The Patho-aetiology of Hip Osteoarthritis

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Abstract

Osteoarthritis of the hip frequently occurs in the absence of osteoarthritis in other large joints, suggesting that local factors are important in its pathogenesis. Hip morphology has been recognised as a potential local biomechanical risk factor for the development of hip osteoarthritis. There are no adequate studies examining osteoarthritis development in the hip. Historical cohorts are either limited by a short follow up or by small numbers.

This thesis explores the natural history of hip osteoarthritis in a large population cohort with particular attention to hip morphology as a predictor of osteoarthritis development.

Software was developed which allows objective measurements of hip morphology in a reproducible manner. Hip morphology was then measured in a 1000 subject cohort. A detailed description of hip morphology is presented in this thesis, with interesting observations of wide variation and a bimodal distribution for alpha angle (a measure of cam-type femoroacetabular impingement). This is suggestive of a discrete pathological entity, which was associated with osteoarthritis in the cross-sectional analysis.

No significant changes exist in terms of morphology during the course of the study and no significant relationship exists between age and hip morphology.

Longitudinal analysis of hip morphology with radiographic osteoarthritis and total hip replacement revealed a significant association between cam-type femoroacetabular impingement and acetabular dysplasia with both outcome measures. Measurements of hip morphology were independently predictive of outcome when controlling for baseline age, BMI and joint space width, and significantly increased our ability to predict osteoarthritis and total hip replacement. Similar associations were seen when considering hip pain and symptomatic osteoarthritis as the outcome measures of interest.

Pincer-type femoroacetabular impingement was not significantly associated with any of the outcome measures of interest and pain remains relatively poorly explained by both hip morphology and/or radiographic change.

The understanding of hip morphology and its role in the natural history of osteoarthritis is significantly improved by this research. Further research is now required to determine whether these morphological abnormalities represent modifiable risk factors for osteoarthritis progression.

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List of Abbreviations

Roman Symbols

α-angle	Alpha Angle
α1(II)	alpha-1 (type II)
ACR	American College of Rheumatologists
AP	Antero-Posterior
AUROC	Area Under Receiver Operator Characteristic
CDH	Congenital Dislocation of the Hip
CI	Confidence Interval
CT	Computerised Tomography
DDH	Developmental Dysplasia of the Hip
DNA	Did Not Attend
FAI	Femoroacetabular Impingement
GDP	Gross Domestic Product
HHGS	Histological-Histochemical Grading System
HTE	Horizontal Toit Externe
ICC	Intraclass Correlation
JSN	Joint Space Narrowing
JSW	Joint Space Width
KL	Kellgren & Lawrence

LCE	Lateral Centre Edge
mPFA	medial Proximal Femoral Angle
MRA	MRI arthrogram
MRI	Magnetic Resonance Imaging
N/R	No Response
OA	Osteoarthritis
OACH	Osteoarthritis Cartilage Histopathology
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
OR	Odds Ratio
PROMs	Patient Reported Outcome Measures
SCFE	Slipped Capital Femoral Epiphysis
THR	Total Hip Replacement
TIH	Triangular Index Height
US	United States
WOMAC	Western Ontario McMaster Universities Osteoarthritis Index

Chapter 1

Introduction

1.1 Anatomical positions and planes

All anatomical descriptions in this thesis are based on standard definitions of the anatomical position and planes.

1.1.1 The anatomical position

A person in the anatomical position:

- is standing upright or lying supine with head, eyes and toes directed anteriorly
- has upper limbs by the side with palms facing anteriorly
- has lower limbs together with the feet directed anteriorly.

1.1.2 The anatomical planes

- The median plane (mid sagittal) is a vertical plane passing longitudinally through the body dividing it into right and left halves
- Sagittal planes are vertical planes that pass through the body parallel to the median plane
- Coronal planes are vertical planes that pass through the body at right angles to the median plane, therefore dividing the body into anterior and posterior portions
- Horizontal planes (also referred to as axial planes) are transverse planes that pass through the body at right angles to the sagital and coronal planes, dividing the body into superior and inferior parts

1.2 The hip

The hip is a synovial joint whose primary function is to support the weight of the body in both static and dynamic postures.

1.2.1 Hip anatomy

The hip joint is a ball and socket joint formed by the articulation of the head of the femur with the acetabulum. The acetabulum is a little less than half a sphere and faces

laterally and somewhat anteriorly.

The articular surface is horseshoe-shaped and covered with hyaline cartilage that is thickest peripherally. The socket is deepened by a peripheral fibrocartilaginous labrum. The femoral head forms approximately two thirds of a sphere. It is covered with hyaline cartilage that is thinnest toward the periphery. Except when considering joint lubrication or the details of transmission of force from one surface to the other, the femoral head may be considered perfectly spherical, and the acetabulum a matching socket. In the adult, the femoral neck normally forms an angle with the femoral shaft of about 125° in the frontal plane and is angled forward approximately 15°.

The muscles that cross the joint can be conveniently grouped into seven major groups:

1. The abductors (gluteus medius, gluteus minimus, tensor fasciae latae)
2. The adductors (adductor magnus, adductor longus, adductor brevis, gracilis, and pectineus)
3. The short extensors (gluteus maximus)
4. The long extensors (long head of biceps, semitendinosus, and semimembranosus)
5. Short flexors (iliopsoas)
6. Long flexors (rectus femoris, sartorius, and tensor fasciae latae)
7. The short external rotators

Rather thick, strong ligaments comprise the hip-joint capsule and extend from the periphery of the acetabulum to the intertrochanteric line and crest of the femur. They are stronger anteriorly and practically unattached to the femur posteriorly. These ligaments are so arranged that they wind up and tighten as the joint is extended and unwind as the joint is flexed.

Hominid evolution has resulted in variants of morphology which facilitate both bipedal gate and birth of a large brained foetus. [1]

1.2.2 Hip movements

Motion of the hip joint varies from individual to individual and with body habitus. Normal passive motion is approximately 140°in the sagittal plan, abduction 40°, adduction 25°, internal rotation 40°and external rotation 50°. Active motion is approximately 25% less than passive motion in all planes.

1.2.3 Hyaline cartilage

Hyaline cartilage, its name being derived from the Greek hyalos meaning glass, is a highly specialised type of connective tissue that occurs on the articular surfaces of bones and within the major airways. Three types of cartilage exist: hyaline, elastic and fibrous, differing in the composition of their matrix or ground substance. Hyaline cartilage is the most widely distributed type of cartilage within the human body.

