Hip Morphology and Osteoarthritis
From anatomical variations to clinical implications

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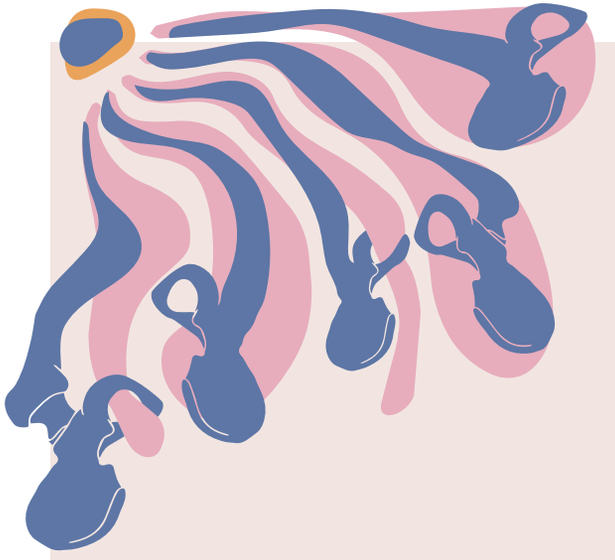
Chapter 1



GENERAL INTRODUCTION

The hip

The skeletal system is the framework of the human body. It protects internal organs and forms the structural foundation for muscles to enable movement. A joint or articulation allows for movement and flexibility in the skeletal system and can be categorized roughly into three types: fibrous, cartilaginous and synovial, of which the latter is the most common. Synovial joints can be categorized anatomically in hinge, pivot or ball-and-socket joints, among others. The hip is a ball and socket joint, and is formed by the proximal femur and the pelvis to connect the lower extremities to the torso. The round femoral head articulates with the cup-shaped acetabulum (Fig. 1) and both articulate surfaces are covered with cartilage(2). The hip is a large and stable joint despite its wide range of motion, which includes flexion, extension, internal and external rotation, adduction and abduction. The stability is largely provided by the surrounding muscles and ligaments of the thighs and glutes (Fig. 2). The labrum, which is a ring of fibrous cartilage, deepens the acetabulum and provides additional stability and shock absorption (3). The hip joint can fall prey to numerous conditions, of which one of the most important is hip osteoarthritis (3-5).

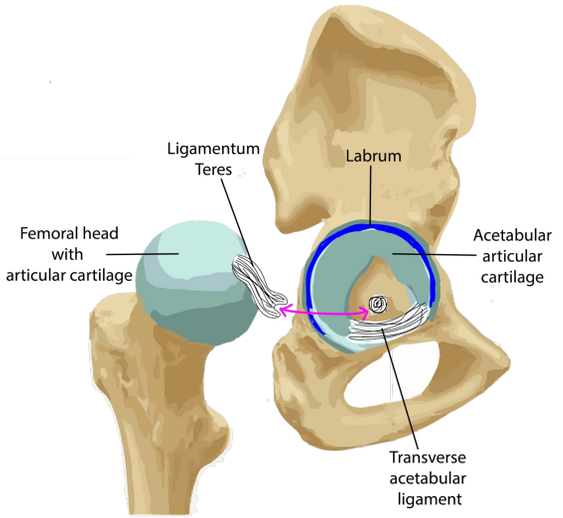


Fig. 1. Schematic drawing of the hip joint.

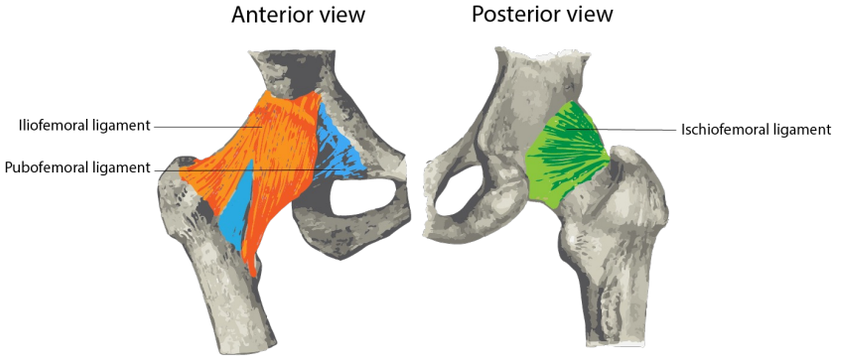


Fig. 2. Schematic drawing of the anterior and posterior view of the hip ligaments. Iliofemoral ligament (orange), pubofemoral ligament (blue) and ischiofemoral ligament (green).

Osteoarthritis of the hip

Osteoarthritis is a complex, chronic, multifactorial joint disease which leads to cartilage degradation, subchondral bone sclerosis, and osteophyte formation, as well as damage to synovium and ligaments (6).

Osteoarthritis may occur in any joint, but of weight-bearing joints the knee the most commonly affected, closely followed by the hip joint (7). Clinically, hip osteoarthritis is characterized by joint pain, crepitus, stiffness and reduced range of motion, which a patient may experience in intermitting phases (8). According to Dutch national guidelines, a diagnosis of hip osteoarthritis can be made based on age (≥45 years), activity-related pain in the hip joint and absence of, or brief morning stiffness in the hip joint. Only when a patient presents with similar but atypical complaints, additional radiographs should be obtained (9). Radiographs may show specific, progressive changes to the joint, such as loss of joint space, osteophytes (bony spurs along the osseus edges of the joint), cysts and bone deformation (10).

The burden of Osteoarthritis

In 2020, it was estimated that osteoarthritis affects over 500 million individuals worldwide, accounting for approximately 7% of the global population (11). In a mere 30 years, between 1990 and 2019, the number of individuals affected by osteoarthritis worldwide increased by 48% (11). An Australian study assessed the national costs of osteoarthritis-related healthcare, and found that they were estimated over $2.1 billion in 2015, but are forecast to exceed $2.9 billion by the year 2030 (12). This in an increase in costs of 38% in only 15 years.

These statistics demonstrate that osteoarthritis is common and costly, but the immense impact on the quality of life of individuals suffering from this disease should be emphasized. Symptomatic hip osteoarthritis can cause significant disability by impairing daily activities such as walking or climbing stairs (13). Osteoarthritis was the 15th highest cause of years lived with disability (YLD) globally in 2019 and responsible for 2% of the total worldwide YLDs (14). Moreover, one in four individuals will develop osteoarthritis of the hip in their lifetime (13).

The incidence of osteoarthritis has been forecasted to increase, which means that the already immense social, personal and financial burden of osteoarthritis will progress. This is the result of the increase in global lifespan, which consequently increases the prevalence of hip osteoarthritis (15,16). The development of effective treatment of osteoarthritis has not progressed at the same pace as treatments for other musculoskeletal diseases, and currently no curative treatment for hip osteoarthritis exists (15). This implies that joint replacement surgery is the only treatment option for end-stage disease when conservative treatment fails (13).

There is a prevailing belief that hip osteoarthritis is an inevitable part of ageing and no effective treatments exist. Research has already shown that modifiable risk factors such as obesity and physically demanding occupations increase the risk of developing, or the progression of, hip osteoarthritis (17,18). Furthermore, the combination of the prevalence of risk factors and the strength of associations have been shown to determine the importance of risk factors in the light of hip osteoarthritis prevention (19). The search for additional modifiable risk factors, and early identification of individuals at risk must be prioritized to reduce the public and economic burden of osteoarthritis, and to increase health benefits for patients suffering from this disease (19-21).

Defining hip osteoarthritis

As mentioned previously, hip osteoarthritis is a heterogeneous and complex disease. This makes it equally complex to define and classify the disease for research purposes. Generally, osteoarthritis of the hip has been classified in two ways: radiographically and clinically (22).

The American College of Rheumatology (ACR) developed clinical criteria for hip pain associated with osteoarthritis. It has been proposed that studies in individuals who have joint symptoms may be more clinically relevant, because not all individuals who have radiographic osteoarthritis have clinical disease, and not all individuals who have joint pain demonstrate radiographic osteoarthritis (22). The ACR criteria classify hip osteoarthritis without the use of radiographs, and are solely based on clinical symptoms with or without laboratory tests. According to the ACR criteria, an individual has hip osteoarthritis if pain was present in combination with hip internal rotation ≥15°, pain present on internal rotation of the hip, morning stiffness of the hip for ≤60 minutes, and age >50 years, or if hip internal rotation <15°and an erythrocyte sedimentation rate (ESR) ≤145 mm/hour. If no laboratory tests are available, ESR may be replaced by hip flexion of ≤115°.

For many years, radiographic osteoarthritis has been accepted as the reference standard for diagnosis. As a result, various methods have been developed to classify hip osteoarthritis based on radiographic findings.

The Kellgren and Lawrence (KL) grading system (Fig 3.) is most well-known and has been in use for over 6 decades (10). The KL grading system defines osteoarthritis severity by five grades (0, normal to 4, severe) using a combination of osteophytes, joint space narrowing (JSN) severity, sclerosis and bone deformity (10). KL grade ≥ 2 is often used as a threshold for defining the presence of radiographic hip osteoarthritis (23-25). The Modified Croft grading system (Fig. 4), which is essentially a modification of the KL grading system, defines OA severity in 5 grades (0–4), and is based on 5 radiographic features: JSN, osteophytes, subchondral sclerosis, cyst formation, and deformity. The cut-off value ≥ grade 2 is generally used to define definite radiographic hip osteoarthritis and requires the presence of at least two of the following features: JSN, osteophytosis, subchondral sclerosis (of >5 mm) or cyst formation (26). This last definition makes the Modified Croft grade depend less heavily on the presence of osteophytes than the KL grading system, for which the Croft classification is celebrated.

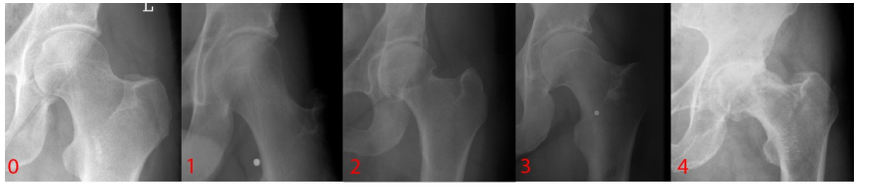


Fig. 3. Kellgren and Lawrence grading. Grade 0: definite absence of radiographic changes of osteoarthritis. **Grade 1:** doubtful joint space narrowing and possible osteophytic lipping. **Grade 2:** definite osteophytes and possible joint space narrowing. **Grade 3:** moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends. **Grade 4:** large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

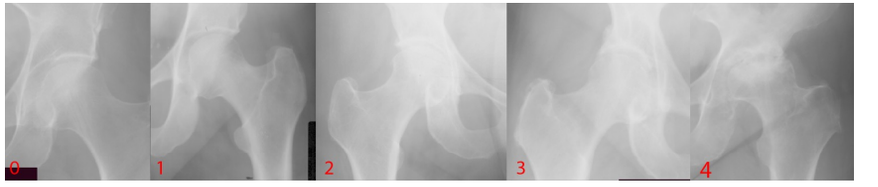


Fig. 4. Modified Croft Grading. Modified Croft: Grading system ranging from grade 0-4. **Grade 0:** absence of osteophytes and JSN. **Grade 1:** Maximum osteophyte ≥1 or maximum JSN ≥1. **Grade 2:** Maximum osteophyte ≥2 and max JSN <2. **Grade 3:** the sum of (maximum osteophytes≥2, maximum JSN≥2, sclerosis≥1, cysts>=1) ≥3 and femoral head deformity=0 **Grade 4:** the sum of (maximum osteophytes≥2, maximum JSN≥2, sclerosis≥1, cysts>=1) ≥3 and femoral head deformity=1.

Croft et al. has also developed a measure of the minimal joint space (MJS) width which has been used to define osteoarthritis of the hip. The MJS, which is the shortest distance on a radiograph between the femoral head margin and the acetabular edge, is measured laterally, superiorly, axial, and medially. Next, the measures are translated into grades, where grade 0 is a MJS ≥2.5 mm, grade 1 is a MJS 2.5mm-1.5 mm and grade 2 is a MJS ≤ 1.5 mm (26,27). Whether these thresholds can be applied to male and female biological sex alike is still under debate.

Alternative imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) may also offer significant benefits in assessing hip osteoarthritis, each with its distinct advantages and disadvantages. MRI proves particularly valuable in diagnosing bone related conditions that lead to rapid escalation of symptoms such as avascular necrosis of the femoral head or subchondral insufficiency fractures, while simultaneously being able to depict surrounding soft tissue (28). MRI classifications for hip osteoarthritis are still undergoing evaluation for their role in defining osteoarthritis and for their application in detecting the effects of disease-modifying interventions. CT scans are faster than MRI, and are able to visualize subchondral bone. Additionaly, CT provides visualization of the hip joint segments that may be difficult to appreciate on radiographs, such as the inferoposterior and posterolateral hip joint (29). It should be kept in mind that these scans expose individuals to ionizing radiation. Optimal selection of the appropriate imaging modality, keeping in mind the advantages and disadvantages of both, will enhance the value of imaging in an epidemiological and clinical setting (28). The same counts for measures of biomarkers of joint metabolism, which have been labeled as important, but are also still being evaluated as a tool to define osteoarthritis for epidemiological studies (22).

Risk factors of hip osteoarthritis

Hip osteoarthritis arises from a complex interaction between genetic, environmental and lifestyle factors (30). Numerous specific risk factors have been identified and include ageing, genetics, biological sex, trauma, physical work load and hip shape (5,31,32). The mechanism underlying joint damage due to ageing is not fully understood, but factors that may play a role include oxidative stress, thinning of cartilage and reduced proprioception (33). Genetics play an important role in development of hip osteoarthritis (5). Not only is this illustrated by ethnic differences in the incidence of the disease, which is for example much less common in Asian compared to Western populations, but genome wide association studies have also identified loci that are associated with development of hip osteoarthritis (34-37). Women are more at risk than men for developing osteoarthritis of the hip. The reason for this is still under debate, but a different distribution of muscle mass, as well as an interplay of hormonal factors has been suggested (5,32). Post-traumatic hip osteoarthritis results from fractures, ligament or capsule injury, or joint dislocation (38). Hip osteoarthritis is associated with physical activities such as with prolonged lifting and standing, but it remains uncertain whether high-impact, high-intensity repetitive movements also lead to an increased risk for hip osteoarthritis (39). Contrary to knee osteoarthritis, the association between obesity or metabolic syndrome and hip osteoarthritis is not as clear (40). Finally, specific shapes of the hip have been shown to increase the likelihood of developing hip osteoarthritis. The varying shape is hypothesized to change the biomechanical loading on the joint and ultimately cause irreversible damage (41,42).

Hip shape as a risk factor

Hip morphology has been marked as an essential risk factors for the development of hip osteoarthritis (41-44). Research shows that the shape and alignment of the hip joint can impact the distribution of loading within the joint, potentially resulting in damage to the cartilage and other surrounding structures (45). These morphological variations can be present on the acetabular or femoral side, or both. Examples of morphologies on the acetabular side are acetabular undercoverage, also known as acetabular dysplasia, or acetabular overcoverage, which is known pas pincer morphology. On the femoral side, a non-spherical head, known as cam morphology may be present. Cam and pincer morphology are associated with femoroacetabular impingement syndrome (46). This thesis focusses primarily on hip shape variations on the acetabular side (acetabular dysplasia and pincer morphology).

Acetabular Dysplasia

Acetabular dysplasia is generally defined as undercoverage of the femoral head by the acetabulum, but encompasses a spectrum of conditions and morphologies that affect the alignment of the hip joint (47,48). It is important to distinguish between developmental dysplasia of the hip and acetabular dysplasia that develops during adolescence.

Developmental dysplasia of the hip is diagnosed in infants or during early childhood. The shallow and/or steep acetabulum fails to adequately cover the femoral head, leading to more lateral and anterior alignment of the femoral head in the socket with an increased risk of dislocation (49). In the Netherlands, all infants undergo screening for this condition, which increases the chance of early detection of developmental dysplasia of the hip (50). Risk factors for developmental dysplasia of the hip include female biological sex, breech position and a positive family history of the condition (51). Timely detection of an incongruent joint is crucial, as this allows for less invasive treatment options (52). To establish a congruent joint, treatment with a Pavlik harness is often sufficient. However, closed or open reduction under anesthesia and surgery to ligaments surrounding the hip joint may also help achieve a stable joint. If the development of the acetabulum is unsatisfactory, additional surgeries such as pelvic and/or femoral osteotomy may be necessary to correct residual dysplasia or subluxation (52).

Acetabular dysplasia is sometimes discovered later in life, often during adolescence (53,54). When exactly these hips develop acetabular dysplasia is still unknown. This thesis primarily focusses on this type of acetabular dysplasia, which is often a milder form compared to developmental dysplasia of the hip (Fig. 5). Being mild, acetabular dysplasia frequently remains undetected until individuals begin experiencing symptoms, such as groin or gluteal pain along with difficulty standing or walking for an extended period of time, related to permanent soft tissue or cartilage damage. Radiographs can aid in the (early) detection of acetabular dysplasia. Common radiographic measures used to assess acetabular dysplasia include the acetabular index, the extrusion index, the Wiberg center edge angle, and the acetabular depth-width ratio (55-57) (Fig. 5).

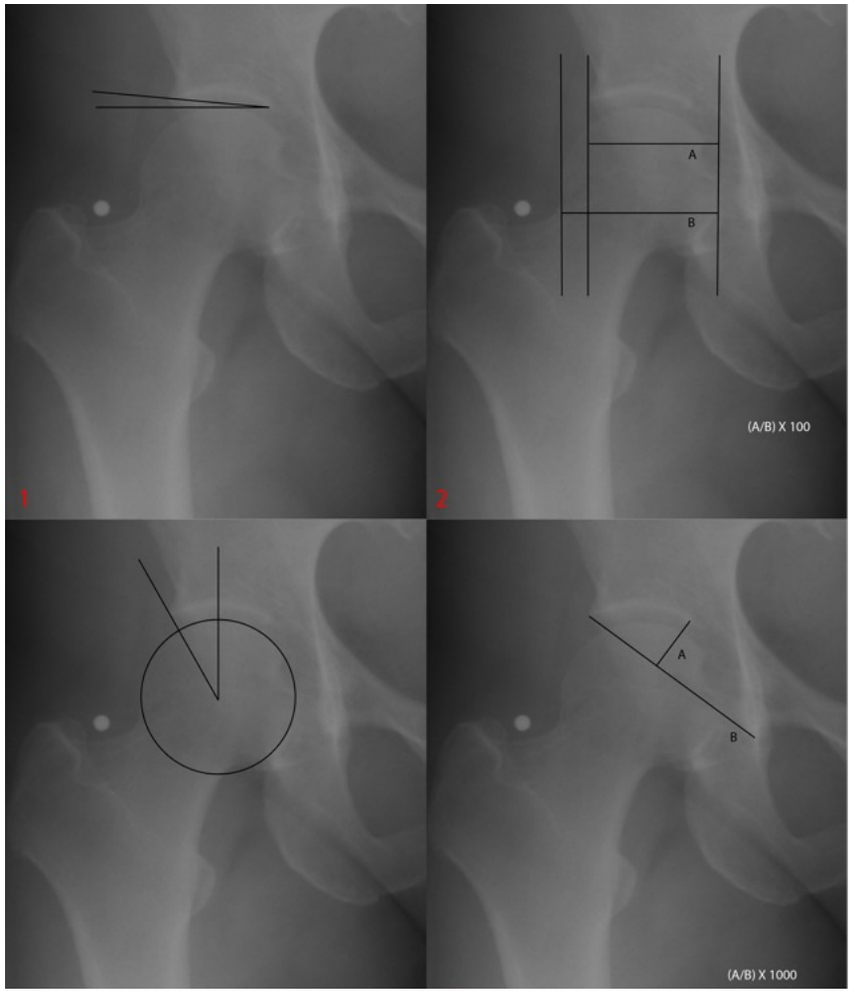


Fig. 5. Radiographic measures of acetabular dysplasia on a right hip radiograph. 1) The acetabular index (AI): angle between the horizontal reference line of the pelvis and a line through the most lateral bony part of the acetabulum. 2) The extrusion index (EI): EI= A/B X 100%, is the ratio between the uncovered part of the femoral head (A) and entire width of the femoral head (B). 3) The center edge angle of Wiberg (WCEA): angle between a vertical line perpendicular to the horizontal reference line of the pelvis, and a line through the femoral head center to the most lateral part of the acetabular sourcil. 4) The acetabular depth width ratio (ADR): (A/B) X 1000, is the ratio between the acetabular width, measured from the most lateral bony part of the acetabulum to the most inferior point of the teardrop and the acetabular depth, measured from the most medial point of the sourcil, perpendicular to the width.

In epidemiological studies, the Wiberg center edge angle is the most commonly used measure to define acetabular dysplasia. A threshold of ≤25° is used to define mild acetabular dysplasia, while a threshold of ≤20° is used to define more severe cases (58,59). However, it should be noted that this measure only quantifies lateral acetabular coverage of the femoral head, whereas acetabular dysplasia involves multiple hip shape variations. The use of multiple measures may therefore provide a more accurate description of the entire morphology in (large) epidemiological studies, but an efficient and reliable method is currently lacking.

Studies have shown that acetabular dysplasia is associated with hip osteoarthritis (24,60-64). The acetabular undercoverage results in a relatively small contact area between the femoral head and the acetabulum, resulting in increased stress on the cranial and ventral acetabular rim (62) (Fig. 6). This altered loading pattern has been shown to increase the risk of labral damage and to ultimately cause hip osteoarthritis. Although many studies have been performed, significant variability in how acetabular dysplasia and hip osteoarthritis are defined exists. This makes it difficult to establish the true importance of acetabular dysplasia as a risk factor.

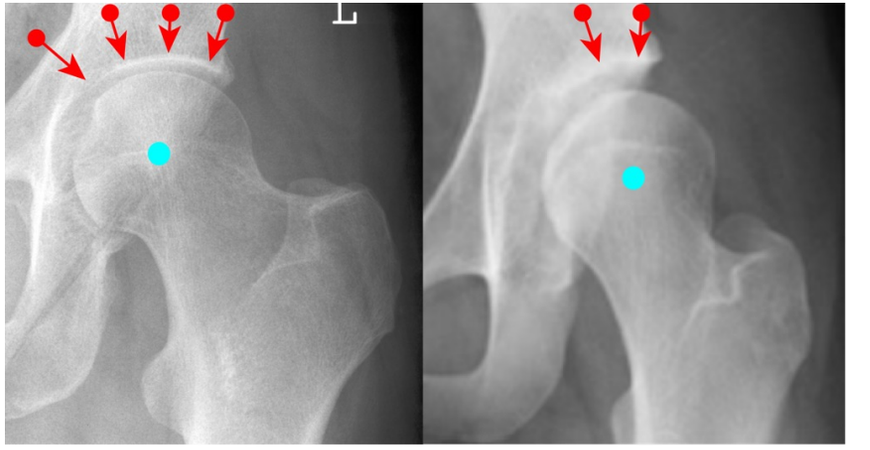


Fig. 6: Left: normal acetabular coverage leads to even force distribution and normal joint loading. Right: reduced acetabular coverage leads to concentrated force on a small surface area and increased stress on the cranial and ventral acetabular rim.

Pincer morphology

Pincer morphology is defined as overcoverage of the acetabulum relative to the femoral head and may either be focal or global (65,66). Focal overcoverage is characterized by a positive crossover sign, posterior wall sign and ischial spine sign on radiographs, which all aim to quantify acetabular retroversion (66). Global pincer morphology may occur with an increased lateral center edge angle, coxa profunda or protrusio acetabuli. Coxa profunda and protrusion acetabuli are characterized by deep acetabular sockets with general overcoverage of the femoral head by the acetabulum (67). Coxa profunda is defined by extension of the acetabular floor over the ilioischial line on an anteroposterior pelvic radiograph. Protrusio acetabuli occurs when there's medial overlap of the femoral head over ilioischial line (Fig. 7) (67).

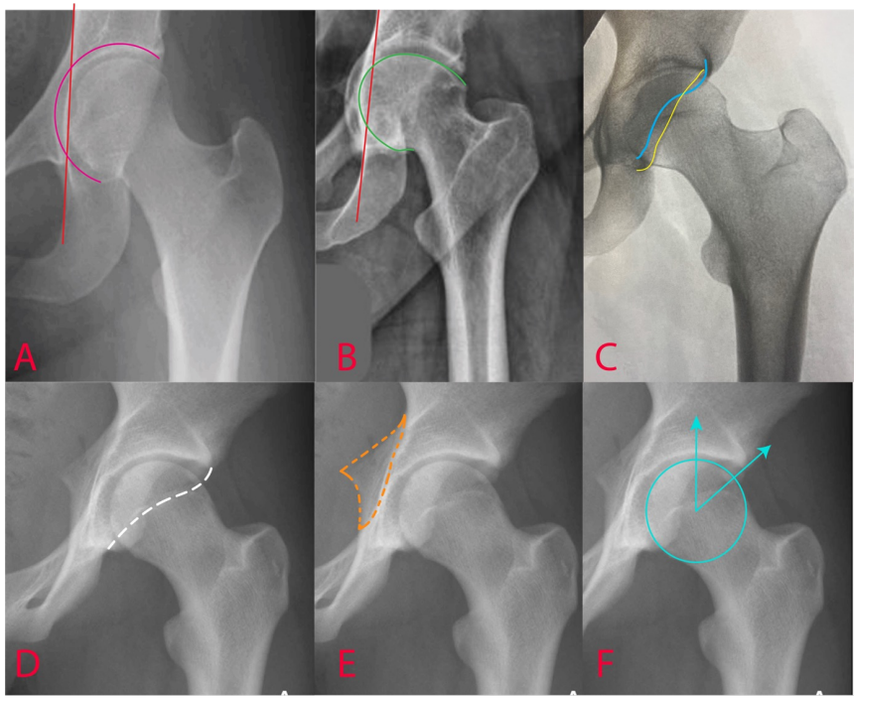


Fig. 7. Radiographic measures that characterize pincer morphology on anteroposterior radiographs.
A: Coxa profunda is characterized by extension of the acetabular fossa (pink) over the ilioischial line (red). **B:** Protrusio acetabuli is present when the femoral head (green) overlaps the ilioischial line (red) medially. **C:** A cross over sign is present when the anterior acetabular wall (blue) and the posterior acetabular wall (yellow) intersect, indicating acetabular retroversion. **D:** The posterior wall sign is positive if the posterior wall runs medially to the center of the femoral head. **E:** The ischial spine sign is positive if the ischial spine is projected medially to the pelvic rim. **F:** The lateral center edge angle measures the amount of acetabular coverage over the femoral head.

In epidemiological studies, pincer morphology is usually quantified using the center edge angle on anteroposterior radiographs. The lateral center edge angle measures the amount of acetabular coverage in degrees. Similarly, pincer morphology is generally defined by a lateral center edge angle ≥40°. The anterior center edge angle can be constructed on a false profile radiograph, which is a lateral view of the hip. Pincer morphology is generally defined by an anterior center edge angle ≥40° (fig. 8) (24,59).

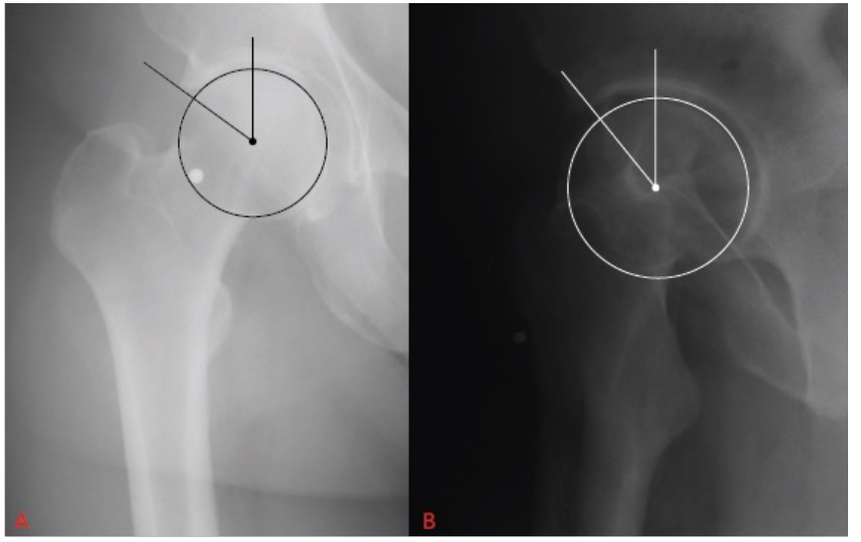


Fig. 8. A) The lateral center edge angle on an anteroposterior radiograph. The lateral center edge angle is calculated as the angle between a vertical line through the femoral head center perpendicular to the horizontal reference line of the pelvis, and a line to the outermost lateral bony part of the acetabulum. **B)** The anterior center edge angle on a false profile radiograph. The angle consists of a vertical line parallel to the radiograph through the femoral head center and a line extending to the outermost anterior bony border of the acetabulum.

Femoroacetabular impingement syndrome

Pincer morphology, along with cam morphology which is defined by a non-spherical femoral head, is a part of femoroacetabular impingement syndrome (FAIS). The concept of FAIS was first proposed by the Swiss Professor Ganz and his colleagues (46). After a surgical method was developed to safely dislocate the hip without risk of avascular necrosis, it was possible to almost completely visualize the femoral head. It was then that Professor Ganz and his research team discovered that a non-spherical femoral head is often accompanied by acetabular chondrolabral damage (68). In 2003, Ganz et al. proposed that the chondrolabral damage was the result of repeated impinging moments between the femoral head-neck junction and the acetabulum during motion, which led to soft-tissue damage (46) (Fig. 9). Either femoral or acetabular morphology can be responsible for the impinging moments; cam morphology on the femoral side and pincer morphology on the acetabular side (Fig. 10) (69).

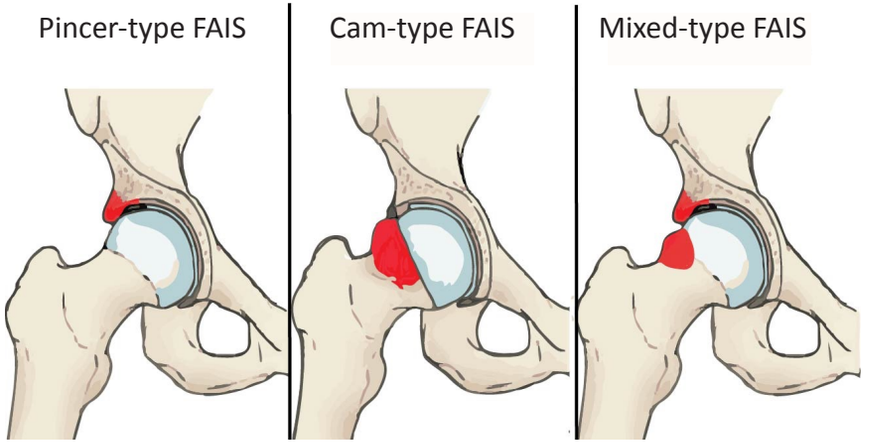


Fig. 9. Types of Femoroacetabular impingement syndrome. Left: pincer-type impingement: acetabular overcoverage leads to impingement on the acetabular rim. Middle: cam-type impingement: the non-spherical femoral head leads to impingement against the acetabular rim especially during flexion and internal rotation. Right: mixed type impingement where both a non-spherical head and excessive acetabular coverage is present. FAIS= femoroacetabular impingement syndrome.

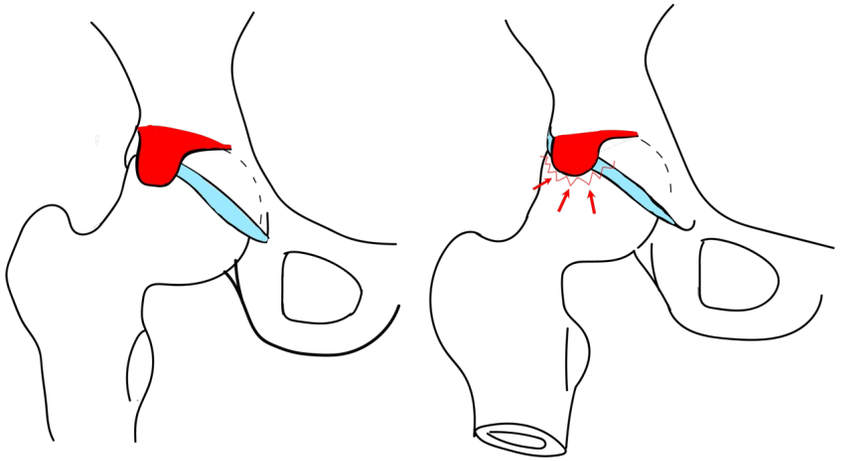


Fig. 10. Mechanism of pincer impingement. Left: pincer morphology (red) on an anteroposterior view. Right: impingement against the acetabular rim during hip flexion and internal rotation causes damage (arrows) to the acetabular cartilage (blue).

A pathophysiological mechanism of how pincer morphology leads to osteoarthritis of the hip has been proposed by Beck et al. in 2005 (69). Pincer morphology is generally present on the anterolateral rim of the acetabulum, which results in impingement of the labrum between the acetabular rim and the femoral neck during motion, causing degeneration and ossification (69). Since then, however, prospective cohort studies have not been able to objectify a significant association between pincer morphology and osteoarthritis of the hip (24,61,70). Multiple reasons for the lack of association have been proposed. First, it's been proposed that pincer morphology may lead to hip osteoarthritis over an extended period of time (much slower than acetabular dysplasia for example) and the follow-up period in prospective cohort studies was insufficient. Only quantifying pincer morphology on an anteroposterior pelvic radiograph with a lateral center edge angle may underestimate the presence of the morphology and be responsible for a lack of association. Finally, it may be the case that pincer morphology on its own does not lead to osteoarthritis of the hip, but only if symptoms and clinicals findings of FAIS are present (66). Before concluding that pincer morphology is not associated with hip osteoarthritis, further research should be conducted.

The importance of studying hip morphology as a risk factor for hip osteoarthritis

To identify risk factors is to understand the causes of disease. This in turn allows for identification of at-risk individuals, which could play a crucial role in preventive and treatment strategies for hip osteoarthritis (43,71,72). Hip morphology is at least partly a modifiable risk factor, as biological pathways within a joint are mechanosensitive, and may therefore be altered (73). It has been hypothesized that conservative treatment (e.g., physical therapy) may be able to influence the loading pattern of the hip, and hip preservation surgery may be able valuable in correcting the aforementioned biomechanical loading patterns.

Valuable insight has been gained through prospective cohort studies. These studies have highlighted the role biomechanics play in the development of hip osteoarthritis that is associated with hip shape variations. The studies that have been published however are limited in several ways. The first limitation is statistical power, which means that currently available prospective cohort studies may only draw conclusions on a group level. The second limitation is variability in quantifying the predictors (hip morphology) and the outcome (hip osteoarthritis), which makes it difficult to draw conclusions on the true magnitude of the risk morphology poses. Individual participant data meta-analysis, a type of meta-analysis in which original data from participants is collected, pooled and re-analyzed may offer a solution to the first limitation. The second limitation may be overcome by using algorithms to automate hip shape quantification. These algorithms must first be validated to appreciate their reliability for which large amounts of data are necessary.

General aim and outline of this thesis

How to accurately quantify hip shape and combine measures with a clinical diagnosis is essential in large population studies, and valid automation of these measures may offer a leap forward. Research shows that the shape of the hip is associated with development of hip osteoarthritis, though associations differ significantly in literature. Recent evidence on this topic shows that acetabular dysplasia may be an important shape variation, but whether this also counts for pincer morphology is unsure presently. In the first part of this thesis we study the automatic quantification of different morphological measures of the hip. In the second part, we study the associations between acetabular dysplasia and pincer morphology and incident radiographic hip osteoarthritis.

The aims of this thesis are:

1. To validate an automated method to quantify hip morphology

2. To study associations between hip morphology and hip osteoarthritis

In **part I** we define radiographic hip osteoarthritis and radiographic measurements for hip morphology. In **chapter 2** we provide a comprehensive and transparent description of the Worldwide Collaboration of OsteoArthritis PrediCtion for the Hip (World COACH) consortium which is used for individual participant data meta-analysis by presenting the consortium design, study population, and data collection. **Chapter 3** validates the automatic calculation and reliability of morphological measurements of the hip. The measurements are based on an automatic search model that annotates the bony outline of the hip. A total of eight measurements were described and include the acetabular depth-width ratio, the acetabular index, the alpha angle, the lateral center edge angle, the Wiberg center edge angle, the migration index, the neck-shaft angle, and the triangular index. In **chapter 4** we determine the additional value of false profile radiographs compared to anteroposterior radiographs alone in the diagnosis of developmental dysplasia of the hip.

Part II focusses on associations between specific hip morphologies and the development of radiographic hip osteoarthritis. For all chapters we studied hip morphology in hips free of osteoarthritis in order to accurately study the association between hip morphology and incident radiographic hip osteoarthritis. In **chapters 5 and 6** we investigated the risk of developing radiographic hip osteoarthritis in hips with acetabular dysplasia and pincer morphology at four different time points in the Cohort Hip and Cohort Knee (CHECK). CHECK consists of individuals with first onset of pain or stiffness in the hip or knee for which they consulted their general practitioner for the first time. Individuals from the same cohort were studied in **chapter 7**, but with an emphasis on clinical osteoarthritis rather than radiographic. In this study, we investigated whether acetabular dysplasia is risk factor for clinically relevant osteoarthritis in addition to radiographic hip osteoarthritis. Finally, in **chapters 8 and 9** we performed an individual participant data meta-analysis in the World COACH consortium to study the association between acetabular dysplasia (chapter 8) and pincer morphology (chapter 9) and incident radiographic hip osteoarthritis. **Chapter 10** provides the general discussion, which addresses the results of all chapters in the light of current literature, and explores potential future research opportunities.

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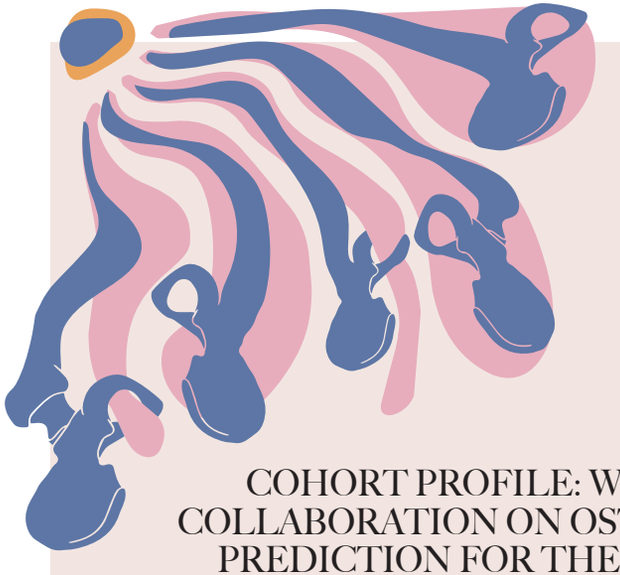
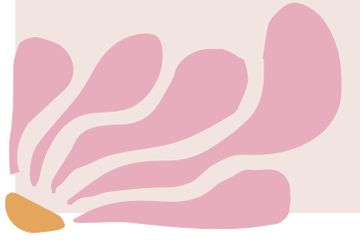
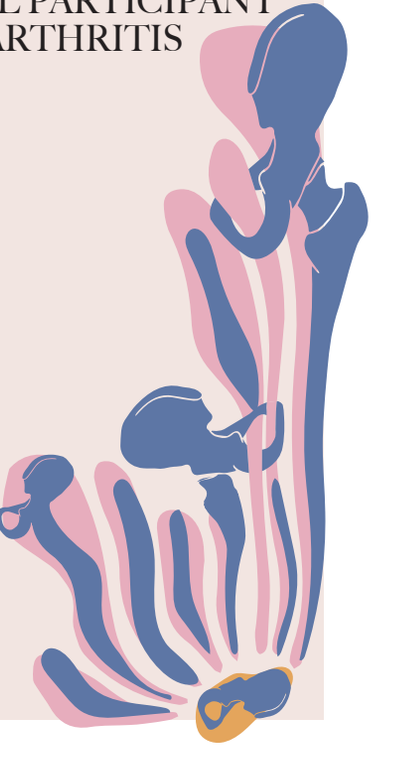


COHORT PROFILE: WORLDWIDE COLLABORATION ON OSTEOARTHRITIS PREDICTION FOR THE HIP (WORLD COACH); AN INTERNATIONAL CONSORTIUM OF PROSPECTIVE COHORT STUDIES WITH INDIVIDUAL PARTICIPANT DATA ON HIP OSTEOARTHRITIS





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Cohort profile: Worldwide Collaboration on OsteoArthritis prediCtion for the Hip (World COACH); an international consortium of prospective cohort studies with individual participant data on hip osteoarthritis.

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Abstract

Purpose: Hip osteoarthritis (OA) is a major cause of pain and disability worldwide. Lack of effective therapies may reflect poor knowledge on its aetiology and risk factors, and result in management of end-stage hip OA with costly joint replacement. The Worldwide Collaboration on OsteoArthritis prediCtion for the Hip (World COACH) consortium was established to pool and harmonise individual participant data from prospective cohort studies. The consortium aims to better understand determinants and risk factors for the development and progression of hip OA, to optimise and automate methods for (imaging) analysis, and to develop a personalised prediction model for hip OA.

Participants: World COACH aimed to include participants of prospective cohort studies with ≥200 participants, that have hip imaging data available from at least 2 time points at least four years apart. All individual participant data, including clinical data, imaging (data), biochemical markers, questionnaires, and genetic data, were collected and pooled into a single, individual-level database.

Findings to date: World COACH currently consists of nine cohorts, with 38,021 participants aged 18 to 80 years at baseline. Overall, 71% of the participants were female and mean baseline age was 65.3 ± 8.6 years. Over 34,000 participants had baseline pelvic radiographs available, and over 22,000 had an additional pelvic radiograph after 8–12 years of follow-up. Even longer radiographic follow-up (15–25 years) is available for over 6,000 of these participants.

Future plans: The World COACH consortium offers unique opportunities for studies on the relationship between determinants/risk factors and the development or progression of hip OA, by using harmonised data on clinical findings, imaging, biomarkers, genetics, and lifestyle. This provides a unique opportunity to develop a personalised hip OA risk prediction model and to optimise methods for imaging analysis of the hip.

Strengths and limitations of this study

- The Worldwide Collaboration on OsteoArthritis prediCtion for the Hip (World COACH) consortium brings patients together with a highly qualified and multidisciplinary team of experts and young investigators in the field of hip osteoarthritis, with backgrounds in orthopaedic surgery, rheumatology, physical therapy, general practice, genetics, epidemiology, biostatistics, technical medicine, biomechanical engineering, radiology, imaging science, and artificial intelligence.
- The World COACH consortium is unique for having harmonised individual participant data on clinical measurements, radiological imaging, biochemical markers, lifestyle and diet, comorbidities, medication, physical and cognitive functioning, quality of life and genetics from over 38,000 people, both from the general population as well as from specific populations at risk for hip osteoarthritis.
- The World COACH consortium has sequential hip radiography available for each participant with a follow-up duration ranging from 5 to over 25 years.
- The main limitations of the consortium are the geographic origins of the included cohorts (Western world) and the heterogeneity in collected data by the cohorts, which may limit the possibilities of harmonisation.

Introduction

Osteoarthritis (OA) is a common disease and a leading cause of disability in adults(1). Over 500 million people are affected by OA worldwide, leading to a global prevalence of around 7%(2). The forecast for OA is alarming; with an ageing population, the prevalence is expected to rise dramatically in the coming decades. The direct healthcare costs of OA in various high-income countries account for 1% - 2.5% of the gross domestic product(3, 4). OA can affect any joint and is most prevalent in the knee and hip, where it also leads to the greatest physical disability(5). Due to a subsequent decrease in physical activity, hip OA also leads to more comorbidities and a higher age-adjusted mortality(6).

Despite the tremendous burden of hip OA, there is no cure available. Therefore, current strategies focus on symptomatic treatment with only a modest effect(7). This may partly result from a lack of knowledge on the aetiology, pathophysiology and risk factors of hip OA. Hip OA is a heterogeneous disease in which the risk factors and aetiology can differ widely from patient to patient. In contrast to knee OA, few large studies have focused on hip OA risk prediction so far. Up until 2022, 31 multivariable prediction models for incident knee OA have been published, while only four exist for hip OA. On top of that, all four have been created with data from Dutch cohort studies only (8). This accentuates the need for more international collaborations in hip OA research.

Additionally, this lack of knowledge regarding person-specific risk factors for hip OA makes efficient and effective preventative and treatment strategies challenging, if not impossible, thus only one-size-fits-all treatment options for hip OA are available to date. Still, some risk factors for hip OA have been identified on a group level, such as age, gender(5), obesity(9), genetics(10), race(11), and hip morphology (such as cam and pincer morphology or acetabular dysplasia)(12, 13). However, each risk factor has only weak or even conflicting associations with hip OA, they have mainly been studied

in single, heterogeneous cohorts, and are typically studied separately from each other. These single studies are underpowered to predict the risk of hip OA on an individual level.

Next to allowing for risk prediction on an individual level, a large dataset also allows for applying techniques from the rapidly emerging field of radiological image processing. These techniques could be used for classification of hip OA or diagnosing hip morphology. This does raise an additional question: how should we make optimal use of these techniques, both in research setting and in clinical practice? Research on the use of artificial intelligence (AI) in hip OA, including the use of machine learning and deep learning, has so far been done in single cohort studies only(14, 15). This may limit the generalisability of the results and the continuation of the research into real-wold applications.

To overcome these challenges, we believe that the prospective cohort study design is ideal to better understand which individuals are at risk of developing hip OA and of progressing to end-stage disease. Harmonising data from multiple cohort studies into an individual participant-level database provides a large sample size, which may allow for individualised or at least subgroup-specific risk estimates. Further, large sample sizes and diverse cohorts from all over the world improve the generalisability of the findings(16). To meet this need, the Worldwide Collaboration on OsteoArthritis prediCtion for the Hip (World COACH) consortium was initiated in 2018. The consortium aims to better understand risk factors for the development or progression of hip osteoarthritis, and to optimise and automate methods for analysing radiological images of the hip. This will be pursued through studying multiple research questions within the consortium.

CONSORTIUM DESCRIPTION

Objectives and research questions

To study the research questions of the World COACH consortium, the consortium currently has five separate work packages. The first work package is **Methodology**, of which the goal is to discover, optimise, automate and validate new methods in OA research, such as an automated pipeline for hip morphological analyses and developing algorithms for the detection of radiographic hip OA (RHOA). This includes the application of AI. **Hip Morphology** is the second work package and it focuses on investigating associations between hip morphology and hip OA. Known morphological risk factors such as acetabular dysplasia, pincer morphology, and cam morphology will be investigated, as well as general hip shape captured with statistical shape modelling. The third work package is **Genetics**, of which the aim is to study associations between genetics, hip morphology, environmental factors, and OA, by applying Genome-Wide Associations Studies (GWAS) among other methods. The fourth work package is **Clinical Measures**, comprising physical examinations, questionnaires, quality of life and blood and urine samples. The aim is to study the associations between these measures and the development of hip OA. Finally, the fifth work package (**Prediction Modelling**) combines data and results from all other work packages to develop a personalised risk prediction model for the development and progression of hip OA, using both conventional and AI-driven methods.

Cohort inclusion and consortium establishment

Prospective cohort studies were considered eligible if they had hip radiography – and optionally computed tomography (CT) and/or magnetic resonance imaging (MRI) – available at two or more points in time, at least four years apart, and if they had a minimum of 200 participants at baseline. These criteria were applied at cohort level, but not participant level, thus having some participants with missing radiographs was not a reason to exclude a cohort.

