is unknown.

Finally, the prospective nature of this cohort study together with the fact that none of the hips showed definite signs of radiographic OA at baseline were of considerable importance. Especially in a more advanced stage of hip OA, the femoral head might become non-spherical as a consequence of OA. The baseline shape aspects that we found to be associated with hip OA at follow-up were most likely the cause of hip OA. Also, we could exclude a cam deformity from being a consequence of OA. These shape aspects might therefore be used in a predictive model that can assess the chances of developing hip OA when somebody visits their GP for their first time with hip complaints.

Statistical shape modelling (SSM)

Hip shape plays an important role in the development of hip OA. Although a pathophysiological explanation has been provided for several abnormal shape aspects of the hip including FAI morphology and dysplasia, there might be other unknown shape aspects that contribute to the development of hip OA. Shape aspects of the hip joint can be captured by predefined measures such as the femoral head diameter, neck-shaft angle, Wiberg angle, or alpha angle.[224,237] However, the measures might reduce the shape of the hip to a limited set of morphological characteristics rather than taking global shape into account.[234,378] As the global shape of the hip joint is a complex structure, it cannot be completely quantified by a combination of several linear measurements. To overcome this problem, statistical shape models (SSMs) have been introduced to quantify the overall bone shape.

The first study using SSM to predict the development of hip OA was performed by Gregory et al. in 2007. This study concluded that certain aspects of hip shape could identify people who are at highest risk of developing OA.[206] Three other studies studies followed, each concluding that certain shape aspects of the hip as quantified by SSM associated with radiographic hip OA and/or THR.[209,213,228] Two other studies showed that the relation between hip shape and OA was influenced by genetics.[217,230] Since a poor association between radiological and clinical definitions for hip OA has been reported,[207] we studied the association between baseline hip shape and clinical OA. In line with other published data, we showed that the shape of the hip can predict THR after 5 years but not clinical OA as defined by the ACR criteria.

SSM is an objective tool to quantify hip shape but the interpretation of the resulting shape variants (modes) is subjective. Some shape variants are clear and explain for example the femoral neck width or length, or the sphericity of the femoral head. However, other shape variants might be more subtle and can be difficult to describe. Furthermore, as all the above-mentioned studies used different shape models, the resulting shape variants cannot be compared with each other. The relevance of the ability to compare the results of different

studies was shown in chapter 4, in which we showed that the association between hip shape and hip OA might be dependent on radiographic protocol, population characteristics and follow-up time. Finally, the strength of association between a mode of shape variation and hip OA usually ranges between 1.5 and 2.5 in terms of odds ratio. When quantifying specific 'at risk' shape aspects by linear measures such as a cam deformity by the alpha angle, the strength of association is usually higher. Therefore, it remains to be determined whether SSM can be used as a predictive tool in clinical practice or whether it is more suitable as a hypothesis generating tool.

Development of a cam deformity

In the introduction it has been outlined that hip shape variants are probably an acquired phenomenon, which means that interactions with the environment after birth might influence the final hip shape. In chapter 9, 10, 11, and 12, we showed that the development of a cam deformity occurs during skeletal maturation, probably as a result of mechanical factors as experienced during high impact athletic activities. To understand the formation of a cam deformity, the factors involved in normal growth and development of the hip must be understood. In the introduction it was explained how the entire cartilaginous proximal femur of the infant hip gradually ossifies until a common growth front arises during mid adolescence consisting of the proximal femoral growth plate, the femoral neck isthmus, and the growth plate of the greater trochanter (figure 3 A-C).[6] Together they contribute for one third to the length of the femur, to the overall neck width, the neck shaft angle, and to more subtle morphological variations of the proximal femur. The process of skeletal growth and thus the resultant hip shape is determined by hormonal, genetic, and mechanical factors. A balance between the growth rates of the three growth plates is necessary for normal growth and is highly determined by forces applied to the hip.[6] An extreme decrease or increase of forces applied to the hip might cause an imbalance between the growth plates and to subsequent morphological abnormalities, as explained in the introduction. Examples of decreased mechanical stimulation of the growth plates that influence hip shape are cerebral palsy and anterior poliomyelitis, diseases characterised by an absence of the abductor muscle forces. The loss of tension in the trochanteric epiphysis tends to close the lateral portion of the growth plate so that the medial part overgrows with resultant coxa valga.[379] An example of increased stimulation of the growth plates are high impact sporting activities, which may lead to the development of a cam deformity.

In chapters 9 and 10 we showed that the formation of a cam deformity is probably a result of frequent high-impact athletic activities during adolescence. This observation is not new and was already suggested by Murray in 1971 who

studied boarding school students with different athletic backgrounds.[23] He found a higher prevalence of cam deformities in the group who were more active in sports during adolescence and therefore concluded that 'excessive athletic activity in adolescence is likely to be an important cause, certainly in males, of degenerative hip disease'. Murray studied this group immediately after skeletal maturation and suggested that the aspherical femoral head was due to a subclinical slipped capital femoral epiphysis (SCFE). However, although the final shape of a SCFE hip after remodelling might mimic a cam deformity, we showed that the majority of cam deformities are probably not a result of a subclinical SCFE. During the stages of skeletal maturation in the soccer players, we could not identify any signs of a SCFE and a cam deformity is therefore probably a consequence of a biomechanically triggered extra bone formation at the anterolateral head-neck junction. This occurs only when the proximal femoral growth plate is open and has the capacity of bone formation. Interestingly, this would also suggest that the formation of a cam deformity can be prevented, as cam deformities hardly exist in a non-athletic population.

Therefore, we sought to determine which specific loading situations during vigorous physical activities stimulate the formation of a cam deformity. In chapter 12 we used a finite element (FE) model of a growing hip and applied different loading patterns to the hip joint. Stresses resulting from flexion and from external rotation while weightbearing modify the distribution of mechanical stimuli such that they might stimulate bone formation at the anterolateral head-neck junction. We also considered three different types of proximal femoral growth plate orientation, as an orientation towards the femoral neck is associated with the presence of a cam deformity,[25] which we confirmed in chapter 10. It has even been suggested that an extension of the growth plate towards the femoral neck precedes a cam deformity,[324] although we could not confirm this in chapter 10. Using the FE model we found that the effects of the different loading scenarios were modulated with the effects of growth plate shape, meaning that certain growth plate shapes (larger extension towards femoral neck) give rise to anomalistic bone growth during flexion and external rotation while weight bearing. Interestingly, the orientation of the proximal femoral growth plate could even be a result of certain loading conditions. Not only a cam deformity but also the extension of the growth plate towards the femoral neck might be a result of external rotation while weight bearing. If the extension of the growth plate is assumed to be relatively small (a horizontal growth plate, figure 3C) at the age of 12 years, which was the case in the soccer players, the distribution of hydrostatic stress shows that relatively large compressive stresses can be found within the growth plate at the lateral side of the femur (figure 3E). According to the Hueter-Volkmann principle, these stresses tend to inhibit bone growth while tensile stresses can be found on the medial side of the growth plate that

stimulate bone growth. As a result of this mismatch between the amount of bone growth at the lateral and medial sides, the growth plate may start to deflect and the extension of the growth plate into the femoral neck may increase (figure 3F). Once the extension of the growth plate increases, the stimulation of bone growth at the anterolateral portion of the head-neck junction as a result of external rotation may further increase (figure 3G,H).