Macroscopically it has a translucent, bluish-white appearance.

1.2.3.1 Constituents of hyaline cartilage

All connective tissues comprise a mixture of cells and intercellular, or ground, substance. Cartilage differs from other forms of connective tissue by virtue of the firmness of the ground substance. This enables it to act as a supportive structure and to bear mechanical stress.

Cartilage cells (chondrocytes), are derived from mesenchymal cells which form part of the undifferentiated loose connective tissue of early embryonic life. Chondrocytes are capable of synthesising and secreting the ground substance that surrounds them. As hyaline cartilage contains no blood vessels, lymphatics or nerves, the properties of the ground substance must allow diffusion of nutrients and waste products to and from the chondrocytes. The latter, located in small lacunae, have multiple short processes extending into the surrounding matrix effectively increasing their surface area.

The ground substance is composed of a mixture of amorphous (non-formed) and fibrous (formed) components. The amorphous component predominantly contains proteoglycans. These consist of polysaccharide chains (glycosaminoglycans) such as keratan sulphate and chondroitin sulphate, which are covalently bound to a protein core. These core proteins are in turn non-covalently bound to a long filament of hyaluronic acid to form large proteoglycan aggregates. Their principle function is to retain water, which is bound to the negatively charged glycosaminoglycans (GAGs), and represents

75% of the total volume of the ground substance. The formed component of the ground substance is composed of collagen fibres that constitute 50% of the dry weight of cartilage. The collagen fibres interact electrostatically with the GAGs to form a cross-linked matrix. The main type of collagen fibre in hyaline cartilage is type II collagen which consists of three alpha-1 (type II) chains [α1(II)] [2]. This differs from the more common type I collagen, which occurs in skin, tendons and bone, in that it contains higher levels of hydroxylysine and is thus more hydrophilic.

1.2.3.2 Histological structure

Histological analysis of hyaline cartilage using polarised light microscopy and transmission electron microscopy reveals a zonal anatomy (Figure 1.1).

1. Tangential layer (superficial zone): The thin superficial or tangential zone contains densely packed collagen fibrils which are orientated parallel to the articular surface. The general orientation is determined by the tensile and compressive forces at the articulating surface.

2. Transitional layer: Below the superficial zone is a transitional zone containing obliquely orientated collagen fibrils, which gradually change with depth to become perpendicular in orientation. Chondrocytes are slightly larger and there is an increase in proteoglycan concentration. This zone forms the transition between the shearing forces of the superficial zone and the comprresive forces of the deeper

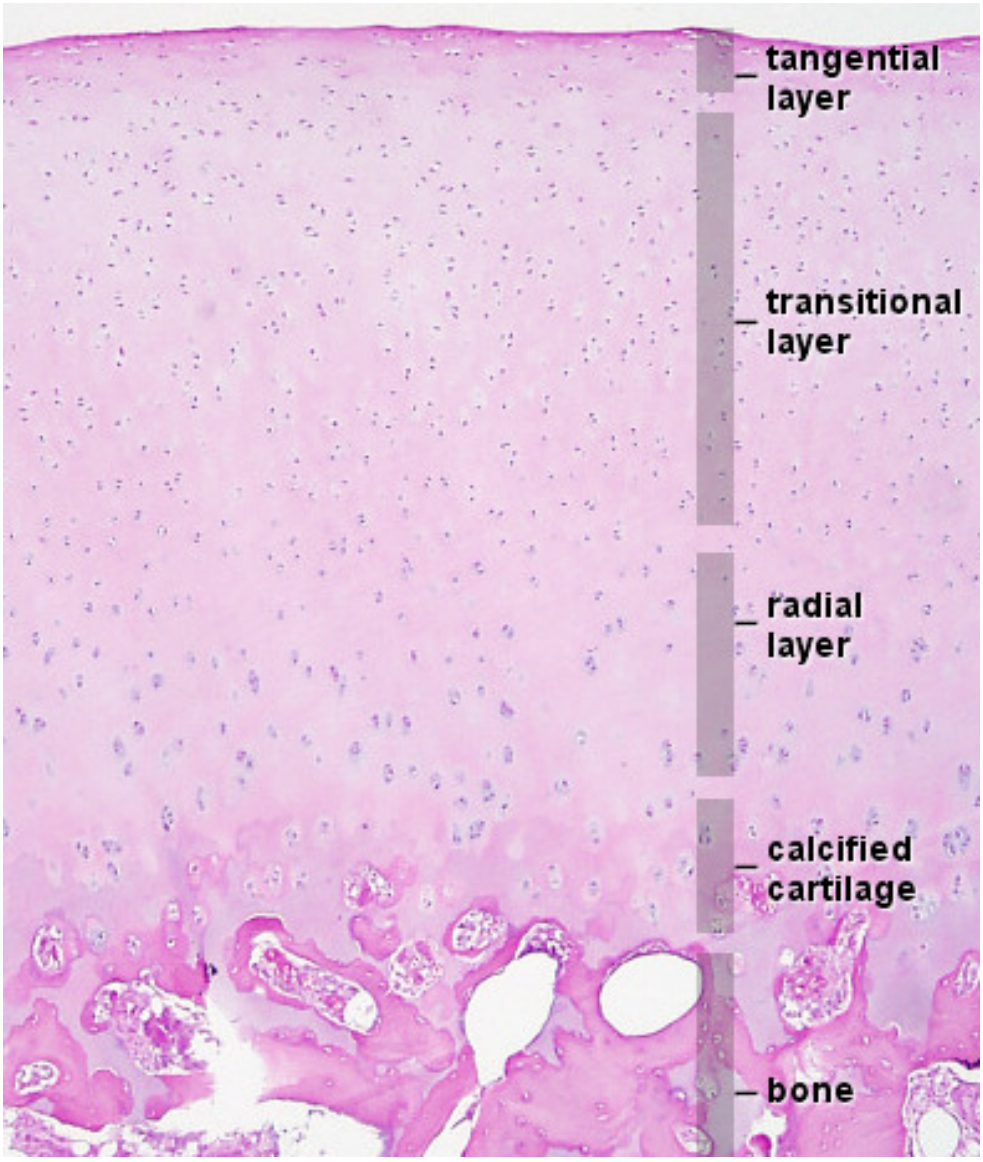


Figure 1.1 – Articular hyaline cartilage: Hematoxylin and eosin stain (from www.labb.anhb.uwa.edu.au).

layers.