A systematic literature search was conducted in Embase, Ovid MEDLINE and Cochrane CENTRAL to identify all studies that fulfilled the inclusion criteria. The search was first carried out in 2017 and was repeated in October 2020 and again in March 2023. Titles and abstracts were screened independently by two researchers (MvB and RA), and all described cohorts were further investigated, both by reading the full texts of the screened references and by additional internet searches. A PRISMA flow diagram of the search and inclusion process is presented in **Figure 1**. In summary, we screened a total of 1,970 records by title and abstract, of which we assessed 195 records in detail. We identified 40 study cohorts, 10 of which we considered eligible for the consortium. Investigators from the eligible cohorts were contacted and asked to collaborate. To date, 9 cohorts have been included in the consortium(17-25), and contact has been initiated with the remaining eligible cohort(26). The systematic search will be repeated every 2 years to identify newly eligible cohorts.

After the first search, the initiator of the World COACH consortium (RA) contacted the principal investigators of the 9 identified cohorts to discuss the consortium's aims. A live meeting with principal investigators of 8 cohorts, as well as other individuals interested in participating in the consortium, was held during the OsteoArthritis Research Society International (OARSI) world congress in Liverpool, 2018. During this meeting, the overall aims of the consortium were presented, and an inventory of the support for initiating the consortium was assessed. With unanimous support for the consortium, we decided to establish this initiative. Legal agreements for data sharing were drafted and executed. Since 2018, quarterly meetings have been held with the collaborators to determine the aims and research plans of the consortium.

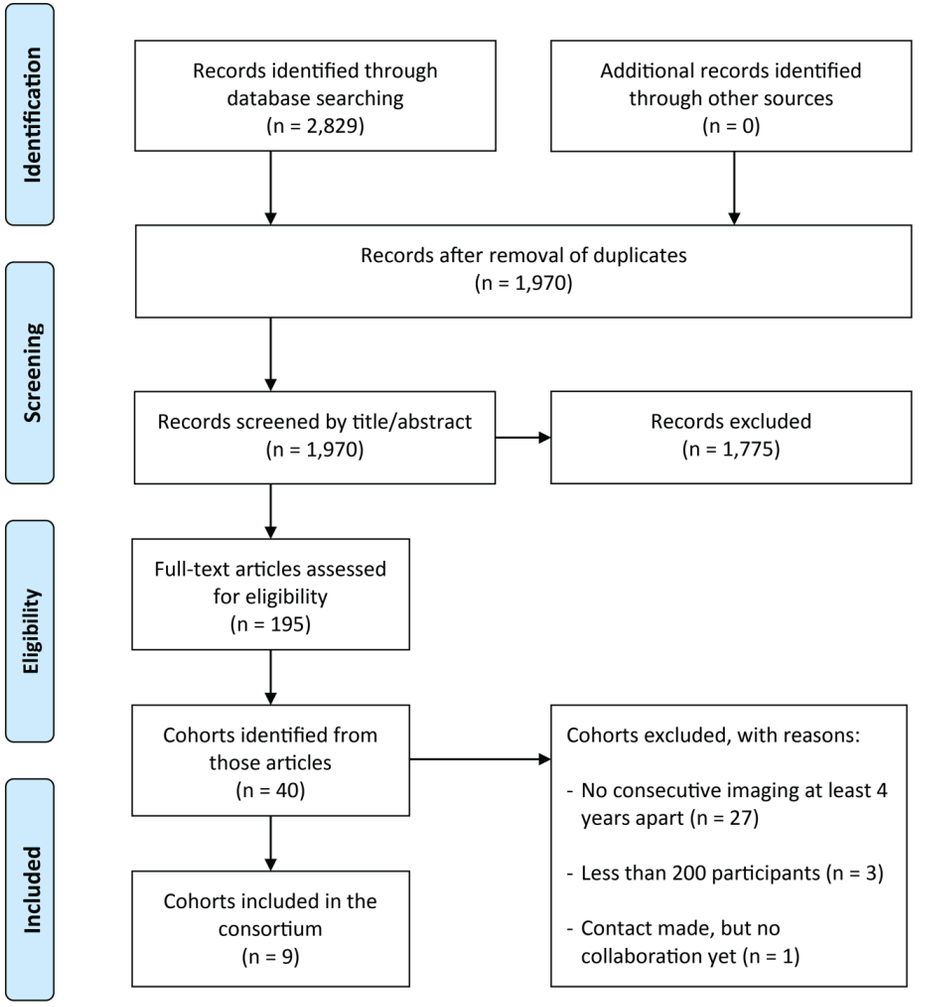

Figure 1: PRISMA flow diagram detailing the literature search, screening, and inclusion process for the World COACH consortium.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; World COACH, Worldwide Collaboration on OsteoArthritis prediCtion for the Hip.

Description of the cohorts

A summary of the included cohorts can be found in **Table 1**. All included studies are prospective cohort studies with a minimum of 5 and a maximum of more than 25 years of follow-up. Some cohorts still have ongoing data collection(17, 20, 24). The earliest data collection in any cohort started in 1986(18), and the most recent baseline data collection started in 2016(20). Most included cohorts are population-based studies. Exceptions are the CHECK cohort, in which participants had hip or knee complaints, MOST and OAI, which both included individuals with or at high risk of knee OA, and FORCe, which included participants with hip and/or groin pain. At least 6 cohorts included non-white individuals, and 6 cohorts studied both men and women. The total World COACH population includes participants from 3 continents. Across cohorts, participants were aged 18 to 80 years at enrolment. The aims and methods of each individual cohort are shortly described below, emphasising those characteristics that correspond with the consortium's inclusion criteria (e.g. radiographic protocols are highlighted, but not CT or MRI).

Table 1: Information and inclusion criteria of the included cohorts.

Cohort	Participants, inclusion criteria & recruitment	Age at enrolment	Races included	Follow-up time	Follow-up status
CHECK	Specific population: First visit to GP with hip/knee pain in the Netherlands Recruited through advertisements, newspaper articles, flyers, GP referral, friends and family	45 – 65 years	W, B, A, O	10 years	Completed
Chingford	General population: asymptomatic women Drawn from the register of a large general practice in Chingford, London, UK	45 – 67 years	NS	19 years	Completed
FORCe	Specific population: Sub-elite soccer and Australian football players with hip and/or groin pain and a physical exam indicative of femoroacetabular inpingement Recruited through advertisements, and from orthopaedic, sports medicine or physical therapy clinics	18 – 50 years	NS	5 years	Ongoing
JoCoOA	General population: Black and White men and women in a rural area Drawn by probability sampling from the population of Johnston County, NC, USA	≥45 years	W, B	25+ years	Completed

MOST	Specific population: Individuals with existing knee OA or those at high risk for it Identified through health insurance companies, voter registration tapes, commercial list brokers, and other sources Recruited by mailings of letters and study brochures to eligible individuals	50 – 79 years	W, B, A, O, NS	7 years	Ongoing
OAI	Specific population: Individuals with existing knee OA or those at high risk for it Recruited through focused mailings, advertisements in local newspapers, presentations at church, community or civic meetings, and a website about knee pain and osteoarthritis	45 – 79 years	W, B, A, O, NS	8 years	Completed
RS	General population: people living in the Ommoord district in Rotterdam, the Netherlands Drawn from the municipal register, after which random clusters of potential participants got invited through a letter sent to their home	≥ 45 years	W, B, A, Mix	25 years	Ongoing
SOF	General population: community-dwelling women Identified through health insurance companies, jury selection lists, voter registration lists, and drivers' licenses and identification cards lists	≥ 65 years	W, B	8 years	Completed

	Recruited by mailings of letters and study brochures to eligible individuals				
TASOAC	General population: community-dwelling men and women Randomly selected from the electoral roll in Southern Tasmania	50 – 80 years	W, NS	10 years	Completed
World COACH	**Mix of individuals from the general population, those with possible early hip or knee OA, those with pre-existent knee OA or at high risk for it, and sub-elite football players with hip/groin pain and possible femoroacetabular impingement**	**18 – 80 years**	**W, B, A, O, Mix**	**5 – 25 years**	**Ongoing**

CHECK = Cohort Hip and Cohort Knee; Chingford = Chingford 1000 women study; FORCe = Femoroacetabular Impingement and Hip Osteoarthritis Cohort Study; JoCoOA = Johnston County Osteoarthritis Project; MOST =Multicenter Osteoarthritis Study; OAI = Osteoarthritis Initiative; RS = The Rotterdam Study; SOF = Study of Osteoporotic Fractures; TASOAC = Tasmanian Older Adult Cohort; World COACH = Worldwide Collaboration on OsteoArthritis prediCtion for the Hip; Race abbreviations: W = white, B = black, A = Asian, O = other, NS = not specified, Mix = admixture

Cohort Hip and Cohort Knee (CHECK) study

The CHECK study was a multi-centre prospective cohort study in the Netherlands that ran from 2002 until 2015 for a total of 10 years follow-up(25). The aim was to study the course, prognosis and underlying mechanisms of early symptomatic OA. The study included 1,002 participants aged 45–65 years, with a first episode of pain in the hip and/or knee. Participants were eligible if they had not yet visited a general practitioner (GP) or were within 6 months of their first visit to the GP for these symptoms, or if they had never visited a GP before for these symptoms, and if there was no other diagnosis that could explain the symptoms at the time of inclusion. Participants were recruited between October 2002 and September 2005, mostly through local newspaper articles and advertisements, and the website of the Dutch Arthritis Society (69% of inclusions). Additionally, eligible individuals were referred by their GP to one of 10 participating general and university hospitals (6%), recruited through a flyer, family member or a friend (12%), and for the remainder it was not recorded. Standardised weight-bearing anteroposterior (AP) hip or pelvic radiographs, using a wedge to get the hips in 15˚ internal rotation, were obtained at baseline and at 2, 5, 8 and 10 years of follow-up. At 10 years follow-up, 87% of the baseline cohort had RHOA scores completed.

The Chingford 1000 women study

The Chingford study was a population-based prospective cohort study that aimed to assess musculoskeletal disease in the female population(19). It ran from 1989 to 2010, having over 20 years of follow-up. The study recruited asymptomatic female participants, aged 45–64 years, from the registry of a large general practice (over 11,000 patients) in Chingford, London, UK. All 1,353 women in that age range were invited to participate, of which 1,003 were included. Standardised supine AP pelvic radiographs, using a small sand bag under the knees to minimise hip rotation, were obtained at year 2, 8 and 20 of follow-up(27). After 8 years, 99% of the participants who had baseline RHOA scores, also had a follow-up score. At 15 years, 77% of the original cohort were still being followed up.

Femoroacetabular impingement and hip OsteoaRthritis Cohort (FORCe) study

The FORCe study is an ongoing prospective cohort study aiming to evaluate changes in hip joint structure in sub-elite soccer and Australian football players with hip and/or groin pain, with a focus on early hip OA features(17). Participants were recruited between August 2015 and October 2018. The study included 239 participants, aged 18-50 years, who were recruited through advertisements at sporting venues and from orthopaedic, sports medicine or physical therapy clinics. Participants were eligible if they had self-reported hip and/or groin pain for >6 months, with a gradual onset, and pain with a score between 3 and 8 on an 11-points numerical rating scale (NRS). They also had to have a positive flexion-adduction-internal-rotation (FADIR) test in at least one hip, indicative of femoroacetabular impingement. At baseline, all participants underwent standardised supine AP pelvic radiographs with the feet in 15˚ internal rotation using a positioning aid, and MRI of the hips. The study is currently inviting participants for a 5-year follow-up visit, that comprises pelvic radiography and MRI according to the same standardised protocols.

Johnston County Osteoarthritis Project (JoCoOA)

The JoCoOA was a population-based cohort study with up to 30 years of follow-up(23, 28). Its aim has been to examine the incidence, prevalence and progression of osteoarthritis in Black and White men and women in a rural county. The study started in 1991 and data collection ended in 2018. Participants, all non-institutionalised black and white men and women, were drawn by probability sampling from the population of Johnston County, North Carolina, USA. The study included 4,337 participants aged ≥45 years. Standardised supine AP pelvic radiographs with the feet in 15˚ internal rotation were obtained at baseline, and then every

5–6 years, except for women under the age of 50 at the time of assessment (per protocol). Follow-up rates over the years have been between 50-60% for each subsequent visit, with the main reason for loss to follow-up being death (around 17% each visit).

Multicenter Osteoarthritis Study (MOST)

MOST is a multicentre prospective cohort study in the USA that started in 2003 and has followed participants for 20 years so far (24). The aim was to study risk factors for the development and progression of knee osteoarthritis and knee pain. Two centres in Birmingham (Alabama) and Iowa City (Iowa) recruited participants with pre-existing knee OA or those at high risk for knee OA from the general population. Eligible individuals were identified through databases from health insurance companies, voter registration tapes, commercial list brokers, and other sources, after which they were sent invitation letters and study brochures. The study included 3,026 individuals aged 50–79 years in its initial phase, with a new cohort of 1,500 individuals included in 2016-2018. A standardised weight-bearing AP full-limb radiograph of the lower extremities (including the pelvis) with the tibial tubercles facing forward and the X-ray beam centred at the knee was obtained at baseline, and again at 5 years of follow-up. Because the pelvis was included in these sequential full-limb radiographs, this cohort study on knee OA was also eligible for inclusion in the consortium. After 5 years, 99% of participants that had baseline RHOA scores, also had follow-up scores completed.

Osteoarthritis Initiative (OAI)

The OAI study was a multicentre prospective cohort study of knee OA in the USA(22, 29). OAI aimed to provide resources to enable a better understanding of prevention and treatment of knee OA. It was initiated in 2002 and the entire cohort finished its 8-year follow-up in 2015, but the follow-up continues for certain subsets of participants. The OAI study has included 4,796 participants with pre-existing knee OA or those at high risk for developing knee OA,

from the general populations of Baltimore (Maryland), Columbus (Ohio), Pittsburgh (Pennsylvania), and Pawtucket (Rhode Island). Participants were aged 45–79 years at enrolment. These participants were contacted through focused mailings, advertisements in local newspapers, presentations at church, community or civic meetings, and a website about knee pain and osteoarthritis. Standardised weight-bearing AP pelvic radiographs using a v-shaped foot-positioning frame to get the feet in 5° of internal rotation were obtained at baseline, 4 years, and 8 years follow-up. The inclusion of pelvic radiography made this knee OA study also eligible for the consortium. RHOA scores were available for 77% at the 4-year follow-up visit, while the 8-year radiographs have yet to be scored for hip OA.

The Rotterdam Study (RS)

The RS is an ongoing prospective population-based cohort study in a district of the city of Rotterdam, the Netherlands(30). It aims to address determinants and occurrence of cardiovascular, neurological, musculoskeletal, ophthalmologic, psychiatric, and endocrine diseases in the elderly. After the pilot in 1989, the study started recruiting in 1990, and it currently has over 25 years of follow-up. The names and addresses of eligible participants were drawn from the municipal register, after which random clusters of potential participants got invited through a letter sent to their home, followed up by a phone call. Up to 2008, the study had included 14,926 participants (72% of 20,744 invitees) aged ≥45 years, divided into three sub-cohorts from different enrolment periods, namely RS-I, RS-II and RS-III. Recruitment of a fourth sub-cohort (RS-IV) started in 2016 and has recently been finished. Data from RS-IV will also be included once they fulfil the inclusion criteria. Standardised weight-bearing AP pelvic radiographs with the feet in 10° internal rotation were obtained at baseline, and then approximately every 4–6 years. Because of the different sub-cohorts with different follow-up schemes, there is no single follow-up rate. The follow-up rate decreases over time, especially after 12 years and over, as can be expected in an ageing population.

Study of Osteoporotic Fractures (SOF)

SOF was a multi-centre prospective population-based cohort study of community-dwelling women aged ≥65 years(18). The primary purpose of SOF was to describe risk factors for osteoporotic fractures. Women were recruited between September 1986 and October 1988 from 4 metropolitan areas in the USA: Baltimore (Maryland), Pittsburgh (Pennsylvania), Minneapolis (Minnesota) and Portland (Oregon). Eligible women were identified in multiple ways: through membership lists from health insurance companies, jury selection lists, voter registration lists, and drivers' licenses and identification cards lists. Women received a letter and brochure inviting them to participate. The original cohort included 9,704 mostly Caucasian women who had not undergone bilateral hip replacement and were able to walk without assistance. The cohort has over 20 years of prospective data about osteoporosis. Standardised supine AP pelvic radiographs with the hips in 15–30˚ internal rotation were obtained at baseline and after 8 years of follow-up. The follow-up rate for RHOA scores was 100%.

Tasmanian Older Adults Cohort (TASOAC) study

The TASOAC study is an ongoing prospective population-based cohort study of 1,099 community-dwelling men and women, aged 50–80 years(21). The study aimed to identify factors associated with the development and progression of OA in multiple joints, including the hip. Eligible participants were randomly selected from the electoral roll in Southern Tasmania, using sex-stratified simple random sampling without replacement (response rate 57%). Participants were excluded if they were institutionalised or if they reported a contraindication for MRI. Enrolment started in 2002 and the cohort had follow-up moments at approximately 2.7 years, 5 years and 10 years. Standardised weight-bearing AP pelvic radiographs with the feet in 10˚ internal rotation were obtained at baseline and after 10 years of follow-up. A subgroup (n=250) had MRI of the right hip in the sagittal plane at 2.7 and 5 years follow-up(31). At inclusion, the TASOAC study did not yet have OA scores available for their 10-year follow-up. These will be added at a later time point.

DATA HARMONISATION

Retrospective harmonisation is an intricate process, considering few original studies have used identical collection methods and procedures. Our harmonisation process will be based both on expert opinion within the consortium, as well as on the Maelstrom Research guidelines for rigorous retrospective data harmonisation(32).

Defining the DataSchema

We started by analysing the present literature on the included studies (e.g. study protocols, published papers) to evaluate sources of study heterogeneity. The next step was to define variables and evaluate the harmonisation potential. All available variables from individual studies within the consortium were identified and systematically entered in a DataSchema(32), categorised in thirteen sections: demographic data, physical examinations and anthropometry, radiographic measurements of OA, questionnaires, family history, procedures, biospecimens, lifestyle and diet, comorbidities, medication, physical and cognitive functioning, quality of life, and genetics. This allowed us to evaluate comparability between studies. Next, all data was catalogued based on their characteristics. All similar variables that indicate the same measurement were grouped together and renamed using a common pooled variable. Finally, the process of data harmonisation was initiated, for which we used and will continue to use one of the established approaches, depending on the data(32):

- **Simple calibration model:** will be used to transform continuous variables into new continuous variables (e.g. transforming height in inches to height in centimetres). The distribution of the values will be compared across cohorts to assess for differences within the measurement.
- **Algorithmic transformation:** will be used to harmonise continuous or categorical variables with combinable ranges or categories (e.g. race or ethnicity, education level).
- **Standardisation model:** will be used to harmonise the same constructs measured with different scales, when there are no bridging items available (e.g. two independent questionnaires on hip symptoms)
- **Latent variable model:** will be used to harmonise variables with different scales that have some bridging items (e.g. OA grade based on the Kellgren-Lawrence (KL), Croft or OARSI atlas classification, which all contain items such as joint space narrowing and osteophytes).

Data storage and processing

After establishing data transfer agreements with each included cohort, all required individual participant data were transferred to a central server. Variables were then prepared to be entered into a relational database using the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) structure(33, 34). The CDM is a 'person-centric' model and is optimised for observational research purposes such as identifying patient populations with certain outcomes (such as hip OA), characterisation of these populations for various parameters (including risk factors), and predicting the occurrence of the outcome in individuals. Variables were clustered in domains using the CDM's standardised vocabularies. Although the variables were mapped to the standardised vocabularies, we also stored the original source values, to ensure that all data entries can be traced when locating or preventing unforeseen errors. The OMOP CDM does not require specific software and can be realised in any relational database software. We currently use an advanced open-source relational database system (PostgreSQL version 15.2, PostgreSQL Global Development Group) which uses the SQL data definition and query language. The stored variables from each cohort and their individual participants include demographics and follow-up visits, along with measurements and procedures performed at each visit. This original data collection setup is used within the relational database model, which contains seven linked tables (**Figure 2**). The person table contains demographics of the included individual, such as biological sex, year of birth, and the originating cohort

identification number, which links to the descriptive cohort table. The visit occurrence table contains the different time points and study sites (where available) at which data was collected from each individual. The measurement and procedure occurrence tables contain harmonised and newly generated World COACH variables for each specific follow-up visit (e.g. harmonised RHOA score based on available KL or modified Croft grades). The harmonisation steps are documented and harmonised values are linked to their source value through the harmonisation key table.

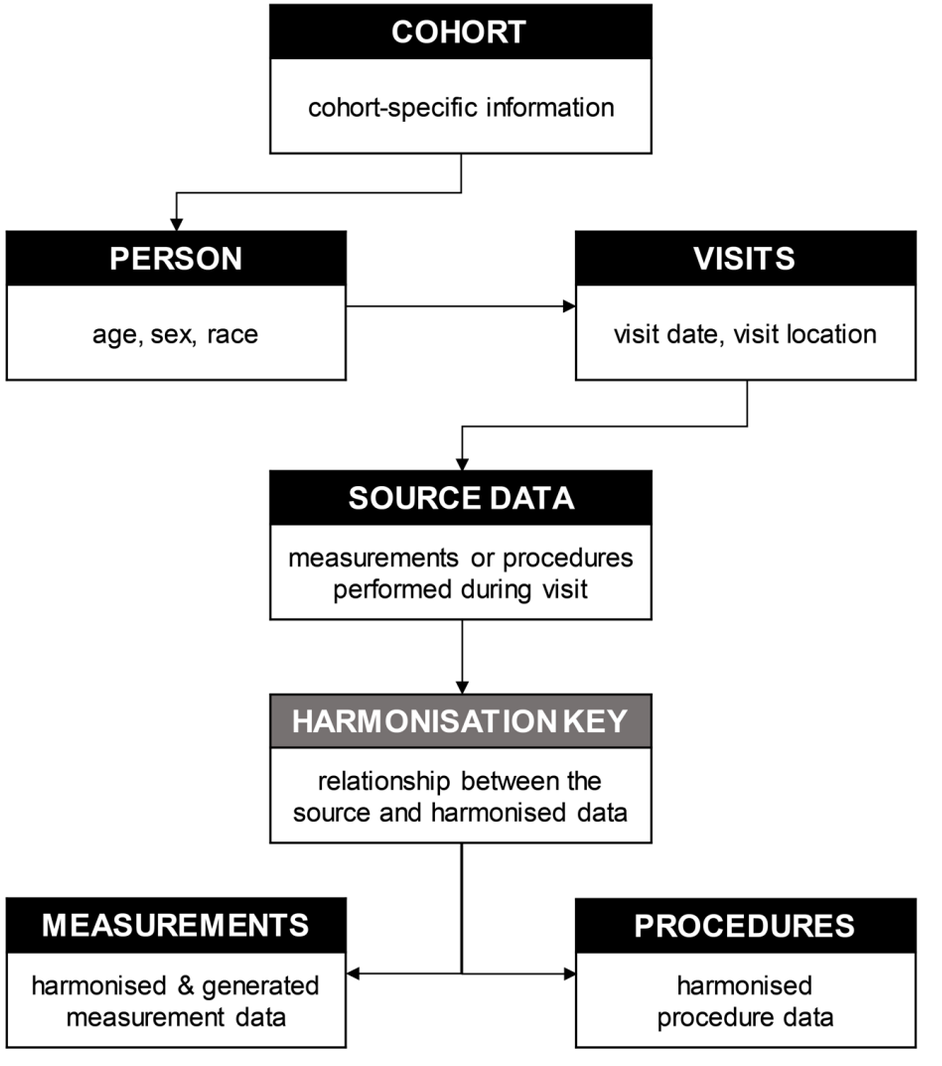

Figure 2: A simplified schema of the relational database used in the World COACH consortium.

World COACH, Worldwide Collaboration on OsteoArthritis prediCtion for the Hip.

Outcome measures

The main outcome is the development of hip OA within the various follow-up periods, although there are several outcomes of interest for secondary analyses. Hip OA could be defined structurally by radiological indices, clinically by pain and/or functional indices, and if possible, by a combination of these two. Radiographs are the only validated and recommended imaging modality to investigate hip OA as a structural outcome(35, 36). Pelvic radiographs have been read for the presence and severity of radiographic OA using either the KL classification(37, 38), the (modified) Croft classification(39-41), or the atlas of individual radiographic features in osteoarthritis (OARSI atlas)(42). The inclusion criterion of having hip radiography available at two or more points in time, at least four years apart, was set to determine the presence or absence of RHOA at both time points. This is necessary to distinguish between incident RHOA (in case of no RHOA at baseline) or progression of RHOA (in case of RHOA at baseline). Different pain scores, such as visual analogue scales (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale, the Hip Disability and Osteoarthritis Outcome Score (HOOS), and other scores will be harmonised into a single pain index if and where possible.

FINDINGS TO DATE

As of submission, the World COACH database contains data on 39,805 individuals. The mean age of all World COACH participants at baseline was 65.4 ± 8.8 years and the study sample consisted of 27,957 (70.2%) women. Mean BMI ranged from 24.6 kg/m2 in the FORCe study to 30.7 kg/m2 in MOST, with an overall mean BMI of 27.5 kg/m2 . The amount of available baseline pelvic and/or hip radiographs is 34,257 (**Table 2**).

The amount of currently available RHOA scores in the included studies is shown in **Supplemental Table S1**, both at baseline and at each of the studies' respective follow-up visits. At baseline, there were almost 60,000 hips with a valid RHOA score available. At both the 4-year and the 5-year mark, 10,000 hips were scored, and around 20,000 hips have a score after 8 years of follow-up. The numbers of hips with a valid OA score logically decreases with longer follow-up times (10, 12, 15, 20 and 25 years of follow-up). The number of RHOA scores available to date may increase in future publications as we plan to score available radiographs that currently miss radiographic OA scores.

Currently available baseline RHOA scores are shown in **Table 3**. Most included cohorts used several methods for RHOA scoring such as KL, (modified Croft), and OARSI individual features. At baseline, 36,065 hips (61.1% of those with available RHOA scores) showed no signs of RHOA (score 0), and 17,778 hips (30.1%) had early or doubtful RHOA (score 1). Definite RHOA or a total hip replacement was present in 5,135 hips at baseline (8.7%). When looking at hips with both baseline and follow-up RHOA scores available, 42,619 hips were free of definite RHOA at baseline. Within this group, 3,207 (8%) of the hips developed incident RHOA at follow-up (**Supplemental Table S2**).

Other available variables of which the harmonisation process is still ongoing (besides those shown in the tables) are: ethnicity/race (all cohorts), socioeconomic status (all cohorts), smoking status (all cohorts), hip pain (CHECK, Chingford, FORCe, JoCoOA, MOST, RS, TASOAC), hip range of motion (CHECK, FORCe, JoCoOA), bone mineral density (Chingford, OAI, SOF, RS, TASOAC), physical activity (CHECK, Chingford, FORCe, JoCoOA, MOST, OAI, RS, TASOAC).

Table 2: Baseline characteristics of the included cohorts.

Cohort	N baseline participants	N participants with data available	N baseline pelvic / hip radiographs	Mean (SD) age, years	Mean (SD) height, cm	Mean (SD) weight, kg	Mean (SD) BMI, kg/m²	% Female
CHECK	1,002	1,002	1,002	55.9 (5.2)	170 (8)	75.5 (13.8)	26.2 (4.0)	79%
Chingford	1,003	1,003	1,003	54.2 (6.0)	162 (6)	66.9 (11.8)	25.6 (4.3)	100%
FORCe	239	239	239	27.2 (5.9)	178 (9)	78.5 (12.8)	24.6 (3.1)	22%
JoCoOA	4,337	4,010	4,004	62.2 (10.0)	166 (10)	81.4 (18.3)	29.5 (6.2)	62%
MOST	3,026	3,026	3,008	62.5 (8.1)	169 (12)	87.9 (18.9)	30.7 (6.0)	60%
OAI	4,796	4,796	4,771	61.2 (9.2)	165 (24)	81.2 (16.4)	28.6 (4.8)	58%
RS	14,926	14,926	11,147	66.0 (10.5)	168 (10)	75.9 (13.9)	26.9 (4.1)	59%
SOF	10,366	9,704	8,291	71.6 (5.2)	159 (6)	67.0 (12.0)	26.4 (4.5)	100%
TASOAC	1,099	1,099	1,099	63.0 (7.5)	167 (9)	77.9 (15.0)	27.9 (4.8)	51%
World COACH	**40,794**	**39,805**	**34,257**	**65.4 (8.8)**	**166 (12)**	**75.7 (14.7)**	**27.5 (4.7)**	**70%**

CHECK = Cohort Hip and Cohort Knee; Chingford = Chingford 1000 women study; FORCe = Femoroacetabular Impingement and Hip Osteoarthritis Cohort Study; JoCoOA = Johnston County Osteoarthritis Project; MOST = Multicenter Osteoarthritis Study; OAI = Osteoarthritis Initiative; RS = The Rotterdam Study; SOF = Study of Osteoporotic Fractures; TASOAC = Tasmanian Older Adult Cohort; World COACH = Worldwide Collaboration on OsteoArthritis prediCtion for the Hip; SD = Standard deviation; BMI = body mass index

STRENGTHS AND LIMITATIONS

The main strength of the World COACH consortium is its rich variety of harmonised, individual participant data from all available prospective cohort studies on hip OA worldwide. Although this offers significant challenges, it has the potential to improve the generalisability of our findings. The large sample size offers unique opportunities to study the relationship between different risk factors and the development and progression of hip OA on an individual level, as well as the identification of high-risk subgroups. It also allows for analysis of interactions between these factors, such as the effect of obesity across different hip shape variations. This will hopefully allow for the creation of the first person-specific and/or subgroup-specific risk estimation of developing hip OA. This personalised model can in turn be used to identify both high-risk individuals and the factors that contribute to this risk. In turn, this provides opportunities for future studies on prevention and individualised OA treatment. Furthermore, the World COACH consortium strives to offer solutions to some of the greatest epidemiological issues in terms of hip OA research by testing, automating, and validating methodological issues related to image analysis, with the potential of providing a benchmark for imaging analysis in hip OA research. Finally, the extensive dataset allows for investigating an array of secondary research questions along with the main aims of the consortium.

Table 3: Indication of radiographic hip osteoarthritis scores at baseline

Cohort	N total hips	Available RHOA scores	0	1	2	3	4	THR	N Missing
CHECK	2,004	KL, (OARSI)	1,225	458	204	13	0	0	104
CHINGFORD	2,006	KL, (OARSI)	1,031	78	152	5	1	1	738
FORCe	465	KL	446	19	0	0	0	0	0
JOCO	8,020	KL, (OARSI)	1,837	4,286	1,493	91	43	0	270
MOST	6,052	KL, (OARSI)	2,194	1,004	354	75	7	0	2,418
OAI	9,592	OA score (based on modified Croft), OARSI	7,121	1,064	543	*NA*	*NA*	*NA*	864
RS1	16,240	KL, (OARSI)	6,406	4,110	426	63	18	216	5,001
RS2	6,024	KL, (OARSI)	3,584	669	105	15	5	62	1,584
RS3	7,878	KL, (OARSI)	5,282	532	58	4	2	42	1,958
SOF	19,414	Modified Croft, (OARSI)	5,725	5,558	262	117	10	0	7,742
TASOAC	1,962	OA score (based on OARSI), (OARSI)	1,214	*NA*	748	*NA*	*NA*	*NA*	0
World COACH	79,657	Mix	36,065	17,778	4,345	383	86	321	20,679

The strength of a relational database is that it is possible to enrich the existing consortium data with data from new cohorts once they meet the inclusion criteria, without the need to restructure the datasets. The flexible structure of relational databases allows for seamless expansion to handle increasing volumes of data and it can easily adapt to frequent updates or deletions.
Limitations of the consortium include the limited geographic selection of cohorts from the Western world (Australia, Europe and the United States). To date, no cohorts have been included from Africa, Asia or South America, which may limit the generalisability of findings. There is some heterogeneity in the populations from

which World COACH participants were originally drawn. Most cohorts have included participants from the general population, albeit with an age restriction (Chingford, JoCo, the Rotterdam Study, SOF and TASOAC), but some cohorts included participants with specific characteristics (CHECK, FORCe, MOST, OAI). This may limit generalisability of the findings and is something we have to account for in future analyses. We will consider the use of different statistical methods that could account for cohort differences and address heterogeneity. Most cohorts included participants aged 45 years or older, while only the FORCe cohort included younger participants. Although people aged over 45 years represent the vast majority of the hip OA population, we will be underpowered to externally validate findings in people younger than 45 years. The World COACH consortium is also limited by the heterogeneity in collection of variables by the cohorts, which was inherently done in slightly different ways. This requires harmonisation of variables, which is mainly based on (potentially subjective) expert-based criteria. On the other hand, pooling of the data creates far greater statistical power than previously possible. Finally, although a subset of the data consists of 3-dimensional imaging data such as CT or MRI, most analyses will be performed using plain AP pelvic radiographs. As stated by the American College of Rheumatologists (ACR, USA)(43), the National Institute for Health and Care Excellence (NICE, UK)(44), and the European Alliance of Associations for Rheumatology (EULAR, EU)(45), imaging is not necessary for the diagnosis of hip osteoarthritis in clinical practice. Still, radiographs probably contain valuable (hidden) predictive information for hip OA, and they are extensively used in daily clinical practice. Radiographs are also the only valid method to diagnose structural hip OA so far and are a simple and inexpensive tool for use in large clinical studies. Findings from this consortium may also guide primary care providers as to which patients should be sent for radiographic imaging, and which patients could start conservative treatment based on a clinical diagnosis of hip OA.

Collaboration

We will provide a harmonised database containing all prospective data on hip OA. We encourage the use of data by third parties, although this is subject to approval by the steering committees of the World COACH consortium and the participating cohorts, as well as to legal boundaries regarding data ownership. To streamline the processing of third-party requests, we have developed a standardised data request form that can be distributed and reviewed uniformly. This will ensure consistency in the way data requests are handled within World COACH.
Our approach to data storage involves the Findable, Accessible, Interoperable and Reusable (FAIR) principles(46). This will be achieved by using unique and persistent identifiers, by adhering to the Observational Health Data Sciences and Informatics (OHDSI) terminology where possible, and by implementing standardised access protocols to make data available upon request. By adhering to the FAIR principles, we aim to promote collaboration and transparency to advance scientific research in the field of hip OA and beyond. The relational database supports data storage that is compatible with other data sources and formats, enabling seamless integration.
Finally, the project will be overseen by two committees: a steering committee and an advisory committee, which have quarterly

meetings regarding the consortium. Both committees consist of a diverse team of experienced researchers and clinicians in the areas of osteoarthritis, rheumatology, epidemiology and image processing. Their combined expertise will provide valuable guidance and ensure the project's success.
More information on the consortium and on data requests can be obtained from the website:

www.worldcoachconsortium.com.

Patient and public involvement

A patient and public committee (PPC) is being formed to ensure that the wider public is represented in World COACH. World COACH aims to ensure that all projects are relevant, meaningful and have impact on the people and patients it aims to serve. This includes not only patients with hip OA, but also families, caregivers and members of the general public. The PPC will be involved in prioritising research questions and in helping to shape the long-term vision of World COACH with particular consideration for the interests of the public and patients with hip OA. Our goal is to engage with a relevant population by promoting our project at various events. Additionally, we have made our research team accessible to the public through the World COACH website, where individuals can contact us directly via email, and through public meetings such as a local "OA cafe". We actively encourage such interactions in our presentations to foster engagement and promote greater understanding of our research to the public, and for the team to better understand what is relevant and important to patients.

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Competing interests statement:

GJ reports personal fees from Novartis outside the submitted work. SBZ reports consulting fees from Pfizer Infirst Healthcare and personal fees for being a Deputy Editor for Osteoarthritis and Cartilage outside the submitted work. CL and TC report a patent for an image processing apparatus and method for fitting a deformable shape model to an image using random forest regression voting. CL reports licensing royalties for this patent from Optasia Medical outside the submitted work. AN is an associate editor for Osteoarthritis and Cartilage and is on the OARSI Board of Directors outside the submitted work. AM is on the Editorial Board for the British Journal of Sports Medicine and the Journal of Science and Medicine in Sport outside the submitted work. HW reports being a minority shareholder of Uplanner BV and Replasia BV outside the submitted work.

Contributors:

RA initiated the study. RA, MvB, NR, MvdB, FB, NA, SBZ, CB, FC, TC, DF, WPG, GJ, SK, NL, CL, JvM, AN, MN, JR, and HW worked on the conceptual design of the study. MvB and RA identified eligible cohorts and contacted cohort investigators for collaboration. MvB, RA, NR, MvdB, HA, KC, JH, SK, JL, JvM, AM, AN, MN, JT and HW collected the existing cohort data. MvB, NR, MvdB, FB, JT, and RA have worked on the database and on the harmonisation process. MvB, NR, MvdB, FB, VA, CB, TC, WPG, CL, JL, JvM, AN, MN, EO, JR, JT, and RA have worked on (preliminary) statistical analyses so far. MvB, NR, MvdB, FB, HA, VA, NA, SBZ, CB, FC, TC, KC, DF, WPG, JH, GJ, SK, NL, CL, L, JvM, AM, AN, MN, EO, JR, JT, HW, and RA critically reviewed and revised the manuscript and contributed to interpretation of the data. All authors read and approved the final version of the manuscript.

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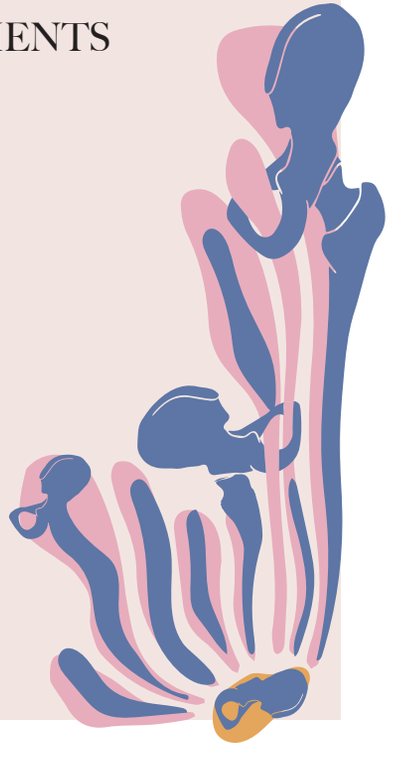
Chapter 3

RELIABILITY AND AGREEMENT OF MANUAL AND AUTOMATED MORPHOLOGICAL RADIOGRAPHIC HIP MEASUREMENTS



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Reliability and Agreement of Manual and Automated Morphological Radiographic Hip Measurements

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Objective

To determine the reliability and agreement of manual and automated morphological measurements, and agreement in morphological diagnoses.

Methods

Thirty pelvic radiographs were randomly selected from the World COACH consortium. Manual and automated measurements of acetabular depth-width ratio (ADR), modified acetabular index (mAI), alpha angle (AA), Wiberg center edge angle (WCEA), lateral center edge angle (LCEA), extrusion index (EI), neck-shaft angle (NSA), and triangular index ratio (TIR) were performed. Bland-Altman plots and intraclass correlation coefficients (ICCs) were used to test reliability. Agreement in diagnosing acetabular dysplasia, pincer and cam morphology by manual and automated measurements was assessed using percentage agreement. Visualizations of all measurements were scored by a radiologist.

Results

The Bland-Altman plots showed no to small mean differences between automated and manual measurements for all measurements except for ADR. Intraobserver ICCs of manual measurements ranged from 0.26 (95%-CI 0 – 0.57) for TIR to 0.95 (95%-CI 0.87 – 0.98) for LCEA. Interobserver ICCs of manual measurements ranged from 0.43 (95%-CI 0.10 – 0.68) for AA to 0.95 (95%-CI 0.86 – 0.98) for LCEA. Intermethod ICCs ranged from 0.46 (95%-CI 0.12 – 0.70) for AA to 0.89 (95%-CI 0.78 – 0.94) for LCEA. Radiographic diagnostic agreement ranged from 47%-100% for the manual observers and 63%-96% for the automated method as assessed by the radiologist.

Conclusion

The automated algorithm performed equally well compared to manual measurement by trained observers, attesting to its reliability and efficiency in rapidly computing morphological measurements. This validated method can aid clinical practice and accelerate hip osteoarthritis research.

Introduction

There is evidence that hip morphology is a leading contributing factor to the development of hip osteoarthritis (OA) (1). Furthermore, studies have shown that specific hip morphologies, such as acetabular dysplasia (undercoverage of the femoral head by the acetabulum), pincer morphology (excessive coverage of the femoral head by the acetabulum) and cam morphology (aspherical femoral head) are associated with radiographic hip OA (1-6).

In order to quantify hip morphology, morphological measurements can be performed on pelvic anteroposterior (AP) radiographs, which are inexpensive and routinely obtained in clinical practice. Manual morphological measurements, however, are time-consuming and can be unreliable when performed by different observers (7). Additionally, a lack of consistency exists in the current definitions for some morphological measurements (8).

Automated morphological measurements could enhance reproducibility while facilitating rapid assessment of multiple measurements per radiograph. Automation, therefore, has the potential to aid clinical practice and allows for the quantification of hip morphology in large cohort studies. There are currently few open-access, publicly available algorithms, and those that are available are sometimes poorly described (9-11).

We aim to study the reliability and agreement of manual and our in-house developed, open-access, automated morphological hip measurements through quantitative and qualitative assessment of both methods. This ensures that results from future studies where this automated method is applied are clinically relevant. The secondary aim was to assess the agreement in making radiographic morphological diagnoses based on manual and automated measurements.

Methods

Participants

The Worldwide Collaboration of OsteoArthritis prediCtion of the Hip (World COACH) consortium is a global collaboration of all prospective cohort studies with available sequential pelvic or hip imaging. The included cohorts are Cohort Hip and Cohort Knee (CHECK), the Multi-center OSteoarthritis sTudy (MOST), the OsteoArthritis Initiative (OAI), the Rotterdam Study-I (RS-I), the Rotterdam Study-II (RS-II), the Rotterdam Study-III (RS-III), the Chingford Study, the Johnston County Project (JoCo), the Study of Osteoporotic Fractures (SOF), and the Tasmanian Older Adults Cohort (TASOAC). The World COACH consortium currently counts 37,732 participants aged 42-100 (mean 65.72 years) at baseline, and 71.33 % are female individuals. The consortium profile and protocol have previously been published in detail (12). From the consortium, 30 baseline radiographs were selected proportionate to the cohort size in the consortium for qualitative and quantitative assessment of the manual and automated morphological measurements. A power analysis was performed assuming type I errors of 0.05, type II errors of 0.20, two replications, a minimally acceptable level of reliability of 0.75 and an expected level of reliability between 0.8 and 0.9, a minimum of 27 inclusions was needed. Therefore, we selected a total of 30 random radiographs for inclusion (13). A flowchart of the radiograph selection is shown in Figure 1. The baseline characteristics were: 18 females (60%), the mean age was 62.5 ± 8.6 years (range 47 – 78), and the mean BMI was 26.5 ± 3.9 kg/m2. All included hips had no definite RHOA as defined by Kellgren and Lawrence classification, modified Croft classification or modified OA score of 0 or 1.

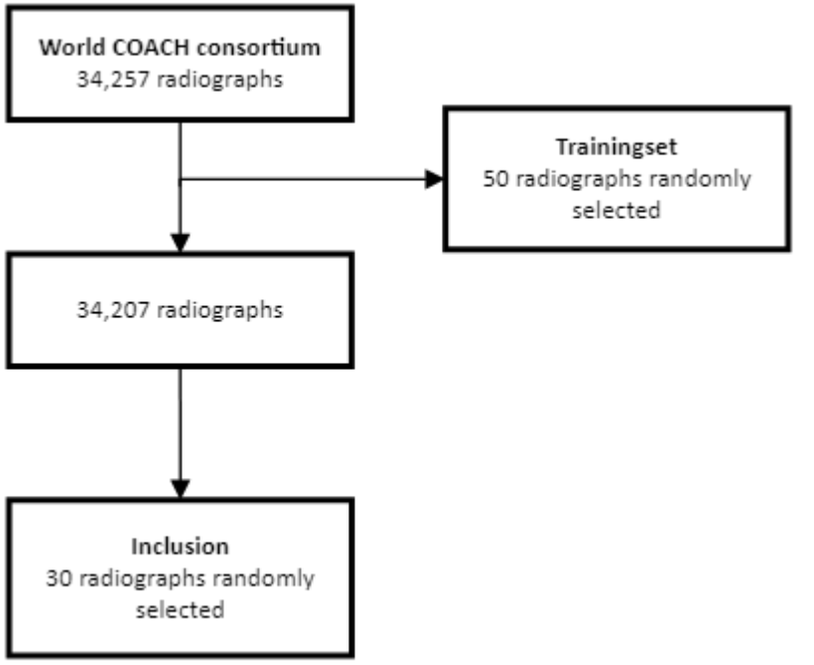


Figure 1. Flowchart of the radiograph selection.

Radiographs

The AP pelvic radiographs were obtained according to a protocol previously decided on by each cohort, and details on cohort-specific radiographic protocols can be found in the World COACH description paper (12). Seven cohorts (CHECK, MOST, OAI, RS-I, RS-II, RS-III, TASOAC) contained weight-bearing AP pelvic radiographs. In contrast, three cohorts (the Chingford Study, JoCo, and SOF) contained supine AP pelvic radiographs.

Hip morphology and morphological measurements

Morphological measures used in this manuscript to determine acetabular dysplasia include the acetabular depth-width ratio (ADR), the modified acetabular index (mAI), the Wiberg center edge angle (WCEA), and the extrusion index (EI) (14-16). The lateral center edge (LCEA) angle determined pincer morphology (17-19). Cam morphology was defined by the alpha angle (AA) and the triangular index ratio (TIR) (4,20,21). The neck-shaft angle (NSA) is used to determine coxa valga and vara (22) All measurements are shown in Figure 2 and are explained in detail elsewhere (23) ; a brief overview, including radiological thresholds for radiographic diagnosis, is provided below.

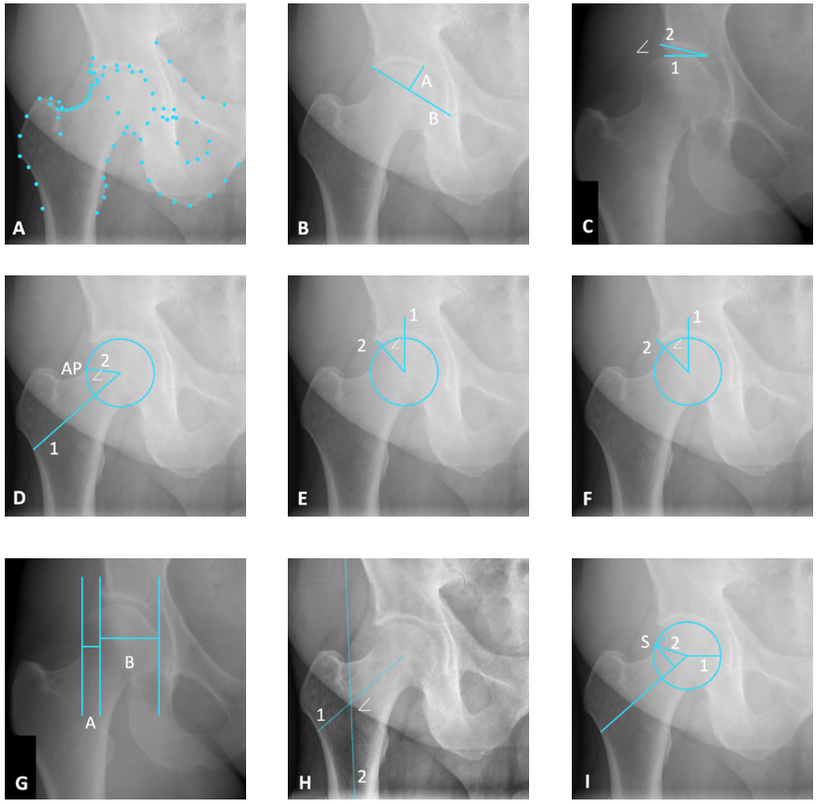


Figure 2: Definition of morphological measurements. A: Overview of the landmarks. **B: Acetabular depth-width ratio (ADR)** – the ratio between the acetabular depth (line A) measured from the most medial point of the acetabular sourcil to line B, and the acetabular width (line B) measured from the most lateral bony edge of the acetabulum to the most caudal point of the teardrop, ADR = A/B*1000. **C: The modified acetabular index (mAI)** – The angle between the horizontal reference line of the pelvis (HRLP) (line 1) and the line between the most lateral bony edge of the acetabulum and the most medial point of the acetabular sourcil (line 2). **D: The alpha angle (AA)** – the angle between the femoral head-neck axis (line 1) and line 2 connecting the femoral head center and alpha point (AP), where the contour of the femoral head-neck junction leaves the best-fitting circle around the femoral head. **E: The Wiberg center edge angle (WCEA)** – The angle between line 1, a vertical line through the femoral head center perpendicular to the HRLP, and line 2 connecting the most lateral point of the acetabular sourcil and the femoral head center. **F: The lateral center edge angle (LCEA)** – The angle between line 1, a vertical line through the femoral head center perpendicular to the HRLP, and line 2 connecting the most lateral bony edge of the acetabulum and the femoral head center. **G: the extrusion index (EI)** –EI = A/(A+B)*100%, where A is the distance between the most lateral point of the femoral head and the most lateral bony edge of the acetabulum, and B is the distance between the most lateral bony point of the acetabulum and the most medial point of the femoral head. **H: The neck-shaft angle** – the angle between the femoral head-neck axis (line 1) and the longitudinal axis of the femoral shaft (line 2). **I: The triangular index ratio (TIR)** – The ratio between the radius of the best-fitting circle around the femoral head (line 1) and the distance between the femoral head center and point S on the femoral head-neck junction at 0.5r along the femoral head-neck axis (line 2).