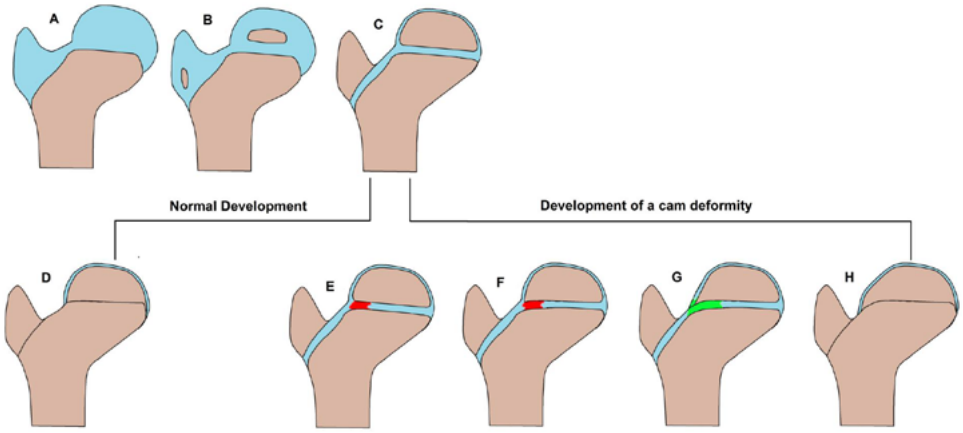


Figure 3. Development of a cam deformity. Skeletal development from infancy (**A**) to childhood (**B**) and early adolescence (**C**, around 12 years of age). At the end of adolescence, the hip is skeletally mature and a spherical femoral head has been formed (**D**). Stresses resulting from high impact athletic activities can modify the distribution of mechanical stimuli thereby stimulating bone formation and influencing the orientation of the growth plate (**E-H**).

This hypothesis can explain the high prevalence of cam deformity in athletes practising high impact sport. It also explains the strong association between a cam deformity and amount of growth plate extension towards the neck, which runs analogous with the formation of a cam deformity, while it does not precede a cam deformity. This is in line with the findings of chapter 10. Finally, it may also explain the higher prevalence of cam deformities in males than in females. In general, fewer females than males practise high impact sports during adolescence. In addition, as females are skeletally mature at a younger age, the intensity they practise sport at the time that a cam deformity develops is probably less.

The finding that a cam deformity does not develop or further increases in size after closure of the growth plate was supported by data from the CHECK and Chingford cohorts, where we did not find an increase in alpha angle between baseline and follow-up. However, it has been shown that the bone mineral density (BMD) of subchondral bone underlying a cam deformity is higher than

the BMD at the same location in hips without a cam deformity.[380] The BMD of the cam deformity under the cartilage layer was similar to or even somewhat higher than normal compact bone in the femoral neck. However, it is unknown if a higher BMD is already present when the cam deformity is formed. When this is not the case, an explanation for the higher BMD might be that the stimulus for bone apposition continuous, but that the newly formed bone is not capable of changing the femoral morphology as it is now surrounded by a cortical envelope that cannot expand. The higher BMD is most likely not explained by the abutment of the cam deformity against the acetabulum, as asymptomatic individuals with a cam deformity showed the same BMD as symptomatic individuals with a cam deformity.[380] This would suggest that before growth plate closure the bone can adapt its morphology (modelling) to mechanical load and after growth plate closure only changes in bone architecture (remodelling) occur.

Combining the results of our studies and other data from literature, I hypothesise that a cam deformity is a bone adaptation and results from high impact athletic activities during skeletal maturation. Loading patterns of especially flexion and external rotation while weightbearing influence bone formation and growth plate orientation, which together have a synergistic effect on the formation of extra bone in the anterolateral head-neck junction.

CONCLUSIONS

We showed that hip shape plays an important biomechanical role in the development of hip OA. By using statistical shape modelling we were able to identify all hip shape variants of participants of the Dutch CHECK cohort. Based on specific shape patterns of the hip in those without OA at baseline, we could make a good prediction of those who will develop future hip OA. Some of these shape patterns could even predict future hip OA in a completely different population from that of the United Kingdom. A broad and short femoral neck are two examples of such shape patterns that are associated with hip OA. We also identified that a non-spherical femoral head could predict the development of hip OA, which has been linked to causing hip OA by a process referred to as FAI. The clinical and radiographic definitions for this pathological entity have been provided in the current thesis. We specifically studied the relationship between cam and pincer impingement and the subsequent risk of developing OA. Pincer impingement did not increase the risk of hip OA, but cam impingement was strongly associated with especially fast progressing hip OA. The presence of a cam deformity can confer up to a 10-fold increased risk for the development of end-stage hip OA. Besides the fact that a cam deformity is probably the most important risk factor of hip OA, it is also a potential modifiable risk factor. We showed that a cam deformity only develops during skeletal maturation most likely as a result of high impact athletic activities during adolescence. More specifically, when the growth plate is open, loading patterns of flexion and external rotation while weight bearing might stimulate the formation of a cam deformity. Regarding the strong association between a cam deformity and development of hip OA and the potential modifiable character of a cam deformity, preventing the development of a cam deformity might substantially decrease the future prevalence of hip OA.

FUTURE PERSPECTIVES

Based on the outcomes of this thesis, three main topics will be discussed in this chapter: 1. The relationship between FAI and OA: what do we not know? 2. The formation of a cam deformity: which future studies are needed to better unravel the etiology of a cam deformity? And 3. Can osteoarthritis be prevented by impeding the development of a cam deformity?

FAI and osteoarthritis

In this thesis, we presented the first prospective studies on FAI and development of OA which showed that cam impingement is a strong –if not the strongest- risk factor for hip OA. Our results should be replicated in other large prospective cohorts to study the strength of association in populations with other characteristics. One of these characteristics is age, because almost all published cohort studies on the relationship between FAI and hip OA consisted of middle-aged individuals. Although cam impingement is strongly associated with the development of OA in patients >45 years of age, there are indications that cartilage damage caused by a cam deformity might already exists from the age of 20 years.[264] This suggests that a cam deformity induces OA changes in the hip well before extensive hip degeneration appears three or four decades later. Long term follow-up of younger cohorts is needed to fully describe the natural history of FAI and hip OA and to determine the relationship between the type and severity of intra-articular damage and the long-term risk of developing clinically significant hip OA. Prospective cohorts should therefore include individuals immediately after skeletal maturation to identify when the first signs of hip OA start to develop. As a cam deformity is present immediately after skeletal maturation, selection bias will be reduced to a minimum and the association between a cam deformity and future hip OA can therefore be studied more reliably. Moreover, prospective cohorts of young individuals will also help to better characterise prognostic parameters for a better or worse outcome which can be used for a better patient selection that require (surgical) treatment.

Magnetic Resonance Imaging (MRI) should also be performed in addition to radiographs, as the cam deformity is usually located in the anterolateral spectrum of the head-neck junction and can therefore be missed on radiographs. Furthermore, sensitive MRI techniques might detect labral and cartilage damage in an earlier stage.

We proposed a definition of a cam deformity based on the alpha angle as measured on AP pelvic radiographs. We also showed that greater alpha angles substantially increase the risk for future OA. This probably indicates that the more pronounced the cam deformity, the higher the risk for development of OA. Although the alpha angle might not be the perfect measure of a cam deformity,

it is the best we have so far in terms of OA prediction. Therefore, future studies should at least include the alpha angle using our proposed threshold values to define a cam deformity, in order to be able to compare the results of future studies. Furthermore, the alpha angle is a 'gross' measure and captures all different shape abnormalities of the head-neck junction that deviate from being a spherical femoral head. This can be an egg-shaped femoral head, a hook-shaped femoral head, a flattened head-neck junction, or a 'pistol grip' deformity. Future studies should focus on these subtle shape differences which we now all classify as a cam deformity. Some of these sub forms of a cam deformity might be more relevant in the prediction of OA than others. To answer this question, SSM might be a suitable tool.