3. Radial layer: The largest zone. Here chondrocytes are arranged in radial colums, orientated perpendicular to articulating the surface. Collagen fibrils are perpendicularly orientated in the upper two thirds, whilst in the lower third there are also numerous curved obliquely orientated fibrils.

4. Calcified cartilage layer (contains the tide mark): Anchors the collagen bundles to the underlying bone and forms a barrier to diffusion from blood vessels supplying the subchondral bone. The tidemark is a basophilic layer that forms the boundary between calcified and uncalcified cartilage straddles.

Water concentration differs slightly between the zones, being 82% in the superficial zone and 76% in the radial zone [3]. The superficial zone is impermeable to water and has a lower proteoglycan concentration than the other zones. This allows higher permeability for fluid flow within the superficial zone itself. The superficial zone may therefore function as a soft cushion, absorbing and distributing the impact of a compressive force. Only prolonged loading forces are purported to be transmitted to the deeper zones [4].

1.3 Osteoarthritis of the Hip

Osteoarthritis (OA) is the commonest disease of human joints and is ten times more common than the second most prevalent, rheumatoid arthritis [3]. It is estimated that 12.1% of the US population aged 25-74 years suffer from OA of some joint [4]. In the Johnston County OA Project 27% of those aged over 45 have mild, moderate, or severe radiographic OA of the hips and 9.2% symptomatic OA [4].

1.3.1 Definition

Kuettner et al. [5], at a workshop sponsored by the American Academy of Orthopaedic Surgeons, the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, the National Institute on Ageing; the Arthritis Foundation, and the Orthopaedic Research and Education Foundation defined OA as:

> OA is a group of overlapping distinct diseases, which may have different etiologies but with similar biologic, morphologic, and clinical outcomes. The disease processes not only affect the articular cartilage, but involve the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane, and periarticular muscles. Ultimately, the articular cartilage degenerates with fibrillation, fissures, ulceration, and full thickness loss of the joint surface.

1.3.2 Classification of Osteoarthritis

The classification and diagnostic criteria for OA remain controversial [6]. Consequently there are several potential classifications in use, each of which has its own strengths and limitations. OA can be defined via (i) histological (ii) clinical, (iii) radiological and (iv) clinical + radiographic criteria.

1.3.2.1 Histological Classification

A clear histological definition of OA has proved difficult [7], but characteristic structural and biochemical changes may be identified. Macroscopically, cartilage changes in OA include softening (chondromalacia), fibrillation, and erosions (ulceration) [8]. Histological features of cartilage breakdown and failed repair include cartilage clefts, loss of the cartilage layers, cellular necrosis, chondrocyte cloning, and a duplication of the tidemark. The superficial zone is affected first in early OA, with loss of proteoglycan content and composition. Proteoglycan architecture is broken down with a higher percentage as non-aggregated (unbound from hyaluronate) proteoglycan leading to a more permeable solid matrix. There is increase in water content and hypertrophy of the matrix, but the increased permeability of the matrix results in a reduction of the hydraulic pressure in early OA cartilage. This causes a reduction in the compressive stiffness of the tissue, which can be identified clinically as the softening of chondromalacia. Cartilage clefts may progress to fissures and as they deepen eventually expose

sub-chondral bone. The local inflammatory response causes an increase in the production of synovial fluid which begins to penetrate into the sub-chondral bone, eventually causing intra-osseous fluid cysts. Local inflammatory mediators may in many cases cause chronic inflammation of the synovial membrane. In addition to degradation and loss of articular cartilage, OA is characterised by hypertrophic bone changes with osteophyte formation and subchondral bone remodelling.

As the understanding of the cellular process of OA pathology develops, several new biomarkers for OA such as Type II collagen C-telopeptide (CTX-II) and human cartilage oligometric matrix protein (HCOMP) have been investigated with variable results [9–11]. Biomarkers for OA have a potential future in early diagnosis, however at present few studies have been able to reliably link them to OA progression in longitudinal studies.

The Mankin Histological-Histochemical Grading System (HHGS) [12] has been the most widely used grading scheme for assessing OA severity and includes 4 parameters (structure, cells, Safranin-O staining, and tidemark integrity) that identify changes within the articular cartilage. Several studies have attempted to validate the Mankin grading system, and these have identified low interobserver and intraobserver reproducibilities, indicating that the scheme is neither reliable nor reproducible [13, 14] and in particular fails to discriminate between normal and mild to moderate OA. The use of end-stage diseased specimens to establish the system has been proposed to account for the lack of sensitivity and specificity [13, 14]. Other schemes, such as the Osteoarthri-

tis Cartilage Histopathology (OACH) scoring system developed by the Osteoarthritis Research Society International (OARSI) [15], and aim to improve upon the Mankin HHGS and evaluation of OA.

1.3.2.2 Clinical Classifications

Typically, patients with OA present with joint pain that is exacerbated by activity and relieved by rest. Pain is typically felt in the groin, but may also occur laterally or be referred distally down the anterior thigh towards the knee. Stiffness or functional limitations are common features due to capsular fibrosis, osteophyte formation and/or joint deformity.

On examination there are a range of clinical signs that are consistent with OA which are listed in Table 1.1.

Table 1.1 – Clinical Signs of Osteoarthritis

Antalgic gait
Trendelenburg test positive
Muscle atrophy & weakness
Leg length discrepency
Fixed flexion deformity
Reduced range of movement (Irritability/Pain on range of movement)
Tenderness over the joint line
Crepitus
Bony enlargement of the joint
Angular deformity (varus/valgus)
Instability of joint
Joint effusion

There are several validated scoring systems or Patient Reported Outcome Measures

(PROMs) used to quantify disease severity and outcomes from the patient's perspective, using both pain and disability with activities of daily living (ADLs). Examples of these scoring systems include the Oxford Hip & Knee Scores [16, 17] and the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) [18].