Acetabular depth-width ratio

The acetabular depth-width ratio (ADR) quantifies the depth of the acetabulum. The acetabular width was defined by a line from the lateral bony edge of the acetabulum to the pelvic teardrop to measure the acetabular opening. Next, the acetabular depth was defined by a line perpendicular to the acetabular width, extending from the most medial point of the sourcil (Figure 2B). The ADR is the depth ratio to the width multiplied by 1000. Acetabular dysplasia is diagnosed by an ADR ≤ 250 (24).

Modified Acetabular Index

The modified acetabular index (mAI) measures the acetabular roof's inclination. The original acetabular index is applied to hips with an open triradiate cartilage; a modified version was created to obtain this measurement in adults. The mAI measures the angle between the line from the medial sourcil to the lateral bony edge of the acetabulum and the horizontal reference line of the pelvis (Figure 2C). Acetabular dysplasia is defined by mAI ≥ 13°, acetabular overcoverage is defined by mAI ≤ 3° (24,25).

Wiberg center edge angle

The degrees of weight-bearing coverage of the femoral head by the acetabulum is measured by the Wiberg center edge angle (WCEA) (24). The WCEA is formed by a vertical line through the center of the femoral head, perpendicular to the horizontal reference line of the pelvis, and a second line from the center of the femoral head to the most lateral weight-bearing part of the sourcil (Figure 2E). Although the threshold has been debated, acetabular dysplasia is generally defined by a WCEA ≤ 25° in prospective studies (1,19,26,27).

Lateral center edge angle

The degrees of bony coverage of the femoral head by the acetabulum is measured by the lateral center edge angle (LCEA) (1,4,28).The LCEA is formed by a vertical line through the center of the femoral head, perpendicular to the horizontal reference line of the pelvis, and a second line from the center of the femoral head to the most lateral bony part of the acetabulum (Figure 2F). Pincer morphology is generally defined by an LCEA ≥ 40° in prospective studies (1,17).

Extrusion index

The extrusion index (EI) quantifies bony femoral head coverage by the acetabulum. The EI is obtained by dividing the horizontal distance of the lateral uncovered femoral head by the total width of the femoral head and multiplying that by 100 to express it as a percentage (Figure 2G). Acetabular dysplasia is defined by an EI ≥ 25% (25).

Alpha angle

The alpha angle (AA) is the most commonly used measurement to define cam morphology and quantify the sphericity of the femoral head-neck junction. The AA is constructed by two lines, one from the femoral head center through the middle of the femoral neck, the femoral head-neck axis, and a second line from the center of the femoral head through the point where the contour of the femoral head-neck junction extends from the best fitting circle around the femoral head (Figure 2D) (29). An AA ≥ 60° threshold is commonly used in literature to define cam morphology (20).

Triangular index ratio

The triangular index ratio (TIR) measures femoral asphericity and defines cam morphology. Compared to the alpha angle, the TIR is measured at a specific point on the femoral head-neck junction. It is the ratio between the radius of the best-fitting circle around the femoral head and the distance between the femoral head center and the femoral head-neck junction at 0.5r along the head-neck axis (Figure 2I). When, for instance, the resultant distance at 0.5r along the axis of the femoral neck at the head-neck junction exceeds the radius of the femoral head, this indicates that, the femoral head is aspherical, possibly indicating the presence of cam morphology (21).

Neck-shaft angle

The neck-shaft angle (NSA) is the angle between the longitudinal axis of the femoral shaft and the femoral head-neck axis (Figure 2H). It has been hypothesized that hips with a more varus neck orientation experience increased subchondral bone stress and, therefore, increased risk of degeneration in individuals with cam morphology (30). Conversely, a relative increase in femoral neck shaft angle combined with acetabular undercoverage also leads to RHOA (30). Coxa valga is generally defined by NSA> 140°, and coxa vara by NSA< 120° (33).

Automated morphological measurements

The bony outline of the proximal femur and acetabulum were annotated automatically on all AP pelvic radiographs with a landmarks (Figure 2A) (BoneFinder® software (www.bone-finder.com;The University of Manchester, UK) (34). The protocol for the 80 landmarks used in this automated hip shape annotation can be found in supplementary material 1. The landmarks were used to automatically derive the hip morphology measurements using in-house-built Python-based software (23)This software is a pipeline to automatically determine radiographic measurements based on radiographic landmarks. The radiographic measurements are performed in accordance to the definitions provided in this manuscript (23). To assess the impact of automated landmark placement on the morphological measurements, a second set of landmarks was created on the same set of radiographs where all landmarks were manually assessed and adjusted, if necessary, after which the morphological measurements were derived again.

Manual morphological measurements

Two researchers (JT and NSR) were trained in performing manual assessment of all previously described morphological measurements. A random set of 50 radiographs from the World COACH consortium was used to train the researchers. Radiographs were selected at random from the consortium such that the number of radiographs chosen from each cohort was proportional to the total number of radiographs available in that cohort. After all measurements were performed on all 50 radiographs by both researchers, measurements were compared under supervision of an experienced orthopedic surgeon (RA), and inconsistencies were discussed. This was repeated 3 times with the same radiographs until both researchers were proficient in performing measurements. Next, the two trained researchers (JT and NSR) performed on the 30 randomly selected radiographs from the World COACH consortium, with the same proportionality as previously mentioned. Information on whether the hips had morphological variations, hip OA, or clinical symptoms was blinded to all researchers. The measurements were repeated on the same radiographs approximately four weeks later. The radiographs were presented to the readers in a different random order each time. Measurements were performed using the DICOM viewer (Synedra View, Version 21.0.0, Synedra Information Technologies). All radiographs were presented in a blinded fashion and random order to the observers. The mean of the individual observers' first and second round of measurements was used for interobserver analyses. The mean of all four manual measurements was used as the reference standard to which the automated method was compared.

Agreement

The agreement within the two rounds of manual measurements for each observer and between observers, and between methods with regard to radiographic diagnoses solely based on morphological measurements of acetabular dysplasia, pincer and cam morphology, and coxa vara and valga was tested.

Qualitative assessment of morphological measurements

A musculoskeletal radiologist (DFH) visually inspected the second round of manual morphological measurements and the automated measurements based on the unadjusted landmarks and qualitatively

rated the measurements as acceptable or unacceptable. "Acceptable" is if the radiologist would measure the same morphological measurements based on the landmark points. "Unacceptable" is if the radiologist would perform the measurements differently. This was done in order to ensure the automated measurements were correct from a clinical perspective of an MSK radiologist. In order to blind the radiologist to which method was used, Printscreens of the manual and automated measurements were visually presented in a way which made it impossible to distinguish between methods and in a random order. Printscreens were used because automated measurements were obtained in Python and manual measurements in Synedra Viewer, which would distinguish between methods. Additionally, this ensured that our reference standard of manual measurements were also approved by the MSK radiologist. An example of the ADR is shown in supplementary material 2. No additional information was disclosed about whether the measurements were performed manually or obtained by the automated method.

Statistical analysis

The agreement between the manual observers and the agreement between the automated and manual methods was visualized using Bland-Altman plots for each morphological measurement. In this study, in order to distunguish between random and systematic error, a mean difference larger than 2.5° was defined as a systematic error for mAI, AA, WCEA, LCEA and NSA. A mean difference larger than 1% of the measurement was defined as a systematic error for ADR, EI and TIR. These thresholds are based on expert agreement. Outliers identified by the Bland-Altman plots were visually inspected to analyze whether consistencies in measurement error occurred.

Intraclass correlation coefficients (ICCs) were used to test reliability and were reported with 95% confidence intervals (CI). Intraobserver reliability was tested with a 2-way mixed-effects model, single rater, absolute agreement ICC. Interobserver reliability between manual observers and between the automated determination of the measurements on the manually adjusted and unadjusted landmarks was tested with a 2-way random-effects model, single rater, absolute agreement ICC. Lastly, intermethod reliability between the mean of all manual and automated measurements on manually adjusted and unadjusted landmarks was tested with a 2-way mixed-effects model, single rater, absolute agreement ICC. ICCs were rated as poor (<0.50), moderate (0.50-0.75), good (0.76-0.90), or excellent (>0.90) (35).

The agreement within and between observers, and between methods with regard to radiographic diagnoses was tested using percentage agreement. Based on the qualitative rating of the measurements by the musculoskeletal radiologist, the percentage of acceptable measurements was determined for each morphological measurement by the two manual observers and the automated method, respectively. The percentage of acceptable measurements was rated as poor (<50%), moderate (50-70%), good (71-90%), or excellent (>90%).

Statistical analyses were performed using R statistical software (v4.1.0; R Core Team 2021). The ggplot2-package in R was used to create Bland-Altman plots (36). The irr-package in R was used to calculate the ICCs and the percentage agreement (37).

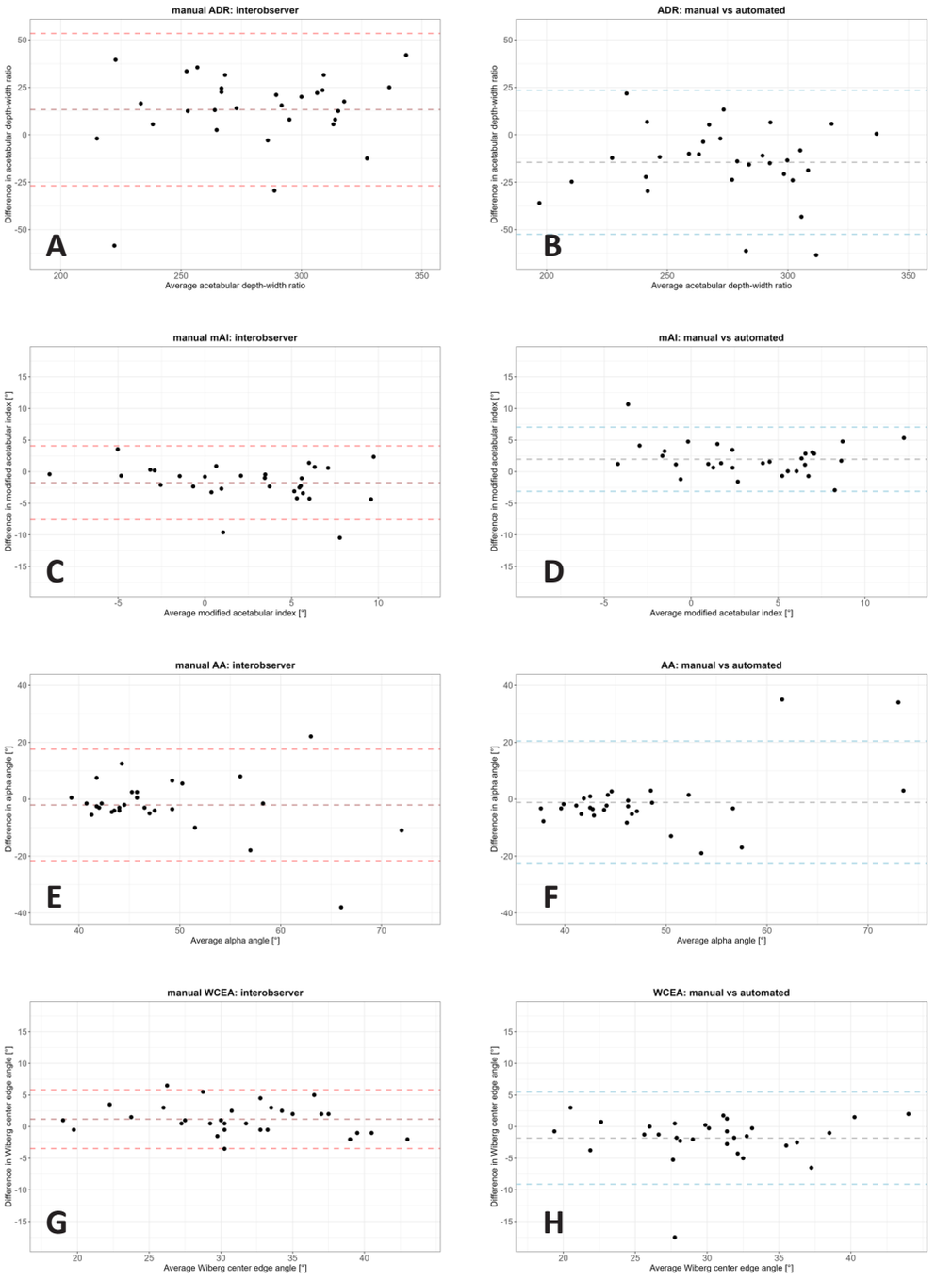
Results

All morphological measurements could automatically be performed in all 30 hips, except for NSA, which could not be performed on two images as too little of the femoral shaft was depicted on the radiograph.

Agreement

The Bland-Altman plots for agreement between the two observers and the agreement between the manual and automated measurements based on unadjusted landmarks are presented in Figure 3, and the corresponding mean difference and limits of agreement are summarized in Table 1. The AA, WCEA, LCEA, mAI, and EI showed no to small mean differences between automated and manual measurements. However, both the interobserver and intermethod agreement of ADR and the interobserver NSA and TIR showed a bias. Observer 1 consistently measured ADR and TIR higher than observer 2, while the opposite was observed for ADR. When comparing the manual and automated ADR, the mean of the manual measurements was consistently higher than the automated measurement.

The intermethod limits of agreement were mainly smaller or similar to the interobserver limits of agreement for all morphological measurements except for WCEA and LCEA.



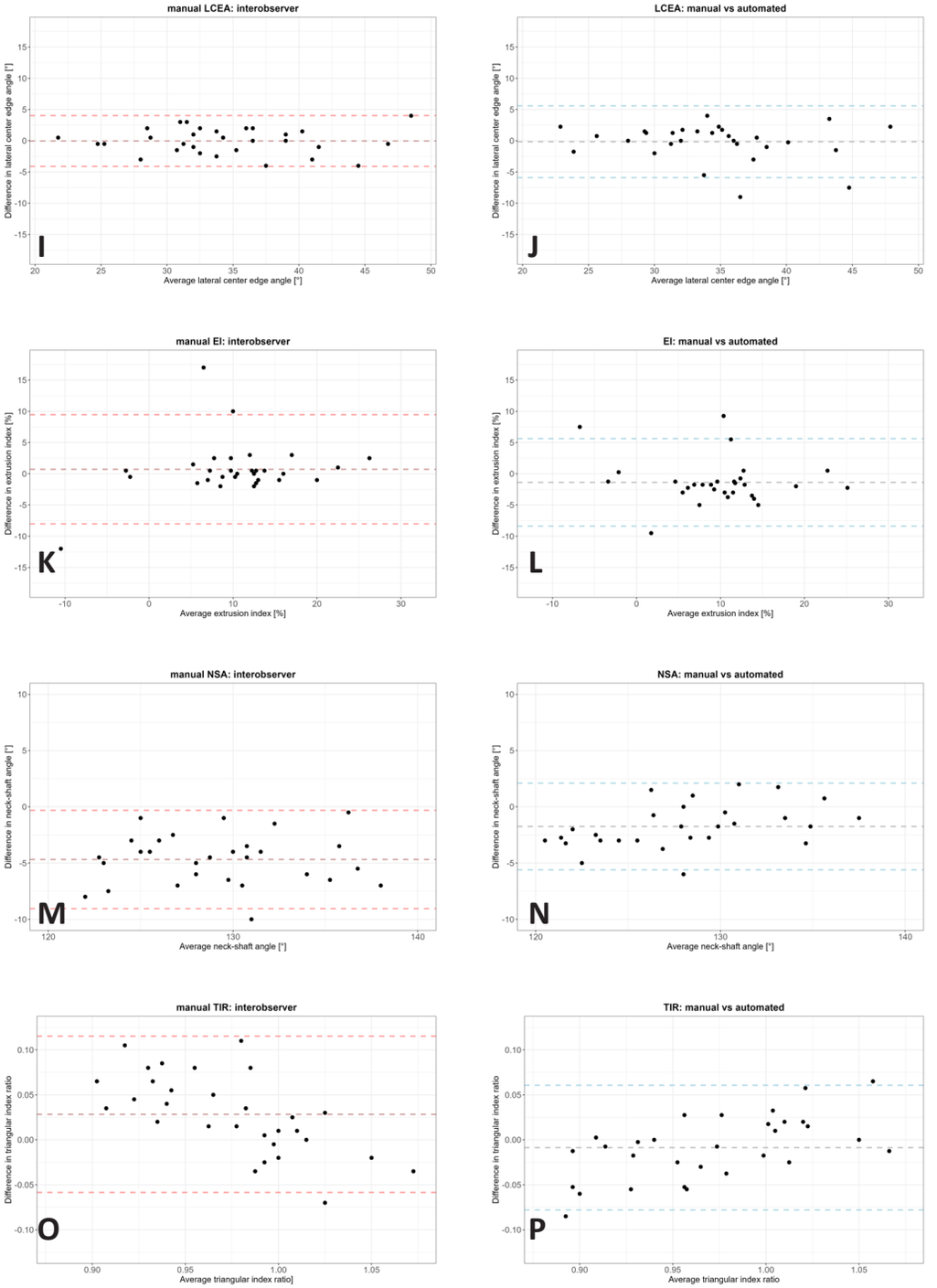


Figure 3: Bland-Altman plots of the morphological measurements. **A:** The acetabular depth-width ratio (ADR) – observer 1 vs observer 2. **B:** ADR – manual vs automated measurements based on unadjusted landmarks. **C:** The modified acetabular index (mAI) – observer 1 vs observer 2. **D:** mAI – manual vs automated measurements based on unadjusted landmarks. **E:** The alpha angle (AA) – observer 1 vs observer 2. **F:** AA – manual vs automated measurements based on unadjusted landmarks. **G:** The Wiberg center edge angle (WCEA) – observer 1 vs observer 2. **H:** WCEA – manual vs automated measurements based on unadjusted landmarks. **I:** The lateral center edge angle (LCEA) – observer 1 vs observer 2. **J:** LCEA – manual vs automated measurements based on unadjusted landmarks. **K:** The extrusion index (EI) – observer 1 vs observer 2. **L:** EI – manual vs automated measurements based on unadjusted landmarks. **M:** The neck-shaft angle (NSA) – observer 1 vs observer 2. **N:** NSA – manual vs automated measurements based on unadjusted landmarks. **O:** The triangular index ratio (TIR) – observer 1 vs observer 2. **P:** TIR – manual vs automated measurements based on unadjusted landmarks.

Table 1 Summary of mean interobserver and intermethod bias and limits of agreement of manual morphological measurements and manual vs automated morphological measurements based on the unadjusted landmarks.

	Manual		**Manual vs Automated**	
Measurement	Interobserver bias (mean)	Interobserver limits of agreement	Intermethod bias (mean)	Intermethod limits of agreement
Acetabular depth-width ratio	13	-27 to 53	-15	-52 to 13
Modified acetabular index [°]	-1.8	-7.6 to 4.1	2.0	-3.1 to 7.0
Alpha angle [°]	-2	-22 to 18	-1	-23 to 20
Wiberg center edge angle [°]	1	-3 to 6	-2	-9 to 5
Lateral center edge angle [°]	0	-4 to 4	0	-6 to 6
Extrusion index [%]	1	-8 to 9	-1	-8 to 5
Neck-shaft angle [°]	-5	-9 to 0	-2*	-6 to 2*
Triangular index ratio	0.028	-0.058 to 0.115	-0.009	-0.078 to 0.061

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Reliability

The intra- and interobserver and intermethod reliability defined by ICCs for all measurements are shown in Table 2. The intermethod reliability between the manual and automated measurements based on both the manually adjusted and unadjusted landmarks was comparable to or better than the interobserver reliability, except for WCEA in which case the manual measurements were more reliable. Additionally, we found that manually adjusted landmarks impacted the ADR and mAI most. This led to lower reliability between manually adjusted compared to unadjusted automated ADR and mAI measurements. These measurements are calculated based on only on few specific landmarks. Conversely, measurements that do not rely on few specific landmarks from the point set like AA, NSA and TIR, showed excellent reliability between the automated measurements performed using the adjusted vs unadjusted landmarks.

Table 2 Intra- and interobserver reliability between manual measurements by observer 1 and observer 2, interobserver reliability between adjusted and unadjusted landmarks and intermethod reliability between manual and automated morphological measurements

	Manual			Automated	Manual vs automated	
	Observer 1	Observer 2	Observer 1 vs observer 2	Adjusted vs unadjusted landmarks	Unadjusted landmarks	Adjusted landmarks
Measurement	Intraobserver ICC (95% CI)	Intraobserver ICC (95% CI)	Interobserver ICC (95% CI)	Interobserver ICC (95% CI)	Intermethod ICC (95% CI)	Intermethod ICC (95% CI)
Acetabular depth-width ratio	0.67 (0.41 – 0.82)	0.89 (0.77 – 0.94)	0.79 (0.49 – 0.91)	0.70 (0.47 – 0.85)	0.78 (0.39 – 0.91)	0.80 (0.60 – 0.90)
Modified Acetabular Index	0.65 (0.36 – 0.82)	0.82 (0.61 – 0.91)	0.77 (0.48 – 0.89)	0.83 (0.67 – 0.91)	0.75 (0.34 – 0.90)	0.82 (0.30 – 0.94)
Alpha Angle	0.36 (0.01 – 0.63)	0.67 (0.42 – 0.83)	0.43 (0.10 – 0.68)	0.98 (0.97 – 0.99)	0.46 (0.12 – 0.70)	0.5 (0.17 – 0.73)
Wiberg center edge angle	0.87 (0.74 – 0.93)	0.94 (0.88 – 0.97)	0.91 (0.78 – 0.96)	0.94 (0.88 – 0.97)	0.77 (0.54 – 0.89)	0.88 (0.70 – 0.95)

Lateral center edge angle	0.89 (0.78 – 0.95)	0.95 (0.87 – 0.98)	0.95 (0.86 – 0.98)	0.91 (0.8 – 0.96)	0.89 (0.78 – 0.94)	0.95 (0.88 – 0.98)
Extrusion Index	0.74 (0.51 – 0.87)	0.80 (0.51 – 0.91)	0.83 (0.67 – 0.91)	0.94 (0.87 – 0.97)	0.86 (0.71 – 0.93)	0.88 (0.65 – 0.95)
Neck Shaft Angle	0.89 (0.78 – 0.94)	0.86 (0.73 – 0.93)	0.58 (0 – 0.87)	0.995 (0.989 – 0.998) *	0.86 (0.44 – 0.95) *	0.88 (0.51 – 0.96) *
Triangular Index Ratio	0.26 (0 – 0.57)	0.88 (0.76 – 0.94)	0.49 (0.12 – 0.73)	0.99 (0.98 – 0.996)	0.78 (0.59 – 0.89)	0.79 (0.61 – 0.89)

Intraclass correlation coefficients (ICC) of intra- and interobserver, and intermethod reliability of the morphological measurements. ICCs are presented with 95% confidence interval (CI). The mean of all four manual measurements was used as the reference standard for the intermethod measurements. Intraobserver reliability was tested with a 2-way mixed-effects model, single rater, absolute agreement ICC. Interobserver reliability between both manual observers, as well as between the automated determination on adjusted and unadjusted landmarks, was tested with a 2-way random-effects model, single rater, absolute agreement ICC. Intermethod reliability was tested with a 2-ways mixed-effects model, single rater, absolute agreement ICC. All ICCs were measured using 30 hips. *ICCs measured using 28 hips. Interpretation: poor (<0.50), moderate (0.50-0.75), good (0.76-0.90), or excellent (>0.90).

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Radiographic diagnostic agreement

Percentage agreement in radiographic diagnosis based on morphological measurements is summarized in Table 3. The intermethod radiographic diagnostic agreement was better than or similar to the interobserver radiographic diagnostic agreement. Except for the radiographic diagnostic agreement of dysplasia based on mAI of the manual versus automated measurements based on the manually adjusted landmarks.

Table 3 Prevalence and diagnostic intraobserver and interobserver agreement between observer 1 and observer 2, interobserver agreement between adjusted and unadjusted automated measurements, and intermethod agreement.

	Manual			Automated	Manual vs automated			
	Observer 1	Observer 2	Observer 1 vs observer 2	Adjusted vs unadjusted landmarks	Reference standard	Unadjusted landmarks	Unadjusted landmarks	Adjusted landmarks
Measurement	Intraobserver percent agreement	Intraobserver percent agreement	Interobserver percent agreement	Interobserver percent agreement	Prevalence	Prevalence	Intermethod percent agreement	Intermethod percent agreement
Acetabular depth-width ratio ≤ 250	90.0	83.3	86.7	93.3	16.7%	26.7%	90.0	90.0
Modified acetabular Index ≥ 13°	96.7	96.7	96.7	90.0	0%	3.3%	96.7	86.7
Alpha Angle ≥ 60°	90.0	90.0	86.7	96.7	10.0%	10.0%	86.7	83.3
Wiberg center edge angle ≤ 25°	100.0	100.0	93.3	90.0	13.3%	23.3%	96.7	93.3
Lateral center edge angle ≥ 40°	90	93.3	93.3	96.7	20.0%	16.7%	96.7	100
Extrusion Index ≥ 25%	96.7	96.7	100	100	0%	0%	100	100
Neck Shaft Angle <120° & >140°	90	96.7	90	96.7	<120°: 0% >140°: 0%	<120°: 3.3% >140°: 0%	96.7	100

The reference standard consists of the mean of all manual measurements. Intermethod percent agreement was determined using the reference standard. n = 30.

Intermethod percent agreement was determined using the mean of all manual measurements as a reference standard.

Qualitative assessment

The results of the qualitative assessment as performed by the MSK radiologist are presented in Table 4. The majority of automated measurements were deemed acceptable by the musculoskeletal radiologist. The percentage of acceptable measurements was moderate to excellent for all measurements, except for the EI measurements by observer 2.

Table 4 The qualitative assessment of the morphological measurements

	Manual		Automated
Measurement	Observer 1	Observer 2	Unadjusted landmarks
Acetabular depth-width ratio	77	80	73
Modified Acetabular Index	70	53	70
Alpha Angle	93	90	77
Wiberg center edge angle	73	80	63
Lateral center edge angle	70	90	80
Extrusion Index	53	47	63
Neck Shaft Angle	93	100	96*
Triangular Index Ratio	63	100	73

Percentage of acceptable measurements. Qualitative assessment was performed on 30 hips.
*Based on only 28 hips. Interpretation: poor (<50%), moderate (50-70%), good (71-90%), or excellent (>90%).

Discussion

This study investigated the agreement and reliability of manual and automated morphological measurements including ADR, mAI, AA, WCEA, LCEA, EI, NSA, and TIR on AP pelvic radiographs. The presented algorithm performed equally well compared to current best practice of manual measurement by trained readers, attesting to its reliability and efficiency in rapidly computing radiological measurements on an AP pelvic radiograph.

The reported intra- and interobserver reliability of morphological measurements varies in literature. The reported ICCs in the present study were compared to the reliability of various morphological measurements in literature. The ICCs reported in literature for the Wiberg and lateral CEA (ICC= 0.7 (95% CI 0.58-0.86) to 0.98 (CI 0.97–0.99) (35,38-41) the NSA (ICC=0.58 (0.31-0.76) to 0.98 (0.95-0.99) (41)), the mAI (or Tönnis angle) (ICC=0.71 (95% CI 0.45-0.83) to 0.92 (95% CI 0.85-0.95) (35,36,38,42)), the EI (ICC= 0.68 (0.57-0.79) to 0.98 (no CI reported) (35,38-40) and the ADR (ICC= 0.62 to 0.84 (40,42,43) are similar to the ICCs found in our study. The reported reliability in literature for the AA (ICC= 0.78 (95% CI 0.61-0.87) to 0.99 (no CI reported) (44-46)) is higher than observed in the present study. No reliability has been reported for the TIR, although one study did report on the triangular index height in 10 individuals (κ = 0.74-0.78) (35)

In terms of reliability and agreement in the current study, the AA showed the worst reliability in the manual method between and within observers, as well as in terms of intermethod reliability. The AA also showed large limits of agreement in the Bland-Altman plots and erratic behavior in the higher AA values (representing cam hips). These results are likely caused by small differences in femoral head circle fit, which may cause large measurement variation due to movement of the alpha point (Fig. 3). Faber et al. showed similar outliers and erratic behavior within the Bland-Altman analysis when comparing manual and automated AA measurements (47).

Similar results, although less extreme, were found for TIR, as expected since this measurement is also largely dependent on the circle fit. However, the erratic behavior observed in the AA Bland-Altman plots in hips with cam morphology is absent in the TIR Bland-Altman plots. This may be caused by the fact that compared to the location of the alpha point, the location of point S (Fig. 2I) is less influenced by the best-fitting circle around the femoral head.

ADR and mAI are two measurements which are calculated based on only two to three landmarks and, therefore highly dependent on correct landmarks recognition and placement. This is reflected in similar reliability and limits of agreement for the intra- and interobserver, and intermethod comparisons. The outliers in these measurements were all caused by different landmarks recognition and placement of both the most lateral bony edge of the acetabulum and the most medial point of the weight-bearing sourcil. Additionally, we found that the mean of the manual measurements by the trained researchers was consistently higher than the automated measurement, implying that we may under diagnose acetabular dysplasia based on manual ADR measurements. Alternatively, it may also be the case that the medial point of the ADR on the sourcil is difficult to identify for the automated measurement. This may also influence the automated ADR.

The correct identification of the most lateral bony edge of the acetabulum also influenced the LCEA and EI measurements. The reliability was good to excellent for all analyses, and the limits of agreement were similar between the interobserver and intermethod analyses.

The WCEA, as determined using the automated method, was slightly worse than the LCEA when comparing the automated method to manual measurements. This is likely due to more difficult assessment of the sourcil, than the more distinct lateral bony acetabular rim. This is also observed in literature with higher reliability for LCEA reported compared to WCEA (34-40). Overall,

this landmark needed more adjustment than the most lateral bony part of the acetabulum during the manual assessment of landmarks placement. This was reflected in the higher reliability of the manual versus automated measurement when the WCEA was performed based on the manually adjusted landmarks.

The majority of manual measurements were deemed acceptable by the musculoskeletal radiologist. This implies that the reported manual measurement ICCs represent clinically acceptable reliability. In terms of automated measurements, we can conclude that the automated ADR, mAI, AA, LCEA, NSA and TIR measurements are valid in a clinical setting and can be applied to establish radiographic morphological hip diagnoses. According to our study, performance of manual as well as automated EI measurements does not reach the threshold for good agreement. We hypothesize that in case of less sphericity of the femoral head, the identification of the most lateral point of the femoral head becomes difficult leading to unreliability in the measurement. As there are other measurements that quantify acetabular coverage, these may be more appropriate in a clinical setting to study hip morphology.

Using automated morphological measurements may advance research and have important clinical implications. First, automated measurements may improve accuracy and consistency in morphological measurements reported in literature. Measurement variability and bias could be reduced dramatically if all measurements are performed uniformly, allowing for comparison of results across studies. This holds especially true in terms of the femoral head circle fit, which is essential in many morphological measurements. The present automated method is published open-access (23), which promotes collaboration in future hip (OA) studies. While the method is still reliant on correct landmark identification, this was also automated to achieve more consistency and speed. This method can be applied in future studies to study whether these measurements are associated with clinical outcomes such

as symptomatic hip OA. The automated method was tested on supine and standing pelvic radiographs from various cohorts in the World COACH consortium, potentially making the results more generalizable to a larger population. Furthermore, the automated method can improve efficiency by accommodating the collection of large amounts of morphological data. This will allow researchers to carry out studies with increased statistical power, advancing our understanding of hip morphology as a risk factor for hip OA.

No gold standard is available for these morphological measurements, so we extensively trained researchers to obtain measurements which could be used as a reference standard. We found order to ensure that these measurements resemble clinical practice, an MSK radiologist visually inspected all manual and automated measurements. Secondly, it should be kept in mind that this study includes a rather small set of 30 hips. A larger dataset would likely show increased variation in hip morphology and therefore provide a more robust assessment of the described methods. Furthermore, as the participants from the World COACH consortium are either from the general population or from a population selected based on having symptoms or risk factors for hip OA, the hips are a representation of the normal population. Therefore, gross bony deformations as seen in hospital populations are underrepresented in the world COACH consortium and results from the automated measures should be validated in this population first. All thresholds used to define radiographic morphological diagnoses are based on literature, but what the "right" threshold is remains unknown (48). With regards to the qualitative assessment, the radiologist evaluated printscreens of measurements, which made it impossible to adjust contrast setting on the images as preferred by the radiologist. As a result of this, the measurements that were impossible to visually inspect were labeled as unacceptable, although in reality they may have been correct. This issue may be avoided in the future by using DICOM images on PACS viewer rather than printscreens of radiographs. Another limitation of this study is

that all morphological measurements were performed on AP pelvic radiographs although it is known that some morphological diagnoses require additional radiographic views to assess hip morphology (19,25,35,40). Furthermore, acetabular morphology is influenced by pelvic orientation, which can vary significantly in terms of tilt (49). This provides a future opportunity to also develop automated measurements in various radiographic views.

In conclusion, automated morphological measurements are a reliable and reproducible method to quantify the ADR, WCEA, LCEA mAI, TIR, EI and NSA. This method makes morphological hip measurements viable in large population studies, as it enables reliable analysis of large amounts of data. Additionally, it may be a useful tool in clinical practice, as it reduces reader bias and the landmarks allow for insightful measurements. Access to fast, externally validated, reliable methods to quantify hip morphology may aid in the quest for modifiable risk factors for hip OA in future studies.

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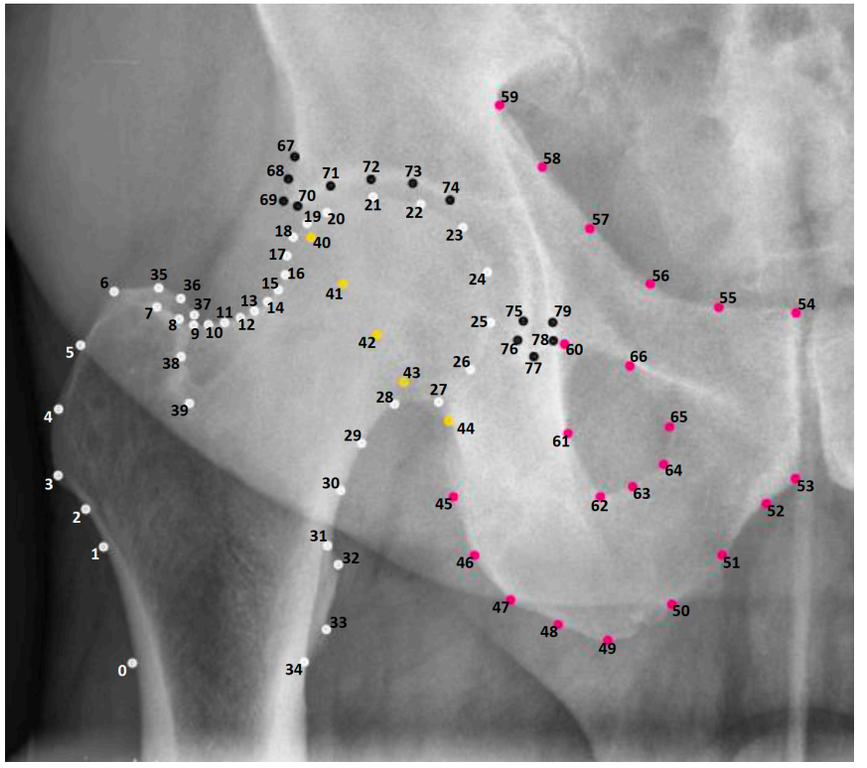
Supplement 1: Protocol for landmark annotation



Proximal femur (white points)

Lesser trochanter

Point **(34)**: Where the lesser trochanter starts bending off the shaft distally. If the lesser trochanter is seen behind the shaft, place this point on the cortex of the shaft at this level. If the lesser trochanter is not visible at all: missing points.

Point (**31**): Where the lesser trochanter joins the shaft proximally. If the lesser trochanter is seen behind the shaft, place this point on the cortex of the shaft at this level. If the lesser trochanter isn't visible at all: missing points.

Point **(32)**+(**33**): Respectively on the lower and upper corners of the lesser trochanter. If there are no clear corners: space them equally between (31) and (34) along the bony contour of the lesser trochanter.

Rest of proximal femur

Point (**0**) + (**1**): Respectively across (34) and (31) on the lateral femoral shaft. If point (1) would be above point (3) based on the position of point (34), place point (1) just under point (3).

Point (**3**): On the lower lateral corner of the greater trochanter.

Point (**2**): Equally spaced between (1) and (3).

Point (**6**): On the upper lateral corner of the (anterior) greater trochanter.

Point (**4**)+(**5**): Equally spaced between (3) and (6).

Point (**7**): On the medial upper corner of the anterior greater trochanter. If not visible, place this point equally spaced between (6) and (8) on the contour of the anterior greater trochanter.

Point (**8**): Where the anterior greater trochanter intersects the femoral.

Point (**18**): On the superolateral side of the femoral head, where the "best fitting circle" around the convexity of the femoral head seems to start. In case of a cam bump, osteophyte, or other irregularity: place (**18**) right after this bump ends, and the circle begins.

Point (**27**): On the inferomedial side of the femoral head, where the convexity of the femoral head seems to end. (The neck bends off after this point).

Point (**20-26**): Place these points equally spaced between (18) and (27) following the femoral head contour, unless there is a clear fovea dip, in which case the adjacent points, usually (24) and (25), are placed just outside of the fovea. Point (23) will be approximately placed halfway across the 'semi'-circle between (18) and (27).

Point (**9-17**): Place these points equally spaced between (8) and (18) following the lateral femoral neck contour. In case of irregularities like a cam bump or osteophyte, follow the outlining contour as closely as possible.

Point (**19**): Place this point equally spaced between (18) and (20) on the femoral head contour.

Point (**28**): At the deepest point of the inferomedial concavity of the femoral neck, so that (27-31) will follow the medial cortex of the femoral neck as closely as possible.

Point (**29**)+(**30**): Place these points equally spaced between (28) and (31), following the medial cortex of the femoral neck.

Greater trochanter, posterior part

** If the posterior greater trochanter is not visible: (35-39) missing points.
Point (**36**): On the upper medial corner of the posterior greater trochanter.
Point (**35**): Between (6) and (36), following the contour. If there is a clear corner, put it there.
Point (**37**): On the medial corner of the posterior greater trochanter, where it starts to drop downwards (caudal). This is independent of the femoral neck, so it can be before or after it dips behind the femoral neck, depending on the rotation of the proximal femur.
Point (**38**): Where the posterior greater trochanter is dropping straight down, right before it bends medially.
Point (**39**): On the end of the sclerotic line right after the medial bend, following the contour of the posterior greater trochanter.

Posterior wall of acetabulum (yellow points)

Point (**40**): On the uppermost visible part of the posterior wall of the acetabulum (usually right below the lateral edge of the weight-bearing surface or lateral osteophyte/pincer).
Point (**44**): Where the posterior wall joins the ischium (where the ischium usually proceeds vertically down).
Point (**41-43**): Place these points equally spaced between (40) and (44), following the contour of the posterior wall of the acetabulum.

Ischium & Pubis (pink points)

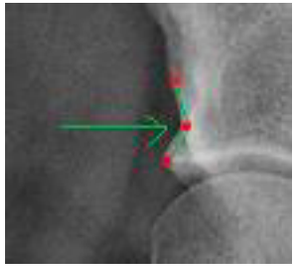
Point (**49**): On the most caudal point of the ischium (ischial tuberosity). If the ischial tuberosity appears as a straight line, put it in the middle of the ischial tuberosity.
Point (**45-48**): Place these points equally spaced between (44) and (49) along the contour of the ischial tuberosity.
Point (52): In the concavity before the symphysis.

Point (**50**)+(**51**): Place these points equally spaced between (49) and (52), following the caudal contour of the inferior pubic ramus.
Point (**53**): On the most caudal point of the pubic symphysis.
Point (**54**): On the most cranial point of the pubic symphysis.
Point (**59**): On the iliopectineal line of the pelvis, at the height where the ilioischial line splits off.
Point (**55-58**): Place these points equally spaced between (54) and (59). Follow the iliopectineal line, ignoring the ischial spine.
Point (**60**): In the superolateral corner of the obturator foramen.
Point (**62**): In the inferolateral corner of the obturator foramen.
Point (**61**): Equally spaced between (60) and (62), following the contour of the lateral rim of the obturator foramen.
Point (**64**): In the inferomedial corner of the obturator foramen.
Point (**63**): Place this point equally spaced between (62) and (64), following the contour/angle of the inferior rim of the obturator foramen.
Point (**65**): In the superomedial corner of the obturator foramen.
Point (**66**): Place this point equally spaced between (65) and (60), following the contour/angle of the superior rim of the obturator foramen.

Acetabulum (black points)

Acetabular roof
** Points (**70-74**) along the weight-bearing zone (sourcil) are placed on the inferior rim of the sclerotic line.
Point (**69**): On the most lateral point of the acetabulum, this can also be a lip/osteophyte.
Point (**70**): On the most lateral point of the weight-bearing zone (sourcil) of the acetabulum (most lateral point of sclerotic line).
Point (**74**): On the most medial point of the **weight-bearing zone** (sourcil) of the acetabulum, this is also the most superolateral point of the acetabular fossa. Usually there is a clear angle in the (sclerotic) line at the transition of weight-bearing zone to fossa. If the acetabular fossa is not visible at all, just place it on the most medial point of the sclerotic line.

Point (**71-73**): Along the underside of the sourcil, place these points equally spaced between (70) and (74), following the contour of the weight-bearing zone
Point (**68**): On the 'dimple' above (70), where the acetabular lip contour has a bend. When the acetabular lip forms a straight line, equally space point (68) and (67) above point (69), with the same distance as points (71-72).



Point (**67**): Above (68), following the most lateral sclerotic line, with a similar distance between points (67-68) as points (71-72).

Pelvic teardrop

Point (**75**): On the superolateral corner of the visible teardrop (on the wall of the acetabular fossa)
Point (**77**): On the most caudal point of the teardrop.
Point (**79**): Across (75) on the other side of the teardrop.
Point (**76**)+(**78**): Across each other between (75-77-79), at the corners of the teardrop, where the more vertical (diverging) lines change direction to more oblique (converging) lines. This can be a very acute angle or more gradual.

Curve model:

Proximal femur curve: 0-1-2-3-4-5-6-7-8-9-10-11-12-13-14-15-16-17-18-19-20-21-22-23-24-25-26-27-28-29-30-31-32-33-34
Greater trochanter curve: 6-35-36-37-38-39
Posterior wall curve: 40-41-42-43-44
Ischium & pubis curve: 44-45-46-47-48-49-50-51-52-53-54-55-56-57-58-59

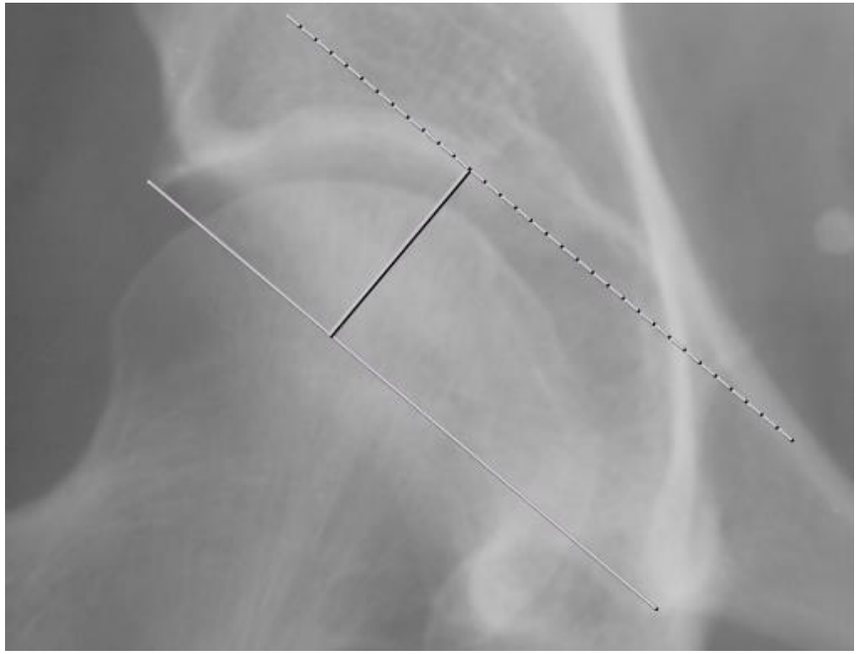
Foramen curve: 60-61-62-63-64-65-66
Acetabular roof curve: 67-68-69-70-71-72-73-74
Pelvic teardrop curve: 75-76-77-78-79

General rules:

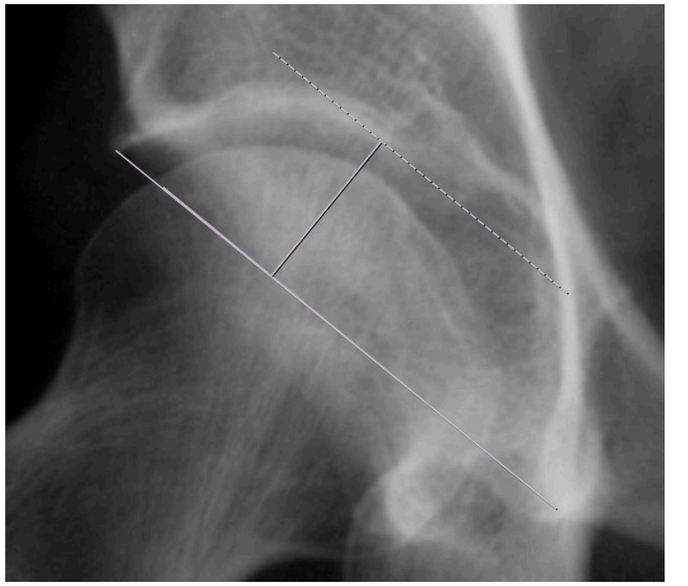
- Osteophytes of the femoral head are included in the model. Follow the outermost contour. We can later correct for these with the radiological assessment data.
- Non-identifiable landmarks: missing points (write in separate log file)
- Only follow clear bony structures, not projecting shadows.
- Every hip is different, so not all anatomical landmarks might be clearly visible in each radiograph. In case of systematic doubt or error: discuss!