Despite the strong association between cam impingement and OA as reported in many studies, even in a large prospective study as part of this thesis, we still can not prove a causal relationship between cam impingement and OA. A causal relationship is likely because (1) a cam deformity is present before the onset of OA, (2) a cam deformity is strongly associated with hip OA, and (3) there is no other reasonable explanation for the typical pattern of cartilage damage. However, the only way to prove a causal relationship is to conduct a randomized controlled trial for the treatment of cam impingement.

The final suggestion to better predict which individuals with a cam deformity are going to develop OA is using a 'personalised' prediction model. Besides morphological parameters this should include the quantification of dynamic impingement and also the activity level of an individual. In the absence of repetitive dynamic impingement events, a cam abnormality probably does not cause OA. Future studies should therefore focus on how to quantify dynamic impingement thereby taking into account the type, frequency and intensity of activities that an individual undertakes.

Formation of a cam deformity

In chapters 9, 10, and 11 we have made a big step towards unravelling the etiology of a cam deformity. However, there are still many things that we do not know. The few studies available on this topic all studied elite or pre-professional athletes participating at a high intensity in high impact sports. One of the main question still to be answered is whether there is a dose-response relationship between the intensity of athletic activities and the prevalence of a cam deformity. Is the prevalence of amateur athletes who practise for example three times a week in between the prevalence of non-athletes (0-10%) and elite athletes (70-90%)? Or is there a certain threshold in terms of athletic intensity from which a cam deformity starts to develop? Another important question is from which age the loading pattern of the hip starts to influence the formation of a cam deformity. Is only the period around the age of 12 years, when a cam

deformity becomes radiographically visible, critical or is it a cumulative result of several years of high hip loading before the age of 12 years? Further, although we assume that stresses as experienced during high impact sports trigger the formation of a cam deformity, there is no data available for low-impact sports such as swimming and cycling. Finally, we do not know if girls will develop a cam deformity when they experience the same loading patterns of the hip as boys when they are in the same stage of skeletal maturation. This information is important when thinking of preventive strategies which will be discussed in the next topic.

Besides the environmental factors that influence the loading pattern of the hip, the role of genetics and hormones in the formation of a cam deformity is unknown. It has been suggested in literature that genetics might play a role, because the prevalence of cam deformity in Asian people is substantially lower than in Caucasian people.[38,272,275,381] Siblings of patients with a cam deformity had a higher risk of having a cam deformity compared with the patients' spouses.[360] Although there are multiple explanations for these differences, more research should focus on the genetic influence on the formation of a cam deformity.[375]

Prevention of hip OA by preventing a cam deformity to develop

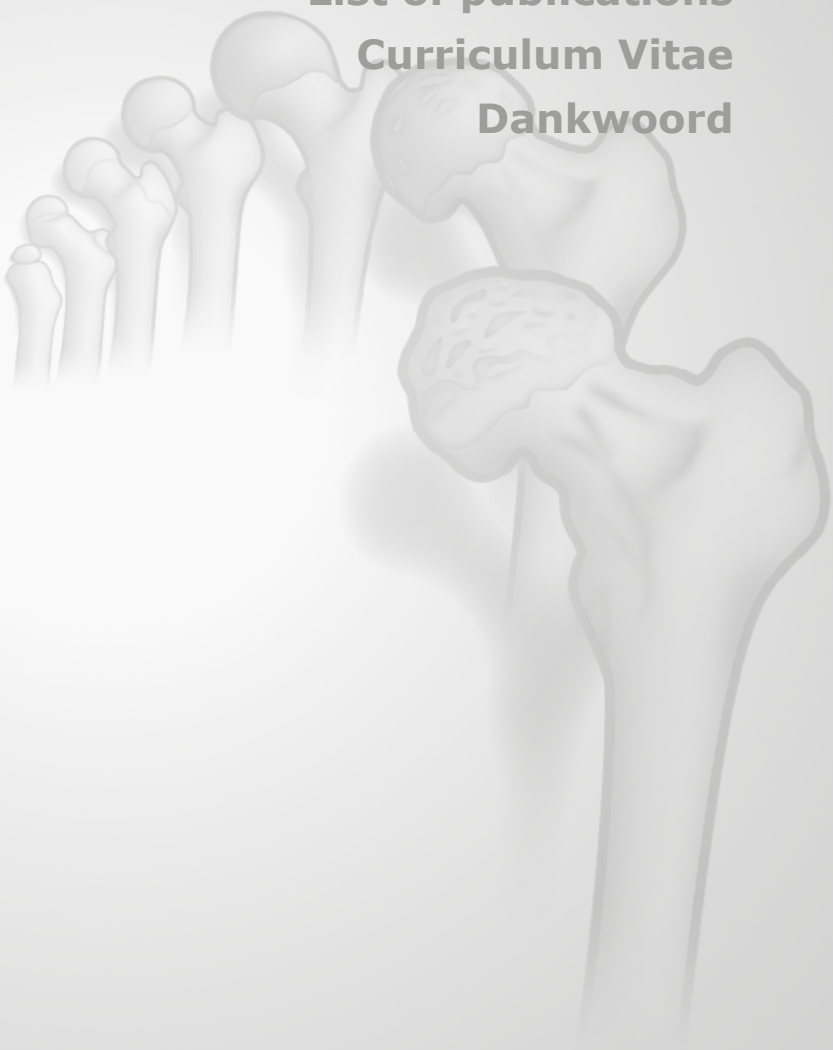
A cam deformity can be modified in two ways thereby potentially decreasing the prevalence of future hip OA. The first option is to surgically removing the cam deformity and the second is preventing the cam deformity from developing. For the first option, an invasive surgical procedure in relatively young individuals is necessary, thus making the second option more promising.

The research in the past 10 years improved our understanding of how to surgically manage cam deformities. Although the surgical treatment is not a topic of the current thesis, there are some interesting and promising future perspectives in this field. Most studies on the treatment of FAI show promising results regarding pain scores, hip function, and most athletes return to their previous level of sport.[166,382] However, most often single surgeon and only case series have been published to date. Furthermore, whether restoring the normal anatomy of the proximal femur can halt or delay the progression towards OA is unknown as there is no long-term follow-up data available. Therefore, although surgery might be a promising solution, randomised controlled trials are highly needed.

The second option is preventing a cam deformity from developing. In this thesis we showed that the formation of a cam deformity is highly influenced by high impact athletic activities during skeletal growth. As cam deformities hardly exist in non-athletic populations, a cam deformity can be prevented by understanding the biomechanical trigger of the hip during skeletal development. One could think of a training schedule in which certain high impact activities are replaced

by low impact activities, such as swimming and cycling. However, to date it is unknown whether there is a dose response interaction between high impact athletic activities and development of a cam deformity, nor do we know how long these high impact activities should be avoided. These uncertainties make preventive strategies impossible at this time and further research in this area is required. If a cam deformity can be prevented from developing in adolescents, this will have a major impact on the incidence of hip pain in young adults and on the incidence of hip OA later in life.