1.3.2.3 Radiological Classifications

Clinical scoring is seldom used in isolation. Radiological diagnosis and grading of OA has long been held as the gold standard in epidemiological studies [19]. Scoring systems such as those described by Kellgren & Lawrence [19], Altman [20] and Croft [21] are based on assessment of radiographs for the presence and severity of individual radiographic features associated with OA which include reduced joint space width, peri-articular osteophytes, subchondral sclerosis and bony cysts. Following the allocation of points for constituent features, individual joints are then given an overall grade allowing relatively straightforward comparison in longitudinal studies. In addition to plain film radiography, computed tomography (CT) scanning and magnetic resonance imaging (MRI) are useful tools in developing our understanding of the pathogenesis and natural history of progression of OA [22–24]. While both have been used to investigate structural progression of OA and links to symptomatic severity [22, 23], neither of these forms of imaging are currently used in the diagnosis of OA or classification of OA for research. Imaging markers from MRI in particular may represent potentially useful biomarkers for the evaluation of OA and research in the future [25, 26].

1.3.2.3.1 Kellgren & Lawrence

The Kellgren & Lawrence (KL) grading system is used in the description of hand, hip and knee OA. The features considered are osteophytes, joint space narrowing with sclerosis of subchondral bone, pseudocysts and altered shape of bone ends. Severity of disease is divided in 5 grades as follows:

- None (0)
- Doubtful (1)
- Minimal (2)
- Moderate (3)
- Severe (4)

The KL grading system is widely used to define the presence or absence of structural change, with Grade 2 commonly held as the threshold for the diagnosis of OA. Advice is given that "to ensure maximum uniformity in grading x-rays in field surveys and therapeutic trials, all readings should be made by the same observer, preferably at a single session".

Problems with the system include its relative insensitivity to change and the importance placed on presence of osteophytes. In addition, interpretations of studies using this grading must be done with care due to discrepancies in interpretations of

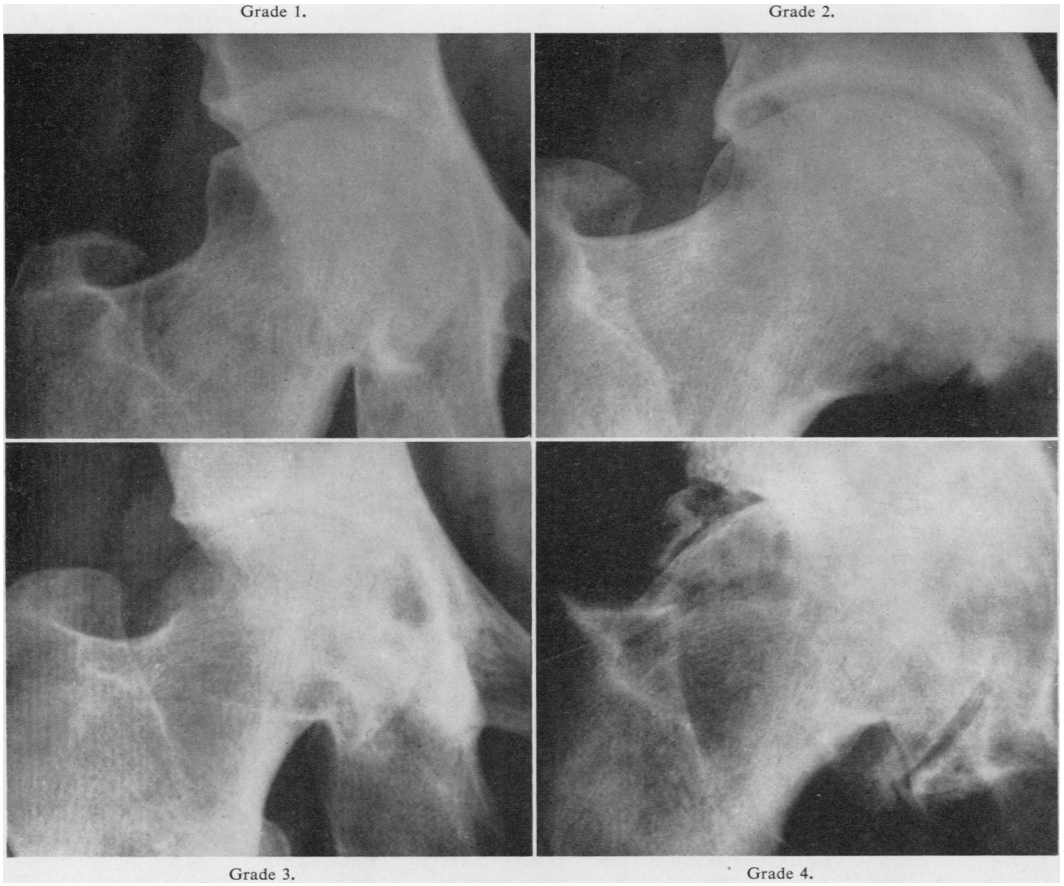


Figure 1.2 – Kellgren & Lawrence Hip Osteoarthritis Reference Grading Radiographs [19].

the original paper. Despite its limitations the KL grading system still appears to be a useful OA definition for epidemiological studies [27, 28]. Reijman et al. considered the validity and reliability of three frequently used radiological definitions of hip OA and found the Kellgren and Lawrence grade showed the highest predictive value for Total Hip Replacement (THR) at follow up [28].

1.3.2.3.2 Croft classification

The Croft classification [21] is a modification of the KL grading system, and again considers the individual radiographic features of minimum joint space width, presence of osteophytes, subchondral sclerosis, and cyst formation. Croft's modification of the KL grading system is shown in Table 1.2. The Croft classification has shown inferior reliability to KL Grading and minimum joint space [28].

Table 1.2 – Croft classification [21]

Grade	Description
0	No change
1	Definite osteophytes only
2	JSN only (defined as an MJS of >2.5 mm)
3	Presence of two of the following: JSN, osteophytosis, subchondral sclerosis (of >5 mm), cyst formation
4	Presence of three of the following: JSN, osteophytosis, subchondral sclerosis (of >5 mm), cyst formation
5	Same as grade 4, but with deformity of the femoral head or total hip replacement due to OA (verified by record view)

JSN: Joint Space Narrowing; MJS: Minimal Joint Space; OA: Osteoarthritis.

1.3.2.4 American College of Rheumatologists Criteria

Thorough clinical history taking and examination of the joints can form a reliable diagnostic pathway in the hands of an experienced clinician, however this lacks objectivity, especially when conducting research.