Supplement 2: Example of the images for qualitative assessment

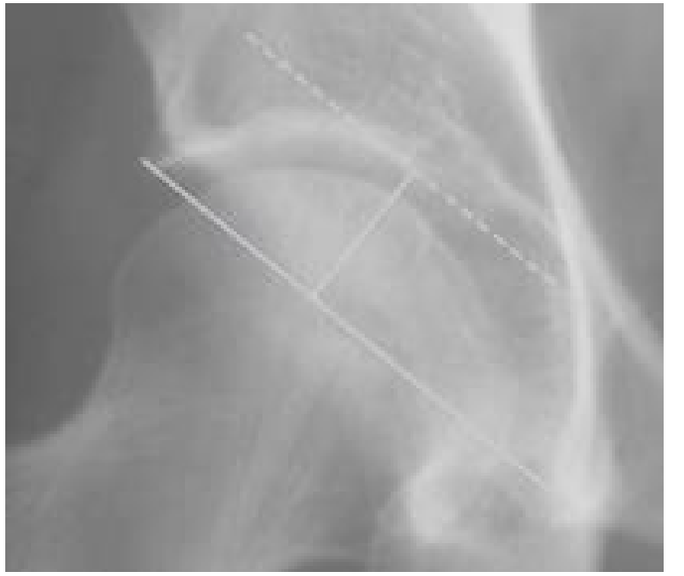
Below are depicted the visualizations of the acetabular depth-width ratio measurements as performed by observer 1, observer 2 and the automated method which were presented to the musculoskeletal radiologist for qualitative assessment of the measurement.



Visualization of the acetabular depth-width ratio measurement as performed by observer 1.



Visualization of the acetabular depth-width ratio measurement as performed by observer 2.



Visualization of the automated acetabular depth-width measurement on unadjusted landmark points.

ADDING FALSE PROFILE RADIOGRAPHS IMPROVES DETECTION OF DEVELOPMENTAL DYSPLASIA OF THE HIP: DATA FROM THE CHECK COHORT

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Adding false profile radiographs improves detection of developmental dysplasia of the hip: data from the CHECK cohort

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Abstract

Objective: To determine the additional value of the false profile (FP) view radiograph in the diagnosis of developmental dysplasia of the hip (DDH), as compared with an anteroposterior (AP) pelvic radiograph only and evaluate the correlation between the Wiberg-lateral centre edge angle(W-LCEA) and Wiberg-anterior centre edge angle(W-ACEA).

Methods: We used baseline data from a nationwide prospective cohort study (CHECK). DDH was quantified on AP pelvic and FP hip radiographs using semi-automatic measurements of the W-LCEA and W-ACEA. A threshold of <20˚ was used to determine DDH for both the W-LCEA and the W-ACEA. The proportion of DDH only present on the FP view determined the FP view additional value. The correlation between the W-LCEA and W-ACEA was determined.

Results: In total 720 participants (1391 hips) were included. DDH was present in 74 hips (5.3%), of which 32 were only present on the FP view radiograph (43.2%). The Pearson correlation coefficient between W-LCEA and W-ACEA of all included hips was 0.547(95%-CI: 0.503 – 0.591) and 0.441(95%-CI: 0.231 – 0.652) in hips with DDH. A mean difference of 9.4° (SD 8.09) was present between the W-LCEA and the W-ACEA in the hips with DDH.

Conclusions: There is a strong additional value of the FP radiograph in the diagnosis of DDH. Over 4 out of 10 (43.2%) individuals DDH will be missed when only using the AP radiograph. In hips with DDH a moderate correlation between W-LCEA and W-ACEA was calculated indicating that joints with normal acetabular coverage on the AP view can still be undercovered on the FP view.

Introduction

Developmental dysplasia of the hip (DDH) is a commonly seen developmental disorder of the acetabulum, leading to undercoverage of the femoral head and increases contact pressure on the joint cartilage. [1] Despite early screening at birth and during infancy, DDH can remain undetected until adulthood, with an estimated prevalence of 0.1% in the United States.[2] DDH has been associated with hip pain and loss of function in young adults, and may lead to an up to six times increased risk of developing hip osteoarthritis (OA) later in life. [3-7]

DDH in adulthood is diagnosed based on a combination of symptoms, signs and imaging findings. [4, 5] Symptoms may include hip and groin pain and instability of the hip joint. Clinical findings include pain provoked with the hip instability tests (hyperextension-external rotation (HEER), Abduction-hyperextension-external rotation (AB-HEER) and the PRONE instability test), abductor fatigue with a positive Trendelenburg sign, and increased range of motion of the hip. [5, 8-11] In order to make the diagnosis of DDH complete, anteroposterior (AP) pelvic radiographs are usually obtained.[12, 13]

The most frequently used parameter to quantify acetabular coverage on an AP pelvic radiograph is the Wiberg Lateral Center Edge Angle (W-LCEA). [12, 14] DDH is generally diagnosed with a W-LCEA < 20°, while an W-LCEA between 20° - 25° is considered borderline DDH. A W-LCEA between 25° and 40° is considered normal. [1, 12-14] The exact threshold values are still under debate and some studies also define a W-LCEA between 18° - 25° as borderline DDH. [15] The original description of Wiberg however states that hips with an LCEA < 20° were considered pathological, hips with an LCEA > 25 ° were normal and hips with an LCEA between 20 and 25 ° were considered uncertain. [14, 16].

However, the W-LCEA only quantifies lateral acetabular coverage and might therefore lead to an underestimation of DDH prevalence, potentially resulting in delayed diagnosis. [7, 17] An additional lateral view, the false-profile (FP) view, can be used to determine the anterior acetabular coverage of the femoral head, which can sbe quantified by the Wiberg Anterior Center Edge Angle (W-ACEA). [8, 12, 13, 18, 19] As DDH is a condition that can be both present laterally and anteriorly an additional value of the FP view radiograph is to be expected.

To the best of our knowledge, the additional value of an FP view as opposed to a sole AP view in the diagnosis of DDH is unclear. Several studies mention the possibility of adding the FP view, but the additional value and correlation with the AP view alone has not yet been established. [8, 12, 20] The primary aim of this study was therefore to evaluate the additional value of an FP view in the diagnosis of DDH as compared with an AP view only. The secondary aim was to investigate the correlation between the W-LCEA and W-ACEA as a surrogate of lateral and anterior dysplasia, respectively.

Methods

Study design and participants

We used data of the Cohort Hip and Cohort Knee (CHECK). CHECK is a Dutch nationwide multi-center prospective cohort study containing 1002 participants, aiming to study the course and risk factors of early hip and knee OA. Participants were eligible for inclusion when they presented with first-onset pain of the hip or knee, were aged between 45-65 years and had not yet consulted their general practitioner for these symptoms, or the first consultation was within six months before entry of the cohort. [21, 22] If symptoms could be explained by other pathology (for hip: previous trauma, fracture, subluxation, rheumatoid arthritis, previous hip surgery, bursitis, tendinitis, previously diagnosed congenital dysplasia, osteochondritis dissecans, septic arthritis or Perthes' disease), or co-

morbidity that did not allow for physical evaluation and/or follow up of at least 10 years was present, if malignancy in the past 5 years was established or participants were unable to understand the Dutch language, they were excluded from the cohort. [21, 22] Participants were included from October 2002 to December 2005. The CHECK study was approved by the medical ethics committees of all participating centers and all participants had signed informed consent forms. For the current study, we used a subset of a previous study [3] which selected participants based on available radiographs of sufficient quality to perform the measurements on baseline and five years follow-up which resulted in 720 participants (1391 hips), see for details Figure 1. For the current study, only the baseline radiographs were used.

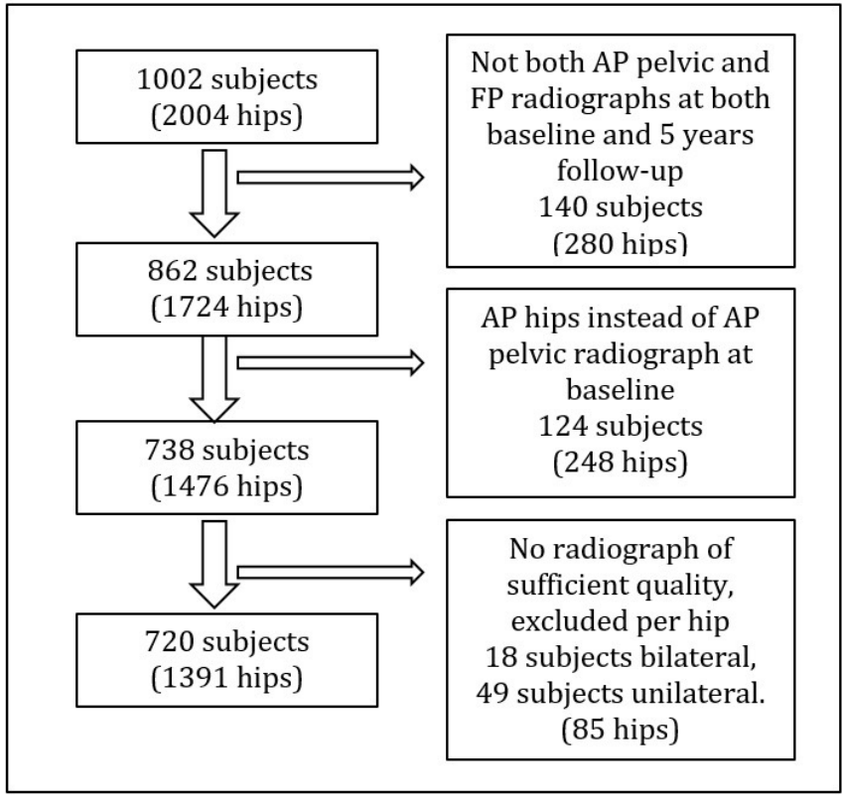

Figure 1. Flowchart of hips from the start of the cohort to the study population

Radiographs

At baseline, both an AP pelvic and FP hip view radiograph were obtained. A standardized protocol was used. [21, 22] (Appendix 1: Radiograph protocol CHECK cohort)

In short, the AP pelvic radiograph was made with the participant in weight-bearing position, placing their feet in 15° internal rotation and centered on the proximal edge of the symphysis pubis. The FP view radiograph was also made in weight-bearing position with a 65° angle between the wall bucky and the participants back (figure 2). [12,20, 21].

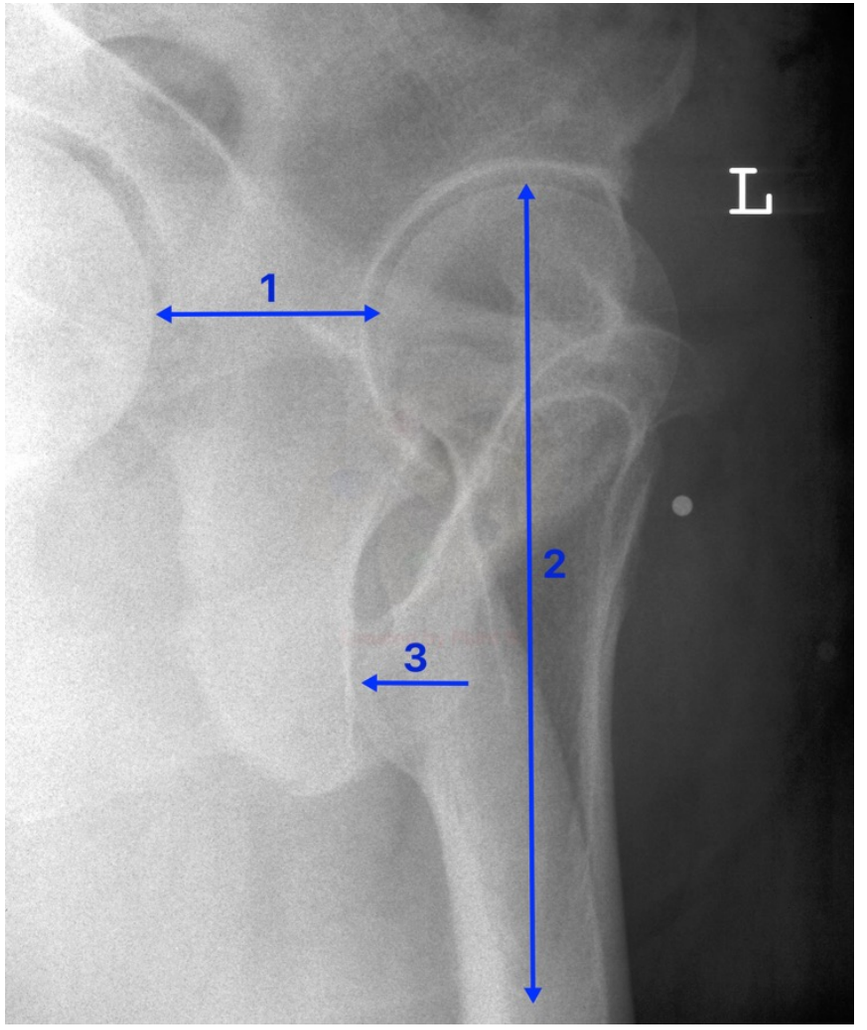

Figure 2. A false profile (FP) radiograph of the hip.
Showing the criteria of a sufficient FP view radiograph: (1) the distance between the two femoral heads should be between two and three thirds of the diameter of the targeted femoral head. (2) The same vertical line could be drawn from the center of the femoral head through the axis of the femoral neck and the femoral shaft. (3) The lesser trochanter minor is visible posteriorly.

Radiographic measurements

The shape of the proximal femur and acetabulum were outlined on both the AP pelvic and FP hip radiographs using statistical shape modeling (SSM) software (ASM tool kit, Manchester University, UK). With this software, a set of landmark points were positioned along the surface of the bone in the image. Each point was placed on the same landmark of the outline. The points were positioned in all radiographs by three researchers. The W-LCEA and W-ACEA were automatically calculated from the point sets of the SSM software using a custom Matlab script (V.7.10). The calculated angle measurement is visible on the radiograph in question and visually checked to confirm correct measurement has taken place.

On the AP pelvic radiograph the W-LCEA is defined as the angle between a vertical line drawn upwards from the most central point of the femoral head and a line from the central point tangential to the lateral margin of the weight-bearing area of the acetabulum (rather than the lateral rim of the acetabulum).[12, 13] The central point of the femoral head was found by drawing a best-fitted circle around the femoral head based on the SSM point sets. The vertical line of the W-LCEA was drawn perpendicular to a horizontal line reference line between both obturator rings. A schematic drawing of measurement of the W-LCEA is visible in figure 3. DDH on the AP view was defined as a W-LCEA <20° and borderline DDH as a W-LCEA between 20-25°. [1, 12, 14, 16]

On the FP view the W-ACEA is the angle between the vertical line starting at the center of the femoral head and a line starting at the center of the femoral head and tangential to the anterior margin of the acetabular roof. [8, 12, 20] A schematic drawing of measurement of the W-ACEA is visible in figure 3. DDH on the FP view was defined as a W-ACEA <20° and borderline DDH as an A-LCEA between 20-25°. [1, 12, 14, 16]

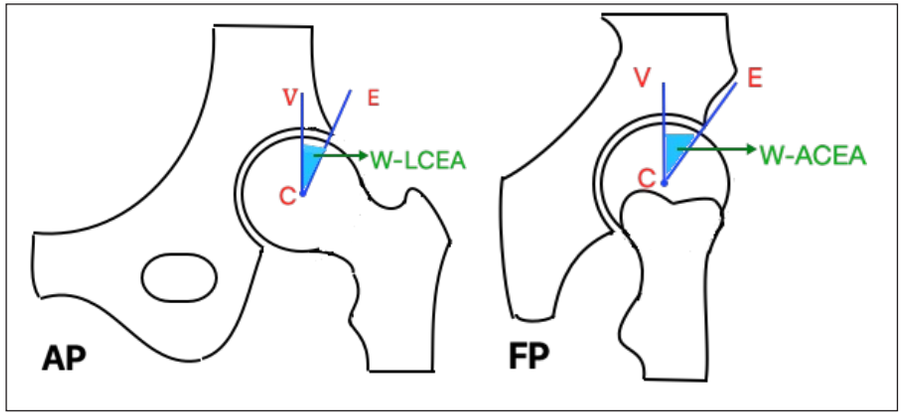

Figure 3. Schematic drawing of the AP (left) and FP (right) view with respectively the Wiberg lateral centre edge angle (W-LCEA) and Wiberg anterior centre edge angle (W-ACEA)
The W-LCEA is the angle between a vertical line(V) from the centre of the femoral head(C) and a second line from C tangential to the lateral margin of the acetabular weight bearing area (E). The W-ACEA is the angle between a vertical line(V) from the center of the femoral head(C) and a line drawn from C anf then tangential to the anterior margin of the acetabular roof (E).

Excellent reliability and reproducibility has been reported previously with inter-observer intraclass correlation coefficients (ICC) 0.97 for the W-LCEA and 0.99 for the W-ACEA, and intraobserver ICCs ranging from 0.91 to 0.96 for the W-LCEA and from 0.97 to 0.99 for the W-ACEA. [3]

Statistical analyses

The additional value of the FP view was assessed by examining the number and proportion of hips that were classified as DDH or borderline DDH on the FP hip view, but not on the AP pelvic view. By using threshold values, it is anticipated that hips can be differently quantified although still quite similar, for example when a W-LCEA of 26° (normal) and a W-ACEA of 24° (borderline dysplasia) is found. In order to determine the linear relationship between the W-LCEA and W-ACEA, the Pearson correlation coefficient (after confirming a Gaussian distribution) was determined in all hips and hips that were classified as DDH, both in all hips with DDH as hips with DDH only visible on the FP view.

Results

Participants

In Table 1, we present baseline characteristics of the included participants. The baseline characteristics (age, gender, height and weight) of the 720 included participants did not differ from those of the 282 excluded participants.

Table 1. Baseline characteristics

	Total n= 720 (1391 hips)	DDH * n=64 (74 hips)	No DDH n= 709(1317 hips)
Age in years: mean (±SD)	56.0 (5.2)	57.4 (4.9)	56.0 (5.2)
Women, No (%)	572 (79.4)	52 (81.3)	563 (79.4)
BMI**,kg/m^2:mean(±SD)	26.1(4.2)	25.2 (3.1)	26.2 (4.2)
Length in cm: mean (±SD)	169.9 (8.2)	170.0 (8.6)	169.9 (8.2)
Weight in kg: mean (±SD)	75.5 (13.3)	72.9 (11.7)	75.3 (13.9)
Left side, No hips(%)	698 (50.2)	27 (36.5)	671 (50.9)
Both hips, No(%)	671 (93.2)	10 (15.6)	608 (85.8)
W-LCEA mean ° (±SD)	32.9 (6.9)	21.9 (6.8)	31.5 (5.7)
W-ACEA, mean ° (±SD)	35.8 (8.8)	21.3 (8.3)	35.5 (8.3)
K&L *** grade 0, No hips (%)	1045 (76.3)	55 (74.3)	990 (76.4)
K&L *** grade 1, No hips(%)	324 (23.7)	19 (25.7)	305 (23.6)

* Dysplasia; W-LCEA and/or W-ACEA were measured <20°
** BMI; body mass index.
***K&L; Kellgren and Lawrence

Additional value of the false profile view

In 74 out of 1391 hips (5.3%) DDH was present. In only 11 of those 74 hips (14.9%) DDH was present on both the AP pelvic and FP hip view. On the AP pelvic view DDH was present in 42 hips (56.8%). However, on the FP view, another 32 (43.2%) hips with DDH were diagnosed. (Table 2) Of the 32 hips with DDH only visible on the FP view, borderline DDH was present in 11 hips on the AP view (W-LCEA 20°-25°) while 21 hips had normal acetabular coverage (W-LCEA>25°) on the AP view. The difference between the W-LCEA and W-ACEA in the hips with DDH established on the FP view ranged from -3.6° to 34.2° with a mean difference of 9.4° (SD 8.09).

Borderline DDH was present in 205 out of 1391 hips (14.7%) on either view. Of those 205 hips with borderline DDH, 21 were already classified as DDH on the other radiographic view (AP or FP), resulting in 184 hips (13.2%) with borderline DDH (W-LCEA and/or W-ACEA between 20° – 25°, and neither below 20°).

Table 2. Distribution of patients with DDH or borderline DDH in groups by means of visibility on either both AP and FP view, only AP or only FP.

Measured on	DDH *	Borderline DDH **
Both AP and FP view, No hips (%)	11 (14.9%)	30 (14.6%)
Only AP, No hips (%)	31 (41.9%)	104 (50.8%)
Only FP, No hips (%)	32 (43.2%)	71 (34.6%)
Total, No hips (%)	74 (100%)	205 (100%)

Thresholds W-LCEA and/or W-ACEA: * dysplasia <20°, **borderline dysplasia 20°-25°,

Correlation between the W-LCEA and W-ACEA

The Pearson correlation coefficient between the W-LCEA and W-ACEA of all included hips was 0.547 (95%-CI: 0.503 – 0.591, p<0.001). The distribution of measurements in all hips is showed in the scatterplot in Figure 4. The Pearson correlation coefficient between the W-LCEA and W-ACEA in hips with DDH only (n=74, W-LCEA and/or W-ACEA < 20°) was 0.441 (95%-CI: 0.231 – 0.652, P<0.001).
In the hips with DDH visible on the FP radiograph (n=32) the Pearson correlation coefficient between the W-LCEA and W-ACEA was 0.017 (95%-CI: -0.389 – 0.356, P =0.928). Distribution of measurement of these hips is showed in the scatterplot in Figure 5.
In the hips where borderline DDH was diagnosed and no DDH was present (n=185, W-LCEA and/or W-ACEA 20-25° + no W-LCEA or W-ACEA < 20°) the Pearson correlation was 0.415 (95%-CI: 0.548– 0.282, p<0.001).

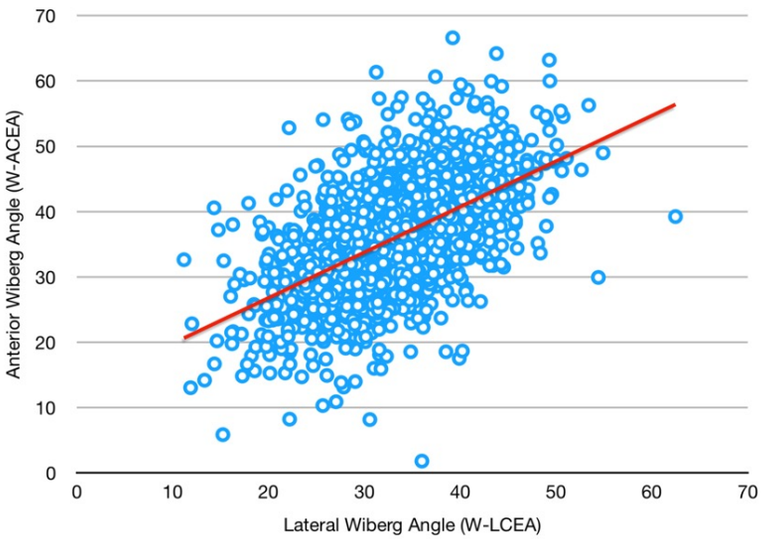

Figure 4. Scatterplot of all hip measurements, showing the W-LCEA (x-axis) and the W-ACEA (Y-axis) and the distribution of measurements. A Pearson correlation coefficient of 0.547 (95%-CI: 0.503 – 0.591, p<0.001) was found.

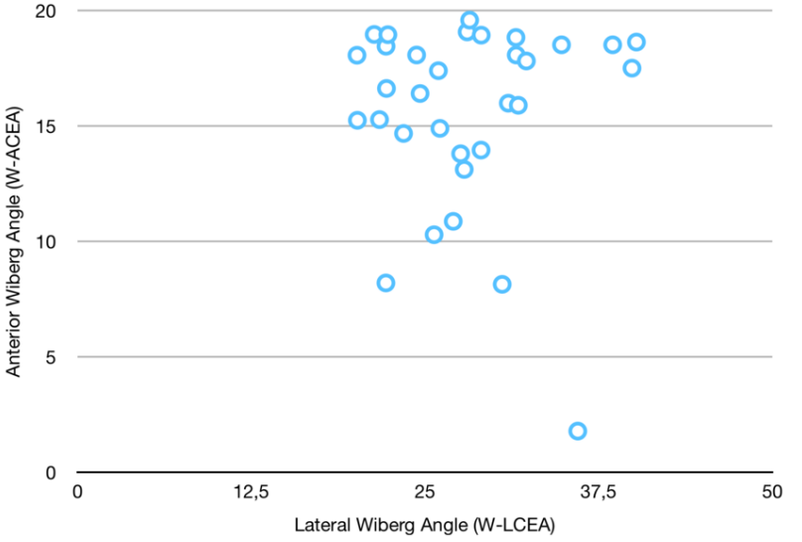

Figure 5. Scatterplot of hips with DDH only found on the FP view. Showing the W-LCEA (x-axis) and the W-ACEA (Y-axis) and the distribution of measurements. A Pearson correlation coefficient of .017 (95%-CI: -0.389 – 0.356, P =0.928).
was found.

Discussion

This study shows an additional value of the FP view in the radiographic identification of DDH. Over 40% of the dysplastic cases in this cohort were only detected on the FP hip view and not on the AP pelvic view. In the DDH diagnosed hips only visible on the FP view we found no linear correlation between the W-LCEA and W-ACEA. This means that the lateral coverage of the acetabulum can be normal while dysplasia can be present anteriorly. Therefore, when only using the W-LCEA, a significant number of hips with DDH will be missed.

Presently there is no consensual diagnostic imaging workup for the hip suspected of DDH. However, the possibility of adding the FP view in the diagnostic workup for DDH has been mentioned in several studies. [8, 12, 20] Schmitz et al. [8] and Beltran et al [12] investigated the ICC of the anterior center-edge angle (ACEA) on the FP view but also pointed out the limitation of the technical adequacy of the images caused by superimposition of osseous structures. Both studies only focused on the ACEA and did not take the W-ACEA into account and therefore could not compare the ACEA on the FP view with the LCEA on the AP view. However, previous studies using 3-dimensional imaging techniques already showed that the acetabulum is a complex acetabular structure in which anterior and lateral coverage or both of importance in DDH. [23-25]

The W-LCEA (also known as the W-CEA[20]) and W-ACEA are often confused with the LCEA and the ACEA. A small important difference is present however. This difference relates to the point where the lateral or anterior part of the acetabulum is defined. When measuring the LCEA, the point through the most lateral bony rim of the acetabulum is used, whereas the W-LCEA is measured through the lateral part of the weight-bearing area of the acetabulum. [14, 20] Therefore, the LCEA expresses the bony acetabular extension laterally while the W-LCEA represents the weight-bearing coverage

(supero)lateral. [20] In case of the ACEA and the W-ACEA the same difference can be mentioned. The difference between the W-LCEA and the LCEA ranges from a mean of 2 to 3 degrees up to much larger differences, mainly in dysplastic hips. [26-28] Using the W-LCEA as a diagnostic tool can therefore been seen as a more sensitive tool in the diagnostic workup for DDH.

Borderline dysplasia is not always described as a LCEA between 20 and 25 degrees. In a previous study of McClincy et al the undetermination surrounding treatment of hips with a LCEA between 18 °and 25 ° is investigated.[15] The original description of Wiberg however states that hips with an LCEA < 20° were considered pathological, hips with an LCEA > 25 ° were normal and hips with an LCEA between 20 and 25 ° were considered uncertain. [14]. This created confusion in the literature concerning the spectrum of dysplasia severity resulting in terms as mild dysplasia and borderline dysplasia using thresholds between 18 and 25°. [15] Our study followed the original thresholds as stated by Wiberg.

The additional value of the FP view has been described in the diagnosis of hip OA. In the study by Lequesne et al. [18], 72% of the hips without joint space narrowing on the AP view, had joint space narrowing on the FP view in the anterosuperior or posteroinferior part of the joint. [18]. Agricola et al. [3] also found a significant association between both lateral and anterior acetabular dysplasia and the development of hip OA. The strength of this association increases when dysplasia is present both anteriorly on the FP view and laterally on the AP view in one hip. [3] Therefore, adding the FP view pelvic radiograph, to assess the presence of dysplasia anteriorly, contributes significantly both to the diagnosis of DDH and the prediction of hip OA development.

DDH is a common disorder of the acetabulum, which can remain undetected despite screening in childhood. Delayed diagnosis or misdiagnosis of DDH can result in early onset of hip OA, and total

hip arthroplasty at a young age. [4, 6, 7] Early detection may allow for non-surgical treatment (such as activity modification, NSAIDs, physical therapy, and intra-articular corticosteroid injections) or surgical treatment and follow-up. Based on the findings of the present study, we recommend to use an additional FP view in the first diagnostic work-up when DDH is suspected, in order to prevent delayed diagnosis.

An extra radiograph besides an AP pelvic view may raise concerns about radiation. The effective dose of a hip or pelvic radiograph is estimated at 0.6 mSv. [30] The background radiation level is about 3 mSv annually. [30,31] Exposure to an individual dose of 50 mSv or a lifetime dose of 100 mSv has not been associated with health risks. [30,31] Therefore, the radiation risk of obtaining one extra radiograph is limited.

The main strength of this study is the large sample size. The CHECK study is the first prospective follow up study that offers a unique population to study hip pain in first presenters. [6] Another strength of this study is the semi-automatic measurements of the W-LCEA and/or W-ACEA. They have been computed automatically from the manually positioned SMM point sets. This has resulted in a high reliability because measurements were not influenced by the subjective assessment of a reader. [3]

An important limitation of this study is that FP view radiographs cannot be adjusted for tilting of the pelvis, whereas on an AP view, a horizontal reference line can be drawn between the obturator rings to adjust for differences in positioning. This could potentially influence the W-ACEA measurement. Also, a two dimensional representation (radiographs) might not always capture the true three dimensional anatomy of the hip. For example, it has previously been shown that the anterior-wall index and posterior-wall index can differ when measures on radiographs as compared with computed tomography scans.[32] A second limitation is the age of the population studied (45 - 65 years), which is older than the typical age that first onset of complaints of DDH become apparent and hence the diagnosis of DDH. Although we cannot be absolutely sure that our results are generalizable to younger populations, we expect similar results in younger, skeletally mature patients. Firstly because DDH remains a condition with involvement of both the anterior and lateral edge of the acetabulum. Secondly, there are no indications that acetabular coverage changes in adulthood after skeletal maturation, except for coxa protrusio. Thirdly, in older populations, (early) OA might cause changes in acetabular coverage, for example by osteophytes. This is why we only included participants without definite OA.

In conclusion, there is a strong additional value of the FP view radiograph in the diagnosis of DDH. Our results show that over 4 out of 10 individuals with DDH could be missed when only performing an AP pelvic radiograph. The correlation between the W-LCEA and W-ACEA is moderate, meaning that hips with completely normal acetabular coverage on the AP view can still have DDH on the FP view. An AP pelvis and a hip FP view should be included in the diagnostic work-up of suspected DDH.

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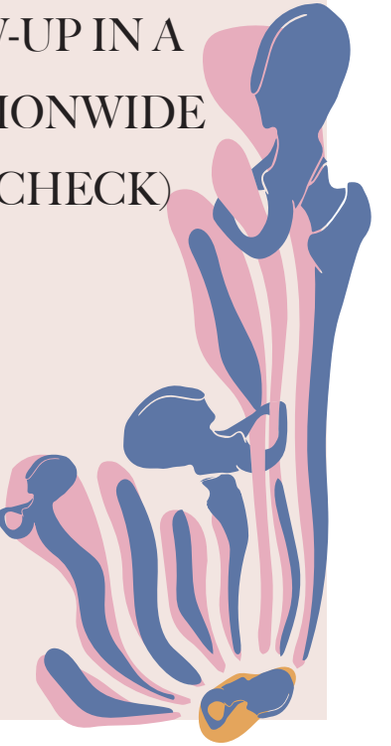
ACETABULAR DYSPLASIA AND THE RISK OF DEVELOPING HIP OSTEOARTHRITIS AT 2,5,8, AND IO YEARS FOLLOW-UP IN A PROSPECTIVE NATIONWIDE COHORT STUDY (CHECK)



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Acetabular dysplasia and the risk of developing hip osteoarthritis at 2,5,8, and 10 years follow-up in a prospective nationwide cohort study (CHECK).

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Abstract

Objective:

To assess the relationship between acetabular dysplasia (AD) and the risk of incident and end-stage radiographic hip osteoarthritis (RHOA) over 2,5,8 and 10 years.

Design:

Individuals (n=1002) aged between 45-65 from the prospective Cohort Hip and Cohort Knee (CHECK) were studied. Anteroposterior pelvic radiographs were obtained at baseline and 2,5,8, and 10-years follow-up. False profile radiographs were obtained at baseline. AD was defined as a lateral center edge angle, an anterior center edge angle, or both <25° at baseline. The risk of developing RHOA was determined at each follow-up moment. Incident RHOA was defined by Kellgren & Lawrence (KL) grade ≥2 or total hip replacement (THR), end-stage RHOA by a KL grade ≥3 or THR. Associations were expressed in odds ratios (OR) using logistic regression with generalized estimating equations.

Results:

AD was associated with the development of incident RHOA at 2 years follow-up (OR 2.46, 95% CI 1.00–6.04), 5 years follow-up (OR 2.28, 95% CI 1.20-4.31), and 8 years follow-up (OR 1.86, 95%CI 1.22-2.83). AD was only associated with end-stage RHOA at 5 years follow-up (OR 3.75, 95% CI 1.02-13.77). No statistically significant associations were observed between AD and RHOA at 10-years follow-up.

Conclusion:

Baseline AD in individuals between 45-65 years is associated with an increased risk of developing RHOA within 2- and 5 years. However, this association seems to weaken after 8 years and disappears after 10 years.

Introduction

Hip osteoarthritis (OA) is a leading cause of poor quality of life (1-8). Therefore, modifiable risk factors must be identified to allow for preventative measures (9,10). Risk factors previously identified include age, genetics, trauma, physical workload, and bone morphology (5,8,11-14). Acetabular dysplasia (AD) was among the bone shapes with the highest risk for the development of radiographic hip osteoarthritis (RHOA) in prospective studies (pooled OR= 2.38 95% CI 1.84 – 3.07) (5).

In hips with AD, the under-coverage of the acetabulum relative to the femoral head leads to concentrated focal stress and increases joint load. Increased joint loading may result in premature cartilage deficiency, increased stress on surrounding soft tissues, and ultimately cause hip OA (6).

There are several measurements to quantify acetabular coverage of the femoral head. The lateral center edge angle (LCEA) is measured on anteroposterior (AP) pelvic radiographs and quantifies lateral coverage of the femoral head by the acetabulum. The anterior center edge angle (ACEA) is measured on false profile (FP) radiographs and quantifies anterior coverage. Although the LCEA is most commonly used to quantify AD, a recent study demonstrated that only considering the LCEA may lead to over 40% of missed AD cases (15). To our knowledge, this is the first study of its kind to also include anterior coverage.

A recent meta-analysis of prospective studies found a pooled odds ratio (OR) of 2.2 in hips with AD to develop RHOA, these results however, were heterogeneous (5). The reported associations in other studies on AD differed, where studies with a long follow-up period seemed to find weaker or no associations between AD and RHOA development (9,16). Available prospective studies had a follow-up period between 6 and 22 years but did not analyze multiple follow-up moments within the study population (9). It is presently unknown how the risk for incident RHOA in the presence of AD varies for different follow-up times.

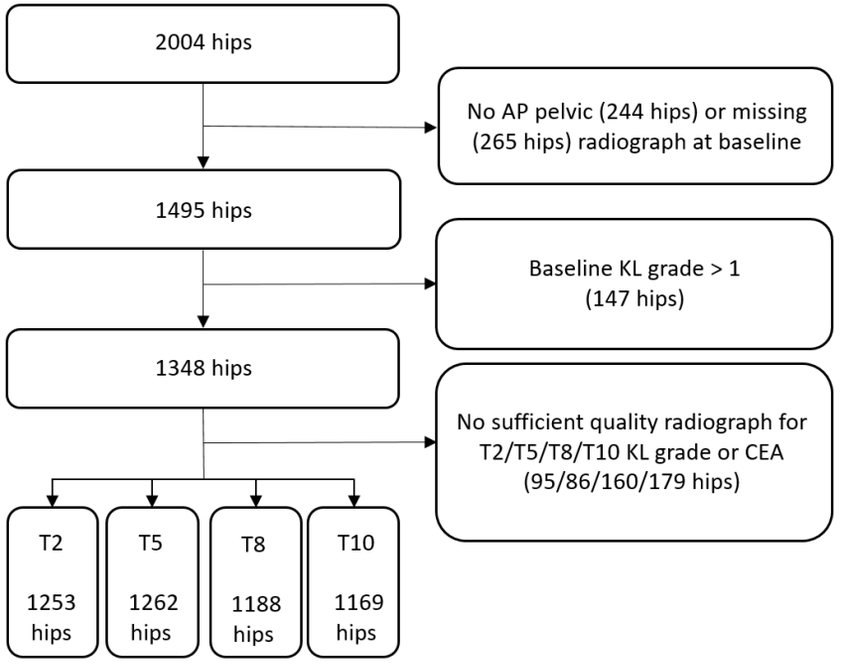
We aim to determine the relationship between anterior and lateral AD at baseline and the risk of developing RHOA at 2,5,8, and 10 years follow-up.

Methods

Study design and participants

All participants were drawn from the Cohort Hip and Cohort Knee (CHECK). CHECK is a prospective, nationwide cohort of 1002 participants (2004 hips) aged 45-65 (mean 55.9 years) at baseline that reported the first onset of pain in either the hip or knee. Participants were recruited by advertisement and referral from general practitioners (GP). Inclusion criteria were; pain or stiffness in the knee or hip and no earlier consultation or a first consultation with a GP within 6 six months for these complaints before entry. Participants were excluded if they had a prior history of hip OA or any other pathological condition that may explain their hip or knee pain. For the hip joints, this includes rheumatic disease, previous hip joint replacement, intra-articular fractures, congenital dysplasia, osteochondritis dissecans, bursitis, septic arthritis, or Perthes' disease (17,18). It should be noted that included individuals in the CHECK cohort represent a mild form of AD, based on abovementioned criteria, as individuals with a known diagnosis of congenital dysplasia were excluded. Participants were also excluded if it was impossible to perform a physical examination due to comorbidity, if they did not understand the Dutch language, or if malignancy had been present in the past 5 years. We included all hips with AP pelvic radiographs at baseline for the current study. The CHECK cohort initially started obtaining AP hip radiographs from the first included participants but switched to AP pelvic radiographs. Hips with AP hip radiographs were excluded as it was not possible to construct the LCEA reliably. Among the selected hips, we included hips without definite signs of RHOA at baseline

(Kellgren & Lawrence (KL) grade = 0 or 1). Finally, we selected all hips with available KL grading at follow-up (fig 1). In case variables such as biological sex, BMI, or age were not recorded at baseline but were recorded at follow-up, these measures were used. Written informed consent was obtained from all participants, and the study was approved by the medical ethical committee of each hospital.



Radiographs

AP pelvic radiographs were obtained at baseline and 2-, 5-, 8- and 10-years follow-up, and FP hip radiographs were obtained at baseline according to a standardized protocol that has previously been published (19). In short, AP radiographs were obtained in a standing position by placing the participant's feet in 15° internal rotation. In addition, it was required for the AP radiograph to depict both obturator rings, femoral necks, and a symmetrical pelvis (20).

The weight-bearing FP radiographs were made by rotating the pelvis 65° relative to the radiographic table. The rotation was ensured by placing a 65° wedge between the patient's back and the table (21,22)

Radiographic measurements

The osseous outline of the proximal femur and acetabulum were drawn on AP and FP radiographs with a point set using statistical shape modeling (SSM) software (ASM tool kit, Manchester University, UK). This point set was used to automize measurements of the lateral center edge angle (LCEA) and the anterior center edge angle (ACEA) using a Matlab script (V.7.10) (23).

The degrees of coverage of the femoral head by the acetabulum are measured by the center edge angle. A best-fitting circle is outlined around the femoral head based on the SSM points to determine the center of the femoral head. From this center, a line is drawn vertically, and a second line is drawn to the most lateral part of the acetabulum—the angle which can be constructed from these two lines in the center edge angle. To construct the LCEA on the AP radiograph, the vertical line is drawn perpendicular to the horizontal reference line connecting both femoral heads (fig. 2). To construct the ACEA on the FP radiograph, the vertical line is drawn perpendicular to the horizontal line of the radiographic film (fig. 3) (24,25). AD was defined as an LCEA, an ACEA, or both of <25° at baseli

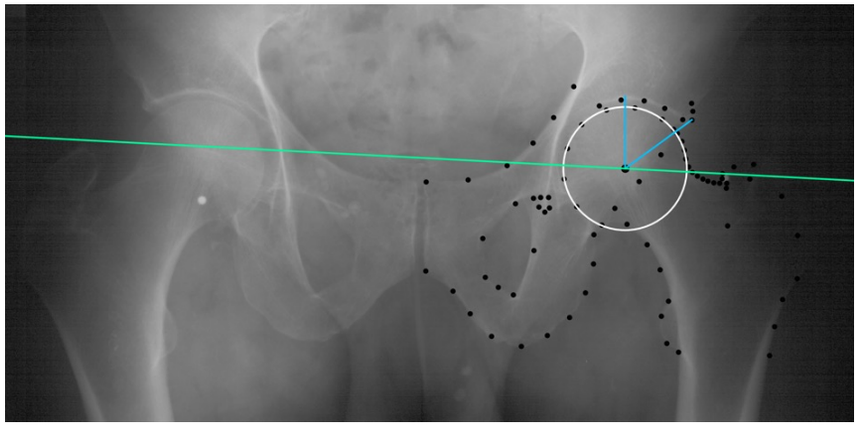


Fig. 2. The lateral center edge angle (LCEA) is measured on an AP pelvic radiograph. The white line represents the best fitted circle around the femoral head. The green line represents the horizontal reference line. The blue lines represent the measurement of lateral acetabular coverage (LCEA). AD was defined as an LCEA<25°.

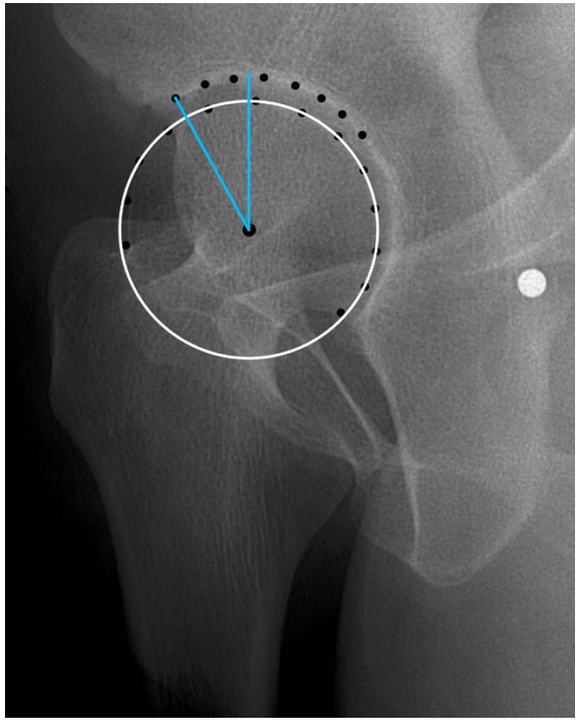


Fig. 3. The anterior center edge angle (ACEA) is measured on an FP radiograph. The white line represents the best fitted circle around the femoral head. The blue lines represent the measurement of anterior acetabular coverage (ACEA). AD was defined as an ACEA<25°.

Reliability measurement of angles

The reliability of measurements in the CHECK cohort has previously been published (26). The intraclass correlation coefficients (ICC) of the three observers who annotated the point set for inter-observer reliability were 0.97 (95% CI 0.94–0.99) for the LCEA and 0.99 (95% CI 0.97–0.99) for the ACEA (26). 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 (26).

Outcome measures

The KL radiographic classification was used to grade all AP radiographs at baseline, 2,5,8, and at 10 years follow-up (27,28). Each participant's radiographs of all time points were scored simultaneously, so that information on all available images was used for the KL scoring at each time point. Disclosing all available images is more reliable than scoring a single radiographic image (28). Incident RHOA was defined by a KL grade ≥2 or total hip replacement (THR) at each follow-up moment. End-stage RHOA was defined by a KL grade ≥3 or THR at each follow-up moment.

Statistical analysis

All statistical analyses were performed in SPSS version 28.0. Univariate baseline differences between included and excluded hips were determined by the independent sample's T-test for age, body mass index (BMI), body height, and body weight and by the chi-square test for biological sex. The association between baseline AD and the development of RHOA was determined using logistic regression with generalized estimating equations (GEE), adjusted for baseline age, biological sex, BMI, and repeated measures within persons, expressed in odds ratios (ORs) with 95% confidence intervals (95% CI).

Results

Participants

1253 hips were included for analysis at 2 years follow-up, 1262 hips at 5 years follow-up, 1188 hips at 8-years follow-up, and 1169 hips at 10-years follow-up. Baseline demographic data is outlined in Table 1. Differences in baseline demographics between included and excluded hips are included.

Table 1. Baseline characteristics and differences between included and excluded hips.

Characteristic	Included hips (n=1265)	Excluded hips (n=739)	p-value
Age in years: mean (±SD)	55.7 (5.2)	56.2 (5.2)	0.06
Women, no. (%)	1038 (82.1)	540 (73.0)	0.01
BMI, kg/m2: mean (±SD)	26.1 (4.1)	26.2 (3.7)	0.76
Length in cm: mean (±SD)	169.5 (8.1)	170.6 (9.0)	0.03
Weight in kg: mean (±SD)	75.1 (13.7)	76.6 (14.1)	0.05
KL grade 0, no (%)	943 (74.5)		
KL grade 1, no (%)	322 (25.5)		
LCEA ≤ 25°, no. (%)	144 (11.4)		
ACEA ≤ 25°, no. (%)	112 (9.0)		
LCEA & ACEA ≤ 25°, no. (%)	47 (3.7)		

RHOA Classification

Incident RHOA had developed in 69 hips (5%) at 2 years, 178 hips (14%) at 5 years, 279 hips (24%) at 8 years, and in 495 hips (42%) at 10 years follow-up. End-stage RHOA had developed in 7 hips (<1%) at 2 years, 22 hips (2%) at 5 years, 43 hips (4%) at 8 years, and in 62 hips (5%) at 10 years follow-up.

Association between acetabular dysplasia and RHOA over time

The associations between acetabular dysplasia and RHOA are summarized in Table 2. At 2 years follow-up, a combination of lateral and anterior AD was associated with incident RHOA. At 5 years follow-up, anterior AD and a combination of lateral and anterior AD was associated with incident RHOA, whereas lateral AD and a combination of lateral and anterior AD was associated with end-stage RHOA. At 8 years follow-up all forms of AD were associated with incident RHOA, whereas none were associated with end-stage RHOA. At 10 years follow-up, no significant associations were found between any forms of AD and neither incident nor end-stage RHOA.