Appendices

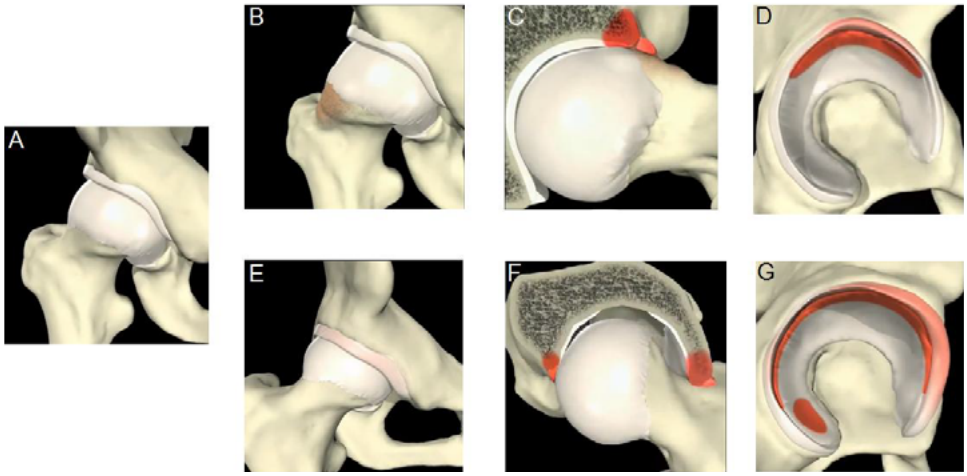


Artrose is een veel voorkomende ziekte met een enorme impact op de kwaliteit van leven. Artrose is een aandoening van de gewrichten die het gewrichtskraakbeen en het onderliggende subchondrale bot aantast. Kenmerken van artrose zijn gewrichtspijn, stijfheid, bewegingsbeperking en deformatie van het gewricht. In de loop der jaren kunnen symptomen van artrose zich ontwikkelen van matige pijn en stijfheid in het beginstadium tot invaliderende pijn en gewrichtsdeformatie in het eindstadium. Artrose kan op elke leeftijd ontstaan maar komt voornamelijk voor boven de 50 jaar waarna de prevalentie stijgt naarmate de leeftijd vordert. Naar schattingen van het Nationaal Kompas Volksgezondheid waren er in 2011 1.2 miljoen Nederlanders bij de huisarts bekend met artrose waarvan 360.000 personen heupartrose hadden. Enerzijds vanwege de ouder wordende bevolking en anderzijds door nog onbekende oorzaken zal het aantal personen met heupartrose de komende jaren nog verder stijgen. De directe kosten (medische zorg) van artrose worden in Nederland geschat op 1,1 miljard euro, waarvan ongeveer 30% toe te rekenen is aan heupartrose. De indirecte kosten van heupartrose, de kosten die niet direct gerelateerd zijn aan medische zorg, bijvoorbeeld doordat patiënten niet kunnen werken, worden nog hoger geschat dan de directe kosten.

Tot op heden bestaat de behandeling bij het beginstadium van artrose alleen uit symptoombestrijding door het onderdrukken van de pijn en eventueel fysiotherapie. Er bestaan geen medicijnen of operatieve ingrepen die heupartrose in een beginstadium kunnen voorkomen of de progressie naar het eindstadium kunnen uitstellen. Voor het eindstadium is een heupprothese wel een effectieve behandeling, maar de levensduur van een prothese is beperkt en er kunnen complicaties optreden. Patiënten die in aanmerking komen voor een heupprothese worden daarnaast steeds jonger en zijn veeleisender met betrekking tot de heupfunctie. Wetenschappelijk onderzoek zou zich daarom moeten richten op de mogelijkheden van oorzakelijke behandeling in een vroeg stadium van artrose of nog beter op het voorkomen van artrose. Om deze uitdagende doelstelling te verwezenlijken is een goed begrip van de ontstaansmechanismen van heupartrose van essentieel belang.

Preventieve maatregelen kunnen alleen genomen worden wanneer beïnvloedbare risicofactoren van artrose ontdekt worden. Echter, de oorzaak of oorzaken van heupartrose zijn grotendeels onbekend. Wel zijn er aanwijzingen in de literatuur dat subtiele vormafwijkingen van de heup een mogelijke risicofactor voor heupartrose zijn. Een goed omschreven vormafwijking is heupdysplasie, waarbij de heupkop niet goed bedekt wordt door het acetabulum (heupkom). Het beperkte oppervlakte tussen heupkop en acetabulum zorgt voor een relatief hogere belasting op een kleiner deel van het acetabulum. Deze statische vorm van overbelasting predisponeert daarom voor kraakbeenschade en mogelijk artrose. Meer recentelijk omschreven vormafwijkingen zijn een overhelling

van het acetabulum (pincer deformiteit) en een asferische heupkop (cam deformiteit). Door deze vormafwijkingen kan de heupkop niet meer soepel in het acetabulum bewegen maar raakt ingeklemd tijdens beweging. Dit wordt femoroacetabulaire impingement (FAI) genoemd (figuur 1). FAI predisponeert mogelijk voor heupartrose maar over deze relatie is slechts weinig bekend. Tenslotte zouden er tot op heden nog onbekende vormvariaties van de heup kunnen zijn die het risico op artrose vergroten.
Het doel van dit proefschrift is drieledig: (1) het bestuderen van de relatie tussen de vorm van de heup en het ontwikkelen van heupartrose 5 jaar later; (2) Het geven van een klinische en radiologische definitie van FAI, en (3) onderzoeken of, en zo ja hoe een cam deformiteit ontstaat tijdens adolescentie.



Figuur 1. Schematische weergave van FAI. **A.** Dankzij een sferische heupkop met een congruent acetabulum heeft de heup een grote bewegingsvrijheid. **B,C,D.** Een cam deformiteit (B) kan vooral tijdens flexie en endorotatie van de heup impingement in het acetabulum veroorzaken (C), wat kan leiden tot schade van het kraakbeen en labrum, met name antero-superieur (D). **E,F,G.** Een pincer deformiteit (E) kan vooral tijdens flexie van de heup leiden tot impingement tegen de femurhals (F), wat tot gegeneraliseerde kraakbeen en labrumschade zou kunnen leiden in het hele acetabulum (G).

DEEL 1. DE RELATIE TUSSEN DE VORM VAN DE HEUP EN HET ONTWIKKELEN VAN HEUPARTROSE

Hoofdstuk 2 is de inleiding van het eerste deel van dit proefschrift, waarin een overzicht van artrose wordt gepresenteerd bestaande uit de epidemiologie, pathogenese, diagnose en behandeling. Tevens speculeren we over potentiële targets voor de preventie van het ontstaan en progressie van artrose. Voor heupartrose zou een chirurgische behandeling van een cam deformiteit mogelijk