The American College of Rheumatologists (ACR) criteria for the classification of patients with hip pain associated with OA were developed through a multicentre study [29], and are advocated as an entry criteria for clinical trials. ACR criteria for hip [29] and knee [30] OA are listed in Table 1.3.

Table 1.3 – American College Of Rheumatology Criteria for classification of Hip [29] & Knee [30] Osteoarthritis

Hip	**Knee**
Hip pain + at least 2 of the following 3 features: - ESR <20 mm/hour - Radiographic femoral or acetabular osteophytes - Radiographic joint space narrowing (superior, axial, and/or medial)	Knee pain + at least 1 of 3: - Age >50 years - Stiffness <30 minutes - Crepitus + Osteophytes

ESR: erythrocyte sedimentation rate

Despite precise and extensive development with reported high sensitivity (89%) and specificity (91%) [31], the ACR criteria have subsequently shown poor reliability and poor cross-validity [27, 28]. This combined with relative complexity has led to poor uptake of the ACR criteria for epidemiological research.

1.3.3 Burden of disease

OA represents a large and expanding burden of disease in our society [32–34]. Treatment-related expenses for OA include all aspects of care ranging from costs of prescription medications to walking aids and from specialist physician consultations to costs of surgical implants. In large joints such as the hip and knee, OA causes severe disability that is responsible for making it the leading indication for total joint arthroplasty [33, 34]. Earnings losses due to disability and direct treatment delivery costs have made OA and other rheumatic conditions among the most expensive of all items in any health budget. In the USA alone, 2003 earnings losses due to arthritis-related disability were US$47.0 billion while total health expenditure towards arthritis-related care was US$321.8 billion [32]. This expenditure figure represents approximately 3% of the country's entire Gross Domestic Product (GDP) which gives some perspective of its scale. Consequently, there is an urgent need to reliably identify high-risk population cohorts who can be targeted for future therapeutic trials, early intervention of modifiable risk factors and ongoing research into the complex disease process and natural history of OA progression.

1.3.4 Surgical Management of End-stage OA

Treatment strategies for hip OA most commonly involve removal of damaged joint tissue and replacement arthroplasty. The majority of OA presents in older individuals with advanced disease and treatment is essentially supportive until joint replacement is required. In this context Total Hip Replacement (THR) remains the preferred surgical treatment for symptomatic end-stage hip OA. Treatment goals are pain relief, improved mobility and quality of life, but are not without risk with regard to morbidity and mortality.

1.3.4.1 Total Hip Replacement

Primary hip replacement is a common operation, with 86,488 performed in the UK last year [35] and over 300,000 in the United States [36] but its history can be traced back almost a century. Pierre Delbet (1861-1925) at La Ferté Gaucher, Departement Seine-et-Marne, France was the first to use a rubber femoral prosthesis to replace one-half of the hip joint in 1919. Ernest W. Hey- Groves (1872-1944) used ivory in the same manner in 1927, but latter described what, in his opinion, was a preferable method to treat hip arthritis [37].

> A better method of altering the disproportion between the ball and the socket of the joint, is to enlarge the socket by cutting away its lower and

anterior margins.

The first attempt at THR was made in 1938 by Philip Wiles (1899-1966) at the Middlesex Hospital in London, using precisely fitted stainless steel components which were fixed to the bone with screws and bolts.

The Judet brothers (Robert (1901-80) and Jean (1905-95)) used an acrylic femoral prosthesis again to to replace one-half of the hip joint in 1948 which was exceptionally susceptible to wear. This design was refined upon by Frederick Reck Thompson (1907-83) and Harold R. Böhlman (1893-1979) with Austin Moore (1899-1963). Both the Thompson and Böhlman-Moore prostheses went on to be the first hip arthroplasty products that were widely distributed and were until recently still widely used for replacement of the femoral head and neck following intracapsular femoral neck fractures in the elderly.

Kenneth McKee (1905-1991) experimented with dental acrylic cement for fixation in the late 1940s and later used the Thompson prosthesis on the femoral side that articulated with a three claw type cup that was screwed into the acetabulum. Peter Ring (b. 1922), in 1964 using cementless components with a metal-on-metal articulation achieved good results. Both the McKee-Farrar and the Ring models were abandoned in the 1970s in favour of the Sir John Charnley's (1911-1982) low friction arthroplasty, which pioneered the use of high density polyethylene for the bearing surface and the routine use of polymethylmethacrylate bone cement. The Charnley low friction arthro-

plasty was the first to be used world wide and these advances may be considered the key stage in evolution to contemporary THR.

Today hip surgeons are faced with a variety of options. Cemented and uncemented fixation for both the femoral and acetabular components are available, as well as combinations of the two. Modularity of components has been introduced as have a selection of bearing surface materials, including ultra high molecular weight polyethylene/highly cross-linked polyethylene, ceramic and metal (cobalt chrome).

The 10th Annual report of the National Joint Registry for England & Wales reports that 539,372 total hip arthroplasty procedures were performed between 1 April 2003 and 31 December 2012 [35]. 92% of THRs performed in 2012 were for OA. THR is a very effective procedure with patient satisfaction reported as good or better by more than 75% of patients [38], but is not entirely risk free.

The 90 day mortality following primary THR varies from 0.16% in the under 55s up to 2.18% in the over 80s. Other complications include dislocation, infection, neurological injury and leg length discrepancy, any of which may compromise the functional results as well potentially necessitate revision surgery. In the longer term aseptic loosening, osteolysis, wear of the bearing surface and periprosthetic fracture predominate as causes for revision surgery.

There were 10,040 hip revision procedures recorded in 2012 of which 88% were single-stage revisions with aseptic loosening as the most commonly recorded indication for revision surgery in 40%. Revision surgery is associated with higher cost and compli-

cation rates than primary THR, with one third of patients graded as ASA (American Society of Anesthesiologists) grade 3 for staged revision surgery. The five-year revision rate for primary THR currently stands at 2.8%. Resurfacing arthroplasty which was introduced for use in younger individuals has unfortunately produced higher revision rates than for stemmed THR (five-year revision rate of 5.2%).

Therefore whilst THR is undoubtedly one of the most effective surgical procedures, it is associated with potential complications and risk of revision is greatest in younger patients.