Table 2. Association between acetabular dysplasia at baseline and RHOA at 2-,5-,8- and 10-years follow-up. Significant associations are in **bold.**

				Incident RHOA		End-stage RHOA	
Total hips per follow-up (n=)	**Hips with incident OA (n=)**	**Hips with end-stage OA (n=)**	**Hips with AD per radiographic view (n=)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
T2 (n=1255)	69	7	LCEA<25 (n=136)	1.71 (0.91-3.19)	1.69 (0.90-3.16)	2.84 (0.54-14.79)	3.02 (0.51-18.00)
			ACEA<25 (n=123)	1.83 (0.90-3.74)	1.93 (0.93-4.01)	1.51 (0.18-12.73)	1.39 (0.17-11.72)
			LCEA & ACEA<25 (n=53)	2.29 (0.95-5.53)	**2.46 (1.00-6.04)**	3.82 (0.45-32.50)	5.73 (0.69-47.69)
T5 (n=1262)	178	22	LCEA<25 (n=157)	1.44 (0.92-2.27)	1.44 (0.90-2.30)	**2.65 (1.07-6.56)**	**2.65 (1.06-6.66)**
			ACEA<25 (n=123)	**1.99 (1.26-3.13)**	**2.07 (1.28-3.34)**	1.39 (0.38-5.07)	1.35 (0.37-4.94)
			LCEA & ACEA<25 (n=53)	**2.28 (1.20-4.31)**	**2.43 (1.25-4.76)**	3.55 (0.97-13.00)	**3.75 (1.02-13.77)**
T8 (n=1188)	279	43	LCEA<25 (n=146)	**1.56 (1.09-2.24)**	**1.56 (1.08-2.26)**	1.52 (0.70-3.29)	1.47 (0.66-3.29)
			ACEA<25 (n=115)	**1.86 (1.23-2.80)**	**1.86 (1.22-2.84)**	0.83 (0.26-2.67)	0.78 (0.24-2.55)
			LCEA & ACEA<25 (n=48)	**1.82 (1.01-3.27)**	**1.88 (1.03-3.42)**	1.91 (0.53-6.88)	1.79 (0.46-7.01)
T10 (n=1169)	495	65	LCEA<25 (n=144)	1.22 (0.88-1.69)	1.21 (0.86-1.69)	1.69 (0.91-3.14)	1.65 (0.87-3.13)
			FP ACEA<25 (n=112)	1.12 (0.77-1.64)	1.11 (0.75-1.66)	1.25 (0.54-2.90)	1.17 (0.50-2.75)
			LCEA & ACEA<25 (n=47)	1.26 (0.71-2.25)	1.29 (0.71-2.35)	1.43 (0.45-4.55)	1.34 (0.40-4.45)

Odds ratios ORs were adjusted for age, BMI, and biological sex at baseline. AD= acetabular dysplasia, LCEA= lateral center edge angle, ACEA= anterior center edge angle, RHOA= radiographic hip osteoarthritis, OR= odds ratio.

Discussion

This prospective cohort study of individuals with the first onset of hip and knee pain without evidence of definite RHOA at baseline showed an increased risk of developing RHOA within 2-8 years in individuals with lateral or anterior AD or a combination of both. Associations between AD and RHOA were observed at 2- and 5-years follow-up, but the association seems to weaken at 8 years follow-up and disappears at 10 years follow-up.

To the best of our knowledge, no other studies have investigated the risk in individuals with AD to develop RHOA at multiple follow-up moments in time. Our results may explain why previous studies have reported conflicting results. A systematic review by van Buuren et al. aimed to summarize the association between hip shape as quantified by statistical shape modeling and the incidence or progression of hip OA and found that the shape variants representing AD were consistently associated with THR and incidence or progression of hip OA (29). These findings did not align with conclusions drawn by studies with a single, long-term follow-up moment. One prospective study with one follow-up moment at 22 years concluded that no AD measure correlated with the onset of OA (14). Jacobsen et al. conducted a case-control study with a single follow-up moment at 10 years follow-up and found no difference in joint space narrowing between individuals with AD and individuals without AD (30). Our results support these findings and suggest that AD is a considerable risk factor for the rapid development of RHOA, while this association blurs at later follow-up moments. Given the steady increase in the prevalence of RHOA over 10 years, individuals without AD at baseline seemed to have developed RHOA at a slower rate and for other reasons.

Our study demonstrates that hips with AD and first complaints of hip or knee pain for which the GP was consulted were at risk of rapidly developing RHOA compared to hips without AD. It is relatively easy to detect AD with AP radiographs, which are already more or less standard of care in the orthopedic setting. Nevertheless, FP radiographs should be obtained considering their added value. In our study, 83 (7% of all included hips), 104 (8%), 98 (8%), and 97 (8%) cases of anterior AD at 2,5,8, and 10 years follow-up, respectively, would have been missed if FP radiographs were not obtained. We studied a population where hips with a known diagnosis of congenital dysplasia were excluded. We likely included hips with a mild form of AD, which had a high prevalence in our population (12%). The results from our study allow healthcare professionals to inform at-risk individuals about potentially developing RHOA and may contribute to preventative strategies (31). AD is an essential risk factor to target, as it may be modifiable, has a high prevalence, and is easy to detect (31).

Our study has several strengths. The first strength is the availability of LCEA and ACEA to define AD. As a result, we obtained a more extensive assessment of the acetabular coverage of the femoral head compared to other large cohorts with only AP pelvic radiographs. A second strength of our paper are the five close follow-up moments. Having multiple follow-up moments within 10 years allowed us to monitor the development of RHOA closely over time. Finally, a third strength is the prospective design of the study.

Our study had several limitations that must be acknowledged. First, it is impossible to construct a horizontal reference line for calculating the ACEA on FP radiographs, as only one hip is depicted. However, an FP view is still more sensitive for the diagnosis of dysplasia when compared to the AP view alone (15). Secondly, the individuals in the CHECK cohort represent a mild form of AD, as individuals with a known diagnosis of congenital dysplasia were excluded from the CHECK cohort. Finally, in our present study, it should be noted that 35% of all participants had developed incident RHOA at 10 years follow-up. This is high compared to other studies where the incidence of developing RHOA was 6-11% (32,33). However, this is can be explained by the inclusion criteria of having pain

or stiffness in the hip or knee at baseline, which could represent the first signs of OA. However, the CHECK cohort is a unique population of individuals first seeking medical help for potential complaints of OA. This offers a unique opportunity to diagnose and treat complaints of OA at the onset.

In conclusion, AD was a risk factor for developing incident and end-stage RHOA within 2-8 years. However, as time passed, the risk of developing both incident and end-stage RHOA disappeared in individuals with AD compared to individuals without this bone shape variation. In addition, as acetabular dysplasia can be diagnosed before severe hip damage occurs, this may provide an opportunity to prevent the development of RHOA in the future.

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Author contributions
N.S. Riedstra: conception and design, analysis and interpretation of the data, drafting of the article, critical revision, final approval, statistical expertise, assembly of data

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J. Herfkens: critical revision, interpretation of data

D. Eygendaal: critical revision, interpretation of data

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J. Runhaar: critical revision, statistical analysis, interpretation of the data

M.M.A. van Buuren: critical revision, interpretation of data

R. Agricola: conception, analysis, and interpretation of the data, final approval, drafting of the article, statistical expertise

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Conflict of interest
No conflict of interest to disclose.

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PINCER MORPHOLOGY IS NOT ASSOCIATED WITH HIP OSTEOARTHRITIS UNLESS HIP PAIN IS PRESENT; FOLLOW-UP DATA FROM A PROSPECTIVE COHORT STUDY (CHECK)

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Pincer morphology is not associated with hip osteoarthritis unless hip pain is present; follow-up data from a prospective cohort study (CHECK).

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Abstract

Objective:

To assess the relationship between pincer morphology and radiographic hip osteoarthritis (RHOA) over 2-,5-,8- and 10-years follow-up, and to study the interaction between pincer morphology and pain in predicting incident RHOA.

Methods:

Individuals from the prospective CHECK cohort were drawn. Anteroposterior pelvic and false profile radiographs were obtained. Hips free of definite RHOA (Kellgren and Lawrence (KL) 0 or 1) at baseline were included. Pincer morphology: lateral or anterior center edge angle, or both ≥40° at baseline. Incident RHOA: KL ≥2 or total hip replacement at follow-up. Multivariable logistic regression with generalized estimating equations estimated the associations at follow-up. Associations were expressed as unadjusted (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (95% CI). An interaction term was added to investigate whether pincer morphology had a different effect on symptomatic hips.

Results:

Incident RHOA developed in 69 hips (5%) at 2 years, 178 hips (14%) at 5 years, 279 hips (24%) at 8 years, and in 495 hips (42%) at 10 years follow-up. No significant associations were found between pincer morphology and incident RHOA (aOR's 0.35 (95% CI 0.06-2.15) -1.50 (95% CI 0.94-2.38)). Significant interactions between pain and anterior pincer morphology in predicting incident RHOA were found at 5- 8- and 10 years follow-up (ORs 1.97 (1.03-3.78) - 3.41 (1.35-8.61)).

Conclusion:

Pincer morphology was not significantly associated with incident RHOA at any follow-up moment. However, an interaction between pain and anteriorly located pincer morphology in predicting RHOA was found.

Significance and Innovations

- Previous studies on pincer morphology as a risk factor for hip osteoarthritis failed to consider important factors, which could influence the reported associations. We considered multiple follow-up moments, both anteroposterior and lateral imaging of the hip joint to quantify pincer morphology accurately and to study the influence of anterior and/or lateral pincer localization to provide a clearer view on the role of pincer morphology in incident hip osteoarthritis.

- We studied pincer morphology as a static concept characterized by acetabular overcoverage, but also as a dynamic concept characterized by acetabular overcoverage and pain.

- We studied only hips free of definite radiographic hip osteoartrtitis at baseline to objectify the role of pincer morphology in developing this disease.

Introduction

Hip osteoarthritis (OA) is a multifactorial disease for which several risk factors, including age, sex, trauma, mechanical workload, and bone shape variation, have been identified (1-5). Hip shapes associated with femoroacetabular impingement syndrome (FAIs), such as pincer morphology, have also been marked as a significant risk factor for hip OA (5). Pincer morphology is defined as excessive femoral head coverage by the acetabulum (5-7).

Pincer-type FAIs results from abutment between the edge of the acetabulum and the femoral head-neck junction during motion, thought to cause intra-articular damage and ultimately lead to hip OA (2,8,9). This hypothesis is supported by arthroscopic studies of symptomatic patients with pincer morphology that found damaged acetabular cartilage in a circumferential band around the labrum during surgery (10-12). Other studies demonstrated that pincer morphology is highly prevalent (13,14). A recent study of 6807 individuals from the UK Biobank found a prevalence in the general population of pincer morphology defined by a LCEA ≥45°, of 8.1% in females and 8.9% in males (15). An even higher prevalence ranging from 27-74% was reported in populations of elite athletes (6).

Conflicting results have been reported on the association between pincer morphology and hip OA (2,10,15-22). A recent systematic review showed that hips with OA were 3.7 times more likely to have pincer morphology in cross-sectional studies, whereas prospective studies did not confirm this (2,5,6,23). Different factors, such as time to follow-up, localization and radiographic quantification of pincer morphology, and hip pain, may explain these conflicting results (6,24,25). Also, studies with a follow-up of less than 10 years may be unable to detect an association between pincer morphology and radiographic hip osteoarthritis (RHOA), as cartilage degeneration caused by pincer morphology is thought to progress slowly (5). Regarding radiographic quantification, the 2018 Zurich

consensus statement recommended lateral imaging to objectify pincer morphology in addition to anteroposterior (AP) imaging (24). Whether pincer morphology is localized only laterally, only anteriorly, or is present on both views may influence the severity of the morphology and could influence the risk of developing RHOA. Finally, it has been hypothesized that symptomatic hips with pincer morphology may be more at risk of developing RHOA (6,26). Currently, no studies consider the abovementioned factors when estimating the risk for hips with pincer morphology to develop RHOA (5,18,19).

Our primary aim was to determine the relationship between anterior, lateral, or a combination of lateral and anterior pincer morphology at baseline and the risk of developing RHOA at 2,5,8, and 10 years follow-up among individuals aged 45-65 with first onset of pain or stiffness in the hip or knee joints. The secondary aim was to study whether there is an interaction between pincer morphology and hip pain at baseline in predicting incident RHOA.

Design

Study design and participants

All participants were drawn from the Cohort Hip and Cohort Knee (CHECK). CHECK is a prospective, nationwide cohort of 1002 participants (2004 hips) aged 45-65 (mean 55.9 years) at baseline that reported the first onset of hip or knee pain. Participants were recruited by referral from general practitioners (GP) or advertisements. Inclusion criteria were: pain or stiffness in the knee or hip and no earlier consultation or a first consultation with a GP for these complaints within 6 six months before entry. Exclusion criteria were: a prior history of hip OA or any other pathological condition that may explain an individual's hip or knee pain. For the hip, this included rheumatic disease, previous hip joint replacement, intra-articular fractures, congenital dysplasia, osteochondritis dissecans, bursitis, septic arthritis, or Perthes' disease (27,28). Individuals were excluded if it was impossible to perform a physical examination due to comorbidity, a lack of understanding of the Dutch language, or if malignancy had been present in the past 5 years. For the current study, we included patients without definite radiographic signs of OA at baseline (Kellgren & Lawrence (KL) grade 0 or 1), who had sufficient quality radiographic data at both baseline and follow-up (Fig. 1). The pelvic radiographs were missing at random, as these individuals instead received single hip radiographs due to a miscommunication between the CHECK investigators and the local centers collecting radiographs in the intial phase of data collection. In case variables such as biological sex, BMI, or age were not recorded at baseline but were recorded at follow-up, these measures were used. Written informed consent was obtained from all participants, and the study was approved by the medical ethical committee of each hospital.

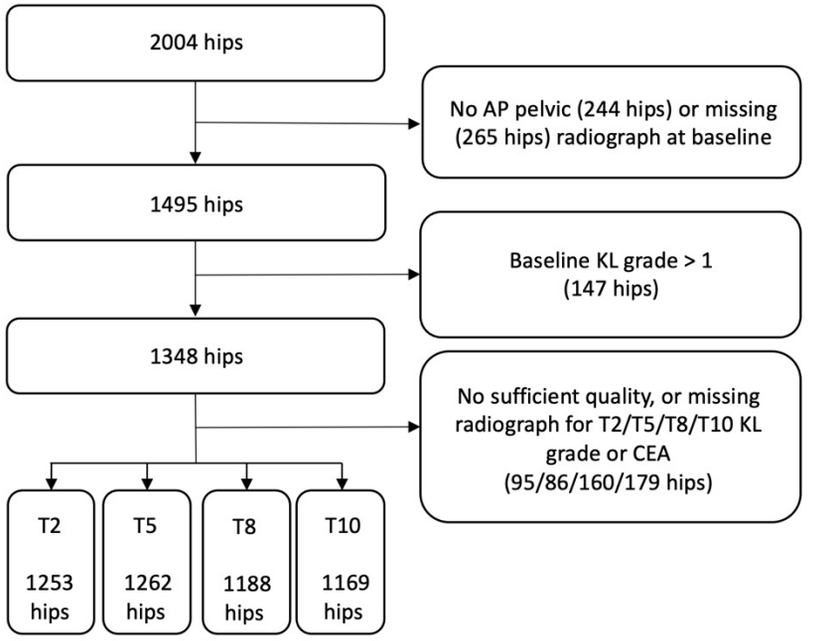

Fig. 1. Flow of hips from cohort inclusion to the final study population at 2- (T2), 5- (T5), 8- (T8), and 10-years (T10) follow-up. AP pelvic radiograph: anteroposterior radiograph. KL grade: Kellgren and Lawrence grade. CEA: center edge angle, the angle necessary to quantify pincer morphology.

Radiographs

AP pelvic radiographs were obtained at baseline and 2-, 5-, 8- and 10-years follow-up. The lateral images, namely the false profile (FP) radiographs, were obtained at baseline. AP and lateral imaging were obtained per a previously published standardized protocol (2). AP radiographs were obtained in a standing position by placing the individual's feet in 15° internal rotation. Weight-bearing FP radiographs were obtained by placing a 65° wedge between the back and the radiographic table, ensuring 25° backward rotation of the pelvis to profile the anterosuperomedial edge of the acetabulum (29,30).

Radiographic measurements

The osseous outline of the proximal femur and acetabulum were drawn on AP and FP radiographs with a point set using statistical shape modeling (SSM) software (ASM tool kit, Manchester University, UK). This point set was used to automize measurements of the lateral center edge angle (LCEA) and the anterior center edge angle (ACEA) using a Matlab script (V.7.10) (31,32).

The LCEA quantifies the lateral coverage of the femoral head by the acetabulum. The LCEA is constructed on an AP pelvic radiograph according to the following steps. First, a best-fitting circle is outlined around the femoral head based on the SSM points to determine the center of the femoral head. Next, a vertical line is drawn perpendicular to a horizontal reference line connecting both femoral heads (fig. 2). The LCEA is the angle between the vertical line and a line drawn from the center of the femoral head to the lateral acetabular rim (33,34) The ACEA is constructed from the FP radiograph in a similar way, except that the vertical line is drawn perpendicular to the horizontal line of the radiographic film (fig. 3) (30,35). Pincer morphology was defined as either an LCEA≥40°, an ACEA ≥40°, or both the ACEA and LCEA ≥40°. Although the threshold of >40° is subjective, it is the most commonly used definition of pincer morphology (36).

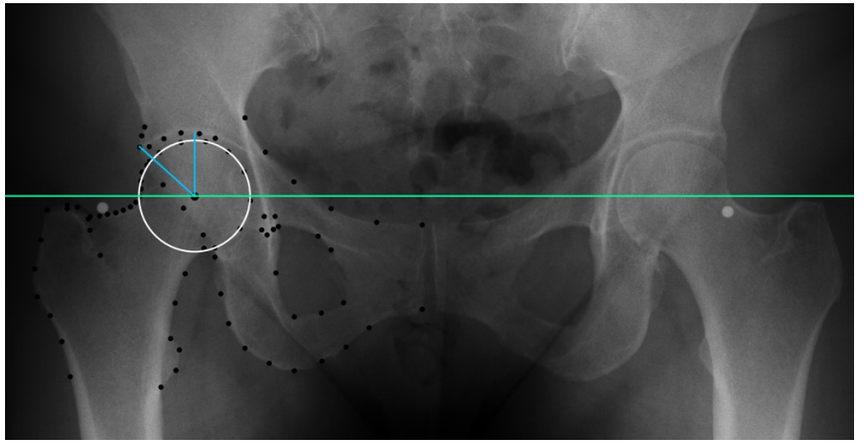

Fig. 2. The lateral center edge angle (LCEA) is measured on an AP pelvic radiograph. The white line represents the best-fitted circle around the femoral head. The green line represents the horizontal reference line. The blue lines represent the measurement of lateral acetabular coverage (LCEA). Pincer morphology was defined as an LCEA≥40°

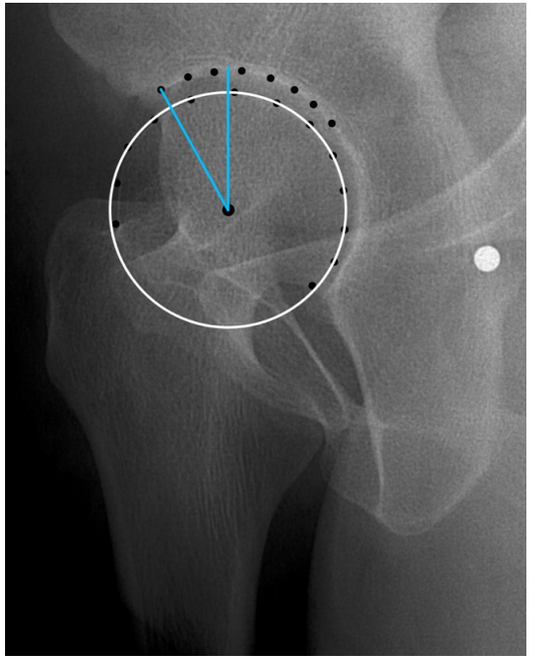

Fig. 3. The anterior center edge angle (ACEA) is measured on an FP radiograph. The white line represents the best-fitted circle around the femoral head. The blue lines represent the measurement of anterior acetabular coverage (ACEA). Pincer morphology was defined as an ACEA≥40°.

The first 122 participants (224 hips) who entered the CHECK cohort had AP hip radiographs instead of AP pelvic radiographs obtained. Therefore, these hips were excluded from the analysis as it was impossible to construct a reference line as described. Reliability measurement of angles

The intraclass correlation coefficients (ICC) of the three observers who annotated the point set for inter-observer reliability were 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 (1,37). The reliability of radiographic OA measurements in the CHECK cohort has previously been published (37).

Independent variables

Hip pain was self-reported by participants of the CHECK cohort with a questionnaire. Participants were asked whether they had experienced any form of pain (yes/no) in the left or right hip or groin region during the past week at baseline. Pincer morphology was categorized into four categories; no pincer morphology (LCEA/ACEA≤40°), lateral pincer morphology (LCEA≥40°), anterior pincer morphology (ACEA≥40°), or both lateral and anterior pincer morphology (LCEA and ACEA≥40°). All groups were mutually exclusive, meaning a single hip could only belong to one category.

Outcome measures

Development of incident RHOA was defined by a KL grade ≥2 or a total hip replacement (THR) at each follow-up moment. Each participant's radiographs of all time points were scored simultaneously so that information on all available images was used for the KL scoring at each time point. Disclosing all available images is more reliable than scoring a single radiographic image (38).

Statistical analysis

Univariate baseline differences between included and excluded hips were determined by the independent sample's T-test for age, body mass index (BMI), body height, and body weight, and the chi-square test for biological sex. The association between baseline pincer morphology (compared to no pincer morphology) and the development of RHOA was determined using logistic regression with generalized estimating equations (GEE), adjusted for baseline age, biological sex, BMI, and repeated measures within persons, expressed in adjusted odds ratios (aORs) with 95% confidence intervals (95% CI). For the interaction analyses, an interaction term between pincer morphology and hip pain at baseline was added to the logistic regression analysis. The exponentiated parameter estimates are presented as ratios of ORs with 95%CIs for each level of the interacting factor. All statistical analyses were performed in SPSS version 28.0.

Results

Participants

Baseline demographic data, including differences between included and excluded hips, is outlined in Table 1. 1253 hips had AP pelvic radiographs at 2 years follow-up, 1262 hips at 5 years follow-up, 1188 hips at 8-years follow-up, and 1169 hips at 10-years follow-up.

Table 1.
Baseline characteristics and differences between included and excluded hips.

Baseline characteristic	Included hips* (n=1265)	Excluded hips (n=739)	p-value
Age in years, mean (±SD)	55.7 (5.2)	56.2 (5.2)	0.06
Women, no. (%)	1038 (82.1)	540 (73.0)	0.01
BMI, kg/m2, mean (±SD)	26.1 (4.1)	26.2 (3.7)	0.76
Height in cm, mean (±SD)	169.5 (8.1)	170.6 (9.0)	0.03
Weight in kg, mean (±SD)	75.1 (13.7)	76.6 (14.1)	0.05
KL grade 0, no. (%)	943 (74.5)		
KL grade 1, no. (%)	322 (25.5)		
LCEA≥40°, no. (%)	144 (11.4)		
ACEA≥40°, no. (%)	112 (9.0)		
LCEA & ACEA ≥40°, no. (%)	47 (3.7)		
Hip pain**	490 (38.7)		

*****Included hips are complete cases at baseline (age, biological sex, BMI, and sufficient quality radiograph for KL grading and pincer morphology (CEA) calculation) and at least one follow-up moment at 2-, 5-, 8-, or 10 years follow-up.
****** individuals were asked if they experienced any form of pain (yes/no) in the left or right hip or groin region during the past week

OA classification

Incident RHOA had developed in 69 hips (5%) at 2 years, 178 hips (14%) at 5 years, 279 hips (24%) at 8 years, and in 495 hips (42%) at 10 years follow-up.

Association between pincer morphology and incident RHOA

The associations between lateral, anterior, or a combination of both lateral and anterior pincer morphology and incident RHOA are summarized in Table 2. No significant associations between any quantification of pincer morphology and incident RHOA were present at 2-,5-,8-, or 10 years follow-up.

Table 2
Associations between pincer morphology at baseline and incident RHOA at 2-,5-,8- and 10-years follow-up. Significant associations are highlighted in **bold.**

			Incident RHOA	
Total hips per follow-up (n=)	**Hips with incident OA (n=)**	**Hips with pincer per radiographic view (n=)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
2 years (n=1255)	69	LCEA ≥40° (n=54)	0.35 (0.06-2.09)	0.35 (0.06-2.15)
		ACEA≥40° (n=235)	0.89 (0.44-1.80)	0.89 (0.43-1.82)
		LCEA & ACEA≥40° (n=125)	1.26 (0.62-2.57)	1.09 (0.51-2.35)
5 years (n=1262)	178	LCEA≥40° (n=54)	1.05 (0.48-2.29)	1.05 (0.48-2.29)
		ACEA≥40° (n=239)	1.10 (0.74-1.63)	1.11 (0.75-1.65)
		LCEA & ACEA≥40° (n=126)	1.43 (0.88-2.33)	1.30 (0.78-2.19)
8 years (n=1188)	279	LCEA≥40° (n=52)	0.82 (0.46-1.48)	0.84 (0.47-1.52)
		ACEA≥40° (n=226)	0.85 (0.61-1.18)	0.84 (0.60-1.18)
		LCEA & ACEA≥40° (n=120)	1.50 (0.97-2.32)	1.50 (0.94-2.38)
10 years (n=1169)	495	LCEA ≥40° (n=52)	0.77 (0.46-1.28)	0.76 (0.45-1.29)
		ACEA≥40° (n=223)	1.01 (0.76-1.35)	1.02 (0.75-1.39)
		LCEA & ACEA≥40° (n=119)	1.37 (0.92-2.03)	1.36 (0.89-2.06)

All odds ratios ORs were adjusted for age, BMI, and sex. LCEA= lateral center edge angle, ACEA= anterior center edge angle, RHOA= radiographic hip osteoarthritis, OR= odds ratio. All pincer groups were mutually exclusive, meaning hips with LCEA≥40° or ACEA≥40° were not included in the LCEA & ACEA≥40° group. Hips without pincer morphology were used as the reference group.

Interaction between hip pain and pincer morphology

Ratios of odds ratios for the interaction between baseline hip pain and pincer morphology are presented in Table 3. A significant association between hip pain at baseline and anteriorly located pincer morphology was observed at all eligible follow-up moments.

Table 3

Analysis of the interaction between hip pain at baseline and pincer morphology in predicting incident RHOA at 2-,5-,8- and 10-years follow-up.

All ratios of ORs were adjusted for age, BMI, and sex. LCEA= lateral center edge angle, ACEA= anterior center edge angle, RHOA= radiographic hip osteoarthritis, OR= odds ratio. All pincer groups were mutually exclusive, meaning hips with LCEA≥40° or ACEA≥40° were not included in the LCEA & ACEA≥40° group. *Limited events (n=69) did not allow for estimating the risk at 2 years follow-up.

				Incident RHOA	
Total hips per follow-up (n=)	**Hips with hip pain at baseline (n=)**	**Hips with incident RHOA (n=)**	**Pincer hips per radiographic view (n=)**	**Absence of hip pain (OR, (95% CI))**	**Presence of hip pain (OR, (95% CI))**
2 years (n=1255)	485	69	No pincer morphology	-*	-*
			LCEA ≥40° (n=54)	-*	-*
			ACEA≥40° (n=235)	-*	-*
			LCEA&ACEA≥40° (n=125)	-*	-*
5 years (n=1262)	489	178	No pincer morphology	Reference group	**1.66 (1.12-2.44)**
			LCEA≥40° (n=54)	1.25 (0.46-3.37)	1.18 (0.23-6.16)‡
			ACEA≥40° (n=239)	0.76 (0.41-1.42)	**3.41 (1.35-8.61)**‡
			LCEA&ACEA≥40° (n=126)	1.18 (0.60-2.34)	2.46 (0.83-7.28)‡
8 years (n=1188)	466	279	No pincer morphology	Reference group	**1.40 (1.04-1.89)**
			LCEA≥40° (n=52)	1.03 (0.50-2.13)	0.80 (0.23-2.11)‡
			ACEA≥40° (n=226)	0.66 (0.41-1.06)	**2.36 (1.03-3.78)**‡
			LCEA&ACEA≥40° (n=120)	1.38 (0.78-2.46)	1.87 (0.64-3.35)‡
10 years (n=1169)	457	495	No pincer morphology	Reference group	**1.42 (1.09-1.85)**
			LCEA ≥40° (n=52)	1.00 (0.51-1.94)	0.69 (0.23-2.11)‡
			ACEA≥40° (n=223)	0.92 (0.63-1.34)	**1.97 (1.03-3.78)**‡
			LCEA&ACEA≥40° (n=119)	1.42 (0.86-2.33)	1.47 (0.64-3.35)‡

Discussion

This prospective study of individuals with the first onset of pain in the hip, knee, or both, without evidence of RHOA at baseline, showed that pincer morphology was not a strong risk factor for incident RHOA in our study population. Hip pain did not seem to moderate this effect significantly. Upon close examination of the reported ORs, it becomes apparent that although not statistically significant, there is a consistent pattern of higher ORs in hips with both lateral and anterior pincer morphology as opposed to those with only lateral or anterior pincer morphology.

Some studies found similar results to ours (2,5,18,19). A systematic review showed that individuals with pincer morphology were not at risk for developing RHOA (LCEA >39°; OR = 1.08, 95% CI: 0.57 to 2.07) (5). The review mentioned three factors that must be considered when interpreting the lack of association; the slow progression of OA, the inability to detect pincer-related OA, and the different acetabular abnormalities associated with pincer morphology. One of the studies in this systematic review was the 5-year follow-up of the CHECK cohort by Agricola et al., where a protective effect for end-stage RHOA was observed if pincer morphology was present both anteriorly and laterally (OR= 0,34; 95% CI: 0,13-0,87) (2). Although this study contained lateral hip imaging, the follow-up may have been too short to find an association. The additional 8- and 10-year follow-up data in the present study of the CHECK population point in the direction that even after a more extended follow-up period, pincer morphology did not seem to be associated with incident RHOA. The prospective study of the Rotterdam Study cohort by Saberi et al. had a relatively long follow-up (mean 9.2 years) but lacked lateral or three-dimensional hip imaging. The conclusions drawn are similar to those in the present study. Finally, a nested case-control study of the Johnston County cohort of 239 hips was able to quantify pincer morphology in several ways, thereby potentially encompassing multiple acetabular abnormalities (crossover sign, protrusion acetabuli, and

coxa profunda) associated with pincer morphology, and also found results consistent with those of the present study (39). It should be mentioned that contrary to pincer-type FAI, all aforementioned explanations as to why an association with RHOA is lacking do not result in a lacking association between cam-type FAI and RHOA (5,15,40).

We hypothesized that the previously reported risk of RHOA in pincer hips may have been underestimated due to the limitations mentioned above (time to follow-up, localization and radiographic quantification of pincer morphology, presence of hip pain) of previous studies that failed to take into account multiple potential risk factors. Despite the notion that the risk of RHOA may increase with time in pincer hips, our findings did not support this hypothesis as neither any significant risk nor a trend towards significance was observed at any time point within 10 years. However, our study was performed in a population of individuals with the first onset of pain in the hip or knee and an average age of 55.7, which should be noted when interpreting our results.

Furthermore, our study evaluated the influence of combined lateral and anterior pincer morphology. We believed this could embody a more severe form of pincer morphology with altered biomechanics and an increased risk of developing RHOA. However, our results did not show a significantly increased risk for RHOA when pincer morphology was present laterally and anteriorly. However, when carefully examining the reported ORs, although not statistically significant, one does notice these are consistently higher in hips with lateral and anterior pincer morphology compared to those with only lateral or anterior pincer morphology. This warrants future research, potentially using 3-Dimensional imaging, to further study the hypothesis that a more severe case of both lateral and anterior pincer morphology does pose a risk factor for RHOA.

Hip pain is a strong predictor for osteoarthritis in our study population. This finding is consistent with prior research (41,42). Interestingly, our study indicates that hip pain and anteriorly located pincer morphology may be an important effect modifier for incident RHOA. Whether isolated anterior localisation of pincer morphology causes more pain, changes the biomechanics of the hip differently, and is more predictive for RHOA than laterally located pincer morphology cannot be concluded from this study, at least partly because the isolated lateral pincers were less common in our study population. Future studies with a large, heterogeneous population and a large number of events should be conducted to provide further insight.

Previous studies have stressed the need to identify factors that predict which hips are at risk of developing RHOA (6,26). This highlights the need for further research to fully understand the risk factors for RHOA in pincer hips and develop appropriate preventive and therapeutic strategies. The current treatment for pincer morphology may either be conservative with physical therapy and pain medication or surgical in severe cases with arthroscopic hip surgery (43). A recent paper by van Klij et al. stressed the need for future studies to monitor whether treatment for FAI syndrome can stop or slow the progression of hip OA (6). Our results showed that these efforts should potentially focus on cam-type FAIs rather than pincer-type FAIs regarding hip OA incidence or progression (19,28,40,44).

One of the strengths of this study is that the FP view radiograph allowed for anterior quantification of acetabular coverage. The additional FP radiograph allowed us to identify up to 226 (19%) additional cases of solely anteriorly located pincer morphology compared to when only studying AP pelvic radiographs. Additionally, it allowed us to study the risk of more "severe" cases of pincer morphology where the bone shape variation was present both laterally and anteriorly. Another strength is the multiple short-term

follow-up moments in time. This allowed us to monitor whether the risk of RHOA increases in hips with pincer morphology as time passes, as previously hypothesized (5)(5). Finally, the CHECK cohort provides a unique population for analyzing bone shape variants and the development of RHOA, as the cohort contains individuals who may have experienced the first signs of OA. Contrary to open population studies, we examined a clinically relevant subgroup of individuals who have shown to require medical care at baseline and are likely to require future medical care.

Our study had several limitations that must be mentioned. First, we could not construct a horizontal reference line for calculating the ACEA on any FP radiographs, as we did for the LCEA on AP radiographs, as only one hip is depicted. Second, in our present study, 35% of all participants had developed incident RHOA at 10 years follow-up, which is high compared to other studies (incidence of hip OA 6-11%) (5,19,45). The reader should bear in mind that all individuals had pain or stiffness in the hip or knee at baseline, which could represent early signs of OA, even though no definite RHOA was present at baseline, and likely explains the high incidence of RHOA at follow-up. On the contrary, the CHECK cohort offers a unique opportunity to gain insight into a population of individuals seeking medical help for the first potential complaints of OA. A CEA of ≥45° is used in some studies to define pincer morphology (15). The threshold of ≥40° might also represent milder cases of pincer morphology. When interpreting the results of this study, it should be taken into consideration that the majority of the included hips belong to female participants. Large population studies have shown that RHOA is more common in males than females, so sex differences may not be elucidated by the present study (46). Finally, our study population may be underpowered to conclude the interaction between pain and pincer morphology and the risk of developing RHOA and should be studied in a larger population.

In conclusion, no significant associations were found between lateral, anterior, or lateral anterior pincer morphology and the development of RHOA within 10 years follow-up. The presence of pain in anteriorly located pincer morphology hips does however seem to influence the association between pincer morphology and RHOA. Pincer morphology, as measured by the LCEA or ACEA, contrary to other hip shape variations such as acetabular dysplasia or cam morphology, does not seem to be an important risk factor for the development of RHOA, although the presence of hip pain may influence this risk. Future research with a large, heterogeneous population should be conducted to confirm or negate our results.

Role of the funding source

The Dutch Arthritis Society funded the CHECK cohort, but there was no funding for the present study.

Competing interest statement

No competing interests do declare.

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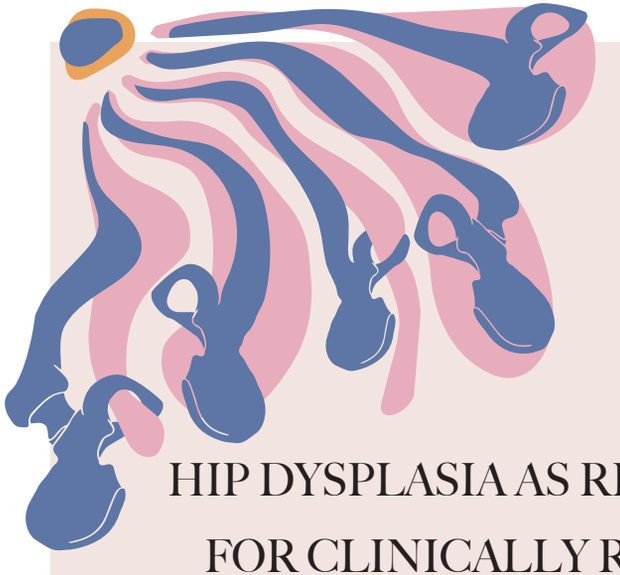

HIP DYSPLASIA AS RISK FACTOR FOR CLINICALLY RELEVANT AND RADIOGRAPHIC HIP OSTEOARTHRITIS: 10-YEAR RESULTS FROM THE CHECK COHORT

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Hip dysplasia as risk factor for clinically relevant and radiographic hip osteoarthritis: 10-year results from the CHECK cohort

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ABSTRACT

Objectives:

To investigate hip dysplasia as a risk factor for clinically relevant and incident radiographic hip osteoarthritis.

Methods:

From a prospective cohort (CHECK) of 1002 middle-aged, new consulters for hip and/or knee pain, 468 hips (251 individuals) were selected based on hip pain, available lateral center edge angle (LCEA) and absence of definite radiographic hip OA (Kellgren and Lawrence grade (KL) <2) at baseline, as well as available follow-up measures. Clinically relevant hip OA was defined by an expert diagnosis based on clinical and radiographic data obtained between year 5–10 from baseline. Incident radiographic hip OA was defined by KL grade ≥2 or a total hip replacement at the 10-year follow-up. Associations between hip dysplasia (LCEA ≤20°) and outcomes were expressed in odds ratios (OR) adjusted for age, sex and BMI.

Results:

At baseline, participants had a mean age of 55.5 years (SD 5.4), 88% were female and, on hip level, the prevalence of hip dysplasia was 3.6% (n=17). After 10 years, hip dysplasia was associated with an increased risk for clinically relevant hip OA (OR 2.80 (95% CI 1.15, 6.79), but not for incident radiographic hip OA (OR 0.78 (95% CI 0.26, 2.30)).

Conclusion:

In the long term, baseline hip dysplasia was associated with an increased risk for clinically relevant hip OA, but not for incident radiographic hip OA. With this in mind, we suggest that future research investigating the link between hip dysplasia and OA strive to include a definition for OA that is clinically relevant.

Key messages

- Dysplasia was associated with increased risk for clinically relevant hip OA in primary care.
- Dysplasia was not associated with increased risk for incident radiographic hip OA in primary care.
- Outcome definitions should be clinically relevant if results are to be implemented in clinical care.

Introduction

Hip dysplasia is a condition defined by acetabular under-coverage of the femoral head. There is growing evidence that hip dysplasia is one of the strongest risk factors for radiographic hip osteoarthritis (OA) and total hip replacement (THR), but the magnitude of the association remains unclear[1, 2]. Previous studies mainly focus on radiographic OA as the sole outcome, while studying a combination of clinical and radiographic findings would have a higher clinical relevance.

The altered biomechanics of dysplastic hips might lead to increased load on the joint, and can cause symptoms such as groin pain, clicking and locking of the hip[3]. Non-surgical treatment for adult hip dysplasia involves lifestyle changes and physiotherapy, although tailored training regimes have not been widely studied[4, 5]. In cases where surgical treatment is advised, the presence or absence of radiographic OA is considered crucial for the choice of surgical method[6]. In the absence of radiographic OA, joint-preserving surgery such as periacetabular osteotomy (PAO) or arthroscopy may be performed with the aim to relieve symptoms[7]. It is hypothesized that such surgical procedures could also protect against OA development. To evaluate possible protective treatments, and to fully understand the link between hip dysplasia and OA, there is probably a need to investigate the natural history of hip dysplasia with focus on clinical relevance.

The purpose of this study was to investigate the long-term association between hip dysplasia and clinically relevant hip OA, defined by an expert diagnosis based on clinical and radiographic data. For comparison, we also aimed to study the long term association with incident radiographic hip OA, defined by Kellgren and Lawrence (KL) grading[8].

Methods

Study population and participants

All participants were drawn from Cohort Hip and Cohort Knee (CHECK), a prospective multicentre cohort study conducted in the Netherlands. On entry, all 1002 CHECK-participants were between ages 45 and 65 years, had pain and/or stiffness in knee and/or hip, and had not consulted a general practitioner for these symptoms yet, or the first consultation was no longer than 6 months ago. They were recruited by general practitioners, through advertisement in local newspapers, on the Dutch Arthritis Foundations' website and on flyers. Potential participants were not included in CHECK if they had comorbidity preventing follow-up over 10 years, malignancy in the last 5 years, inability to understand the Dutch language or any present or past history of a medical condition, other than possible early arthritis, that could explain their musculoskeletal symptoms (for hip: trauma, rheumatoid arthritis, congenital hip dysplasia, Perthes disease, subluxation, osteochondritis dissecans, fracture, septic arthritis, KL grade 4 or total hip replacement, previous hip surgery, and individuals having only symptoms of bursitis or tendinitis)[9]. 10 medical centres participated to collect questionnaires, radiographs and clinical examinations at baseline, year 2, 5, 8 and 10 for the 1002 participants. Only 145 participants (14%) were lost to follow-up during the CHECK study. More details about CHECK can be read elsewhere[10, 11].

For the current study, we included CHECK-participants who presented with hip pain at baseline, had an available center edge angle measured on an anteroposterior (AP) pelvic radiograph and available KL grading with absence of radiographic hip OA (KL grade <2) at baseline, as well as available KL grading and expert diagnosis at the 10-year follow-up.

Radiographs

A standardized protocol was used to acquire weight bearing AP radiographs of the pelvis with the feet positioned in 15° internal rotation[12].

Lateral center edge angle (LCEA)

Three observers outlined the bony contour of the proximal femur and pelvis by manual positioning of 75 landmark points along the surface of the bone, using statistical shape modelling (SSM) software (ASM tool kit, Manchester University, Manchester, UK). The LCEA was then calculated automatically from the landmark points using a Matlab script (version 7.10, MathWorks Inc, Natick, MA, USA). The LCEA was defined as the angle between two lines drawn through the center of the femoral head, the first line drawn vertical and the second line drawn to the lateral subchondral sclerotic zone of the acetabular roof (the "sourcil")[13]. The vertical line was drawn perpendicular to a horizontal line between the femoral heads. Inter-observer and intra-observer variability were assessed with intraclass correlation coefficients (ICC) and were 0.97 (95% CI 0.94, 0.99) and 0.91–0.96 respectively[14]. Hip dysplasia was defined as a LCEA ≤20° at baseline.

Kellgren and Lawrence grading

Baseline grades were initially scored by members of the CHECK steering committee, consisting of senior researchers with substantial expertise in radiographic OA. Over the course of the CHECK study, KL grading was performed after each follow-up by trained observers who were provided radiographs and grades from all previous time points, including their chronological order. Four trained observers scored the grades in year 2 and 5. Five trained observers scored the grades in year 8 and 10. These trained observers were medical students with extensive training by an experienced musculoskeletal radiologist and a general practitioner

(GP) with expertise in radiographic reading and OA, including a PhD in early OA. The GP maintained supervision over the trained observers throughout the study.
After the last follow-up, the trained observers reviewed the full set of grades, with known chronological order, and reassessed grades when considered appropriate. Thereafter, the above-mentioned GP reviewed all grades to check missing data and resolve remaining uncertainties[15]. Inter-observer variability between the trained observers and the experienced observer (the GP) was tested for radiographs from the 5-year follow-up and showed an average prevalence and bias adjusted kappa of 0.8 (range 0.71–0.91)[16].

Outcome measures

Clinically relevant hip OA was determined on hip level, based on an expert-based diagnosis. The group of 24 experts consisted of GPs, rheumatologists and orthopaedic surgeons with extensive experience in management of OA patients. The decision basis consisted of questionnaires, results from physical examinations and radiographs performed 5, 8 and 10 years after enrolment. The questionnaires consisted of pain and stiffness scales (Likert) of the Western Ontario and McMaster Universities OA Index (WOMAC) and questions on physical activity, current presence of hip pain and subluxation. The physical examination evaluated the presence of pain and range of motion at passive flexion, internal rotation, external rotation, and abduction. The radiographic data consisted of AP and faux profil (FP) oblique view radiographs and accompanied grades for the presence of femoral osteophytes (grade 0–3), for joint space narrowing (JSN) in the medial and superior aspects of the hip joint (grade 0–3) and KL grading (grade 0–4). The outcome for each hip was assessed by one expert pair (one GP and one secondary care clinician). First, the experts in each pair individually evaluated the data to determine whether clinically relevant OA was present or not. Instead of providing a set definition for clinically relevant OA, the experts were asked to make the assessment based on their expertise. In addition, they were asked to state their certainty of the assessment from 1 (definitely not clinically relevant OA) to 100 (definitely clinically relevant OA). Next, the agreement within the expert pair was assessed to determine the actual outcome. If the expert pair agreed, the matter was settled (not clinically relevant hip OA / clinically relevant hip OA). If the expert pair's answers disagreed and both had stated that they were uncertain (>30 to <70) the outcome was reported uncertain. For all other cases with disagreement, the assessment was repeated by the expert pair during a consensus meeting. If consensus could not be met, the outcome was reported as uncertain. It should be noted that the outcome of clinically relevant hip OA was not limited to one follow up, as it was determined based on data collected from year 5–10 from baseline. Further details on the expert diagnosis can be read elsewhere[17].

The additional outcome incident radiographic hip OA was defined as a KL grade ≥2 or THR at the 10-year follow-up.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 28 (IBM Corp, Armonk, NY, USA). All continuous variables were normally distributed and are presented as means (SD). Categorical variables are presented as frequencies. Differences in baseline characteristics between included and excluded cases were assessed by Student's t-test for age and BMI, by chi-square test for sex and prevalence of dysplasia defined by the LCEA, and by logistic regression with generalized estimating equations (GEE) for KL grades. For interferential statistics, a significance level of <0.05 was chosen. Logistic regression with GEE was used to assess the association between the predictor (hip dysplasia) and the two outcomes (clinically relevant hip OA and incident radiographic hip OA). The strength of association was expressed in odds ratios (OR) with 95% confidence intervals (CI). In the main analysis, the association with each outcome was adjusted for age, sex and BMI. Sensitivity analyses were run without any adjustment and with KL grade 1 at baseline added as confounder in addition to age, sex,

and BMI (Supplementary Table S1). For clinically relevant hip OA, uncertain cases were deemed OA cases in the main analysis as this was found true for the knee cases in a previous study on data from the CHECK cohort[18]. To confirm this assumption, we performed a sensitivity analysis described in Supplementary Table S2.

Report

The STROBE guidelines for cohort studies were used for the reporting of this study[19].

Results

Baseline characteristics

The selection of 468 hips (251 individuals) for analyses from the entire CHECK cohort of 2004 hips (1002 individuals) is presented in a flow-chart in Figure 1. Baseline characteristics are summarized in Table 1. Of the 251 included individuals, 88% were female. The mean age was 55.5 years (SD 5.4) and the mean BMI 26.4 kg/m2 (SD 4.2). On hip level, the prevalence of hip dysplasia (LCEA ≤20°) was 3.6% (n=17). The majority of hips (69.4%, n=325) had KL grade 0, the remaining had KL grade 1 (30.6%, n=143). Baseline characteristics were comparable for included and excluded individuals/hips, with the exception that the prevalence of females was lower in the excluded group (Table 1).