preventief kunnen zijn. Tijdens deze behandeling wordt het additionele bot van de asferische heupkop verwijderd zodat er weer een sferische heupkop ontstaat. Echter, de lange termijn resultaten van deze ingreep zijn nog niet bekend en tot op heden zijn er nog geen gerandomiseerde studies uitgevoerd. In **hoofdstuk 3** hebben we de associatie van de algemene heupvorm op baseline en het risico op het ontwikkelen van artrose na 5 jaar bestudeerd. Hiervoor hebben we gebruik gemaakt van het CHECK cohort, een Nederlands cohort van 1002 mannen en vrouwen tussen de 45 en 65 jaar die werden geïncludeerd wanneer ze voor het eerst bij de huisarts kwamen met klachten van pijn en/of stijfheid in de knie en/of heup. De algemene vorm van de heup werd op anteroposterior (AP) röntgenfoto's gekwantificeerd met Statistical Shape Moddelling (SSM). Deze software 'herkent' op basis van statistische principes alle vormvariaties die in een populatie aanwezig zijn. Hierdoor is het mogelijk om zonder een vooraf gedefinieerde hypothese over welke vormaspecten relevant zijn, van alle vormvariaties op baseline de kans op het krijgen van heupartrose te berekenen. Tijdens de 5-jaars follow-up werd artrose gedefinieerd volgens de American College of Rheumatology (ACR) criteria en tevens als het hebben van een heupprothese op follow-up. Wij lieten zien dat bij mensen die op baseline nog geen artrose hebben, specifieke vormaspecten kunnen voorspellen of iemand een heupprothese heeft na 5 jaar. Vooral een brede en korte femurhals, een geretroverteerd acetabulum en een cam vorm van de kop-hals overgang konden voorspellen of iemand een heupprothese na 5 jaar zou hebben. Alhoewel de heupvorm niet kon voorspellen of iemand tijdens follow-up aan de ACR criteria zou voldoen, kon het wel twee ACR criteria afzonderlijk voorspellen, namelijk het hebben van een beperkte endorotatie en heuppijn tijdens follow-up. Gebaseerd op deze resultaten werd in **hoofdstuk 4** de generaliseerbaarheid van deze vormaspecten bestudeerd. Door een identiek shape model in het Chingford cohort (een open populatie cohort van vrouwen tussen 45 en 65 jaar uit Londen) te gebruiken, konden we vergelijken hoe consistent de voorspellende vormaspecten van het CHECK cohort zijn. In overeenstemming met de literatuur vonden we zowel in het CHECK cohort als in het Chingford cohort voorspellende vormaspecten van de heup voor het krijgen van een heupprothese. Eén van deze vormaspecten was significant voorspellend voor het krijgen van een heupprothese in zowel het CHECK cohort als het Chingford cohort. Daarnaast vertoonden twee vormaspecten die significant geassocieerd waren met een heupprothese in het CHECK cohort ook een sterke trend in dezelfde richting in het Chingford cohort. Dit wil zeggen dat bepaalde vormaspecten bij vrouwen generaliseerbaar zijn in de voorspelling van het krijgen van een heupprothese, ongeacht de karakteristieken van de populatie, het röntgenprotocol of de follow-up tijd (5 jaar in het CHECK cohort en 19 jaar in het Chingford cohort). Daarentegen zijn andere vormaspecten die geassocieerd zijn met een heupprothese juist wel

afhankelijk van deze factoren. Op basis van de bevindingen uit hoofdstuk 3 en 4, worden in de volgende hoofdstukken meer specifieke vormaspecten in het CHECK cohort bestudeerd zoals heupdysplasie en FAI gerelateerde vormaspecten. In **hoofdstuk 5** onderzochten we of de mate van acetabulaire bedekking van de heupkop op baseline geassocieerd was met het ontwikkelen van artrose na 5 jaar. We onderzochten heupdysplasie (te weinig acetabulaire bedekking) en een pincer deformiteit (teveel acetabulaire bedekking). Heupdysplasie is al langer een bekende aandoening en in overeenstemming met de literatuur vonden wij voor een geringe dysplasie (lateral centre edge angle <25° op een AP opname) een licht verhoogd risico op het ontwikkelen van heupartrose (met odds ratios (ORs) tussen de 2.5 en 3.8 afhankelijk van de definitie van artrose). Echter, in tegenstelling tot andere studies konden wij heupdysplasie ook kwantificeren op een laterale opname. Wanneer heupdysplasie op baseline zowel op de AP opname als op de laterale opname aanwezig was, werd de associatie met artrose behoorlijk sterker (ORs tussen de 4.9 en 6.5). Over de associatie tussen een pincer deformiteit en artrose is tot op heden veel minder bekend. Op dit gebied zijn een aantal retrospectieve en cross-sectionele studies gepubliceerd maar die laten tegenstrijdige resultaten zien. Wij vonden een significant beschermend effect op het ontwikkelen van een beginstadium van heupartrose wanneer een pincer deformiteit zowel op de AP als op de laterale opname aanwezig was (OR van 0.34 voor Kellgren & Lawrence (K&L) graad ≥2). Deze bevinding werd ondersteund door het feit dat geen van deze heupen met een pincer deformiteit na 5 jaar eindstadium artrose had ontwikkeld (K&L graad 3, 4 of een heupprothese). Studies waarin symptomatische FAI patiënten worden bestudeerd suggereren dat pincer impingement kan leiden tot heuppijn en gewrichtsschade. Echter, onze data suggereren dat pincer impingement epidemiologisch gezien niet met artrose is geassocieerd. In **hoofdstuk 6** onderzochten we of een cam deformiteit geassocieerd was met het krijgen van heupartrose. Ondanks het feit dat retrospectieve en cross-sectionele studies allen consistent een associatie tussen het hebben van een cam deformiteit en heupartrose laten zien, zijn er tot op heden geen prospectieve studies bekend. Het hebben van een cam deformiteit werd gekwantificeerd met de alpha hoek, die de mate waarin de heupkop afwijkt van sferisch meet (vanaf 60° noemen we het een cam deformiteit). Wij toonden aan dat een cam deformiteit sterk geassocieerd is met het ontwikkelen van heupartrose. Deze associatie werd sterker naarmate de cam deformiteit groter was (OR van 3.9 bij een alpha hoek >60° en een OR van 9.7 bij een alpha hoek van >83°). Daarnaast hebben we getracht heupen te selecteren die daadwerkelijk impingement ervaren, door een radiologische cam deformiteit te combineren met een beperkte endorotatie (<20°, een klinisch teken van cam impingement). Van alle heupen die op baseline aan deze radiologische en klinische criteria van cam impingement voldeden, ontwikkelden 53% artrose binnen 5 jaar. Dit resulteerde in een OR van 25.2.

DEEL 2. DEFINITIE VAN FEMOROACETABULAIRE IMPINGEMENT (FAI)

Vanaf het moment dat ruim 10 jaar geleden het mechanisme van FAI voor het eerst werd beschreven, is de hoeveelheid aan literatuur op dit gebied exponentieel gestegen. Dit heeft geleid tot een beter begrip over de rol van FAI in de etiologie van artrose, zoals in voorgaande hoofdstukken beschreven, maar ook over de prevalentie en de associatie met heuppijn en een beperkte bewegingsvrijheid. Het erkennen en herkennen van FAI en de (chirurgische) behandelmogelijkheden hebben het klinisch handelen in de afgelopen jaren behoorlijk beïnvloed. Ondanks de toenemende belangstelling voor FAI en het feit dat iedereen zich wel iets kan voorstellen bij het mechanisme, is er tot op heden nog geen heldere definitie van FAI. Het doel van **hoofdstuk 7** was het formuleren van een operationele definitie van FAI om te kunnen gebruiken in klinische trials. Op basis van consensus kwamen we met een groep van klinische en wetenschappelijke experts op het gebied van FAI tot de volgende definitie: 'een klinische entiteit waarbij een pathologisch mechanisch proces heuppijn veroorzaakt wanneer morfologische afwijkingen van het acetabulum en/of femur, gecombineerd met krachtige beweging van de heup (vooral in de eindfase), leiden tot repetitieve botsingen die de intra-articulaire weke delen beschadigen'. Deze definitie bevat vijf essentiële elementen: (1) morfologische afwijking van het femur (cam deformiteit) en/of het acetabulum (pincer deformiteit), (2) abnormaal contact tussen deze twee structuren, (3) vooral krachtige, suprafysiologische bewegingen die resulteren in dit abnormale contact, (4) repetitieve botsingen die leiden tot een voortdurend beschadigen en (5) het aanwezig zijn van weke delen schade. De meest bestudeerde subcategorie van FAI is cam impingement. Echter, er is geen consensus over hoe een cam deformiteit radiologisch te definiëren. Het wordt veelal gekwantificeerd door de alpha hoek; hoe groter de alpha hoek des te meer wijkt de heupkop af van sferisch. Echter, er is geen consensus over welke afkapwaarde te gebruiken om een cam deformitiet te definiëren. In **hoofdstuk 8** stellen wij alpha hoek afkapwaardes voor om zowel de aanwezigheid van een cam deformiteit te definiëren als om te definiëren wanneer een cam deformiteit pathologisch wordt. De alpha hoeken van het CHECK cohort en Chingford cohort werden gecombineerd, zodat bijna 3000 heupen werden geanalyseerd. Opvallend was dat de alpha hoek in deze grote groep bimodaal was verdeeld, wat suggereert dat er twee verschillende populaties zijn: één met een cam deformiteit en één zonder een cam deformiteit. Een alpha hoek van 60° discrimineerde het beste tussen deze twee populaties, zodat deze afkapwaarde werd voorgesteld om een cam deformiteit mee te definiëren. Aangezien een grotere alpha hoek (grotere cam deformiteit) het risico op artrose substantieel verhoogt, hebben we ook een pathologische afkapwaarde bepaald gebaseerd op het ontwikkelen van