A relatively small proportion of patients with OA have clear predisposing risk factors which might be amenable to modification and/or present early enough for any intervention to be effective.

1.4 Paediatric Hip Disease

1.4.1 Developmental Dysplasia of The Hip (DDH)

DDH formerly described as 'Congenital Dislocation of the Hip (CDH), is a common cause of secondary OA in young adults and is responsible for up to 29% of THR in people below 60 years of age and 9% of all THR procedures [39]. DDH encompasses a spectrum of morphological derangements. The most severe are teratological malarticulations which are rare. Next are developmental dislocation and subluxation, which

describe unstable/dislocatable hips and poorly developed acetabula at birth and may be identified by specific clinical tests. These abnormalities will generally be identified and treatment initiated in infancy. Finally, acetabular dysplasia, which is the mildest form. This may be the end result of a treated dislocated or subluxed hip, but is commonly subclinical, presenting with symptoms in adult life. Acetabular dysplasia is discussed in more detail in section 1.5.1.

DDH is estimated to occur in between 1 and 5 in 1000 live Caucasian births, with females affected 5 to 8 times more commonly than males. In addition to female sex, risk factors include breech positioning, a large neonate, first born child, Downs syndrome, congenital muscular torticollis and positive family history (daughters of fathers with DDH, have 12 times the risk of developing the condition themselves) [40, 41].

Several grading systems exist for quantifying severity on AP pelvis radiographs. The Crowe [42] classification is one such system that classifies hips on the basis of acetabular depth and femoral head location. This categorises DDH based on the degree of proximal migration of the femoral head (Grade I: <50% subluxation; Grade II: 50-75% subluxation; Grade III: 75-100% subluxation; Grade IV: >100% subluxation).

Several retrospective and cross-sectional studies support an association between DDH and OA [43, 44], though degenerative hip disease in adults does not always correlate with the magnitude of adult acetabular dysplasia [45–47].

1.4.2 Slipped Capital Femoral Epiphysis (SCFE)

SCFE is a disorder of the proximal femoral physis that leads to abnormal alignment of the epiphysis (femoral head) relative to the femoral neck. The epiphysis remains in the acetabulum while the neck displaces anteriorly and externally rotates. Slippage occurs though the hypertrophic zone of the physis caused by weakness of the perichondral ring.

In terms of epidemiology SCFE commonly effects adolescent hips and is found in 10 per 100,000 individuals. It is more common in boys (with a male to female ratio of 3:2), obese children, African Americans, Pacific Islanders and bilateral in 17% to 50%. Renal failure (osteodystrophy of chronic renal failure) and endocrine conditions, such as hypothyroidsm are also risk factors.

SCFE shows a clear association with an increased risk of OA. Carney et al [48] report 10% of patients with SCFE develop OA at a mean follow-up of 41 years, while Crowe et al [49] reported one third of all patients with SCFE followed for 17 years manifested radiographic OA. A radiographic study considering the aetiology of idopathic OA of the hip indicated that 39% could have developed OA secondary to SCFE [50], and other authors have also reported estimates in the range of 10 to 40% [51–53]. A cadaveric study of over two thousand adult skeletons found a subclinical SCFE type appearance in 8%, and osteoarthritic changes were more common in hip joints with SCFE [54]. This finding has been opposed by Resnick who argues that these associations may be

as result of secondary deformity, due to OA mimicking the deformity seen in SCFE [55].

1.4.3 Legg-Calvé-Perthes Disease

Legg-Calvé-Perthes Disease is an idiopathic avascular necrosis of the proximal femoral epiphysis, typically affecting children between 4-8 years and is thought to be associated with a disruption in vascular supply with subsequent revascularisation. The prevalence is in the region of 1 in 1200, with a male to female ratio of 5:1. Increased risk is seen with positive family history, low birth weight, abnormal birth presentation, children exposed to second hand smoke as well as in individuals of Asian and Central European decent. The pathologic stages exhibit characteristic appearances over several years. Initially there is infarction which produces a smaller, sclerotic epiphysis with medial joint space widening, progressing through fragmentation and reossification and remodelling, the femoral head typically becomes flattened whilst the femoral neck becomes short and broad [56].

Stulberg et al. noted that progression of degenerative change in Perthes was related to the final sphericity, and the congruence of the head and acetabulum [57]. Gower and Johnston reported at an average follow-up of 36 years that 25 of 30 patients treated non-operatively with Perthes disease manifested radiological signs of OA. Poorest prognosis is in those with collapse of the femoral head in childhood [58]. Approximately half of

patients with a history of Perthes develop premature osteoarthritis secondary to an aspherical femoral head, most commonly in the fifth or sixth decade of life [59]. In patients undergoing THR for end-stage OA, 3% have a history of Perthes disease. [51]

1.5 Morphological Deformities of the Hip

1.5.1 Acetabular Dysplasia

Acetabular dysplasia refers to the presence of an underdeveloped or shallow, upwardly sloping acetabulum, which may occur with varying degrees of deformity of the proximal femur such as excessive femoral neck anteversion, coxa valga or femoral neck cam deformity. The aetiology of acetabular dysplasia dysplasia is obsure and the criteria for its definition controversial. The condition shares aetiological factors with the more severe forms of DDH, but it is important to appreciate that not all acetabular dysplasia is due to DDH. Acetabular development may be affected by a variety of conditions including cerebral palsy, hereditary motor and sensory neuropathy, poliomyelitis, hyperlaxity, and Downs and Ehlers-Danlos syndromes. Skeletal dysplasias, proximal femoral focal deficiency and Perthes disease can also affect acetabular development, while the triradiate cartilage can be injured by sepsis or trauma, which can also cause incomplete lateral acetabular growth.

1.5.2 Femoroacetabular Impingement (FAI)

Femoroacetabular impingement (FAI) is a pathological hip condition characterised by abnormal contact between the acetabulum and femoral head-neck junction [60, 61]. The term FAI did not appear in the English literature until 1999, when it was described by Myers et al. [62], but was perhaps first recognised in 1898 a few years after the introduction of the roentgenogram in association with slipped capital femoral epiphysis [63]. Poland reported a case in which, without reducing the displacement, the projecting anterosuperior margin of the neck was trimmed away, a description not dissimilar to modern osteochondroplasty, discussed in Section 1.5.3.2. Howorth in 1957 [64] highlights the above article, whilst also noting reports of similar cases in relation to SCFE by Whitman [65] in 1909 and Vulpius and Stffel in 1913. The concept of impingement as a cause of hip pain in adults was also reported by Smith-Peterson in 1936 [66]. Some thirty years later R. O. Murray described "tilt" deformities of the proximal femur in relation to the aetiology of OA. Several studies have since proposed the concept of FAI as a cause for degenerative changes leading to idiopathic hip OA in later life [67–71].