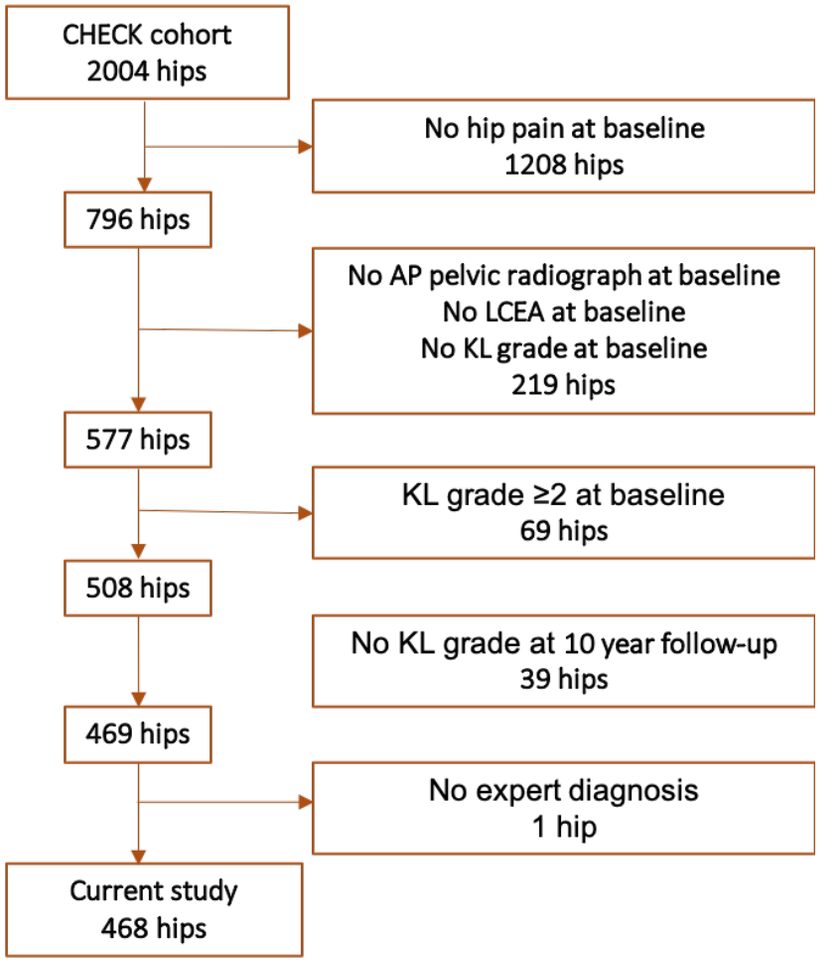

Figure 1. Inclusion of hips from the CHECK cohort for the current study. Inclusion was based on the following inclusion criteria: hip pain at baseline, available LCEA measured on an AP pelvic radiograph at baseline, available KL grade at baseline, KL grade at baseline <2, available KL grade and expert diagnosis at follow-up. The expert diagnosis for clinically relevant hip OA was based on clinical and radiographic data obtained from year 5–10. The CHECK cohort initially collected AP hip radiographs before shifting to collecting AP pelvic radiographs, which explains the relatively large group that was excluded in the second step of the flowchart. CHECK = Cohort Hip and Cohort Knee, LCEA = lateral center edge angle, AP = anteroposterior, KL = Kellgren and Lawrence.

Table 1
Baseline characteristics of included and excluded cases from CHECK, and comparison between the two groups. For the KL grades, included cases ranged between grade 0–1 as one of the exclusion criteria for the current study was definite radiographic osteoarthritis at baseline (KL grade ≥2). Excluded cases had the full range of grade 0¬–3 represented in the CHECK cohort.

		Included cases (n=468 hips, 251 individuals)	**Excluded cases** (n=1536 hips, 751 individuals)	**Difference** (p-value)	**Difference** (mean difference (95% CI))
Individual level					
Female (%)		88.0 (n=221/251)	76.0 (n=571/751)	0.001	
Mean age (SD)		55.5 (5.4) (n=251)	56.1 (5.1) (n=751)		-0.59 (-1.34, 0.15)
Mean BMI (SD)		26.4 (4.2) (n=244)	26.1 (3.9) (n=735)		0.35 (-0.30, 0.93)
Hip level					
LCEA ≤20 (%)		3.6 (n=17/468)	4.4 (n=51/1166)	0.497	
LCEA ≤25 (%)		13.2 (n=62/468)	13.4 (n=156/1166)	0.944	
KL grade (%)	0	69.4 (n=325/468)	63.3 (n=958/1514)	0.486	
	≥1	30.6 (n=143/468)	36.7 (n=556/1514)	0.486	

CHECK = Cohort Hip and Cohort Knee, LCEA = lateral center edge angle, KL = Kellgren and Lawrence, CI = confidence interval, SD = standard deviation, LCEA = lateral center edge angle.

OA incidence
After ten years of follow up, clinically relevant hip OA was fulfilled by 31.0% (n=145) and radiographic hip OA by 45.9% (n=215) of the hips. Forty three percent (n=202) fulfilled neither outcome and 20.1% (n=94) of the hips fulfilled both outcomes.

Association between hip dysplasia and OA
Baseline hip dysplasia was associated with clinically relevant hip OA (adjusted OR 2.80 (95% CI 1.15, 6.79), but not with incident radiographic hip OA (adjusted OR 0.78 (95% CI 0.26, 2.30) after 10 years of follow up (Table 2).

Table 2. Association between hip dysplasia and OA. Two different definitions were used for OA. Clinically relevant hip OA was defined by an expert diagnosis based on clinical and radiographic data obtained from year 5–10. Incident radiographic hip OA was defined by a Kellgren and Lawrence grade ≥2 at year 10. Hip dysplasia was defined as a lateral center edge angle ≤20°.

	Hip dysplasia
	OR (95% CI), adjusted for sex, BMI, age
Clinically relevant hip OA	2.80 (1.15, 6.79)
Incident radiographic hip OA	0.78 (0.26, 2.30)

OA = osteoarthritis, OR = odds ratio, CI = confidence interval, BMI = body mass index.

Sensitivity analyses

Adjusted ORs obtained with KL grade 1 at baseline as an additional confounder, as well as unadjusted ORs, were comparable to the ORs in the main analysis (Supplementary Table S1).

The association between hip dysplasia and uncertain clinically relevant hip OA was strong and in the same direction as the association between hip dysplasia and certain clinically relevant hip OA (Supplementary Table S2). These results indicate that the uncertain cases were likely OA-cases, as was assumed.

Discussion

In this prospective study of participants aged 45-65 years, who were new consulters for hip pain, hip dysplasia was a risk factor for clinically relevant hip OA, but not for incident radiographic hip OA, 10 years from baseline.

To our knowledge, this is the first prospective study to investigate the association between hip dysplasia and hip OA, where hip OA was defined based on both radiographic and clinical data. In the pursuit to understand the natural history of hip dysplasia, it is reasonable to include a radiographic definition for OA as it is the most objective method and consequently enables comparison between studies. However, it is well known that the correlation between radiographic OA and clinical symptoms at a given time is poor[20]. In the setting of clinical practice, symptoms and clinical findings should therefore also always be considered. As we have shown in this study, the choice of definition of OA has an important impact on the obtained long-term association between hip dysplasia and OA. Much research is still needed to fully understand the link between hip dysplasia and OA, not least if there are any interventions that can modify the increased risk for OA development. On this quest, we suggest including a clinically relevant definition for OA.

In contrast to our findings, the 5-year results from the CHECK cohort showed an association between hip dysplasia and incident radiographic hip OA (OR 2.83 (95% CI 1.54, 5.20)14. It should be noted that the inclusion criteria of the current study of the 10 year-data, differ from the inclusion criteria used by Agricola et al. when analysing the 5-year data. Agricola's study population consisted of a mixed group of symptomatic and asymptomatic hips. With the aim to make the results of the current study more clinically applicable, we only included hips with hip pain at baseline. We used a cut off value for the LCEA of 20° instead of 25°, not to include borderline dysplastic hips in our definition of hip dysplasia. Furthermore, the

reassessment of the KL grades that was performed when the 10-year radiographs became available resulted in a slight increase in cases with baseline OA15. Whether this reassessment corrected previous underestimations or overestimated the current grades is debatable. However, a known chronological order in a series of radiographs has been shown to be more sensitive to structural changes[21, 22]. Even though the two studies are not identical, the discrepancy between them supports previous findings that hip dysplasia is a risk factor for rapid development of OA especially among younger individuals[23, 24], and with an aging study population and a longer follow-up duration, the association may therefore become weaker[25].

Beside studies based on the CHECK cohort, there are several other prospective studies investigating the association between hip dysplasia and incident radiographic hip OA. Reijman et al. studied a sample representative of the general population, with a mean age of 65.6 (SD 6.5) years and a mean time to follow-up of 6.6 years, of which 16.9% had developed incident radiographic hip OA at follow-up (OR for hip dysplasia 2.4 (95% CI 1.2, 4.7))[26]. Thomas et al. studied female participants sampled without regard to hip symptoms, with a median age of 54 years (IQR 49–60) and 11% of their hips had developed incident radiographic hip OA after 20 years. They found that the risk of incident radiographic hip OA at the follow-up increased with 13% for each degree of reduction of the LCEA below 28 degrees (OR 0.87 (95% CI 0.78, 0.96))[27]. Saberi Hosnijeh et al studied two different cohorts representative of the general population, with mean ages of 65.1 (SD 6.4) and 62.9 (SD 6.4), and found that the incidence of radiographic hip OA after a mean follow up for 9.2 years was 10.5 and 7.4% respectively (pooled OR for hip dysplasia 2.19 (95% CI 1.50–3.21). In comparison to these studies, incident radiographic hip OA was seen in almost 50% of the hips at year 10 in the current study. As our participants were included based on the presence of hip pain, and pain is a possible sign of early OA, it is not surprising that we found a high incidence of radiographic hip OA. However, hip dysplasia was apparently not causing the development of radiographic hip OA 10 year after baseline in our population.

This study has several limitations to be considered. The inter-observer variability for the KL grading was tested for the 5-year gradings, but not for the 10-year gradings that were used in the current study. However, the same method was used at both time points, and therefore the variability can be expected to be comparable. Furthermore, the presence of a THR at the 10-year follow-up was used as a criterion for incident radiographic OA although the reason for THR was not obtained at the 10-year follow-up in the CHECK cohort. Therefore, there may be a few cases who received THR due to other reasons than OA, such as a hip fracture. At the 5-year follow up however, the reason for THR was obtained, and all were due to OA[9]. In the current study, 70% (n=7) of new cases with THR at 8-year follow up and 63% (n=5) of new cases with THR at 10-year follow-up had KL grade ≥2 at the previous follow-up. These results suggest that the new THR-cases from year 5–10 were likely also due to OA.

We chose strict criteria both for inclusion in the study and for the definition of hip dysplasia in order to achieve high clinical relevance for our results. As an effect, the prevalence and absolute number of hips with hip dysplasia were relatively low (3.6%, n=17). Studying an exposure with low prevalence leads to a loss of precision of risk estimates[28], and this effect probably explains why we obtained relatively wide confidence intervals for the risk estimate of hip dysplasia for clinically relevant hip OA in the main analysis (adjusted OR 2.80 (95% CI 1.15, 6.79)). Not surprising, the confidence interval became wider when the majority of events were excluded (OR 3.9 (95% 1.01, 15.1)) and narrower when all uncertain events were excluded (OR 2.13 (95% CI 1.00, 4.50)) in the sensitivity analyses. Future studies that investigate the magnitude of association between hip dysplasia and clinically relevant hip OA should aim to do so with an even higher precision.

Lastly, the expert diagnosis that was used to obtain the outcome clinically relevant hip OA may be difficult to reproduce. It could be argued that the American College of Rheumatology (ACR) criteria, should have been used instead as it is an established classification system that combines clinical (hip pain) and radiographic features[29]. However, the presence of hip pain is not constant in OA, especially in early-stage OA, and therefore the fulfilment of the ACR criteria can fluctuate back and forth although OA is considered to be a progressive disease[30]. This can be seen in the CHECK cohort, where the ACR criteria based on only clinical data were fulfilled by 16% of participants at baseline and 16% of participants at 10-year follow-up, but only 4% (95% CI 1, 7) fulfilled the criteria at all time points[10]. In the current study, we aimed to define hip OA based on clinical and radiographic findings in a more definite way. We therefore used an expert diagnosis based on extensive clinical and radiographic data gathered between year 5–10 from the participant's first primary care consultation due to hip pain. This approach is clinically relevant as it has obvious similarities with assessments made in real life.

Conclusion

In the setting of primary care, middle-aged new consulters for hip pain had an increased long-term risk for clinically relevant hip OA, but not for incident radiographic hip OA, if they had hip dysplasia at baseline. With this in mind, we suggest that future research investigating the link between hip dysplasia and OA strives to include a definition for OA that is clinically relevant.

Statements

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Disclosures

We declare no conflicts of interest.

Ethics

The CHECK cohort has been approved by the Medical Ethics Committee of the University Medical Center Utrecht (02/017-E) and all patients provided informed consent prior to data collection.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Acknowledgements

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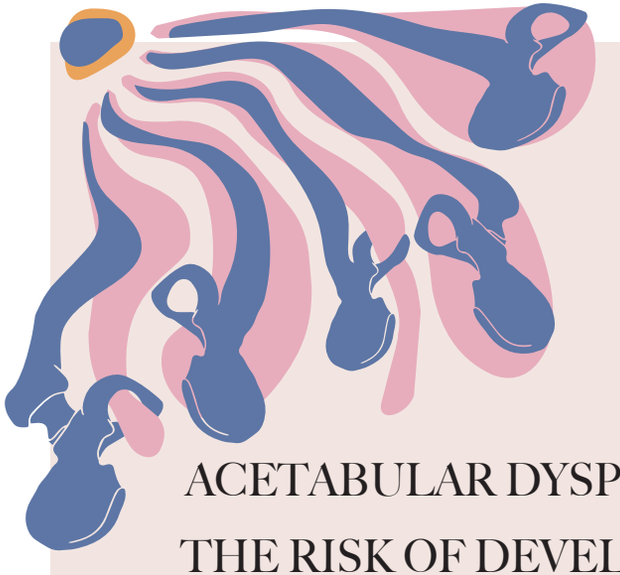

ACETABULAR DYSPLASIA AND THE RISK OF DEVELOPING HIP OSTEOARTHRITIS WITHIN 4-8 YEARS; AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS OF 18,807 HIPS FROM THE WORLD COACH CONSORTIUM

Submitted to Osteoarthritis and Cartilage

Acetabular dysplasia and the risk of developing hip osteoarthritis within 4-8 years; an individual participant data meta-analysis of 18,807 hips from the World COACH consortium.

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Summary

Objective

To study the association between various radiographic definitions of acetabular dysplasia (AD) and incident radiographic hip osteoarthritis (RHOA), and to analyze in subgroups.

Methods

Hips free of RHOA at baseline and with follow-up within 4-8 years were drawn from the World COACH consortium. The Wiberg center edge angle (WCEA), acetabular depth width ratio (ADR), and the modified acetabular index (mAI) were calculated. AD was defined as WCEA≤25°, and for secondary analyses as WCEA≤20°, ADR ≤250, mAI ≥ 13°, and a combination. A logistic regression model with generalized mixed effects with 3 levels adjusted for age, biological sex, and body mass index (BMI) was used. Descriptive statistics stratified by age, biological sex and BMI were reported.

Results

18,807 hips were included. Baseline characteristics: age 61.84 (± 8.32) years, BMI 27.40 (± 4.49) kg/m², 70.1% women. 4,766 hips (25.3%) had WCEA≤25°. Within 4-8 years (mean 5.8 ±1.6) follow-up, 378 hips (2.0 %) developed incident RHOA. We found an association between AD and RHOA (aOR 1.80 95% CI 1.40-2.34). In secondary analyses, all other definitions of AD were also associated with incident RHOA (aOR ranging from 1.52 95% CI 1.19-1.94 to 1.96 95% CI 1.26-3.02). Descriptive statistics showed that the relative risk in AD hips to develop RHOA was higher compared to non-AD hips in age group 61-70 (RR 1.70), BMI<25 (RR 1.66), and in female hips (RR 1.73).

Conclusion

AD was consistently associated with incident RHOA. AD hips in women and in the age group 61-70 years are more at risk of developing RHOA compared to non-AD hips.

Key Words
Hip imaging, hip shape, risk factor, developmental dysplasia, harmonized, big data, epidemiology

Introduction
There is no curative nonsurgical treatment available for hip osteoarthritis OA (1,2). Therefore, prevention is critical, but there is a lack of knowledge on risk factors for the development of radiographic hip OA (RHOA). Identifying risk factors for this disease should be prioritized.

Subtle features of hip shape may predate the development of OA by many years and might therefore be a preventative target (3,4). Acetabular dysplasia (AD) has previously been identified as a risk factor for developing RHOA (5,6). AD is defined by insufficient coverage of the femoral head by the acetabulum (7). Concentrated focal stress on a relatively small area of the acetabulum (7) is thought to lead to early mechanical failure of the cartilage, and to eventually cause hip OA (6,8-10).

A systematic review on hip morphology and osteoarthritis found an association between AD and RHOA (OR 2.38, 95% CI: 1.84 to 3.07) (9). However, when analyzing individual studies, these have yielded conflicting results and highlight the need for robust analysis, avoiding inconsistencies in measurements and definitions (8,9,11-13). Single cohorts are likely to be underpowered to determine whether specific high-risk subgroups are responsible for the associations found (9). Likely due to the overall low number of included individuals and therefore decreased statistical power, existing prospective cohort studies include hips free of RHOA as well as those with doubtful RHOA at baseline, which may bias the presently known associations. Hips with doubtful RHOA already show mild radiographic changes (possible joint space narrowing and signs of osteophytes), which may influence the radiographic measures of AD and represent the first signs of potential osteoarthritic changes (8,11,13).

Using an individual participant data (IPD) meta-analysis, we aimed to investigate the association between AD, defined by the Wiberg center edge angle (WCEA) ≤25° at baseline, and developing incident RHOA within 4-8 years follow-up. For secondary analyses, we investigated whether other measures of AD and other threshold values to quantify AD were associated with incident RHOA. Finally, we performed subgroup analyses stratified by age, biological sex, and body mass index (BMI) to assess potential high-risk subgroups.

Methods
Study design and participants.
Participants were drawn from the Worldwide Collaboration on OsteoArthritis prediCtion for the Hip (World COACH) consortium. The World COACH consortium is an international collaboration of all worldwide available prospective cohort studies with sequential pelvic or hip imaging. The consortium profile has previously been published in detail elsewhere (14).

For the present study we included all cohorts with a follow-up anteroposterior (AP) pelvic radiograph within 4-8 years of a baseline radiograph. This led to inclusion of 9 cohorts (Cohort Hip and Cohort Knee (CHECK), Multi-center Osteoarthritis Study (MOST), Osteo Arthritis Initiative (OAI), Rotterdam Study-I (RS-I), Rotterdam Study-II (RS-II), Rotterdam Study-III (RS-III), the Chingford Study, The Johnston County Project (JoCo) and the Study of Osteoporotic Fractures (SOF)), and exclusion of one cohort (Tasmanian Older Adults Cohort (TASOAC), Femoroacetabular impingement and hip osteoarthritis cohort (FORCe)).

We included hips with known BMI, biological sex, and age at baseline. Next, we excluded hips without an original baseline RHOA score. We then excluded radiographs of insufficient quality for automated AD measurement calculation and all AP hip radiographs as they

did not allow for constructing a horizontal reference line to adjust for pelvic rotation. Next, we included only the hips with an original RHOA score at follow-up and excluded all baseline hips with pincer morphology (acetabular overcoverage) as determined by a lateral center edge angle (LCEA) ≥40°. We chose to do the latter to compare hips with AD to a reference group with normal acetabular coverage, and because studies have found an association between pincer morphology and RHOA or total hip replacement (THR) (9,11). Finally, we included only hips free of any signs of RHOA at baseline (any score=0). Studying a population completely free of RHOA at baseline allows for determination of true predictors of RHOA, as existing osteophytes may affect the measurement of AD and bias the association between AD and incident RHOA. Furthermore, excluding hips with doubtful RHOA isolates the effect of AD on incidence RHOA rather than the effect of AD on progression in hips that likely already have some form of RHOA. This led to a total inclusion of 18,807 hips.

Radiographs

AP pelvic radiographs were taken at baseline and at follow-up between 4-8 years in each included cohort, according to cohort-specific protocols which have been published previously (15-19) (Supplementary material 1). To study the impact of the full-limb films from the MOST cohort on the associations between AD and RHOA, that are otherwise studied on pelvic radiographs, sensitivity analyses were performed excluding hips from the MOST cohort from the primary analysis.

Radiographic measurements

To avoid measurement variability across cohorts, for the present study all AD measurements were calculated uniformly on baseline radiographs. The bony outline of the proximal femur and acetabulum were automatically annotated on the AP pelvic radiographs with a point set using the BoneFinder® software (www.bone-finder.com; The University of Manchester, UK) (20). This point set was used to perform automated radiographic measurements using a previously published Python script, which was adapted and validated for World COACH data, for which a detailed description can be found elsewhere (21,22).

Radiographic measurements to define AD are depicted (Fig. 1). The amount of weight-bearing coverage of the femoral head by the acetabulum is measured by the center edge angle of Wiberg (WCEA) (9,11,23). AD was defined as a WCEA ≤ 25° in the primary analysis and in subgroup analyses, and additionally by WCEA≤20° for secondary analyses (8,12). The acetabular depth-width ratio (ADR) is a measure of depth of the acetabulum. AD was defined as an ADR ≤ 250 for secondary analyses (24). The modified acetabular index (mAI) measures the inclination of the acetabular roof. AD was defined as an mAI ≥ 13° for secondary analyses (24). In secondary analyses the radiographic definitions of AD were studied individually and combined.

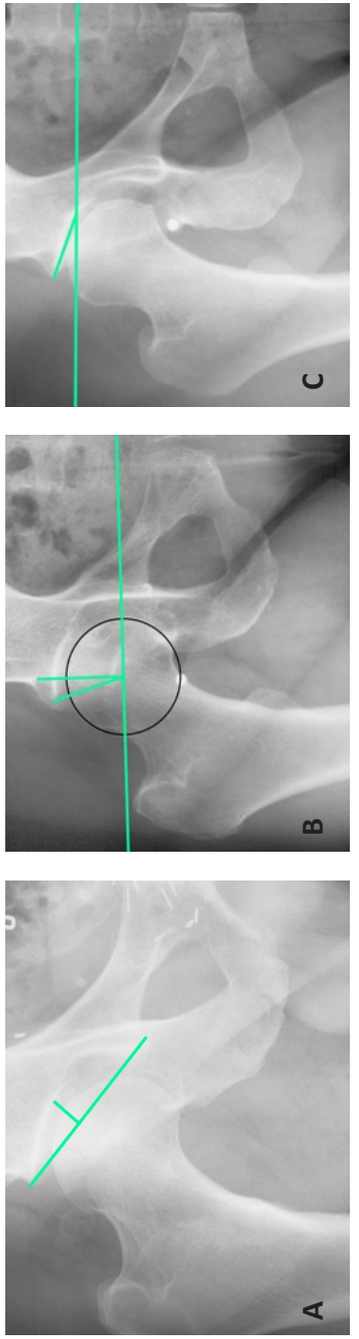


Fig. 1. Anteroposterior in pelvic radiographs with three radiographic measurements to define AD.
A: The acetabular depth-width ratio (ADR): The acetabular width was defined as a line across the length of the acetabular opening, extending from the lateral edge of the acetabulum to the pelvic teardrop. Next, the acetabular depth was determined by constructing a line perpendicular to the acetabular width, extending from the most medial point of the sourcil. The ADR is defined as the ratio of the depth to the width, multiplied by 1000. **B: The Center Edge Angle of Wiberg (WCEA)**: To determine the center of the femoral head, a best fitting circle is outlined around the femoral head based on the SSM points. The WCEA is then formed by a line drawn vertically through the center of the femoral head, perpendicular to the horizontal reference line, the second is drawn from the center of the femoral head to the most lateral weight-bearing part of the sourcil. **C: The modified acetabular index (mAI)**: The mAI measures the acetabular roof inclination. The measure is modified, as the original acetabular index is applied to hips with an open triradiate cartilage. The mAI measures inclination from the medial sourcil to the lateral bony part of the acetabulum.
Horizontal reference line (B+C): To correct for pelvic rotation, a horizontal reference line is calculated based on the average of 4 lines, between 1) both femoral head centers, 2) the most cranial points of the foramen obturator, 3) the most caudal points of the ischial tuberosity and 4) the most caudal points of the pelvic teardrop.

Radiographic Hip Osteoarthritis Grading

At baseline and follow-ups, all included radiographs had scores available by either the Kellgren and Lawrence (KL) classification (CHECK, Chingford, JoCo, MOST, RS-I, RS-II, RS-III) (25), the modified Croft classification (SOF) (26), or a modified OA score (OAI) (27).

The KL grading system defines OA severity in five grades (0-4) using a combination of osteophyte, joint space narrowing (JSN) severity, sclerosis and bone deformity (25). The modified Croft grading system defines OA severity in five grades (0–4) and is based on 5 radiographic features: JSN, osteophytes, subchondral sclerosis, cyst formation, and deformity (28). The modified OA grades are based on the modified Croft grades and defines OA in 3 grades (0-2), where 0 marks hips free of RHOA, 1 defines doubtful RHOA and 2 is definite RHOA (27).

Original OA scores per cohort were defined as "free of RHOA" (any score 0), "doubtful RHOA" (any score 1), or "definite RHOA" (KL ≥2, Modified Croft ≥2, Modified OA=2, or total hip replacement (THR)) (8,29,30).

Outcome measurements

The outcome was incident score "definite RHOA" within 4-8 years follow-up. Additionally for secondary analyses RHOA was defined as an ordinal outcome "free of RHOA", "doubtful RHOA" and "definite RHOA".

Statistical Analysis

All statistical analyses were performed in R version 4.1.1. Univariate differences in baseline characteristics between complete included and excluded cases were inspected. This means that we compared the included hips to the hips that were excluded because of OA score of 1 or 2 at baseline (Fig. 2). The associations between baseline AD, defined by the WCEA≤ 25°, and incident RHOA

were estimated with mixed effects logistic regression models. Mixed effects were added to account for the clustering in the data on three levels; hip, patient and cohort. The cohort was added as a level in this multi-level model to adjust for possible residual confounding by study differences. The model accounted for the difference between an open population cohort (Chingford, JoCo, RS-I, RS-II, RS-III), and closed population cohort (CHECK, OAI, MOST, SOF). The results are expressed as adjusted (aOR) and unadjusted (OR) odds ratios with 95% confidence intervals (CI) and were adjusted for baseline age, sex, and BMI. Additionally, a mixed model for ordinal data, namely RHOA classified as "free of RHOA", "doubtful RHOA", and "definite RHOA" was created using a forward build continuation ratio model to assess the impact of doubtful RHOA. Random effects were added to adjust for clustering, and the model was adjusted for baseline age, sex, and BMI. The ordinality assumption was relaxed for acetabular dysplasia, allowing the effect of acetabular dysplasia to be different for each level of RHOA at follow-up. The results were presented as an effect plot of the marginal probabilities marginalized over the random effects for women, with mean baseline age and BMI and randomly selected left hip side. Secondary analyses were performed using the same model and 5 definitions of AD: 1) WCEA ≤ 20°, 2) ADR ≤ 250, 3) mAI ≥ 13°, 4) three combined measures (WCEA ≤ 25° and ADR ≤ 250 and mAI ≥ 13°), and 5) a pooled definition of any of the three measures (WCEA ≤ 25° or ADR ≤ 250 or mAI ≥ 13°). In the secondary analysis when using a WCEA≤20° as the predictor, hips with a WCEA>20° and WCEA≤25° were excluded from the reference group to compare AD hips to a clean population of hips completely free of AD. In the secondary analysis when using any of the three measures for AD, the reference group contained hips free of AD and hips with only one or two measures of AD. We used descriptive statistics to explore whether specific subgroups may be more at risk to develop RHOA. Because of limited outcomes, it was not possible to perform subgroup analyses using logistic regression. We reported absolute risk (AR) and relative risk (RR) in AD and non-AD hips of developing RHOA stratified by age groups 40-50, 51-60, 61-70 and >70 years of age, by BMI by studying groups with a BMI>25 and BMI≤25, and by biological sex. The following packages in R were used: Logistic regression was performed using the lme4-package (31). The continuation ratio model was created using the GLMMadaptive package (32). The effect plot was created using the ggplot2-package (33).

Results

Participants

The flow of hips from those available in World COACH to the current final study population is depicted (Fig. 2). 18,807 hips free of any signs of RHOA at baseline were included. The mean interval between the baseline and follow-up radiograph across all cohorts was 5.8 ± 1.6 years. Baseline demographic data stratified per cohort are presented in Table 1. Our study population was younger than the excluded hips (61.84 ± 8.32 versus 64.56 ± 8.49 years, respectively); all other baseline characteristics and predictors were similar across included and excluded hips.

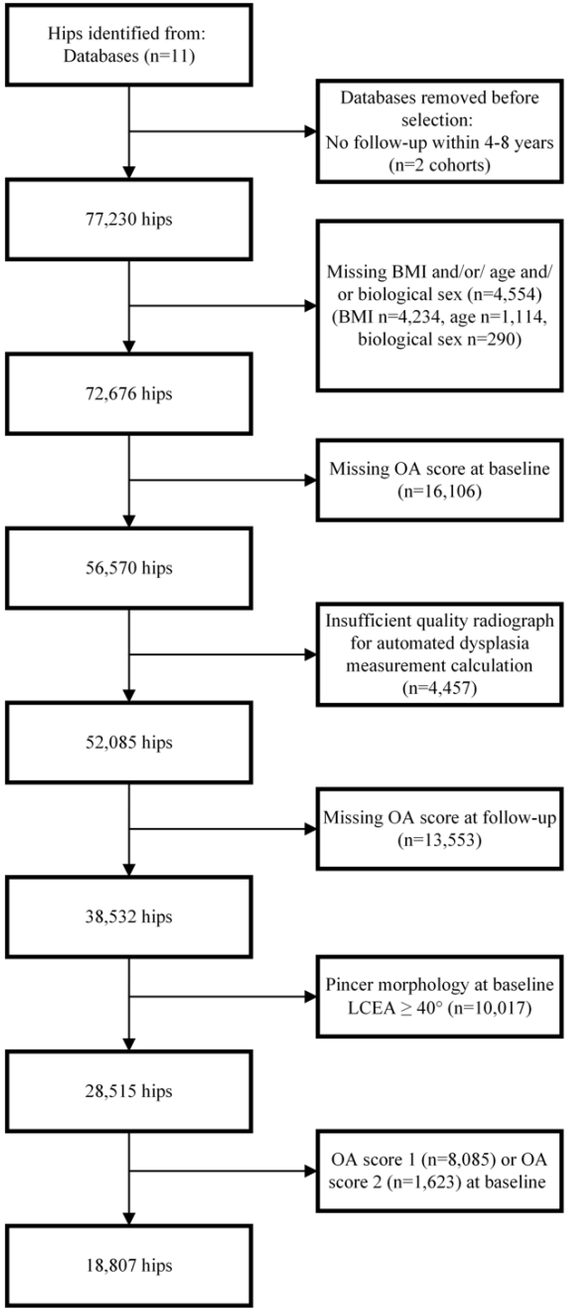


Fig 2. Flow of hips from consortium inclusion to final study population. OA: osteoarthritis. LCEA: lateral center edge angle. AP: anteroposterior. BMI: body mass index.

Table 1. Baseline characteristic of included hips, stratified per cohort.

	CHECK	Ching	JoCo	MOST	OAI	SOF	RS-I	RS-II	RS-III	Total incl.	Total excl.*
Hips, n (%)	753	727	614	1,776	4,552	3,547	2,460	1,810	2,568	18,807	9,708
Age, mean (sd) years	55.65 (5.24)	53.09 (5.59)	58.21 (8.49)	60.84 (7.43)	59.96 (8.90)	70.07 (4.27)	64.84 (6.46)	62.75 (6.15)	56.13 (4.85)	61.84 (8.32)	64.56 (8.49)
BMI, mean (sd) kg/m2	26.11 (4.02)	25.44 (4.09)	29.62 (6.01)	29.60 (5.03)	28.12 (4.60)	26.42 (4.37)	26.37 (3.53)	27.20 (3.86)	27.46 (4.08)	27.40 (4.49)	27.59 (4.73)
Men, n (%)	117 (15.5)	0 (0)	298 (48.5)	501 (28.2)	1,895 (41.6)	0 (0.0)	955 (38.8)	756 (41.8)	1,109 (43.2)	5,631 (29.9)	3,158 (32.5)
XWCEA ≤20°, n (%)	48 (6.4)	43 (5.9)	18 (2.9)	274 (15.4)	234 (5.1)	106 (3.0)	161 (6.5)	106 (5.9)	174 (6.8)	1,164 (6.2)	510 (5.3)
WCEA ≤25°, n (%)	218 (29.07)	173 (23.8)	130 (21.2)	795 (44.8)	1,085 (23.8)	575 (16.2)	628 (25.5)	453 (25.0)	709 (27.6)	4,766 (25.3)	2,105 (21.7)
ADR ≤250, n (%)	248 (32.9)	212 (29.2)	159 (25.9)	715 (40.3)	1,273 (28.0)	955 (26.9)	857 (34.8)	651 (36.0)	847 (33.0)	5,917 (31.5)	2,694 (27.8)
mAI ≥ 13°, n (%)	14 (1.9)	26 (3.6)	11 (1.8)	72 (4.1)	84 (1.8)	54 (1.5)	50 (2.0)	35 (1.9)	51 (2.0)	397 (2.1)	191 (2.0)
OA score=2 follow-up, men/women (%/%)	101 (13.4)	61 (8.4)	39 (6.4)	10 (0.6)	21 (0.5)	60 (1.7)	22 (0.9)	7 (0.4)	57 (2.2)	77/301 (1.4/2.3)	2,390 (24.6)

CHECK= Cohort Hip and Cohort Knee, MOST= Multi-center Osteoarthritis Study, OAI= Osteo Arthritis Initiative, RS-I= Rotterdam Study-I, RS-II=Rotterdam Study-II, RS-III= Rotterdam Study-III (RS-III), Ching= the Chingford Study, JoCo=The Johnston County Project, SOF= Study of Osteoporotic Fractures, WCEA= Wiberg Center Edge Angle, ADR= Acetabular Depth-Width Ratio, mAI= Modified Acetabular Index. OA score: 0= no RHOA, 1= Doubtful RHOA, 2= Definite RHOA.

*Excluded hips are defined as all eligible hips for analysis but with OA score 1 or 2 at baseline

Acetabular Dysplasia

At baseline, 4,766 (25.3%) hips had AD defined by a WCEA ≤25°. 1,164 (6.2%)
according to a WCEA ≤20°, 5,917 (31.5%) hips had an ADR ≤250 and 397 (2.1%) hips had an mAI ≥ 13°. The overlap between measures is illustrated in supplementary material 2.

Incident radiographic hip osteoarthritis

378 hips (2.0%) developed incident RHOA within 4-8 years follow-up. The incidence of RHOA at follow-up per cohort were: CHECK: 13.4% Chingford: 8.4%, JoCo: 6.4%, MOST 0.6%, OAI: 0.5%, SOF: 1.7 %, RS-I: 0.9%, RS-II: 0.4%, RS-III: 2.2%.

Primary analysis: association between acetabular dysplasia and radiographic hip osteoarthritis

A significant association (aOR 1.80 (95% CI 1.40-2.34) between AD (WCEA ≤25°) and incident RHOA within 4-8 years was observed. The association remained statistically significant after adjustment for covariates.

The effect plot of the marginal probabilities from the mixed model for ordinal data is shown in figure 3. All marginal probabilities were calculated for hips free of RHOA, in women aged 62 years with a BMI of 27.4 kg/m2 at baseline. The marginal probability for hips with AD to develop doubtful RHOA within 4-8 years is 0.15 (95% CI 0.10-0.20), compared to 0.17 (95% CI 0.11-0.23) for hips free of AD. The marginal probability for AD hips to develop definite RHOA within 4-8 years is 0.03 (95% CI 0.01-0.08), compared to 0.02 (95% CI 0.01-0.06) for AD-free hips.

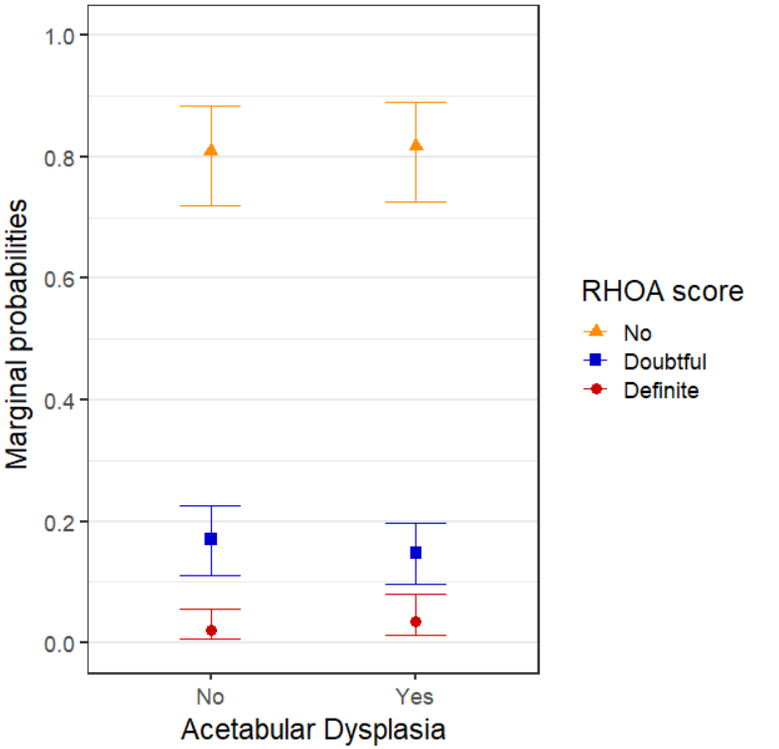


Fig. 3: Marginal probabilities of RHOA score within 4-8 years for women aged 62 years and BMI of 27.4 kg/m2 in hips with AD (WCEA ≤25°) or without AD. The probabilities were marginalized over the random effects, i.e., cohort and individual and the model was adjusted for age, BMI, biological sex, and hips side.

Sensitivity analysis excluding MOST

The study population excluding MOST resulted in a total of 17,031 hips. A significant association was found (aOR 1.89 95%CI 1.45 -2.47) between hips with AD (WCEA ≤25°) and incident RHOA in the study population excluding hips from the MOST cohort.

Secondary analyses: association between various measures of acetabular dysplasia and radiographic hip osteoarthritis

Significant associations between AD defined by WCEA ≤20°, ADR≤250 or either WCEA ≤25° or ADR ≤250 or mAI ≥ 13°) and incident RHOA within 4-8 years were observed. The associations remained statistically significant after adjusting for covariates. Because of a limited number of events (14 hips), it was not possible to calculate the association in the AD defined by mAI≥ 13° group. All ORs are summarized in Table 2.

Table 2. Associations between various radiographic definitions of AD and incident RHOA. Significant associations are printed in **bold.**

Definition of AD	Hips with AD at baseline, n	Hips with incident RHOA at follow-up, n	Absolute risk (%)	Unadjusted OR (95% CI) *	Adjusted OR (95% CI)
WCEA ≤25°	4,766	127	127/4,766 (2.7)	**1.73 (1.33-2.25)**	**1.80 (1.40-2.34)**
WCEA ≤20°	1,164	34	34/1,164 (2.9)	**1.80 (1.28-2.52)**	**1.96 (1.26-3.02)**
ADR ≤250	5,917	144	144/5,917 (2.4)	**1.48 (1.15-1.90)**	**1.53 (1.19-1.96)**
mAI ≥ 13°	397	14	14/397 (3.5)	-****	-****
WCEA ≤25° & ADR ≤250 & mAI ≥ 13°**	351	14	14/351 (4.0)	-****	-****
WCEA ≤25° or ADR ≤250 or mAI ≥ 13°***	7,480	176	176/7,480 (2.4)	**1.47 (1.16-1.88)**	**1.52 (1.19-1.94)**

Odds ratios ORs were adjusted for age, BMI, biological sex, and hip side, and were accounted for by clustering cohort and individual. WCEA: Wiberg center edge angle. ADR: acetabular depth-width ratio. mAI: modified acetabular index. OR: odds ratio. CI: confidence interval.

* The unadjusted odds ratios are calculated using the logistic regression model with generalized mixed effects with 3 levels (cohort, person and -hip side correlation) unadjusted for age, biological sex, and BMI.

**The reference group contained hips free of AD and hips with only 1 or 2 measures of AD.

*** The reference group contained hips free of any measure to define AD.

**** Too few cases with both predictor and outcome to calculate an OR

Subgroup analyses

Descriptive statistics stratified by age group, biological sex, and BMI are summarized in Table 3. The relative risk for hips with AD to develop RHOA was highest in age group 61-70, in hips with BMI<25, and in women.

Table 3. Absolute and relative risk of hips with acetabular dysplasia (WCEA ≤25°) to develop incident radiographic hip osteoarthritis stratified by age group, BMI, and biological sex.

Strata	Total hips in group, n	Hips with AD (WCEA ≤25°), n	Hips with incident RHOA, n	Hips with AD and incident RHOA, n	Absolute Risk, % *	Relative Risk, % (95% CI) **
Age group (years)						
40-50	1,753	526 (30.0)	35 (2.0)	11	0.6	1.07 (0.53-2.17)
51-60	6,738	1,921 (28.5)	159 (2.4)	57	0.8	1.40 (1.02-1.93)
61-70	7,192	1,691 (23.5)	128 (1.8)	44	0.6	1.70 (1.19-2.44)
70+	3,124	628 (20.1)	56 (1.8)	15	0.5	1.45 (0.81-2.61)
BMI						
<25	5,874	1,380 (23.5)	142 (2.4)	48	0.8	1.66 (1.18-2.34)
≥25	12,933	3,386 (26.2)	236 (1.8)	79	0.6	1.42 (1.09-1.85)
Biological sex						
Men	5,631	1,369 (24.3)	77 (1.4)	14	0.2	0.69 (0.39-1.23)
Women	13,176	3,397 (25.8)	301 (2.3)	113	0.9	1.73 (1.37-2.18)

*The absolute risk was calculated using the following equation: (number of hips with pincer morphology and RHOA/Total number of hips in subgroup)

**The relative risk was calculated using the following equation: (number of hips with pincer & RHOA/(number of hips with pincer & RHOA + number of hips with pincer only)) / (number of hips with RHOA without pincer morphology/ (number of hips with RHOA without pincer morphology + number of hips without pincer morphology or RHOA))

Discussion

This IPD meta-analysis on the association between AD and incident RHOA in a large prospective study of 18,807 hips free of any RHOA at baseline, demonstrated a significant association between AD defined by a WCEA ≤25° and incident RHOA within 4-8 years. Additionally, hips with AD were more likely to progress from being RHOA-free to definite RHOA rather than doubtful RHOA compared to non-AD hips. Secondary analyses showed that other measures of AD (WCEA ≤20°, ADR ≤250 and a combination of WCEA≤25° and ADR ≤250) were also associated with an increased risk of developing RHOA. Descriptive statistics show that AD hips in women, individuals aged 61-70 and individuals with BMI<25 have a higher relative risk to develop RHOA.

Several studies have shown that AD is associated with the development of RHOA. The strength of associations in prospective cohort studies ranged from aOR 1.56 (95% CI 1.09-2.24) to aOR 5.45 (95% CI 2.40-12.34) (8,9,11,12,34,35). Conversely, a number of studies (case-control, prospective and cross-sectional) have failed to find such an association (13,36,37). Our results support the finding that AD is associated with RHOA, although the association in the present study is not as strong as previously reported. This may be explained by the fact that the present study population only included hips free of any RHOA at baseline, whereas previous prospective cohort studies also included hips with doubtful RHOA at baseline, in which the stronger associations may reflect an association between AD and progression of RHOA, rather than incident RHOA (8,9,11,12,34,35). Furthermore, publication bias may have played a role in selective publication of (strong) associations between AD and RHOA previously, and negative results may have been disfavored (38). Time to follow-up as well as how AD and RHOA are measured and defined may also have contributed to variable strengths of associations in prospective studies or absence of an association in cross-sectional studies.

Although generalizable evidence is lacking, it has been hypothesized that AD leads to RHOA only in younger individuals (11). Saberi et al. studied hips from RS-I and RS-II with an average age of 65 years at baseline and found that the magnitude of the association AD and RHOA was stronger in persons aged ≤65 years at baseline (OR 2.59 95% CI 1.62-4.16) compared to those aged > 65 years (OR 1.74 95% CI 0.90-3.37). On average, the population in this IPD meta-analysis is younger (61.84 years) which is likely because only hips completely free of RHOA were included at baseline, whereas the aforementioned study also included hips with doubtful RHOA at baseline. Our study lacked sufficient statistical power to stratify associations by age. However, the descriptive subgroup statistics showed that hips with AD aged 61-70 at baseline had an increased relative risk (1.70 95% CI 1.19-2.44) of developing incident RHOA, which was lower in other age groups although the CI overlaps (age 40-50 RR: 1.07 95% CI 0.53-2.17, age 51-60 RR: 1.40 95% CI 1.02-1.93, age 70+ RR: 1.45 95% CI 0.81-2.61). This finding suggests that younger individuals with AD may not be more at risk, but future studies with sufficient power should further analyze these associations.

The prevalence of AD defined by a WCEA ≤25° in our study population was similar in women (25.8%) compared to men (24.3%) in the study population. Although acetabular undercoverage was equally common in men and women in our study, we found that the relative risk is significantly lower in men with AD to develop RHOA (RR 0.69 95% CI 0.39-1.23) compared to women (RR 1.73 95% CI 1.37-2.18). It has been hypothesized that women have different joint alignment and thus joint load distribution than men. Estrogen metabolism, or pregnancy related pelvic instability may play a role in sex differences (39).

We hypothesized that a higher overall body weight may lead to higher joint load and therefore increase the risk of RHOA in overweight individuals with AD. Descriptive statistics show a slightly increased

relative risk for AD hips in individuals who have a BMI<25 (RR 1.66 95% CI 1.18-2.34) compared to AD hips of individuals with BMI ≥25 (RR 1.42 1.09-1.85) in our study population, but CIs overlap meaning this is likely not significant. Interestingly, a recent study in children found a negative association between being overweight and developing dysplasia (40). A previous study in the Rotterdam Study also reported low BMI as a risk factor for AD hips to develop RHOA (23).

The sensitivity analysis excluding the MOST cohort, as this contained long-limb radiographs rather than AP pelvic radiographs, yielded similar results to the primary analysis. Excluding MOST led to an aOR of 1.89 (95%CI 1.45 -2.47) for the association between AD and RHOA, compared to the primary analysis which does include the MOST cohort of aOR 1.80 (95% CI 1.40-2.34). By including the hips from the MOST cohort in the primary analysis, we argue that the reported aORs contribute to generalizable results considering the added variation of a different radiographic view. Furthermore, the confidence intervals largely overlap, from which we conclude that there are no statistically important differences between the study population including and excluding the hips from the MOST cohort.

Quantification of AD may have impacted the previously reported associations between AD and RHOA (24). In the present study, WCEA rather than LCEA was employed, as we argue that the weight-bearing surface, rather than the entire bony femoral head coverage, is under stress as a result of AD. Secondly, the threshold to define AD also vary in the literature. We used a threshold of WCEA ≤25° which indicates mild AD and should be kept in mind when interpreting the results. The association between AD when defined by WCEA ≤20° increased, which may indicate that more severe AD increases the risk of developing RHOA. Finally, we found that most studies only use acetabular coverage as a measure of AD, but for the present study we examined if acetabular depth or roof inclination

influenced the reported associations. We found that both acetabular undercoverage as well as a shallow acetabulum were significantly associated with RHOA at follow-up in the present population. Whether acetabular roof inclination is also associated with RHOA could not be concluded from the present study, but future studies with long-term follow-up and therefore likely a higher incidence of RHOA may shed light on this measurement as a predictor.

A comprehensive definition of hip osteoarthritis in epidemiological studies is still lacking (41). Commonly used RHOA classification systems are the KL and (modified) Croft grading systems (25,26,30,41), for which good interclass correlation coefficients (ICC's) (κ = 0.55-0.92) have been reported in the World COACH cohorts (16,17,25,26,30,41,42). The inevitable variability in RHOA grading was corrected for in the logistic regression model by accounting for within-cohort effects. The incidence of RHOA in the present study of 2.01% (range per cohort 0.5-13.4%) is relatively low compared to similar studies (8,11,12,42,43). Interestingly, the cohorts with the highest incidence of RHOA at follow-up (CHECK (22.6%), JoCo (10.9%) and Chingford (8.6%) were on average younger at baseline than the cohorts with the lowest incidence (OAI (0.5%), RS-II (0.4%) and RS-III (0.2%). The overall low incidence of incident RHOA is likely related to the exclusion of hips with doubtful RHOA at baseline.