eindstadium artrose tijdens follow-up. Een pathologische cam deformiteit werd gedefinieerd als een alpha hoek groter dan 78°, aangezien deze afkapwaarde resulteerde in de maximale oppervlakte onder de ROC curve (hoogste som van sensitiviteit en specificiteit), welke 0.69 voor eindstadium heupartrose bedroeg.

DEEL 3 HET ONTSTAAN VAN EEN CAM DEFORMITEIT

Onderzoek in de afgelopen 10 jaar heeft onze kennis over hoe een cam deformiteit intra-articulaire schade kan veroorzaken en hoe een cam deformiteit chirurgisch te behandelen is behoorlijk vergroot, maar over de etiologie van een cam deformiteit is nog weinig bekend. Gezien de sterke associatie met heuppijn, een beperkte heupfunctie en het ontwikkelen van heupartrose is een beter inzicht in hoe een cam deformiteit ontstaat van groot belang. In **hoofdstuk 9** hebben we de prevalentie van een cam deformiteit en op welke leeftijd een cam deformiteit zichtbaar wordt bestudeerd bij jeugdvoetballers en bij niet sportende controles. Van de 89 jeugdvoetballers tussen de 12 en 19 jaar werden AP en Lauenstein röntgenopnames van de heup gemaakt en er werd een klinisch heuponderzoek verricht. Controles (n=92) werden geselecteerd uit een radiologie database op basis van dezelfde röntgenopnames en waarbij in de status geen heuppathologie of sportactiviteit werd vermeld. We toonden aan dat een cam deformiteit in de vroege adolescentie zichtbaar is vanaf 13 jarige leeftijd. Tevens was de prevalentie van een cam deformiteit hoger bij de jeugdvoetballers dan bij de controles en de cam deformiteiten waren ook meer uitgesproken bij de jeugdvoetballers. De prevalentie van cam deformiteiten leek bij de jeugdvoetballers met de leeftijd toe te nemen. In **hoofdstuk 10** presenteerden wij de 2,5 jaars follow-up van de jeugdvoetballers. Het doel van deze studie was om te kijken of een cam deformiteit groter kan worden in de tijd en of een cam deformiteit alleen ontstaat tijdens skeletale groei. Het tweede doel was het bestuderen van de vraag of er radiologische en klinische factoren geassocieerd zijn met, of voorspellend zijn voor het ontstaan van een cam deformiteit. Er waren 63 jeugdvoetballers bereid en in de mogelijkheid om deel te nemen aan de follow-up, waarbij dezelfde röntgenfoto's werden gemaakt en hetzelfde klinisch heuponderzoek werd verricht. Wij toonden aan dat een cam deformiteit geleidelijk ontstaat bij adolescenten en alleen tijdens skeletale groei. Het algemene patroon was dat de heupkop op 12 jarige leeftijd rond is, daarna ontstaat tot ongeveer 14 jarige leeftijd een afvlakking van de kophals overgang en tenslotte ontwikkelt deze afvlakking zich tot aan het einde van de skeletale groei bij een substantieel aantal voetballers door tot een bult. Na het sluiten van de proximale femorale groeischijf verandert de vorm van het proximale femur niet meer tijdens follow-up. Het ontstaan van een cam deformiteit is daarom waarschijnlijk een adaptatie van het bot ten gevolge van de hoge belasting van

de heupen tijdens voetballen in de periode van skeletale groei, wanneer het skelet gevoelig is voor mechanische belasting. Het afbuigen van de groeischijf tot in de femurhals, een kleinere collum-schacht hoek (meer varus positie) en een beperkte endorotatie van de heup op baseline waren allen geassocieerd met het hebben van een cam deformiteit op baseline. In de heupen zonder een cam deformiteit op baseline waren een kleinere collum-schacht hoek en een beperkte endorotatie zelfs voorspellend voor het ontwikkelen van een cam deformiteit tijdens follow-up. Aangezien een cam deformiteit alleen ontstaat tijdens skeletale groei en zeer prevalent is bij jeugdvoetballers terwijl het nauwelijks voorkomt bij niet-sporters, zou het ontstaan van een cam deformiteit mogelijk voorkomen kunnen worden. Daarom was het doel van **hoofdstuk 11** te onderzoeken welke mechanische factoren het ontstaan van een cam deformiteit kunnen verklaren. Hiervoor gebruikten we eindige elementen (FE) modellen om te bestuderen welke specifieke belastingspatronen (lopen, endorotatie, exorotatie en flexie) het ontstaan van een cam deformiteit kunnen verklaren. Tevens namen we voor al deze belastingpatronen drie verschillende vormen van de groeischijf in acht, van horizontaal tot doorlopend in de femurhals. Mechanische stimuli werden voor alle combinaties berekend en uitgedrukt in een zogenaamde 'osteogenic index', een index die aangeeft in welke mate het weefsel vervormt onder een mechanische belasting. In feite wordt met deze index de vervormingsenergie per volume weefsel in elke locatie van het bot bepaald en wordt verondersteld dat de botaanmaak wordt gestimuleerd bij een hoge vervormingsenergie en geremd bij een lage vervormingsenergie. Zowel exorotatie als flexie zouden het ontstaan van een cam deformiteit kunnen veroorzaken, doordat deze belastingspatronen de mechanische stimuli bij een open groeischijf dusdanig veranderen dat er een trigger voor botaanmaak in de anterolaterale kophals overgang ontstaat. Dit effect wordt versterkt wanneer de groeischijf verder doorloopt in het femurhals. Deze bevindingen bevestigen de resultaten van hoofdstuk 9 en 10. In **hoofdstuk 12** bespraken we de huidige kennis omtrent FAI waarbij de focus op het ontstaan van een cam deformiteit en de associatie met heupartrose lag. Door deze principes in het juiste perspectief te plaatsen, speculeerden we over preventieve mogelijkheden voor het ontwikkelen van een cam deformiteit en de daaruit voortvloeiende heupartrose. Tenslotte bespraken we de verschillen tussen radiologische en klinische tekenen van FAI, hoe deze begrippen geïnterpreteerd moeten worden en hoe dit de associatie met toekomstige heupartrose beïnvloedt.