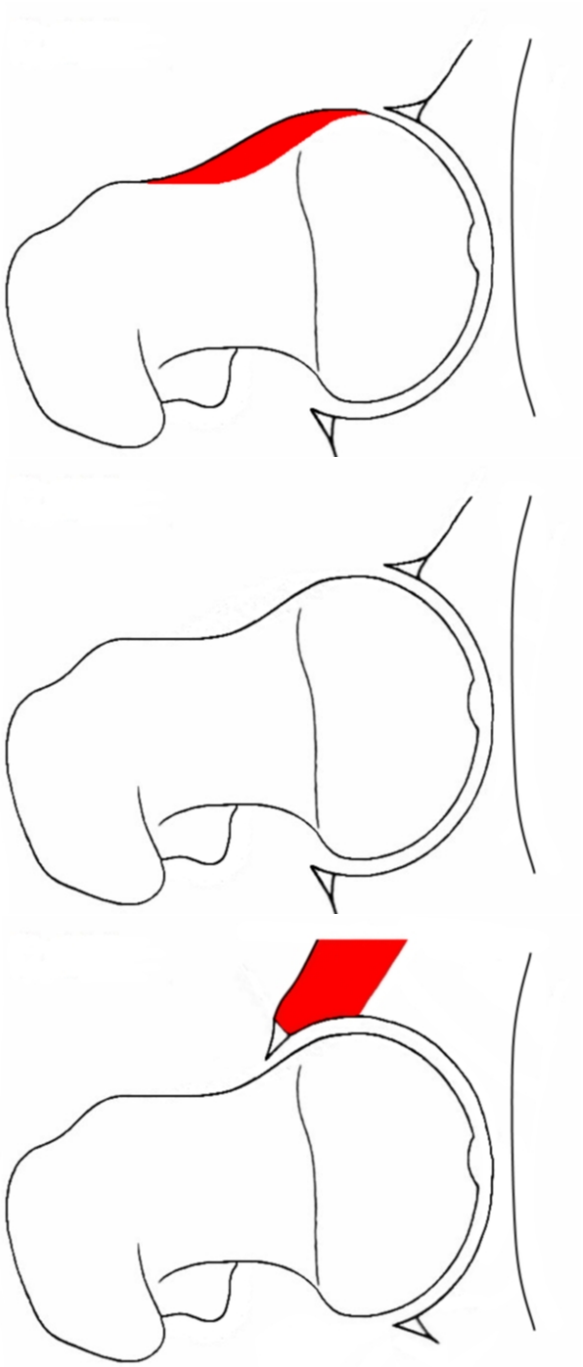
FAI can occur within the normal physiological range of motion as a result of osseous abnormalities described as either cam or pincer deformities. Cam deformities describe an abnormal anterosuperior femoral head-neck junction, whereas pincer deformities describe abnormalities in the shape or orientation of the acetabulum (Figure 1.3).

These deformities exist across a spectrum of severity. Some are very mild and may remain subclinical, whilst others lead to severely debilitating joint pathology in early adulthood. Some patients have both deformities, designated mixed pathology [68]. Impingement can also occur in a morphologically normal hip as a result of extreme range of motion activities, such as in ballet dancers or gymnasts.

Repeated abutment of the femoral neck against the acetabular rim can result in injury to the labrum and adjacent cartilage [72]. Over time these focal lesions may progress to more extensive degenerative disease [67, 70]. There is a scarcity of robust data on its prevalence, especially since it is thought that a large portion of individuals remain subclinical until they present with end-stage OA, but one large cross-sectional population study reports that cam and/or pincer deformities were found in 71% of men and 37% of women with hip osteoarthritis [71].

1.5.2.1 Presentation

FAI commonly presents in healthy, active adults, most frequently between the ages of 25 and 50. In older patients it is more frequently accompanied by osteoarthritis. Cam-type FAI is more common in men whilst, Pincer-type FAI presents more commonly in middle-aged women. Deep intermittent discomfort, during or after activity is the most common presenting complaint. The first step in assessment involves a comprehensive pain history. Intermittent discomfort in the groin during or after repetitive or persistent hip flexion is characteristic of anterior impingement resulting from either cam



(a) Cam deformity

(b) Normal

(c) Pincer deformity

Figure 1.3 – Illustrative axial cross-section of the right hip joint showing a) cam deformity with additional bone at the anterior femoral head-neck junction (shown in red) b) normal hip c) pincer deformity with additional bone at the anterior acetabular rim (shown in red). The deformities in a) and c) cause the femoral neck to impact against the labrum and acetabular rim on flexion and internal rotation.

or pincer deformities. Sprinting or kicking sport, hill climbing or prolonged sitting in low chairs are common exacerbating activities. Pain may be referred to the anterior thigh, symphysis pubis or the ipsilateral testicle in men. Pincer deformities may also give rise to posterior impingement with pain experienced in the buttock or sacro-iliac region and are often difficult to differentiate from pain referred from the lower back or sacro-iliac joint. Repeated hyperextension with such activities as fast-walking, or walking downhill are common exacerbating activities. Posterior hip pain during intercourse is also a frequent complaint in women. Associated mechanical symptoms such as catching or clicking may be seen when labral tears are also present. Duration of symptoms is variable, and patients sometimes report an inciting event.

1.5.2.2 Examination

Antalgic or Trendelenberg gait patterns may be observed. Internal rotation with the hip at 90 of flexion is typically markedly limited. Flexion and abduction are also often limited, although this is a less consistent feature. The hip impingement test is performed with the patient supine with hip and knee flexed to 90°, the hip is progressively rotated from external rotation to internal rotation while moving from abduction to adduction. A positive test elicits a sudden, sharp pain in the hip. Patients often report that the manoeuvre recreates their typical symptoms. A positive impingement test has been shown to be present in more than 90% of patients who go on to have FAI confirmed either radiologically or at the time of surgery [67, 73], in addition it has a

high positive predictive value for labral pathology [74].