The primary strength of the present study is the design. IPD meta-analysis created increased statistical power, reduced publication bias, and allowed for investigation of subgroup effects (44). As RHOA is a heterogeneous disease, identifying subgroups for interventions is likely a promising way forward in clinical research. A second benefit of IPD meta-analysis compared to meta-analysis alone is that we were able to choose confounders for all included hips. This allowed us to correct for the same covariates across all cohorts and perform uniform analyses. IPD also helped improve data quality by combining studies with different follow-up and

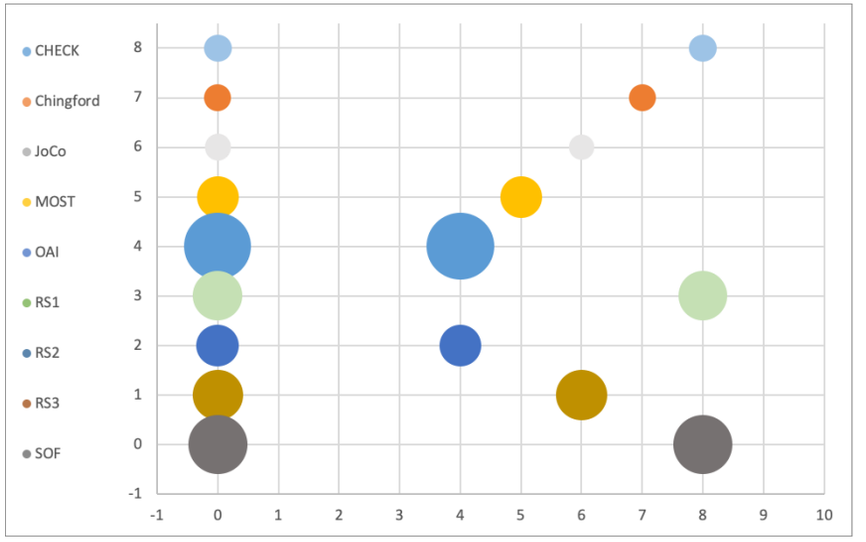
outcomes, to improve generalizability of findings (45,46). A second strength is the use of multiple, uniform radiographic measurements to quantify AD. Although the WCEA proved to be the only measure of AD significantly associated with incident RHOA in our analysis, we argue that by additionally studying the ADR and mAI, we captured more of the AD characteristics compared to studies only employing a CEA (11,34). A third strength is the uniformity of automated measurements, which removed variability compared to manual measurements and allowed for objective AD measurements across all cohorts (9).

This study was subject to limitations. The primary limitation is the subjective nature of original OA grading systems, as they rely on subjective assessment of OA features. We accounted for variability in OA scores per cohort in our statistical model and argue that, as these grading systems are still primarily used in a clinical setting, our study represents best current clinical practice. A second limitation is the variety of radiographic protocols per cohort, such as supine vs. weight-bearing radiographs. However, a recent study showed that for JSN, no difference in measurements between weightbearing or supine AP radiographs was found (47) A horizontal reference line allowed for standardization of all other measurements, which reduced variability to a minimum. A limitation of IPD meta-analysis is that it may become prone to selection bias when IPD are only sought for a specific subset of studies. The World COACH cohorts however have been recruited based on a systematic literature search, which has been repeated recently (14). Clinicians, researchers, and patients are also actively involved to help identify studies that should be included in the consortium. We therefore argue that publication bias was minimized in our study. We used definitions of AD only in one plane, thereby potentially neglecting anatomical abnormalities that may exist at different planes simultaneously (48). We argue however, that by using multiple measurements to define AD, we were still able to capture a wide array of anatomical variability, in line with current clinical practice.

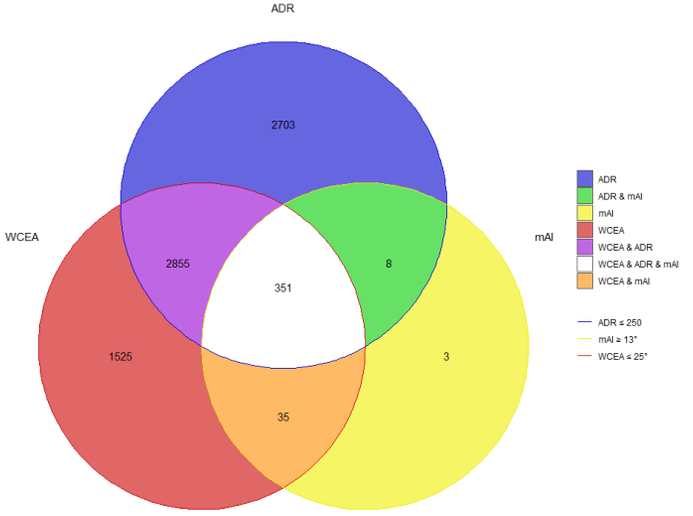
In future studies, identification of modifiable risk factors is essential for prevention of hip osteoarthritis, as well as improving quality of life by advancing individualized care and identification of new treatments. Hip dysplasia is recognized as a potentially modifiable risk factor. It has been hypothesized that there are two distinct forms of hip dysplasia; developmental dysplasia of the hip (DDH) which is diagnosed during infancy, and AD, which is diagnosed later in life (49). A recent study found demographic differences between patients diagnosed with DDH in infancy and adults with AD, supporting this hypothesis (50). Examination of newborns for hip instability exemplifies prevention for hip osteoarthritis in DDH hips, as the plastic hip joint can be stabilized to produce a congruent joint . This study showed that AD in the adult population was highly prevalent depending on the definition used, but the association with RHOA in general may be weaker than previously thought. It is therefore warranted to further our understanding of which individuals with AD specifically are at high risk of developing hip osteoarthritis, and, assuming that two distinct forms exist, investigate whether one form is clinically more relevant.

In conclusion, this study demonstrated that AD is a risk factor for incident RHOA in hips free of RHOA at baseline. This IPD meta-analysis allowed for a robust analysis of the association between AD and RHOA, due to the large sample size, uniform measurements of AD across all baseline radiographs, and harmonized outcome of RHOA. Identification of modifiable risk factors is essential for prevention of hip osteoarthritis in the future, as well as improving quality of life by advancing individualized care and identification of new treatments.

Supplementary material



Supplementary material 1: Radiographs per cohort at baseline and follow-up within 4-8 years. The size of the dot is proportionate to the number of included individuals at baseline and at each follow-up moment.



Supplementary material 2: Venn diagram of all AD measures. ADR: acetabular depth-width ratio ≤250. mAI: modified acetabular index ≥13°. WCEA: Wiberg center edge angle ≤25°.

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Data sharing statement

Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. We encourage the use of data by third parties, although this is subject to approval by the steering committees of the World COACH consortium and the participating cohorts, as well as to legal boundaries regarding data ownership. A standardised data request form is available for which will be reviewed uniformly in order to consistetenly handle World COACH data requests.

Competing interests

GJ reports personal fees from Novartis outside the submitted work. SBZ reports consulting fees from Pfizer Infirst Healthcare and personal fees for being a Deputy Editor for Osteoarthritis and Cartilage outside the submitted work. CL and TC report a patent for an image processing apparatus and method for fitting a deformable shape model to an image using random forest regression voting. CL reports licensing royalties for this patent from Optasia Medical outside the submitted work. AN is an associate editor for Osteoarthritis and Cartilage and is on the OARSI Board of Directors outside the submitted work. AM is on the Editorial Board for the British Journal of Sports Medicine and the Journal of Science and Medicine in Sport outside the submitted work. HW

reports being a minority shareholder of Uplanner BV and Replasia BV outside the submitted work.

Patient and public involvement

Patient involvement is ongoing in the World COACH consortium as they co-determine and prioritize research questions to be answered within World COACH. World COACH researchers attend annual conferences for patients with OA in the Netherlands (Artrose Gezond) and engage in open dialogue with OA patients to form research goals. The potential of the consortium to discover risk factors and potential treatment options are explained to patients, and both patients and public are encouraged to share ideas and questions they want answered through www.worldcoachconsortium.com.

Ethical approval

This study involves human participants but was excepted from ethical approval (Erasmus MC Medical Ethics Review Committee) as it uses previously collected observational data for which the participants had originally given informed consent, and all cohort studies included in this consortium already had ethics approval from their respective committees. Participants gave informed consent to participate in the study before taking part.

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PINCER MORPHOLOGY IS ASSOCIATED WITH INCIDENT HIP OSTEOARTHRITIS: PROSPECTIVE INDIVIDUAL PARTICIPANT DATA FROM 18,935 HIPS FROM THE WORLD COACH CONSORTIUM

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Pincer morphology is associated with incident hip osteoarthritis: prospective individual participant data from 18,935 hips from the World COACH consortium

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Summary

Objective

To assess the relationship between pincer morphology and incident radiographic hip osteoarthritis (RHOA). The secondary aim is to study specific subgroups.

Methods

Hips completely free of RHOA at baseline and with follow-up within 4-8 years were drawn from the World COACH consortium. The lateral center edge angle (LCEA) was calculated uniformly on all baseline radiographs. Pincer morphology was defined as a LCEA≥40°, and LCEA≥45° in sensitivity analyses. The primary outcome was incident RHOA defined by a harmonized OA score. A logistic regression model with generalized mixed effects with 3 levels (within- cohort, -person and -hip side correlation) adjusted for age, biological sex, and BMI was employed. Descriptive statistics are reported for age, biological sex and BMI.

Results

18,935 hips from 9 cohorts were included. 4,894 hips (25.8%) had pincer morphology. Within 8 years (mean 6.0 ± 1.7 years), 352 hips (1.9%) developed RHOA. Pincer morphology (LCEA≥40°) was not associated with RHOA (OR 1.15 (0.87-1.51), whereas LCEA≥45° was associated with RHOA (OR 1.50 95% CI 1.05-2.15). Pincer morphology in groups aged 40-50 (RR 2.67) and BMI ≥25 (RR 1.21) had a higher risk compared to non-pincer hips. Women (RR 1.15) with pincer morphology seem to be more at risk than men (RR 0.92).

Conclusion

The odds of developing RHOA within 8 years for hips with pincer morphology defined by LCEA≥45° is 1.50 times higher than pincer-free hips, whereas an LCEA≥40° was not significantly associated with RHOA. Younger individuals and increased BMI in hips with pincer morphology may increase the risk for RHOA.

Introduction

Osteoarthritis (OA) is a debilitating disease that significantly impacts quality of life (1). It is therefore essential to identify risk factors for OA, which can potentially be targeted in prevention and treatment strategies (2-4). Risk factors for hip OA that have been identified include age, biological sex, genetics, physical workload and hip shape (2,3,5,6).

Pincer morphology is a hip shape characterized by acetabular over coverage of the femoral head, and is associated with femoroacetabular impingement syndrome (FAIs), a motion related clinal disorder of the hip (7-9). Pincer morphology may cause repeated abutment between the proximal femur and the acetabulum during terminal motion of the hip (Fig. 1) (8). It has been proposed that the repeated impingement leads to intra-articular damage (e.g., cartilage and labral pathology), and ultimately to hip OA (7,8).

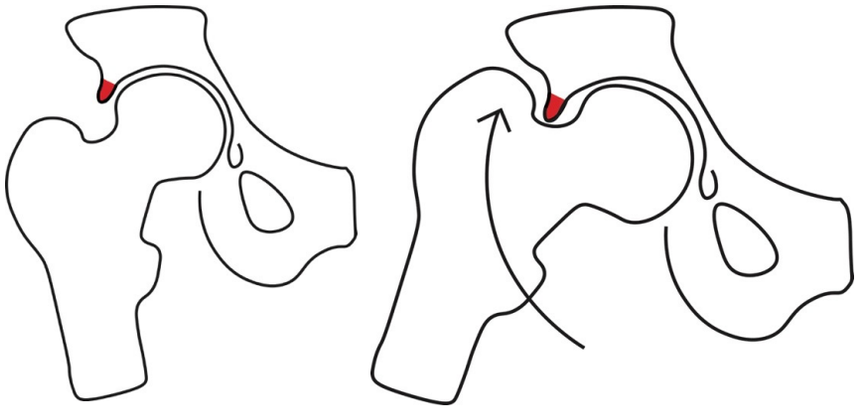

Fig. 1 The mechanism of pincer impingement. The anatomy of the pincer hip leads to an abnormal linear contact between the overcovered acetabular rim and the femoral neck during terminal motion of the hip, which may lead to impinging moments. When motion causes repetitive impingement moments, the acetabular cartilage is thought to damage over time.

Contrary to other hip shapes such as cam morphology (an aspherical femoral head) or acetabular dysplasia (AD) (acetabular undercoverage of the femoral head), it is unclear whether an association between pincer morphology and the development of radiographic hip osteoarthritis (RHOA) exists (3,10-14). A recent systematic review did not find a higher likelihood of developing hip OA over a median of 9.2 years in hips with pincer morphology as defined by a lateral center edge angle (LCEA) ≥40° than in hips with a LCEA <40° in prospective studies, whereas cross-sectional studies showed that hips with OA were 3.7 times more likely to have a LCEA ≥40° (3). However, substantial heterogeneity (I2 60%) was observed between the results of the prospective studies, making it difficult to draw conclusions from this meta-analysis (3). Furthermore, study populations and how pincer morphology is defined and measured varies across studies, which may influence the reported associations.

Our aim is to perform an individual participant data (IPD) meta-analysis on the association between pincer morphology at baseline and the risk of developing RHOA within 4-8 years follow-up. Additionally, we will study this association in subgroups stratified by age, biological sex and BMI.

Methods

Study design and participants

Participants were drawn from the Worldwide Collaboration on OsteoArthritis prediCtion for the Hip (World COACH) consortium. The World COACH consortium is a global collaboration of all available prospective cohort studies with prospective pelvic or hip imaging. The consortium profile has previously been published in detail elsewhere (15).

In this study we included all cohorts with a follow-up anteroposterior (AP) pelvic radiograph within 4-8 years of a baseline radiograph, and therefore included 9 cohorts (Cohort Hip and Cohort Knee (CHECK), Multi-center Osteoarthritis Study (MOST), Osteo

Arthritis Initiative (OAI), Rotterdam Study-I (RS-I), Rotterdam Study-II (RS-II), Rotterdam Study-III (RS-III), the Chingford Study, The Johnston County Project (JoCo) and the Study of Osteoporotic Fractures (SOF)), and excluded two cohorts (Tasmanian Older Adults Cohort (TASOAC), Femoroacetabular impingement and hip osteoarthritis cohort (FORCe)).

All included hips needed to have known BMI, biological sex, and age at baseline. Next, hips without an original baseline RHOA score at baseline were excluded. All radiographs of insufficient quality for automated pincer morphology measurements and all AP hip radiographs were excluded as they did not allow for constructing a horizontal reference line to adjust for pelvic rotation. Next, we excluded all hips lacking an original RHOA score at follow-up and excluded all baseline hips with AD as determined by a Wiberg center edge angle (WCEA) ≤25°. We chose to do this in order to compare the pincer hips to a clean reference group of hips with normal acetabular coverage. Furthermore, multiple studies have demonstrated a significant association between AD and RHOA (4,11,16). Finally, we included only hips free of any signs of RHOA at baseline (any OA score=0). We chose to focus on a population of hips completely free of RHOA to identify the true predictors of this disease. This led to a total inclusion of 18,935 hips.

Radiographs

AP pelvic radiographs were obtained by cohorts at baseline and at follow-up between 4-8 years (Fig.2). All radiographs were obtained based on a cohort-specific predetermined protocol established by each cohort. Detailed information about specific radiographic protocols, was previously published (15). Five cohorts (CHECK, OAI, RS-I, RS-II, RS-III) had weight-bearing AP pelvic radiographs, one cohort (MOST) had weight-bearing full-limb radiographs, and three cohorts (the Chingford Study, JoCo, and SOF) had supine AP pelvic radiographs.

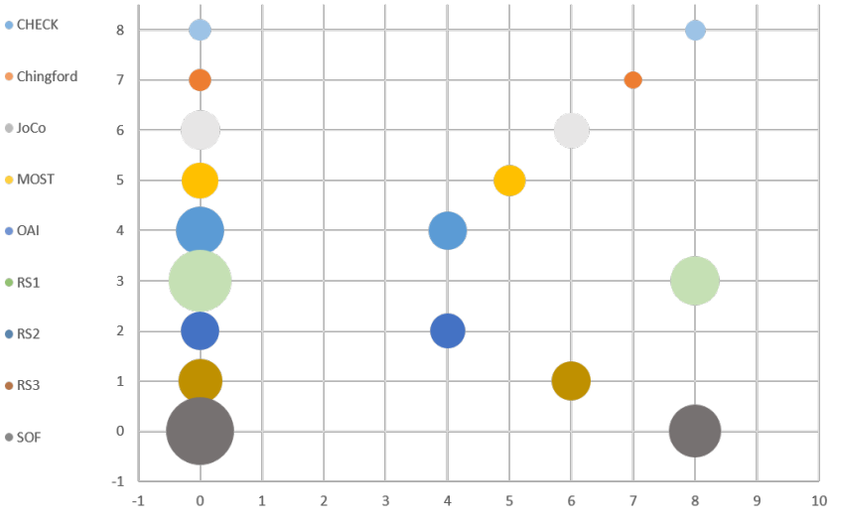

Fig. 2 Radiographs per cohort at baseline and follow-up within 8 years. The size of the dot is proportionate to the number of included individuals at each follow-up moment. *Weight-bearing AP pelvic radiographs. †Supine AP Pelvic radiographs. ∞ full-limb radiographs.

Radiographic measurements

Lateral Center Edge Angle

To avoid measurement variability across cohorts, uniform pincer morphology measurements were performed on all baseline radiographs. The bony outline of the proximal femur and acetabulum were annotated on the AP pelvic radiographs with a point set using the BoneFinder® software (www.bone-finder.com; The University of Manchester, UK) (17). This point set was used to perform automated radiographic measurements using a previously published Python script, which was adjusted and validated on World COACH data (18,19).

The LCEA quantifies bony coverage of the femoral head by the acetabulum (Fig. 3) (20). Pincer morphology was defined as a LCEA ≥40°. Sensitivity analyses with an LCEA threshold of ≥45° were performed to determine whether increased acetabular overcoverage influences the risk of developing RHOA.

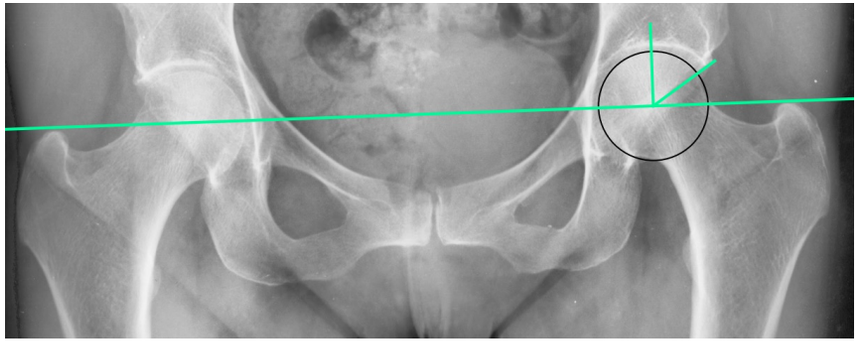

Fig. 3. The lateral center edge angle (LCEA) is measured on an AP pelvic radiograph. The LCEA was constructed according to the following steps. A horizontal reference line is constructed to correct for pelvic tilt in the radiograph, and is based on the average of 4 lines, between 1) both femoral head centers, 2) the most cranial points of the foramen obturator, 3) the most caudal point of the ischial tuberosity and 4) the most caudal point of the pelvic teardrop. To determine the center of the femoral head, a best fitting circle is drawn around the femoral head based on the SSM points. The LCEA is then formed by two lines drawn from the center of the best fitting circle. The first line is drawn vertically through the center of the femoral head, perpendicular to the horizontal reference line. The second line is drawn from the center of the best fitting circle to the most lateral bony point of the acetabulum.

Radiographic Hip Osteoarthritis Grading

Radiographs from seven cohorts (CHECK, Chingford, JoCo, MOST, RS-I, RS-II, RS-III) were graded using the Kellgren and Lawrence (KL) classification system. The KL grading system defines OA severity in five grades (0-4), combining osteophytes, joint space narrowing (JSN) severity, sclerosis and deformity (21). Definite RHOA is defined by KL grade ≥ 2 (4,22). One cohort (SOF) had used the modified Croft classification to score RHOA on radiographs. The modified Croft grading system defines OA severity in five grades (0–4) and is based on five radiographic features: JSN, osteophytes, subchondral sclerosis, cyst formation, and femoral head deformity. The cut-off value ≥ grade 2 is used to define RHOA and requires the presence of maximum osteophyte grade >=2 and/or maximum JSN grade <2 (22). One cohort (OAI) used an adaptation of the modified Croft score, referred to as "modified OA score" in the original studies (23). The grading system ranges from grade 0-2 with the following definitions: a score of 0 indicates no evidence of OA, 1 represents doubtful OA, and 2 represents definite OA.

Original OA scores per cohort were harmonized into "free of RHOA" (any score 0), "doubtful RHOA" (any score 1), or "definite RHOA" (KL ≥2, Modified Croft ≥2, Modified OA=2, or total hip replacement (THR)) (4,22,24).

Outcome measurements

The primary outcome was "definite RHOA" defined by the harmonized RHOA score (OA score = 2) within 4-8 years follow-up from baseline. Additionally, RHOA was defined as an ordinal outcome "free of RHOA", "doubtful RHOA" and "definite RHOA" in secondary analyses.

Statistical Analysis

All statistical analyses were performed in R version 4.1.1. Univariate differences in baseline characteristics between complete included and excluded cases were inspected, meaning the included hips were compared to the hips that were excluded because of an OA score of 1 or 2 at baseline (Fig. 3.) The association between baseline pincer morphology defined by LCEA≥40° and incident RHOA was estimated using a one-stage logistic regression model with generalized mixed effects with 3 levels: hip side (left/right), individual and cohort. We corrected for the cohort in this multi-level model in order to adjust for possible residual confounding by study differences. The model accounted for the difference between open (Chingford, JoCo, RS-I, RS-II, RS-III), and closed population cohorts (CHECK, OAI, MOST, SOF). The inclusion criteria for various population types vary notably, with a key distinction centered on enrollment characteristics. In an open population cohort, the participant count is adaptable, recruitment is ongoing, and research objectives are diverse. Conversely, a closed population cohort maintains a predetermined participant group

from the study's outset, featuring more defined inclusion criteria and focused research goals. This primary difference underscores the dynamic nature and versatility of open population cohorts, contrasted with a more static structure and specificity of closed population cohorts. The results are expressed as adjusted (aOR) and unadjusted odds ratios (OR) with 95% confidence intervals (95% CI) and were adjusted for baseline age, biological sex, and BMI. A sensitivity analysis was performed using LCEA≥45°. In the sensitivity analysis hips with a 40°≤LCEA<45° were excluded from the reference group in order to compare pincer hips to a clean population of hips free of pincer morphology by any definition. Additionally, a continuation ratio model with ordinal outcome RHOA classified as "free of RHOA", "doubtful RHOA" and "definite RHOA" was created to assess the influence of doubtful RHOA as reference group. Again, random effects were added to adjust for clustering of cohorts and individual, and the model was adjusted for baseline age, sex, and BMI. Pincer morphology was defined as LCEA≥40°. The model was built in a forward fashion and a relaxed ordinality assumption for pincer morphology, allowing the effect of pincer morphology to be different for each level of the outcome RHOA within 4-8 years. The results were presented as an effect plot of the marginal probabilities with reference to the random effects for females, with mean baseline age and BMI and randomly selected left hip side. Because of limited outcomes, it was not possible to perform subgroup analyses using the same logistic regression model. We reported absolute risk (AR) and relative risk (RR) in pincer morphology and non-pincer hips to develop RHOA stratified by age (40-50, 51-60, 61-70 and >70 years of age), by BMI (BMI>25 and BMI≤25), and by biological sex. Logistic regression was performed using the lme4-package (25). The continuation ratio model was created using the GLMMadaptive package (26). The effect plot was created using the ggplot2-package (27)

Patient and public involvement

Continuous patient engagement is a fundamental aspect of the World COACH consortium. Together, patients actively participate in shaping and prioritizing research inquiries within the consortium. World COACH researchers actively attend annual conferences, such as Artrose Gezond in the Netherlands, fostering open dialogues with osteoarthritis (OA) patients to collaboratively define research objectives. Patients are informed about the consortium's capacity to identify risk factors and explore treatment options, and a platform at www.worldcoachconsortium.com encourages both patients and the public to contribute their ideas and questions for future research.

Participants

The flow of World COACH hips to the current final study population is depicted (Fig. 4). 18,935 hips were included for analysis. The average time between the baseline and follow-up radiograph across all cohorts is 6.0 ± 1.7 years. Baseline demographic data stratified per cohort are presented in Table 1. The excluded hips were on average slightly older (65.68 years vs 62.66 years at baseline) and had a higher prevalence of pincer morphology as defined by both thresholds.

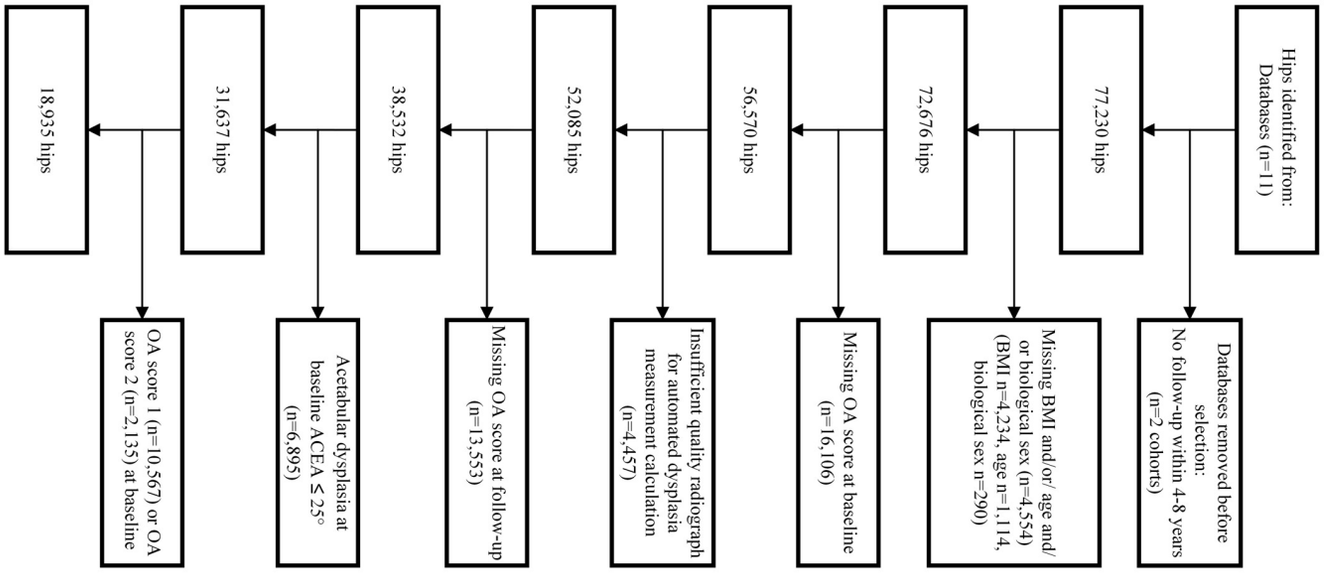

Fig 4. Flow of hips from consortium inclusion to final study population.

Table 1. Baseline characteristic of included hips, stratified per cohort.

	CHECK	Ching	JoCo	MOST	OAI	RS-I	RS-II	RS-III	SOF	Total incl.	Total excl.*
Hips, n (%)	678	815	633	1,202	4,481	2,719	1,797	2,381	4,229	18,935	12,702
Age, mean (sd) years	55.64 (5.28)	53.62 (5.73)	59.25 (8.72)	61.09 (7.24)	60.66 (8.92)	65.21 (6.33)	63.00 (6.40)	56.34 (4.85)	70.38 (4.36)	62.66 (8.36)	65.68 (8.32)
BMI, mean (sd) kg/m2	26.29 (4.23)	25.38 (3.97)	29.60 (6.02)	29.93 (5.13)	28.27 (4.64)	26.15 (3.45)	27.11 (3.83)	27.56 (4.17)	26.38 (4.31)	27.30 (4.49)	27.51 (4.75)
Men, n (%)	114 (16.8)	0 (0.0)	282 (44.5)	378 (31.4)	1,860 (41.5)	1,120 (41.2)	795 (44.2)	1,065 (44.7)	0 (0)	5,614 (29.6)	3,444 (27.1)
LCEA ≥40°, n (%)	143 (21.1)	261 (32.0)	149 (23.5)	221 (18.4)	1,014 (22.6)	887 (32.6)	440 (24.5)	522 (21.9)	1,257 (29.7)	4,894 (25.8)	5,099 (40.1)
LCEA ≥45°, n (%)	33 (4.9)	73 (9.0)	35 (5.5)	55 (4.6)	204 (4.6)	230 (8.5)	93 (5.2)	108 (4.5)	290 (6.9)	1,121 (5.9)	1,815 (14.3)
OAscore=2 follow-up, male/female (%/%)	19/ 63 (16.8/11.2)	0/72 (0.0/8.8)	18/36 (6.4/10.3)	3/4 (0.8/0.5)	3/10 (0.2/0.4)	1/11 (0.1/0.7)	2/4 (0.3/0.4)	36/17 (3.4/1.3)	0/53 (0.0/1.3)	82/270 (1.5/2.0)	3,025

CHECK= Cohort Hip and Cohort Knee, MOST= Multi-center Osteoarthritis Study, OAI= Osteo Arthritis Initiative, RS-I= Rotterdam Study-I, RS-II=Rotterdam Study-II, RS-III= Rotterdam Study-III (RS-III), Ching= the Chingford Study, JoCo=The Johnston County Project, SOF= Study of Osteoporotic Fractures, LCEA= Lateral Center Edge Angle. OA score: 0= no RHOA, 1= Doubtful RHOA, 2= Definite RHOA.
*Excluded hips are defined as all eligible hips for analysis but with OA score 1 or 2 at baseline

Pincer morphology

4,894 (25.8%) hips had pincer morphology defined by LCEA≥40° and 1,121 (5.9%) hips had a larger pincer morphology defined by a threshold LCEA≥45°. 3,542 (26.6%) female hips had pincer morphology defined by LCEA≥40°, and 810 (6.1%) by LCEA≥45°. 1,352 (24.1%) male hips with pincer morphology defined by LCEA≥40°, and 311 (5.5%) by LCEA≥45°.

Incident radiographic hip osteoarthritis

Definite RHOA had developed in 352 hips (1.9 %) within 8 years follow-up. The distribution of RHOA incidence per cohort is 82 hips (12.1%) in CHECK, 72 hips (8.8%) in Chingford, 54 hips (8.5%) in JoCo, 7 hips (0.6%) in MOST, 13 hips (0.3%) in OAI, 12 hips (0.5%) in RS-I, 6 hips (0.4%) in RS-II, 53 hips (2.2%) in RS-III and 53 (1.9%) in SOF.

Association between pincer morphology and radiographic hip osteoarthritis

No significant association between pincer morphology (LCEA ≥40°) and incident RHOA within 8 years was observed. However, a significant association between pincer morphology defined (LCEA≥45°) and incident RHOA was observed. The associations between pincer morphology and incident RHOA are summarized in Table 2.

Table 2. Associations between LCEA measures using two cutpoints to define pincer morphology and RHOA. Significant associations are printed in bold.

Definition pincer morphology	Hips with pincer morphology (%)	Hips with incident RHOA at follow-up (%)	Absolute risk (%)	Unadjusted OR (95% CI) *	Adjusted OR (95% CI)
LCEA ≥40°	4,894	101	101/4,894 (2.1)	1.18 (0.95-1.47)	1.15 (0.87-1.51)
LCEA ≥45°	1,121	31	31/1,121 (2.8)	**1.57 (1.10-2.24)**	**1.50 (1.05-2.15)**

Fig. 5 shows the effect plot of the marginal probabilities from the continuation ratio model with ordinal outcome RHOA.
All marginal probabilities were calculated for hips free of RHOA, in women aged 63 years with a BMI of 27 kg/m2 at baseline. The marginal probability for hips with pincer morphology (LCEA ≥40°) to develop doubtful RHOA within 4-8 years is 0.20 (95% CI 0.14-0.28), compared to 0.17 (95% CI 0.11-0.24) for hips free of pincer morphology. The marginal probability for pincer hips (LCEA ≥40°) to develop definite RHOA within 4-8 years is 0.03 (95% CI 0.01-0.06), compared to 0.02 (95% CI 0.01-0.06) for pincer-free hips.

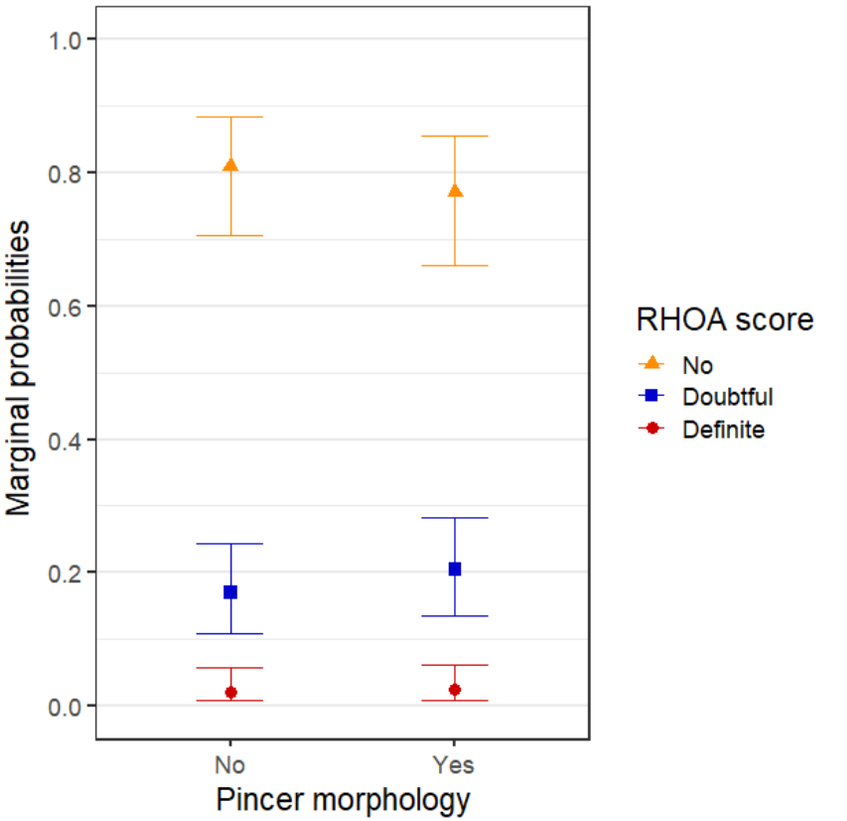

Fig. 5: Effect plot of the marginal probabilities of RHOA within 4-8 years for females aged 63 years and BMI of 27 kg/m2 in hips with pincer morphology (LCEA ≥40°) or without pincer morphology. The probabilities were marginalized over the random effects (cohort and individual), and adjusted for baseline age, BMI, biological sex, and hips side.

Sensitivity analysis excluding the MOST cohort.

The study population excluding the MOST cohort comprised a total of 17,733 hips. Of all hips in the study population, only 7 hips develop RHOA within 8 years in the MOST cohort. No hips with pincer morphology develop RHOA. The non-significant association between hips with pincer morphology (LCEA ≥ 40°) and incident RHOA was 1.18 (95% CI 0.95-1.47) in the remaining study population (n=17,733) when hips from the MOST cohort were excluded.

Subgroup analyses

Descriptive statistics stratified by age group, biological sex, and BMI are summarized in Table 3. The RR for pincer hips (LCEA ≥ 40°) to develop RHOA was highest in age group 40-50 (RR 2.67 (95% CI 1.43-4.95)), in hips with BMI ≥25 (RR 1.23 (95% CI 0.98-1.71)), and in female hips (RR1.20 (95%CI 0.93-1.56)).

We were unable to perform subgroup analyses using logistic regression as there were only 16 cases with both pincer morphology at baseline and RHOA at follow-up in age group 40-50, only 12 cases in age group 70+, only 31 cases in BMI<25 group, and 19 males with pincer morphology and incident RHOA.

Table 3. Absolute and relative risk of hips with pincer morphology (LCEA ≥ 40°) to develop incident radiographic hip osteoarthritis stratified by age group, BMI, and biological sex.

Strata	**Total hips in group, n**	**Hips with pincer (LCEA ≥40°), n**	**Hips with incident RHOA, n**	**Hips with pincer (LCEA ≥40°), and incident RHOA, n**	**Absolute Risk, % ***	**Relative Risk, % (95% CI) ****
Age (years)						
40-50	1,534	307 (20.0)	40 (2.6)	16	1.0	2.67 (1.43-4.95)
51-60	6,180	1,363 (22.1)	149 (2.4)	47	0.8	1.63 (1.16-2.29)
61-70	7,557	2,056 (27.2)	110 (1.5)	26	0.3	0.93 (0.54-1.28)
70+	3,664	1,168 (31.9)	53 (1.4)	12	0.3	0.62 (0.33 to 1.17)
BMI						
<25	6,094	1,600 (26.3)	125 (2.1)	31	0.5	0.79 (0.62-1.38)
≥25	12,841	3,294 (25.7)	227 (1.8)	70	0.5	1.23 (0.98-1.71)
Biological sex						
Male	5,614	1352 (24.1)	82 (1.5)	19	0.3	0.95 (0.57-1.58)
Female	13,321	3,542 (26.6)	270 (2.0)	82	0.6	1.20 (0.93-1.56)

*The absolute risk was calculated using the following equation: (number of hips with pincer morphology and RHOA/Total number of hips in subgroup)

**The relative risk was calculated using the following equation: (number of hips with pincer & RHOA/(number of hips with pincer & RHOA + number of hips with pincer only)) / (number of hips with RHOA without pincer morphology/ (number of hips with RHOA without pincer morphology + number of hips without pincer morphology or RHOA))

Discussion

This first IPD meta-analysis in a large prospective consortium of 18,935 hips completely free of RHOA at baseline, did not find significant association between pincer morphology defined by LCEA ≥40° and incident RHOA within 8 years. However, sensitivity analysis showed that pincer morphology defined by LCEA ≥45° was significantly associated with RHOA. Hips with pincer morphology (LCEA ≥40°) may also be more likely to progress to doubtful RHOA within this follow-up compared to non-pincer hips, although no conclusions on clinical significance can be drawn. Subgroup statistics point in the direction that hips with pincer morphology in younger persons (aged 40-50) and with higher baseline BMI (≥25) are more at risk of developing RHOA compared to non-pincer hips. Additionally, hips in females with pincer morphology were slightly more at risk to develop RHOA within 8 years compared to hips in males.

To date, prospective cohort studies have not been able to demonstrate an association between pincer morphology and RHOA (3). A study of over 4,000 hips by Saberi Hosnijeh et al. in the Rotterdam Study with a mean follow-up of 9.2 years, did not find a significant association between pincer morphology defined by an LCEA≥40° and RHOA (11). The authors hypothesized that the follow-up period may have been too short to observe a significant association, as pincer morphology has been hypothesized to lead to slow degeneration of the joint. Similarly, a recent study of 1,002 hips in the CHECK cohort with 10 years follow-up did not find an association, although this association was modified by the presence of hip pain at baseline, in which case acetabular overcoverage did increase the risk of developing RHOA (28). Contrastingly, in a cross-sectional study, hips with OA were 3.7 times more likely to have pincer morphology, indicating that pincer morphology could in fact play a role in development of OA (3). Previous results from the Rotterdam Study demonstrated that pincer morphology increased the risk of developing RHOA only in hips completely free of RHOA at baseline (KL grade 0) (11). In the present study we observed a similar result in sensitivity analyses, where LCEA≥45° was significantly associated with developing RHOA. Furthermore, a cross sectional study by Faber et al. found that pincer morphology was associated with an increased risk of JSN, which further supports the notion that pincer morphology poses a risk in hips to develop RHOA (14).

In the present study, the average BMI was 27.4 kg/m2. Conflicting evidence has been published on the relationship between increased BMI and hip osteoarthritis., Although a systematic review confirmed that the risk of hip OA increases with BMI and a dose–response relationship exists (29). Subgroup statistics in our study show that hips with a baseline BMI ≥25 kg/m2 when pincer morphology is present have a higher RR (1.23 vs 0.79) compared to non-pincer hips.

Our study population consists mostly of female hips (70%), but the incidence of pincer morphology was similar in female and male hips (26.6% and 24.1% respectively). Whether the risk of developing RHOA in hips with pincer morphology differs between male and female individuals is presently unknown. Research shows that women have greater pelvic obliquity and less vertical center of mass displacement compared to men, which may influence biomechanics of the hip joint, and could potentially lead to a RHOA higher risk in female hips with pincer morphology (30). Unfortunately, it was not possible to perform regression analyses in subgroups by biological sex in the present study, as only 19 male hips with pincer developed RHOA within 8 years. As our study may represent a relatively short period of time for hips free of RHOA at baseline to develop radiographic disease, future studies with longer follow-up may be able to shed light on the association between pincer morphology and RHOA by stratified by biological sex.

It is possible that definition of pincer morphology has a direct impact on its association with RHOA. This is illustrated by the significant association between pincer morphology defined by LCEA≥45° and incident RHOA, which was not present in the current population when pincer morphology was defined by LCEA≥40°. Most studies have relied on a LCEA≥40° to define pincer morphology, but based on results from the present study with almost 19,000 hips, we argue that this threshold may be too low to be clinically relevant. A recent study of 6,807 individuals from the UK Biobank found a prevalence in the general population of pincer morphology defined by a LCEA ≥45°, of 8.1% in females and 8.9% in males (14). This is similar to the prevalence in this study (LCEA≥45° 6.1% in female hips and 5.5% in male hips). In the excluded hips from the present study, a prevalence of 14.3% of hips with LCEA≥45° was found. These hips were only excluded from analysis because they were not free of RHOA at baseline. It may be that these hips had already developed RHOA as a result of acetabular overcoverage. Subsequent studies should aim to conduct sensitivity analyses employing this threshold, which may elucidate a more clinically relevant study population in the search for modifiable risk factors for RHOA.

It should be kept in mind that the definition of pincer morphology as a static concept defined by radiological excessive acetabular coverage differ from the dynamic concept of pincer type-FAIs. The definition of FAIs as stated by the 2016 Warwick Agreement, does not only pertain to radiological findings, but to a triad of radiological signs, clinical signs (hip impingement tests, limited range of motion) and symptoms (motion or position related pain in the hip or groin) (9). This is essential as the treatment of FAIs ranges from conservative care (education, lifestyle and activity modification, physiotherapy) to surgical care (arthroscopic surgery to improve hip morphology and joint alignment). There are currently no prospective studies available that study the triad of FAIs and the association with RHOA, which implies that treatment of pincer morphology should presently only be carried out to relieve

symptoms rather than for RHOA prevention. Furthermore, to date there are no randomized controlled trials investigating the role of resection of pincer morphology specifically for OA prevention. The results from the present study can only be interpreted in the light of static pincer morphology.

This study has several strengths. The first is the inclusion of hips completely free of any signs of RHOA at baseline, which differs from some previous prospective studies (3,4,11). This allowed us to study associations that were unbiased by pre-existing doubtful RHOA. Though previous prospective studies generally correct for baseline RHOA grade in statistical models, we believe risk factors are best demonstrated when RHOA-free hips are followed until a subset develops disease. Furthermore, LCEA measurements may be affected by the presence of osteophytes as it is possible that spurious osteophytes are mistaken for pincer hips. We were able to rule out the presence of osteophytes at baseline as all included hips were completely free of RHOA. The second strength is the study design using IPD meta-analysis. By collecting, pooling and analyzing original cohort data, we achieved great statistical power which allowed for subgroup and sensitivity analyses. The results from the present study, we believe, are a robust estimate of the risk pincer morphology poses to RHOA-free hips within 8 years. They can therefore be used to inform patients with this bone shape variation, and may aid in future treatment and preventative strategies for hip OA. A third strength is the use of uniform automated measurements. Using a validated algorithm to quantify acetabular coverage of all hips on baseline radiographs reduces variability and bias in predictor measurements.

This study is subject to a number of limitations that must be acknowledged. First, it has been suggested that pincer morphology potentially only leads to RHOA when mixed with other shape features, or specific subtypes of pincer morphology which were not captured by the LCEA only (31). Radiographs are

2-dimensional images, which limit the ability to detect differences in pincer morphology in multiple planes. The LCEA however, is presently the most commonly used and reliable measurement of pincer morphology (32). Furthermore, a recent study compared radiographs to computed tomography (CT) scans and found similar sensitivity and specificity in defining pincer morphology when comparing radiographs to CT scans (33). A second limitation is that we included both supine and weight bearing radiographs, which may influence RHOA grading. However, a study comparing the JSW on weight bearing and supine radiographs found that how the radiograph was obtained does not significantly impact JSW measurements (34). Finally, we only studied RHOA in the present study, which may differ from clinically relevant hip OA where symptoms are taken into account. Elucidating the association between pincer morphology and a clinical definition of hip OA should be prioritized in future research.

Identification of modifiable risk factors is essential for prevention of hip osteoarthritis in the future. Pincer morphology is a potentially modifiable risk factor for hip osteoarthritis, as physical therapy may increase strength and stability of the joint, activity modification may help avoid excessive joint-loading and surgical interventions may help improve the joint shape and could potentially aid in preventing osteoarthritis, although this is presently unknown. Prevention of hip osteoarthritis can improve overall quality of life and aid in relieving the substantial and increasing societal burden of this disease (35).

To the best of our knowledge, our IPD meta-analysis is the first study of its kind to investigate the relationship between pincer morphology and the risk of developing RHOA, and elucidates that pincer morphology defined by a LCEA≥45° is significantly associated with incident RHOA in a population of RHOA-free hips at baseline. This study offers new insight into a potentially modifiable risk factor for RHOA in specific subgroups, which contributes to discovering targets for prevention and treatment of hip osteoarthritis in the future.

Key messages

- What is already known on this topic: Pincer morphology, or acetabular over-coverage, is not consider a risk factor for RHOA in existing literature. However, inconsistencies in literature complicate the interpretation of reported associations in prospective studies. Various methods and thresholds are used to measure and define the predictor (pincer morphology) and the outcome (hip osteoarthritis), and inclusion criteria and participant demographics amongst cohorts vary significantly. Furthermore, manually performed measurements may introduce reader variability.

- What this study adds: Pincer morphology defined by a lateral center edge angle of 40° is not associated with radiographic hip osteoarthritis, whereas pincer morphology defined by a lateral center edge angle of 45° is significantly associated with radiographic hip osteoarthritis. This study represents a robust and thorough analysis, where inconsistencies in radiographic measurements were avoided and variations in defining the outcome were accounted for in the statistical model. Only hips free of RHOA were included at baseline which is unprecedented in a large prospective cohort study.

- How this study might affect research, practice or policy: This study showed that overcoverage of the femoral head by the acetabulum by 45° or more in a general population poses a risk for individuals with radiographic hip osteoarthritis. As osteoarthritis is a common condition associated decreased quality of life, it is warranted to further our understanding of which individuals with pincer morphology are at high risk of developing disease, as this is a potentially modifiable risk factor.

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Data sharing statement

Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. We encourage the

use of data by third parties, although this is subject to approval by the steering committees of the World COACH consortium and the participating cohorts, as well as to legal boundaries regarding data ownership. A standardised data request form is available for which will be reviewed uniformly in order to consistetenly handle World COACH data requests.

Competing interests

GJ reports personal fees from Novartis outside the submitted work. SBZ reports consulting fees from Pfizer Infirst Healthcare and personal fees for being a Deputy Editor for Osteoarthritis and Cartilage outside the submitted work. CL and TC report a patent for an image processing apparatus and method for fitting a deformable shape model to an image using random forest regression voting. CL reports licensing royalties for this patent from Optasia Medical outside the submitted work. AN is an associate editor for Osteoarthritis and Cartilage and is on the OARSI Board of Directors outside the submitted work. AM is on the Editorial Board for the British Journal of Sports Medicine and the Journal of Science and Medicine in Sport outside the submitted work. HW reports being a minority shareholder of Uplanner BV and Replasia BV outside the submitted work.