Conclusie

Wij hebben aangetoond dat de vorm van de heup een belangrijke etiologische rol speelt in het krijgen van heupartrose. Met SSM konden wij alle heupvorm variaties in het CHECK cohort kwantificeren en met een aantal specifieke vormvariaties een goede voorspelling maken van welke heupen na 5 jaar artrose zouden ontwikkelen. Een aantal van deze vormvariaties zijn generaliseerbaar naar andere populaties en konden ook voorspellen welke heupen in het Chingford cohort na 19 jaar artrose zouden ontwikkelen. Een brede en korte femurhals zijn twee voorbeelden van heupvormen die geassocieerd zijn met artrose. Naast het bestuderen van algemene vormvariaties hebben we aangetoond dat heupdysplasie geassocieerd is met het krijgen van artrose. Tenslotte hebben we FAI gedefinieerd en onderzocht of pincer impingement (overhelling van het acetabulum door een pincer deformiteit) en cam impingement (asferisch femurkop door een cam deformiteit) geassocieerd waren met artrose. Pincer impingement was niet geassocieerd met het ontwikkelen van heupartrose (het beschermt juist), terwijl cam impingement wel sterk geassocieerd was met heupartrose. Personen met een cam deformiteit hadden grofweg een 10-voudig verhoogde kans op het krijgen van artrose. Bovendien is een cam deformiteit een mogelijk vermijdbare risicofactor. Wij hebben namelijk aangetoond dat een cam deformiteit vanaf 13 jarige leeftijd ontstaat en veel vaker voorkomt bij jeugdvoetballers dan bij 'niet sportende controles'. Tevens ontwikkelt een cam deformiteit alleen maar tijdens skeletale groei en verandert de heupvorm niet meer nadat de proximale femorale groeischijf gesloten is. In de periode van botrijping leidt een te hoge belasting van de heup, waarschijnlijk vooral door bewegingen van flexie en exorotatie, tot adaptatie van het bot waardoor een cam deformiteit ontstaat. De sterke associatie van een cam deformiteit met artrose in combinatie met het feit dat het onstaan van een cam deformiteit mogelijk vermijdbaar is, suggereert een potentiële preventieve target om heupartrose in de toekomst te voorkomen.

Appendices

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Appendices

Summary of PhD training and teaching activities

Name PhD student:	R. Agricola	PhD period:	01-10-2010 – 30-04-2013
Erasmus MC Department:	Orthopaedics	Promotor(s):	Prof.dr. H. Weinans,
Research School:	Molmed		Prof dr. J.A.N. Verhaar
		Supervisor:	dr. J.H. Waarsing

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication	2011	4.0
- BROK cursus (good clinical practice)	2011	1.0
- Biostatistical Methods 1: Basic Principles (CCO2, NIHES)	2012	5.7
- Writing grant proposals, of which one entitled 'femoroacetabular impingement and early arthritis' was approved by the Australian government National Health and Research Council (co-applicant, $900,000.00)	2013	8.0
In-depth courses		
- Statistics: Cohort studies (ESP 39, NIHES)	2012	0.7
- Statistics: Logistic regression (ESP 66, NIHES)	2012	1.4
Seminars and workshops		
- Get Out of your Lab days (Molmed), Bunnik, the Netherlands	2011	2.0
- Breakout session 'FAI: definition of disease and role in pathophysiology of hip OA', Chicago, United States	2012	0.5
- Breakout session: 'FAI: clinical science priorities and clinical trial designs', Chicago, United States	2012	0.5
- Writing a successful grant proposal	2012	1.0
- Literature meetings orthopaedic lab	2010-2013	4.0
(Inter)national conferences: invited lectures		
- Radiological FAI development in youth football players, Aspetar sports groin pain conference, Doha, Qatar	2013	1.0
- Sporten, een oorzaak van heupartrose?, Vereniging Sport en Geneeskunde jaarcongres, Ermelo, the Netherlands	2013	1.0
- Heupimpingement en artrose, ROGO dag, Tilburg, the Netherlands	2013	1.0
- Cam impingement bij sporters, pathogenese, behandeling en prognose, Masterclass 'liespijn bij voetballers', Arnhem, the Netherlands	2014	1.0

	Year	Workload (Hours/ECTS)
(Inter)national conferences: podium presentations		
- Cam laesie bij jeugdvoetballers, Werkgroep NOTS (sportorthopaedie), Amersfoort, the Netherlands	2011	1.0
- The development of cam-type deformity in adolescent and young male soccer players, European Orthopaedic Research Society, Vienna, Austria	2011	1.0
- De ontwikkeling van cam laesies bij jonge voetballers, Vereniging Sport en Geneeskunde jaarcongres, Kaatsheuvel, the Netherlands	2011	1.0
- De ontwikkeling van cam laesies bij jonge voetballers, Nederlandse Orthopaedische Vereniging jaarcongres, Den haag, the Netherlands	2012	1.0
- Total hip replacement can be predicted by shape variants of the hip: a nationwide prospective cohort study, European Orthopeadic Research Society, Amsterdam, the Netherlands	2012	1.0
- Total hip replacement but not clinical osteoarthritis can be predicted by shape variations of the hip: a prospective cohort study (CHECK), Osteoarthritis Research Society International, Barcelona, Spain	2012	1.0
- Cam impingement causes end-stage osteoarthritis of the hip: a nationwide prospective study (CHECK), European Hip Society, Milano, Italy ***Awarded*** *for best oral presentation and scientific content*	2012	1.0
- Pincer deformities and mild acetabular dysplasia: the relationship between acetabular coverage and development of hip OA in the nationwide prospective CHECK cohort, Osteoarthritis Research Society International, Philadelphia, United States	2013	1.0
- Pincer deformity is not associated with osteoarthritis of the hip, Nederlandse vereniging voor arthroscopie jaarcongres, Den Bosch, the Netherlands	2013	1.0
- A cam deformity only develops during growth: a prospective 2-years follow-up study, Nederlandse vereniging voor arthroscopie jaarcongres, Den Bosch, the Netherlands	2013	1.0
- Een cam laesie ontstaat en ontwikkelt zich geleidelijk tijdens de groei: een prospectieve studie met een minimum follow-up van 2 jaar, Nederlandse Orthopaedische Vereniging jaarcongres, Rotterdam, the Netherlands	2014	1.0

	Year	Workload (Hours/ECTS)
(Inter)national conferences: poster presentations		
- The development of cam-type deformity in adolescent and young male soccer players, Osteoarthritis Research Society International, San Diego, United States	2011	1.0
- Cam-type deformities strongly predict total hip replacement within 5 years in those with early symptomatic OA: a prospective cohort study (CHECK), Osteoarthritis Research Society International, Barcelona, Spain	2012	1.0
- A radiographic cam deformity is gradually and exclusively acquired during skeletal maturation:	2014	1.0
- a prospective study with minimum 2 years follow-up, European Congress of Radiology, Vienna, Austria		
- Validation of statistical shape modelling to predict hip osteoarthritis in females: data from two prospective cohort studies (CHECK and Chingford), Seville, Spain	2014	1.0
Other		
- Reviewer for international journals (on a regular basis) for: Annals of the Rheumatic Diseases, British Journal of Sports Medicine, Plos One, Journal of hip preservation surgery	2013-2014	3.0
- Fellowship (3 months) at the Nuffield department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences (Botnar research institute, epidemiology research group), University of Oxford, Oxford, United Kingdom	2013-2014	15.0

2. Teaching activities

	Year	Workload (Hours/ECTS)
Supervising practicals and excursions		
- Supervising practical assignment for third year medical students attending the minor 'Orthopaedic Sports Traumatology'	2012–2013	1.0
- Tutoring anatomy lessons (upper and lower limbs) for fourth year medical students attending the Erasmus Anatomy Research Project	2011-2013	5.0
Supervising Master's theses		
- Supervising medical and technical students (Roeland H. Roze and Pauline Roels) in their scientific period	2012-2013	8.0

Appendices

LIST OF PUBLICATIONS

Glyn-Jones S, Palmer AJR, Agricola R, Price A.J, Vincent TL, Weinans H, Carr AJ.Osteoarthritis: Is it possible to diagnose and treat early disease? Lancet. Accepted for publication

Roels P, Agricola R, Oei E, Weinans H, Campoli G, Zadpoor AA. Mechanical factors explain development of cam-type deformity Osteoarthritis and Cartilage. Accepted for publication.