Patient and public involvement

Patients and public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Patient and public involvement section for further details.

Ethical approval

This study involves human participants but was excepted from ethical approval (Erasmus MC Medical Ethics Review Committee) as it uses previously collected observational data for which the participants had originally given informed consent, and all cohort studies included in this consortium already had ethics approval from their respective committees. Participants gave informed consent to participate in the study before taking part.

Contributorship

NSR, FB and RA initiated the study. NSR, FB and RA worked on the conceptual design of the study. MMAvB and RA identified eligible cohorts and contacted cohort investigators for collaboration. MMAvB, RA, NSR, FB, HA, AM, KC, JH, SK, JAL, JVM, ABM, AEN, MN, JT and HW collected the existing cohort data. MMAvB, NSR, FB, JT and RA have worked on the database and on the harmonisation process. NSR, FB, and RA have worked on statistical analyses. NSR and FB wrote the manuscript under supervision of RA. All authors critically reviewed and revised the manuscript and contributed to interpretation of the data. All authors read and approved the final version of the manuscript. NR acts as guarantor and accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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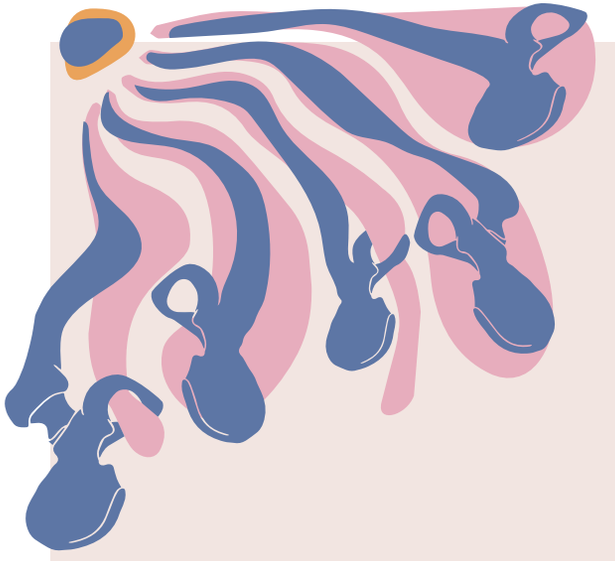
Chapter 10

GENERAL DISCUSSION



General discussion

The general aim of this thesis was to investigate the relationship between hip morphology and hip osteoarthritis. In the first part, we validated an automated method to quantify hip morphology, which can be used in large epidemiological studies and in a clinical setting. In the second part, we investigated the association between various acetabular hip morphologies and osteoarthritis of the hip. The findings, the future perspectives and the challenges I faced during the completion of this thesis will be discussed and elaborated on.

Defining hip osteoarthritis

From 1990 to 2019, the worldwide incidence of hip osteoarthritis increased from 0.74 million to 1.58 million, an increase of 115.4%. Similarly, the disability-adjusted life years of hip osteoarthritis increased from 0.46 million to 1.04 million, an increase of 126.7% (1). In the Netherlands, osteoarthritis in general is forecasted to become the most prevalent disease by 2040, surpassing cardiovascular disease and diabetes (2). The overall burden increased in nearly all global countries, and governments and health policymakers have been urged to increase awareness and prioritize research on the topic of disease prevention (1). In order to find solutions, risk factors and the magnitude to which they contribute to the development or progression of hip osteoarthritis must be studied.

In order to study hip osteoarthritis and its risk factors, the disease as an outcome must be clearly defined. Despite numerous published (epidemiological) studies, a gold standard to define hip osteoarthritis is still lacking (3). A systematic review by Reijman et al. summarised articles addressing the validity, reliability, applicability of definitions of hip osteoarthritis in epidemiological studies (3). The included definitions were the Kellgren and Lawrence grading system, Croft's grading system, minimal joint space according to Croft, joint space according to Resnick and Niwayama, three sets of criteria

of the American College of Rheumatology, a clinical definition of hip osteoarthritis (radiological osteoarthritis combined with pain in the hip region), and the radiographic index grade according to Lane. The authors concluded that the validity of the studied definitions had barely been investigated, even though they are commonly applied throughout existing literature (3). A later study by Kim et al. from 2015 investigated the concordance between hip pain and radiographic hip osteoarthritis defined by the Kellgren and Lawrence grading (4). The authors concluded that hip pain was not present in many hips with radiographic hip osteoarthritis and vice versa. Moreover, most older participants in this study who had a high suspicion of clinical hip osteoarthritis did not have radiographic findings (4). Besides concerns on the validity, the Kellgren and Lawrence grading system has been shown to be susceptible to subjective grading, with reported intra-rater interclass correlation coefficients (ICCs) of 0.66-0.89, and inter-rater ICCs of 0.40-0.75 (3,5,6). These are important factors to keep in mind when interpreting results in the present thesis as these classifications were also used to define the outcome, and the results may be impacted by the shortcomings of these grading systems. The foremost way in which the results are impacted are that radiographic hip osteoarthritis does not necessarily equal clinical hip osteoarthritis, and that cases may be missed when diagnosis is solely based on radiographs. Presently the Kellgren and Lawrence grading system, among others such as the (modified) Croft grading system, for lack of a better alternative, are commonly applied and accepted in epidemiology. Subjective grading was overcome by correcting for the cohort that assigned radiographic grades in all individual participant data meta-analyses.

Studies investigating the correspondence between existing radiographic grading systems should be conducted. The following example, although pertaining to osteoarthritis of the knee, demonstrates why it is essential to evaluate correspondence between methods. A study compared the severity of osteoarthritis

in the knee using two grading systems, the Kellgren and Lawrence grading system and the OARSI atlas of individual features (7). Theoretically, one would anticipate that the severity classification from both systems would be relatively similar, since the Kellgren and Lawrence grading system takes into account the specific characteristics outlined by the OARSI atlas of individual features (8). However, this study found that radiographic tibiofemoral osteoarthritis was almost twice as common using the individual OARSI criteria compared to the KL system (7). This implies that there is subjectivity involved in evaluating knee radiographs, and the same is likely true for hips, although there haven't been any studies examining the agreement between grading methods for hip osteoarthritis at present. This holds significant value considering it would allow for more accurate comparison of outcomes across different studies.

The World COACH consortium has the potential to serve as a foundation for a comprehensive definition of hip osteoarthritis. As we formulated the harmonized OA score in the World COACH meta-analyses in chapter 8 and 9, we concluded that all existing grading systems and definitions of hip osteoarthritis are flawed, but currently represent the best available options. Considering the size of the World COACH consortium (over 40.000 participants) and the extensive clinical and radiographic data collected per individual, the World COACH consortium has the potential to develop and validate a comprehensive hip osteoarthritis grading system. We propose that the first step towards a comprehensive hip osteoarthritis definition will be to thoroughly study and explain what the limitations of current methods, such as those described in the paper by Reijman et al. are (3). Next, the correspondence between existing grading systems and the World COACH method should be studied in terms of sensitivity, specificity and positive predictive value for pain and other symptoms or total hip replacement. It is essential to include the latter factors, as only considering radiographic signs of osteoarthritis may underestimate the disease

in its entirety. Moreover, Dutch general practitioner guidelines advise against obtaining radiographs to diagnose hip osteoarthritis, which emphasizes that hip osteoarthritis as a disease entails much more than radiographic findings (9). Finally, the validity can be tested by comparing the World COACH method to a gold standard of expert opinion or obvious hip osteoarthritis characterized by a total hip replacement (3). By automating the method though an algorithm that analyzing radiographs, subjective grading and reader variability may be reduced in future studies.

Defining hip morphology

Acetabular dysplasia

A wide array of definitions for acetabular dysplasia has been employed in literature and although all measurements were performed on anteroposterior radiographs, the variability may still influence the reported results (10-13).

The first factor in variability is how the center edge angle, a measure of acetabular coverage, is defined. Studies interchanged the lateral and the Wiberg Center edge angle, which differ significantly as the Wiberg center edge angle (WCEA) extends from the center of the femoral head to the lateral weight bearing edge of the acetabulum, whereas the lateral center edge angle (LCEA) extends from the center of the femoral head to the outermost bony part of the acetabulum, which is not necessarily the same anatomical landmark as the weight bearing landmark (14,15). When both anatomical landmarks are not in the same location on the radiograph, the LCEA point is always placed more laterally than the WCEA point, which means that the WCEA is always equal to or smaller than the LCEA in degrees. This may significantly impact whether acetabular dysplasia is marked as present on a radiograph, as this is generally categorized dichotomously based on a predefined threshold rather than continuously in degrees (10,11,13,16). Depending on whether the LCEA or WCEA is used, the inclusions may therefore vary across studies.

The second way in which variability is introduced, is in the thresholds used to define acetabular dysplasia. This is especially important in a clinical setting. A threshold of ≤ 20° may be employed to define acetabular dysplasia or ≤25° to define borderline acetabular dysplasia, but a systematic review of arthroscopic studies found that the thresholds vary as much as ≤ 16°-27° and ≤ 18°-28° respectively (17). A threshold of ≤ 25° is more common than ≤ 20°, which increases the incidence of acetabular dysplasia in large cohort studies, but should also be kept in mind when interpreting results. For example, surgical treatment of individuals with borderline acetabular dysplasia remains controversial due to the relatively high risk of reoperation, with conversion to total hip replacement of up to 28% within 2.5 years (18).

How acetabular dysplasia should be defined in research, repeatedly led to a discussion concerning biomechanical aspects. We hypothesize that using the WCEA is more logical to define acetabular dysplasia, as the weight-bearing surface is likely what is most compromised by the increased joint loading on a small surface area of the joint, rather than the most lateral bony part of the acetabulum (19). Any threshold to define acetabular dysplasia can be used, but the clinical implications of results should be stated in the discussion of a manuscript. Finally, to reduce variability and increase efficiency, automated measurements should be used in large epidemiological studies. Using lateral imaging increases the incidence of acetabular dysplasia and strengthens the association between this morphology and hip osteoarthritis, which should be kept in mind for future data collection (13).

Pincer morphology

In the present thesis, pincer morphology was defined as acetabular overcoverage by an LCEA≥40° and sensitivity analyses were performed using a threshold of ≥45°. Pincer morphology in literature is heterogeneously defined, hence why the prevalence

of this morphology differs greatly among populations (20). Pincer morphology has been described as a collection of bone shape variations, which includes coxa profunda (a deep acetabulum), protrusio acetabuli (protrusion of the acetabulum into the pelvic cavity), acetabular retroversion (posterior rotation of the acetabulum), or even osteophytes as a result of osteoarthritis (21). Pincer morphology if defined only by acetabular overcoverage or by the orientation of the acetabulum, is a static concept. Pincer morphology as a part of femoroacetabular impingement syndrome, however, is dynamic and involves repeated impinging moments during motion and radiographic findings. The distinction between pincer morphology and pincer type femoroacetabular impingement syndrome is essential when interpreting scientific results and may impact studies on the association between pincer morphology and hip osteoarthritis depending on the definition used.

The association between hip morphology and hip osteoarthritis

The CHECK cohort provides important information about the development of hip osteoarthritis in a population of individuals with first complaints of stiffness or pain in the hip or knee joint. These complaints may represent the first signs of osteoarthritis of the hip. The world COACH consortium contains mostly data from open population cohorts, and provides important information about an unprecedented number of hips completely free of radiographic signs of osteoarthritis, which allows for research into modifiable risk factors.

Acetabular dysplasia

Previous prospective studies have suggested an association between (mild) acetabular dysplasia and hip osteoarthritis (10-13). However, evidence from studies with a cross-sectional and retrospective design regarding this relationship, was conflicting (16,22). This conflicting

evidence is potentially due to variability in study methods, inclusion criteria and definitions of acetabular dysplasia in literature (23).

In chapter 5 in the CHECK cohort, we found that acetabular dysplasia was a significant risk factor for incident radiographic hip osteoarthritis, with the highest odds ratios at 2- and 5-years follow-up, a weaker association at 8 years follow-up and no association after 10 years. We found that the lack of association between acetabular dysplasia and radiographic hip osteoarthritis at 10 years follow-up in chapter 5 did not count for clinically relevant hip osteoarthritis at 10 years follow-up (OR 2.80 95% CI 1.15-6.79) in chapter 7. In chapter 8 in the World COACH consortium, we found that odds of incident radiographic hip osteoarthritis were 1.80 times as high in hips with acetabular dysplasia compared to those without acetabular dysplasia within 8 years follow-up. It should be mentioned that the average age of 61.84 (± 8.32) years may have impacted the strength of the association, as studies have shown that acetabular dysplasia poses an important risk for total hip replacement in younger individuals (24). The results from all studies nonetheless fortify the notion that acetabular dysplasia is a risk factor for radiographic hip osteoarthritis.

It is known that female biological sex is an important risk factor for developmental dysplasia of the hip (25). Unfortunately, it was not possible to perform logistic regression analyses stratified by biological sex in chapter 8. As the etiology of acetabular dysplasia in the adult hip is presently unknown, it may be that decreased acetabular coverage is the result of subclinical developmental dysplasia of the hip during infancy, despite thorough screening programs. A second hypothesis is that acetabular dysplasia develops later in life. A recent study confirms that there are demographic differences between individuals with hip dysplasia diagnosed during infancy and during adulthood, which supports the notion that there are two distinct forms of acetabular dysplasia (26). It is therefore necessary to study the development of the femoral head and acetabular roof prospectively in children to provide further insight. The etiology of acetabular dysplasia in the adult hip should be unraveled, as this thesis confirms that it is a risk factor for developing radiographic hip osteoarthritis. Regardless of when acetabular dysplasia develops, it is a potentially modifiable risk factor as pediatric hips are highly plastic, and adult hips may benefit from physical therapy or surgical intervention prior to developing end-stage disease.

Pincer morphology

The concept of femoroacetabular impingement causing osteoarthritis proposed by Ganz et al. has permeated scientific literature (27). Although this concept is biomechanically logical and has been shown to hold true for cam morphology (10,20,28,29), no prospective evidence to support this claim for pincer morphology was available until recently (27). In chapter 6 we studied pincer morphology in the CHECK cohort, and found results in line with previous research, unless hip pain at baseline was present. Yet when we studied the association in the World COACH consortium, we found that the odds of developing incident radiographic hip osteoarthritis in pincer hips as defined by LCEA≥45° was 1.50 times higher compared to hips with normal acetabular coverage.

The IPD meta-analysis in the world COACH consortium was the first prospective study to find a relation between pincer morphology and radiographic hip osteoarthritis, although this association only became apparent when performing sensitivity analyses with an increased LCEA threshold of 45°. We believe that earlier studies were underpowered to include only osteoarthritis-free hips at baseline, which partly resulted in a lack of association. The presence and severity of osteoarthritis negatively impacts morphological measurements to define femoroacetabular impingement syndrome, which pincer morphology is a part of (30). It has therefore been advised that epidemiological studies on hip morphology are performed in healthy hips with no signs of osteoarthritic changes

(30). The World COACH analyses were performed in hips completely free of any radiographic hip osteoarthritis. We were therefore able to find a robust estimate of pincer morphology as risk factor for hip osteoarthritis. Further research into biomechanical differences between male and female hips is therefore warranted.

Pincer morphology is highly prevalent, but most individuals with this bone shape variation will never experience symptoms or develop radiographic hip osteoarthritis as a result of pincer morphology (20). This, and the results from chapter 9 led us to question whether the threshold to define pincer morphology of LCEA≥40° is clinically relevant. Future research should therefore concentrate on distinguishing factors that can predict which individuals with pincer morphology will also develop hip osteoarthritis by identifying effect modifiers. Potential factors that may be of interest include range of motion, walking patterns, other measures or the degree of pincer morphology and physical workload. In doing so, modifiable risk factors for hip osteoarthritis in individuals with pincer morphology may be discovered which can in turn help in the prevention or slowing the process of disease.

It may also be possible that previous prospective cohort studies have not been able to demonstrate an association between pincer morphology and hip osteoarthritis as a result of a mismatch between individuals with radiographic pincer morphology, and those who truly suffer from repetitive impinging moments, or repeated exposure to movement beyond a normal range of motion (athletes, dancers). Using clinical information on range of motion or pain may provide further insight into whether this hypothesis holds true. It had previously been proposed that only extreme overcoverage leads to impingement and therefore development of hip osteoarthritis (20). This was confirmed by our study in chapter 9, where an increased lateral center edge angle led to a significant association between pincer morphology and incident hip osteoarthritis.

In our studies in chapter 6 and 9 we only used two-dimensional imaging in one or two different planes. The Warwick agreement states that in order to study pincer-type femoroacetabular impingement syndrome, lateral imaging should be included in studies (21). Moreover, future studies with three-dimensional imaging can capture the entire hip shape, which may provide further information on the association between focal or global acetabular overcoverage and hip osteoarthritis. On the other hand, this thesis shows that an inexpensive anteroposterior pelvic radiograph can provide substantial information on morphological risk factors for hip osteoarthritis, which can help inform individuals in a clinical setting, as well as provide important data for epidemiological studies.

Implications for clinical practice

Although most studies in this thesis have an epidemiological nature, translations to clinical practice can be made. First, it important to recognize that an anteroposterior radiograph does not always suffice to establish morphological diagnoses. When acetabular dysplasia, pincer morphology or femoroacetabular impingement syndrome are included on the differential diagnosis, requesting a lateral radiograph with routine radiographic imaging is of additional value. The use of automated measurements to quantify hip morphology may reduce bias in clinical practice. In chapter 3 we argued that bias in measurements is introduced when an observer sees the bone shape variation on radiographs prior to carrying out the measurement. Relying on validated algorithms in clinical practice may help inform clinicians and aid in making non-biased treatment decisions. When translating results from studies on hip osteoarthritis to clinical practice, it is important to keep in mind the distinction between radiographic hip osteoarthritis and clinically relevant hip osteoarthritis. As demonstrated in chapter 6, the definitions of osteoarthritis used in studies do not always translate to what is clinically important for patients. Moving forward, a clinically relevant, comprehensive definition of hip osteoarthritis must be

developed. The individuals with acetabular dysplasia that seek out medical help may experience severe complaints, have osteoarthritic changes at a young age on radiographs and are sometimes treated with extensive surgeries including periacetabular osteotomies. The complaints these patients experience and potential treatment they may undergo have an immense impact on their quality of life, and are therefore regarded by clinician as very serious cases. This sentiment is further enhanced by findings from some prospective studies investigating the associations between acetabular dysplasia and hip osteoarthritis. One cannot help but wonder whether the cases that reach the doctor's office are in some way different from the hips with acetabular dysplasia in the general population. This is supported by the findings in chapter 8, where the odds for hips with acetabular dysplasia to develop radiographic hip osteoarthritis in a large population are, although increased, not very high. Research into which individuals with acetabular dysplasia are more at risk and will require medical attention in the future should be prioritized. Previous studies were unable to demonstrate a significant association between pincer morphology and radiographic hip osteoarthritis. In our study in chapter 9 we were able to demonstrate a mild significant association for healthy pincer hips at baseline with LCEA≥45° to develop incident radiographic hip osteoarthritis within 8 years follow-up. In terms of clinical practice, it is essential to investigate whether this risk can be reduced or eliminated with preventative strategies, which may be either surgical or non-surgical. Whether operative elimination of pincer morphology reduces the risk of developing hip osteoarthritis later in life is presently unknown.

Automated measurements are the way forward in epidemiological studies

In chapter 3 we presented an open-access, automated method to determine radiographic measurements on anteroposterior pelvic radiographs. When working with large datasets, algorithms are essential to quantify hip morphology. They offer a fast and reliable

alternative to manual measurements, and as our study shows in chapter 3, they perform equally well compared to the current reference standard of trained human readers. The speed of calculating the measurements will allow future population-based studies to quantify hip shape using more measures simultaneously. It has been hypothesized that this will capture the overall hip shape more accurately, and will allow for more accurate estimation of the risk factors (21). The algorithms used in the present thesis were programmed to calculate measurements on anteroposterior pelvic radiographs, but future studies may be able to develop algorithms on other radiographic views (such as the false profile view used in chapter 5 and 6 or 3D imaging such as CT or MRI). We strongly urge researchers in the field of osteoarthritis to publish such algorithms open access and to promote collaboration so we can further advance research of morphological hip features.

Individual participant data meta-analysis and epidemiological hip osteoarthritis research

Individual participant data (IPD) meta-analysis involves including all original data such as demographic data for each individual such as age, sex, health status and details about exposures or treatment from eligible studies into one analysis. The data is collected, centrally analyzed and combined in a meta-analysis.

A reason to consider undertaking an IPD meta-analysis may be when the available published data do not permit a good quality review or are insufficient for thorough analysis (31). Previously published studies on morphological risk factors for hip osteoarthritis were generally underpowered for analysis of high-risk subgroups. By collecting and combining original data for IPD analysis, it was possible to increase statistical power and perform thorough analyses. In light of the present thesis, the quantification of hip morphology also posed an issue for undertaking meta-analysis with aggregate data. Whenever (manual) measurements are performed by multiple

analysists, or when different definitions to quantify hip morphology are used, some form of measurement variability will be inevitable. By collecting all original radiographs from the included cohorts in the World COACH consortium and using in-house algorithms to quantify predictors, we were able to conduct a review with consistent measurements.

Over recent decades the use of IPD meta-analysis has gained momentum. Although this method of analyzing data is not able to answer all questions, it provides a method to systematically study individual level-factors. IPD offers flexibility in analytical methods, which allows researchers to investigate how participant level covariates alter the impact of treatment or exposure (31). The risk of bias can also be assessed more thoroughly, which ultimately provides robust estimates and context when interpreting evidence which may even differ from results based on aggregate data (32). IPD meta-analysis however, has been shown to be resource- and time consuming. This means that an IPD review usually takes longer and costs more than a conventional systematic review, making time and funding necessary before undertaking such research projects. This statement holds true for the World COACH consortium. Despite the immense efforts invested in building a harmonized IPD database, we argue that this is the future of epidemiological research into hip osteoarthritis. The power of IPD meta-analysis should therefore be kept in mind when research groups undertake new studies and collect data to make future IPD endeavors more efficient. One way to do this, may be by utilizing the Observational Health Data Sciences and Informatics (OHDSI) documentation, which will make harmonization of data easier in the future, and will allow us to learn more from the already collected data (33).

Future perspectives of hip osteoarthritis research

Hip morphology plays a crucial role in the development and progression of hip osteoarthritis. Not all hips with bone shape

variations however, develop osteoarthritis. This highlights the complex nature of hip osteoarthritis as a disease, where an interplay of risk factors results in joint degeneration. Extensive research into individual risk factors has been carried out, but the next point on the horizon should be to unravel the interplay of risk factors at the individual level. This calls for research into aforementioned phenotypic definitions of osteoarthritis patterns as well as complex analyses that take interrelationships among risk factors into account.

Individual risk prediction models estimate the likelihood of the incidence of developing disease. They may assist health professionals by complementing clinical decision-making and help inform patients. Moreover, risk prediction models contribute to public health by identifying future healthcare needs and potentially permitting the modification of risk factors while patients remain free of disease. This information aids in the search for preventative strategies and individualized treatment options, thereby lowering health care costs.

Risk prediction models have been developed for osteoarthritis, but research efforts have heavily focused on the knee joint (34). The four models that exist for hip osteoarthritis are based on a median number of 994.5 hips, and only included age, biological sex, BMI and radiographic parameters as variables (34). For a complex disease like hip osteoarthritis, this poses two limitations. The first in the small number of variables being taken into account, and the second is the small number of hips studied. Aspects of hip morphology will add important predictive value but currently have limited availability in routine records for general populations (34). Clinical data on range of motion or pain may further enhance these predictive models. The World COACH consortium has the potential to overcome aforementioned limitations. In the first place by combining an immense amount of individual participant data from prospective cohort studies, which results in unrivaled statistical power and will result in generalizability of results. The

available (harmonized) data transcends patient demographics, and also includes detailed clinical data spread across multiple follow-up moments. Using the automated tools to quantify hip morphology uniformly for all radiographs will further enhance predictive value.

Although deep learning prediction models are a promising tool, and research seems to await a bright future considering recent advances in artificial intelligence, we must remain cautious of its application in a clinical setting until proven valuable. Deep learning models may result in uninterpretable results (known as the "black-box") when applying the most seemingly accurate and complex models. For World COACH studies to render clinically relevant results, it is necessary to run conventional statistical models first, so researchers can understand the data and results. The world COACH studies in this thesis are therefore building blocks in the foundation of hip osteoarthritis research within the consortium, and serve as a stepping stone for future studies and hypotheses. All building blocks will ultimately result in an individualized risk prediction model, which will, once validated, provide crucial information to healthcare professionals, patients, policy makers, insurance companies, and health economists in terms of understanding the etiology of hip osteoarthritis and accurately forecasting disease behavior.

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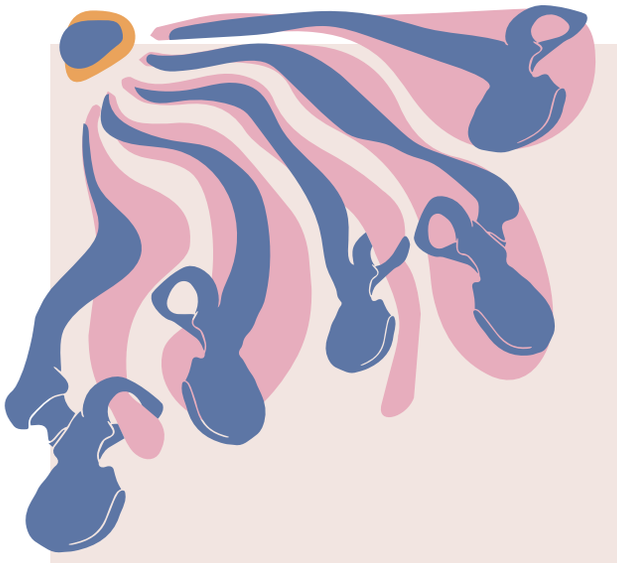

APPENDICES

Takeaways from this thesis

Part I

- Automated methods to quantify hip morphology perform equally well as trained human readers and should be applied in epidemiological studies as they eliminate human measurement error and bias, are faster and therefore cheaper than trained human readers.
- A comprehensive definition of hip osteoarthritis is still lacking. It should be investigated how to define hip osteoarthritis that is clinically meaningful and feasible for epidemiological studies.
  The false profile radiograph in addition to the anteroposterior radiograph has an additional value of 43% in the diagnosis developmental dysplasia in adults.

Part II

- A study in the CHECK cohort demonstrates that acetabular dysplasia was not associated with radiographic hip osteoarthritis, but did pose a significant risk for clinically relevant hip osteoarthritis after 10 years follow-up.
- A study in the World COACH consortium of 18,807hips demonstrates that acetabular dysplasia may not be as strong of a risk factor (OR 1.80 95% CI 1.40-2.34) for radiographic hip osteoarthritis as previously thought.
- A Wiberg Center Edge Angle (WCEA) ≥25° was significantly associated with incident radiographic hip osteoarthritis, but other measures to quantify acetabular dysplasia such as a WCEA≥20°, an acetabular depth-width ratio ≥250, a modified acetabular index ≤13°, or a combination of these measures was not associated with radiographic hip osteoarthritis within 8 years.
- Further research is necessary to identify which individuals with acetabular dysplasia are at risk of developing (early) radiographic hip osteoarthritis. Acetabular dysplasia is a potentially modifiable risk factor, which may make this hip shape variation an important target for preventative and treatment strategies for hip osteoarthritis.

- A study in the CHECK cohort found that neither time to follow-up nor the presence of anterior, lateral or both anterior and lateral overcoverage did not lead to a significant association between pincer morphology and radiographic hip osteoarthritis at 2,5,8 and 10 years follow-up. Yet when hip pain was present, a significant association between pincer morphology and RHOA was found.
- A study in the World COACH consortium was the first prospective study to demonstrate a significant association between pincer morphology (LCEA≥45°) and radiographic hip osteoarthritis (OR 1.50 95% CI 1.05-2.15).). This is the first study to investigate hips completely free of radiographic hip osteoarthritis at baseline, which may explain why previous studies were unable to find an association as they also included hips with doubtful hip osteoarthritis at baseline. Hips with pincer morphology aged 40-50 (RR 2.67) and with BMI ≥25 (RR 1.21) had a relatively higher risk of developing RHOA compared to non-pincer hips.

Summary

Osteoarthritis is a leading cause of pain, disability, and decreased quality of life worldwide (1). Not only does this pose a significant burden on individuals suffering from disease, osteoarthritis also represents a financial burden for society (2). A study that estimated the lifetime risk of developing symptomatic hip osteoarthritis, found that one in four individuals develops this condition by the age of 85 (3). Presently there is no cure of hip osteoarthritis in the form of disease modifying drugs or preventative surgical interventions, which makes total hip replacement the only treatment option for end-stage disease. It is therefore essential to study early treatment options and preventative strategies for hip osteoarthritis. In order to advance research, we must identify modifiable risk factors to target. Hip morphology has been recognized as an important risk factor, as an altered hip shape changes the biomechanical forces acting on the joint, which leads to soft tissue and ultimately cartilage damage associated with hip osteoarthritis. In order to investigate the associations between hip morphology and hip osteoarthritis, both the predictor and outcome must be defined clearly in epidemiological studies. Here I provide a summary of the chapters covering the two aims of this thesis. The first aim was to validate an automated method to quantify hip morphology. We describe the World COACH consortium, a collection of all worldwide available cohorts with prospective hip imaging available, we validate an automated method to study hip morphology in the consortium, and investigate the additional value of false profile radiographs compared to anteroposterior radiographs alone in the diagnosis of developmental dysplasia of the hip. The second aim was to study associations between hip morphology and hip osteoarthritis. We specifically researched acetabular dysplasia (undercoverage of the femoral head by the acetabulum) and pincer morphology (overcoverage of the femoral head by the acetabulum).

Part I – Validating an automated method to quantify hip morphology

In chapter 2 we present the consortium profile of the Worldwide Collaboration of OsteoArthritis prediction for the Hip (World COACH). The consortium was initiated to increase knowledge on the etiology and risk factors associated with hip osteoarthritis. By pooling and harmonizing individual participant data of nearly 40.000 participants, we aim to develop a personalized prediction model for hip osteoarthritis. In the prediction model factors such as clinical findings, imaging, biomarkers, genetics and lifestyle data will be incorporated. In chapter 3 we validate a previously developed automated method to quantify hip morphology. The eight validated measures are the acetabular depth-width ratio, the acetabular index, the alpha angle, the lateral center edge angle, the Wiberg center edge angle, the migration index, the neck-shaft angle, and the triangular index. We found that automated morphological measurements are reliable compared to measurements by trained readers, and offer a faster, cheaper and more objective alternative. In chapter 4 the additional value of the false profile radiograph, which visualizes a lateral view of the hip joint, in the diagnosis of developmental dysplasia of the hip was compared with only using the anteroposterior radiograph for diagnosis. Data was drawn from Cohort Hip and Cohort Knee (CHECK), which is a prospective nationwide cohort study. Developmental dysplasia of the hip was quantified on anteroposterior and false profile radiographs using a semi-automated method, and the additional value was the proportion of developmental dysplasia only present on the lateral images. We found a strong additional value of the false profile radiograph, as 43.2% of diagnoses will be missed when only using anteroposterior radiographs.

Part II – The associations between hip morphology and hip osteoarthritis.

In chapter 5 we studied the association between acetabular dysplasia and radiographic hip osteoarthritis over 4 different time points within 10 years in the CHECK cohort. The average age of our population at baseline was 55.7 years of age. We used both the LCEA as well as the anterior center edge angle (ACEA) to quantify anterior and lateral acetabular coverage. Acetabular dysplasia was present when either the LCEA, the ACEA or both were ≤ 25° (4). Our study showed that individuals with the first onset of hip and knee pain without evidence of definite radiographic hip osteoarthritis at baseline had an increased risk of developing radiographic hip osteoarthritis within 2-8 years. The observed associations were strong when acetabular dysplasia was present both anteriorly and laterally at at 2- and 5-years follow-up (OR 2.46, 95% CI 1.00–6.04 and 2.28, 95% CI 1.20-4.31, respectively), but seemed to weaken at 8 years follow-up (OR 1.86, 95%CI 1.22-2.83), and disappeared fully at 10 years follow-up. We concluded that as time passed, the risk of developing both incident and end-stage radiographic hip osteoarthritis disappeared in individuals with acetabular dysplasia compared to individuals without this bone shape variation. In chapter 6 we studied pincer morphology and whether it is associated with the development of radiographic hip osteoarthritis. A previous study in the CHECK cohort at 5 years follow-up found a protective effect for end-stage radiographic hip osteoarthritis if pincer morphology was present both anteriorly and laterally (OR= 0,34; 95% CI: 0,13-0,87) (5). As we hypothesized that the previously reported risk of radiographic hip osteoarthritis in pincer hips in existing literature may have been underestimated due to limitations such as time to follow-up, localization and radiographic quantification of pincer morphology and presence of hip pain, we conducted a long-term follow-up study in the CHECK cohort investigating this association. Our findings in chapter 6 however, did not support this hypothesis as no significant association was observed at any time point within 10 years. However, hip pain did moderate this effect significantly, which warrant further research into clinical symptoms that should be studied along with morphological variety in determining the risk of developing radiographic hip osteoarthritis. In chapter 7 we studied whether acetabular dysplasia was a risk factor for clinically relevant and radiographic incident hip osteoarthritis in the CHECK cohort. Clinically relevant hip osteoarthritis was defined by an expert diagnosis based on clinical and radiographic data obtained between 5-10 years follow-up from baseline. As in chapter 5, acetabular dysplasia was not associated with radiographic incident hip osteoarthritis at 10 years follow-up in this cohort, but it was associated with clinically relevant hip osteoarthritis (OR 2.80, 95% CI 1.15-6.79). This led to the conclusion that a clinically relevant definition of hip osteoarthritis must be included in future studies. In chapter 8 we performed an individual participant data meta-analysis on the association between acetabular dysplasia and incident radiographic hip osteoarthritis in 18,807 hips free of doubtful and definite radiographic hip osteoarthritis at baseline. We demonstrated an independent association (OR 1.80 95% CI 1.40-2.34) between acetabular dysplasia defined by a WCEA ≤25° and incident radiographic hip osteoarthritis within 8 years. Additional measures of acetabular dysplasia (WCEA≤20°, ADR ≤250, or a combination of both) were also associated with an increased risk of developing radiographic hip osteoarthritis. In chapter 9 we conducted an individual participant data meta-analysis of World COACH data, investigating the association between pincer morphology and radiographic hip osteoarthritis within 8 years. Contrary to previous results from prospective cohort studies, we found a significant association between pincer morphology defined by LCEA≥45° (OR 1.50 95% CI 1.05-2.15), but not when pincer morphology was defined by LCEA≥40° (OR 1.15 95% CI 0.87-1.51).

Nederlandstalige samenvatting

Artrose vormt wereldwijd een vooraanstaande oorzaak van pijn, invaliditeit en verminderde levenskwaliteit (29). Dit legt niet alleen een aanzienlijke last op degenen die lijden aan de aandoening, maar vormt tevens een financiële belasting voor de maatschappij (93). Een studie die het levenslange risico op het ontwikkelen van symptomatische heupartrose heeft geschat, ontdekte dat één op de vier personen deze aandoening ontwikkelt tegen de leeftijd van 85 jaar (12). Momenteel bestaat er geen genezing voor heupartrose in de vorm van medicatie of preventieve chirurgische ingrepen, wat tot gevolg heeft dat een heupprothese vaak de enige behandeloptie is voor het eindstadium van de ziekte. Het is daarom essentieel om vroegtijdige behandelopties en preventieve maatregelen voor heupartrose te bestuderen. We moeten daarom modificeerbare risicofactoren identificeren. Heupmorfologie is erkend als een belangrijke risicofactor, aangezien een veranderde heupvorm de biomechanische krachten die op het gewricht inwerken beïnvloedt, wat leidt tot beschadiging van omliggend weefsel en uiteindelijk kraakbeenschade geassocieerd met heupartrose. Om de verbanden tussen heupmorfologie en heupartrose te onderzoeken, moeten zowel de heupvorm als artrose duidelijk worden gedefinieerd in epidemiologische studies. Hier geef ik een samenvatting van de hoofdstukken die de twee doelstellingen van dit proefschrift beslaan. Het eerste doel was het valideren van een geautomatiseerde methode om heupmorfologie te kwantificeren. We beschrijven het World COACH consortium, een verzameling van alle wereldwijd beschikbare cohorten met prospectieve heupbeeldvorming, we valideren een geautomatiseerde methode om heupmorfologie in het consortium te bestuderen, en onderzoeken de aanvullende waarde van faux profile röntgenfoto's in vergelijking met alleen anteroposterieure röntgenfoto's bij de diagnose van heupdysplasie. Het tweede doel was het bestuderen van verbanden tussen verschillende heupmorfologieën en heupartrose. Acetabulaire dysplasie (onvoldoende bedekking van de femurkop door het acetabulum) en pincermorfologie (overmatige bedekking van de femurkop door het acetabulum) werden onderzocht.

Deel I – Validatie van een geautomatiseerde methode voor het kwantificeren van heupmorfologie

In hoofdstuk 2 wordt het consortium profile van the Worldwide Collaboration of OsteoArthritis prediction for the Hip (World COACH) gepresenteerd. Het consortium is opgezet om kennis over de etiologie en risicofactoren geassocieerd met heupartrose te vergroten. Door individual participant data van bijna 40.000 deelnemers te bundelen en te harmoniseren, wordt ernaar gestreefd om een gepersonaliseerd voorspellingsmodel voor heupartrose te ontwikkelen. In dit voorspellingsmodel zullen factoren zoals klinische bevindingen, beeldvorming, biomarkers, genetica en leefstijlgegevens worden meegenomen. In hoofdstuk 3 wordt een eerder ontwikkeld geautomatiseerde methode om heupmorfologie te kwantificeren gevalideerd. De acht gevalideerde metingen zijn de acetabular depth-width ratio, the acetabular index, the alpha angle, the lateral center edge angle, the Wiberg center edge angle, the migration index, the neck-shaft angle, and the triangular index. Daaruit bleek dat automatische morfologische metingen een betrouwbaar, snel en goedkoop alternatief blijken voor handmatige morfologische metingen.
In hoofdstuk 4 wordt de aanvullende waarde van de faux profile röntgenfoto onderzocht. De faux profile rontgenfoto geeft een lateraal beeld van het heupgewricht weer, en wordt vergeleken met de anteroposterieure (standaard) röntgenfoto voor het stellen van de diagnose van heupdysplasie bij volwassenen in het prospectieve Cohort Heup en Cohort Knie (CHECK). Heupdysplasie werd gekwantificeerd op anteroposterieure en faux profile röntgenfoto's met behulp van een semi-geautomatiseerde methode, en de aanvullende waarde is gedefinieerd als het percentage heupdysplasie dat enkel aanwezig was op de faux profile foto's. Een sterke aanvullende waarde van de faux profile röntgenfoto werd

aangetoond, aangezien 43,2% van de diagnoses gemist zou worden bij het enkel gebruiken van enkel anteroposterieure röntgenfoto's.

Deel II – De associatie tussen heupmorfologie en heupartrose.

In hoofdstuk 5 werd de associatie bestudeerd tussen acetabulaire dysplasie en radiografische heupartrose op 4 verschillende tijdstippen binnen 10 jaar in het CHECK cohort. De gemiddelde leeftijd van de studiepopulatie bij aanvang was 55,7 jaar. Zowel de lateral center edge angle (LCEA) als de anterior center edge angle (ACEA) zijn gebruikt om de anterieure en laterale acetabulaire bedekking te kwantificeren. Acetabulaire dysplasie was aanwezig wanneer de LCEA of ACEA of beiden ≤ 25° waren (94). Onze studie toonde aan dat individuen met de eerste tekenen van heup- en kniepijn zonder aanwijzingen voor definitieve radiografische heupartrose bij aanvang een verhoogd risico hadden om binnen 2-8 jaar radiografische heupartrose te ontwikkelen. De associaties waren sterk wanneer acetabulaire dysplasie zowel anterieur als lateraal aanwezig was bij de follow-up na 2 en 5 jaar (OR 2,46, 95% BI 1,00-6,04 en 2,28, 95% BI 1,20-4,31 respectievelijk), maar leken af te zwakken bij de follow-up na 8 jaar (OR 1,86, 95% BI 1,22-2,83) en verdwenen volledig bij de follow-up na 10 jaar. We concludeerden dat naarmate de tijd verstreek, het risico op het ontwikkelen van zowel incidentele als eindstadium radiografische heupartrose verdween bij individuen met acetabulaire dysplasie in vergelijking met individuen zonder acetabulaire dysplasie. In hoofdstuk 6 is de associatie tussen pincermorfologie en de ontwikkeling van radiografische heupartrose bestudeerd. Een eerdere studie in het CHECK-cohort na 5 jaar follow-up vond een beschermend effect voor eindstadium radiografische heupartrose als pincermorfologie zowel anterieur als lateraal aanwezig was (OR = 0,34; 95% BI: 0,13-0,87) (23). Omdat we vermoedden dat het eerder gerapporteerde risico op radiografische heupartrose bij pincer heupen in bestaande literatuur mogelijk is onderschat vanwege beperkingen zoals

follow-up tijd, lokalisatie van de pincermorfologie, radiografische kwantificatie van pincermorfologie en aanwezigheid van heuppijn, hebben we een lange termijn follow-up studie uitgevoerd in het CHECK-cohort om deze associatie verder te onderzoeken. Er werd geen significante associatie tussen pincermorfologie en radiografische heupartrose waargenomen op enig tijdstip binnen 10 jaar. De aanwezigheid van heuppijn op baseline had echter een significante invloed dit effect, en zorgde ervoor dat er op 5,8 en 10 jaar wel een significant associatie was tussen pincermorfologie en radiografische heupartrose. In hoofdstuk 7 werd onderzocht of acetabulaire dysplasie een risicofactor is voor klinisch relevante en radiografische incidentie van heupartrose in het CHECK-cohort na 10 jaar follow-up. Klinisch relevante heupartrose werd gedefinieerd door een deskundige op basis van klinische en radiografische gegevens verkregen tussen 5-10 jaar follow-up. Zoals in hoofdstuk 5 was acetabulaire dysplasie niet geassocieerd met radiografische heupartrose na 10 jaar follow-up in dit cohort, maar het was wel geassocieerd met klinisch relevante heupartrose (OR 2,80, 95% BI 1,15-6,79). Dit leidde tot de conclusie dat een klinisch relevante definitie van heupartrose moet worden opgenomen in toekomstige onderzoeken.

In hoofdstuk 8 hebben we een meta-analyse uitgevoerd van individuele deelnemersgegevens over de associatie tussen acetabulaire dysplasie en het optreden van radiografische heupartrose bij 18,807 heupen zonder radiografische heupartrose op baseline. We hebben een onafhankelijke associatie aangetoond (OR 1.80, 95% CI 1.40-2.34) tussen acetabulaire dysplasie gedefinieerd door een WCEA ≤25° en het optreden van radiografische heupartrose binnen 8 jaar. Overige maten van acetabulaire dysplasie (WCEA ≤20°, ADR ≤250, of een combinatie van beide) waren ook geassocieerd met een verhoogd risico op het ontwikkelen van radiografische heupartrose. In hoofdstuk 9 hebben we een meta-analyse uitgevoerd van individuele deelnemersgegevens van World COACH data, waarbij we de associatie tussen pincermorfologie en radiografische heupartrose binnen 8 jaar hebben onderzocht. In tegenstelling tot eerdere

resultaten uit prospectieve cohortstudies vonden we een significante associatie tussen pincermorfologie gedefinieerd door LCEA ≥45° (OR 1.50, 95% CI 1.05-2.15), maar niet wanneer pincermorfologie werd gedefinieerd door LCEA ≥40° (OR 1.15, 95% CI 0.87-1.51).

Abbreviations

2D	Two dimensional
3D	Three dimensional
AA	Alpha angle
ACR	American College of Rheumatology
AD	Acetabular dysplasia
ADR	Acetabular depth-width ratio
AI	Acetabular index
BMI	Body mass index
CHECK	Cohort Hip and Cohort Knee
CI	Confidence interval
CT	Computed tomography
DALY	Disability-Adjusted Life Year
FAIs	Femoroacetabular impingement syndrome
IPD	Individual participant data
LCEA	Lateral Center Edge Angle
MI	Migration index
MOST	Multicenter Osteoarthritis STudy
MRI	Magnetic resonance imaging
NSA	Neck shaft angle
OA	Osteoarthritis
OAI	OsteoArthritis Initiative
OR	Odds ratio
QALY	Quality-Adjusted Life Year
RHOA	Radiographic hip osteoarthritis
ROM	Range of motion
RS	Rotterdam Study
SOF	Study of Osteoporotic Fractures
TASOAC	TASmanian Older Adult Cohort study
THR	Total hip replacement
TI	Triangular index
WCEA	Wiberg Center Edge Angle
World COACH	Worldwide Collaboration of OsteoArthritis prediction for the Hip

PhD TrainingCourses	Year	ECTS*
Statistical Shape Modeling	2022	2
Introduction to SQL	2022	1.2
NIHES Logistic Regression	2022	3
Biostatistics 1	2022	4.5
Biomedical English Writing	2022	2
Scientific Integrity	2022	0.3
Conferences		
Oral presentations		
OARSI conference	2022	2
Science Day Dept. of Orthopaedics and Sports Medicine	2022	0.7
NOV congress	2023	2
Poster presentations		
OARSI	2022	1.5
MolMed PhD Day	2022	1.5
OARSI	2023	1
OARSI	2023	1
Teaching activities		
Minor Orthopedics writing course	2022	2
Scientific internship for medicine master student education	2023	2
Other		
Reviewer Osteoarthritis and Cartilage	2023	0.3
Chair World COACH consortium meetings	2022-2023	1
Training SQL	2022	2.5
Soup and Science presentation	2022	0.5
Journal club department of Orthopedics and Sports Medicine	2022-2023	2.5
Attendance ESOC	2023	0.3
Master of ceremonies (Dagvoorzitter) NOV/ NOF congress	2024	-

*1 ECTS (European Credit Transfer System) equals a 28-hour workload.

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Curriculum vitae

Noortje Sophie Riedstra werd op 22 mei 1995 geboren te Amsterdam. Zij verhuisde in 2000 naar Brugge in België waar zij de lagere school afrondde. In 2007 verhuisde zij met haar familie naar Lake Bluff, Illinois in de Verenigde Staten waar zij op Lake Forest High School zat. In 2011 verhuisde Noortje naar Breda en behaalde haar vwo-diploma op het Mencia de Mendoza Lyceum in 2013. In datzelfde jaar ging zij geneeskunde studeren aan de rijksuniversiteit Groningen.
In 2017 studeerde zij een jaar als exchange student aan de University of Sydney in Australië. Noortje liep haar coschappen in het Universitair Medisch Centrum Groningen, gevolgd door het Isala Ziekenhuis te Zwolle. Daar werd haar interesse voor de Orthopedie gewekt, wat zich verder uit heeft gebreid tijdens het laatste jaar van haar studie bij de Orthopedie en Sportgeneeskunde in het Erasmus MC en het Sophia Kinderziekenhuis. In 2021 behaalde Noortje haar artsendiploma en werkte aansluitend een jaar als ANIOS Orthopedie in het Dijklander Ziekenhuis te Hoorn. In januari 2022 startte zij haar PhD traject op de afdeling Orthopedie en Sportgeneeskunde in het Erasmus MC onder begeleiding van co-promotor dr. Rintje Agricola en promotors professor dr. Sita Bierma-Zeinstra en professor dr. Denise Eygendaal. In oktober 2023 zal zij haar vooropleiding algemene heelkunde starten in het Albert Schweitzer ziekenhuis te Dordrecht (opleider Dr. Avontuur). Haar opleiding tot orthopaedisch chirurg zal in 2025 aanvangen en zij zal gaan werken in het Erasmus MC te Rotterdam (opleider dr.Bos) en in het Elizabeth Twee Steden ziekenhuis te Tilburg (opleider dr. van der Jagt).

Dankwoord

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