Siebelt M, Agricola R, Weinans H, Kim YJ. The role of imaging in early hip osteoarthritis. Osteoarthritis and Cartilage. 2014 Oct;22(10):1470-80

Agricola R, Waarsing JH, Thomas GE, Carr AJ, Reijman M, Bierma-Zeinstra SMA, Glyn-Jones S, Weinans H, Arden NK. Response to letter to the editor: cam impingement defining the presence of a cam deformity by the alpha angle: Data from the CHECK cohort and Chingford cohort. Osteoarthritis and Cartilage. Accepted for publication

Agricola R. Is osteoarthritis the price to be paid for a professional football career or can we prevent it? Aspetar Sports Medicine Journal. 2014 June;3(4):266-271

Agricola R, Heijboer MP, Ginai AZ, Roels P, Zadpoor AA, Verhaar JAN, Weinans H,Waarsing JH. A cam deformity is gradually acquired during skeletal maturation in adolescent and young male soccer players: a prospective study with a minimum of 2 years follow-up. American Journal of Sports Medicine. 2014 Apr;42(4):798-806

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Sankar WN, Nevitt M, Parvizi J, Felson DT, Agricola R, Leunig M. Femoroacetabular impingement: defining the condition and its role in the pathophysiology of osteoarthritis. Journal of the American Acadamy of Orthopaedic Surgeons. 2013;21 Suppl 1:S7-S15

Agricola R, Waarsing JH, Arden NK, Carr AJ, Bierma-Zeinstra SMA, Thomas GE, Weinans H, Glyn-Jones S. Cam impingement of the hip - a risk factor for hip osteoarthritis. Nature Reviews Rheumatology 2013 Oct;9(10):630-4

Agricola R, Heijboer MP, Roze RH, Reijman M, Bierma-Zeinstra SMA, Verhaar JAN, Weinans H. 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 and Cartilage 2013 Oct;21(10):1514-21

Agricola R, Reijman M, Bierma-Zeinstra SMA, Verhaar JAN, Weinans H, Waarsing JH. Total hip replacement but not clinical osteoarthritis can be predicted by the shape of the hip: a prospective cohort study (CHECK). Osteoarthritis and Cartilage 2013 Apr;21(4):559-64

Agricola R, Heijboer MP, Bierma-Zeinstra SMA, Verhaar JAN, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Annals of the Rheumatic Diseases. 2013 Jun;72(6):918-23

Agricola R, Bessems JH, Ginai AZ, Heijboer MP, van der Heijden RA, Verhaar JAN, Weinans H, Waarsing JH. The development of cam-type deformity in adolescent and young male soccer players. American Journal of Sports Medicine. 2012 May;40(5):1099-106

Weinans H, Siebelt M, Agricola R, Botter SM, Piscaer TM, Waarsing JH. Pathophysiology of per-articular bone changes in osteoarthritis. Bone 2012 Aug;51(2):190-6

Agricola R, Leyland KM, Bierma-Zeinstra SMA, Thomas GE, Emans PE, Spector TD, Weinans H, Waarsing JH, Arden NK. Validation of statistical shape modeling to predict hip osteoarthritis in females: data from two prospective cohort studies (CHECK and Chingford) Rheumatology. Revision submitted.

Tak I, Weir A, Waarsing JH, Langhout R, Stubbe J, Kerkhoffs G, Agricola R. The relationship between the frequency of football practice during skeletal growth and the presence of a cam deformity in adult elite football players. British Journal of Sports Medicine. Revision submitted.

Mosler AB, Agricola R, Weir A, Holmich P, Crossley KM. Factors differentiating athletes with and without hip and groin pain- a systematic review and meta-analyses. Submitted.

Roze RH, Bierma-Zeinstra SMA, Agricola R, Oei EHG, Waarsing JH. Sex related differences in MRI features of between two different osteoarthritis subpopulations: data from the Osteoarthritis Initiative. Submitted

Spil van WE, Agricola R, Meijer R, Drossaers-Bakker KW, Weinans H, Lafeber FPJG. Associations of markers of metabolism and inflammation and adipokines with cam impingement of the hip and their relation with future osteoarthritis. Submitted.

Appendices

CURRICULUM VITAE

Rintje Agricola werd geboren op 25 november 1986 te Heerenveen waar hij tevens in 2005 zijn VWO diploma aan het Bornego College behaalde. In datzelfde jaar ging hij bewegingswetenschappen studeren aan de Rijksuniversiteit Groningen. Na het behalen van zijn propedeuse startte hij in 2006 de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens zijn afstudeeronderzoek naar de ontwikkeling van cam-deformiteiten bij de afdeling orthopaedie van het Erasmus MC, werd zijn belangstelling gewekt voor wetenschappelijk onderzoek. In 2011 heeft hij zijn doctoraal behaald. Toen vervolgens de mogelijkheid zich voordeed om zijn afstudeeronderzoek als promovendus voort te zetten, greep hij die kans vol enthousiasme. Onder begeleiding van prof.dr.ir. H. Weinans, prof.dr. J.A.N. Verhaar en dr.ir. J.H. Waarsing heeft hij 2.5 jaar onderzoek gedaan naar morfologische risicofactoren van heupartrose en hoe deze ontstaan in de jeugd. In 2013 is hij gestart met zijn co-schappen in diverse ziekenhuizen in de regio Rotterdam. Zijn co-schappen werden 2.5 maand onderbroken om een fellowship te volgen in het Nuffield Orthopaedic Centre en Botnar Research Centre aan de University of Oxford. Onder begeleiding van prof. N.K. Arden heeft hij zijn kennis op het gebied van morfologische kwantificatie van de heup verder kunnen uitbreiden. In februari 2015 zal hij zijn artsdiploma in ontvangst mogen nemen en aansluitend een fellowship in Doha, Qatar volgen. In juli 2015 zal hij met zijn vooropleiding algemene heelkunde starten in het IJsselland ziekenhuis te Capelle aan den IJssel (opleider dr. I. Dawson). Zijn opleiding tot orthopaedisch chirurg zal in 2017 aanvangen en hij zal gaan werken in het Erasmus MC te Rotterdam (opleider prof. dr. J.A.N. Verhaar) en in de Reinier de Graaf Groep te Delft (opleider dr. R.M. Bloem).

Appendices

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Tot slot mijn dank aan alle mensen die een bijdrage hebben geleverd aan de totstandkoming van dit proefschrift. Een aantal mensen wil ik in het bijzonder bedanken.

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Paranimfen, beste Michiel en Jasper, de cumulatieve opbrengst van de vruchtbare Boudewijn meetings hebben al zeker 30 papers opgeleverd. Michiel, mentor, vriend, gelukkig kan ik je op deze wijze op papier bedanken, zodat je geen bescheiden weerwoord kan geven. Naast alle mooie dingen die we hebben beleefd ben jij degene die mij heeft gescout; bedankt daarvoor. Jasper, fiets- en reismaatje, vriend, van flauwe grappen tot serieus wetenschappelijk overleg, ik heb me geen seconde verveeld met jou als kamergenoot.

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Drs. Heijboer, u was de eerste bij wie ik op de deur klopte met de vraag: 'kan ik onderzoek bij Orthopaedie doen'? Heel veel dank dat u mij het vertrouwen schonk en die deur voor mij hebt geopend.

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