1.5.2.3 Investigation

Plain radiology may identify morphological abnormalities as well as degenerative change. Whilst there are no commonly used radiological classification systems for FAI there are several constituent morphological measurements which have been used in the literature to quantify severity. Alpha (α) angle [75], femoral head:neck ratio [76] and Gosvig's Triangular index [77] are examples of three such measurements.

MRI arthrogram (MRA) with intra-articular contrast is the investigation of choice in a clinical setting. In addition, intra-articular injection of local anaesthetic and steroid at the time of MRA is safe and of diagnostic value. 3D reconstruction of Computerised Tomography (CT) scans has proved useful in the recognition of subtle femoral deformities and in preoperative planning during the management of complex deformities.

1.5.3 Treatment of Morphological Deformities

Non-operative management incudes rest, anti-inflammatory medication and modification of activity, avoiding excessive range of hip movement. Pincer impingement might be amenable to sports therapy that focuses on modifying dynamic hip flexion by maintaining core stability and a more upright stance during activity [78]. Surgical therapies

are targeted at restoring normal morphology in order to prevent development of OA. Additionally, there are a variety of intra-articular soft tissue therapies that can be used to optimise outcome. Some surgical procedures related to DDH and FAI are discussed below.

1.5.3.1 Acetabular Dysplasia

Surgical treatment for acetabular dysplasia involves addressing damage to the labrum and articular cartilage as well as underlying morphological abnormalities. Intra-articular pathology may be addressed arthroscopically but corrective surgical treatment for morphological abnormalities requires an open approach. Femoral and acetabular osteotomies are employed in paediatric practice, whilst periacetabular osteotomy (PAO) described by Ganz et al. [79], is most commonly employed in adult patients. The principles of these procedures are to correct deformity whilst avoiding over-correction that may lead to impingement. These are significant procedures, not without risk, but encouraging medium to long term results have been reported [80–82].

1.5.3.2 Femoroacetabular Impingement

Operative management and has been shown to be effective in providing symptomatic relief and functional improvement [83–85]. Treatment strategies, both open and arthroscopic, are aimed at correcting underlying structural deformity. Despite evidence that

FAI predisposes to OA [86], thus far there is no evidence that intervention will alter the natural history of the disease or the future need for arthroplasty.

The arthroscopic approach is minimally invasive with the faster rehabilitation and a lower incidence of complications, but access to some areas of the joint is difficult. Complications of this approach include transient neuropraxias and fluid extravasation [87]. Labral repair is possible and areas of chondral damage can be debrided or regenerative techniques implemented such as microfracture. Osteochondroplasty can be performed in cam impingement to reshape the head-neck junction, while acetabular rim trimming can be used to reshape the acetabulum with reattachment of the labrum. Open hip dislocation (utilising a trochanteric slide osteotomy) allows the procedures listed above to be performed and may provide better access to the postero-inferior portion of the hip. This is however a major operation and carries a longer rehabilitation period and slightly higher complication rates [88].

1.6 Aetiology of hip osteoarthritis

Many epidemiological risk factors for OA have previously been identified. Age, sex, body mass index (BMI), previous joint injury, high-level sporting activity, occupational activity levels and presence of Heberden's nodes have all been shown to have some association with hip OA. Using these factors to select high-risk populations for future studies is important. Equally, defining what we classify as osteoarthritis affects how

results are received.

The pathogenesis of OA in the hip is multifaceted and involves articular cartilage failure induced by an interplay of genetic, metabolic, biochemical, and biomechanical factors [89]. Following this failure, a cyclical cascade of inflammation, repair and further degeneration unfolds. The hallmark radiological feature of OA is the change in bone - osteophyte formation, proliferation, sub-chondral sclerosis and cyst formation. These features are perpetuated by local and systemic factors.

Risk factors for OA in the hip include age, Caucasian race, female gender and elevated BMI as well as high impact activities and other hip pathologies, though discrepancies exist between studies with regard to the strength and significance of these associations. Trauma both intra-articular and peri-articular as well as supraphysiological activity levels such as those sustained during gymnastics or contact sports, represent the type of high impact activities that are associated with OA. Finally, osteonecrosis, biological susceptibility (e.g. Legg-Calfé-Perthes disease), soft tissue laxity and biomechanical factors represent the local hip-related risk factors. Soft tissue laxity and biomechanical factors are very broad risk factors and include conditions such as developmental dysplasia of the hip (DDH) and femoroacetabular dysplasia (FAI). However, despite some well established risk factors, OA continues to be a very difficult disease to predict [90–93]. At present, accurately identifying healthy individuals who are at high risk of developing incident hip OA is impossible, with only age and early radiological evidence of OA significantly associated with OA progression[94].

Whilst there is ongoing investigation into all areas of this complex and broad pathogenesis, the focus of the present study is on the biomechanical factors and specifically morphological variation within the hip joint.

1.6.1 Epidemiological surveys

Associations have been made between idiopathic hip OA and several constitutional risk factors including age, gender, obesity, heredity, joint injury, occupational activity, high-level sporting activity, and the presence of Heberden's nodes [33, 95–99]. A major limitation of most epidemiological surveys on hip OA is their focus on asymptomatic individuals with radiographic signs of OA. The natural history of OA is poorly understood and there are few long-term studies.

It is believed that OA progresses from an asymptomatic form, in which histological changes develop first and are later accompanied by radiographic changes, to symptomatic disease of varying severity culminating in "end-stage" OA warranting joint replacement. However, cross-sectional studies of subjects over the age of 55 years with the most severe radiographic grading of OA, demonstrate that only approximately one third of men and half of women have symptoms [100, 101]. Therefore the relevance of epidemiologically-determined risk factors, as identified for asymptomatic joints, to "end-stage" OA of the hip is questionable. Since the thrust of medical involvement in OA is directed towards patients with symptoms, there is an important need to charac-

terise disease-associated factors relevant to OA in such individuals. The few existing studies describing the aetiology of advanced OA of the hip have significant limitations. Studies have described "idiopathic" and "secondary" OA together [102, 103], been limited in size and scope [104–106] or failed to describe selection criteria for patients studied [51].

1.6.1.1 Age

One of the most striking features of radiographic surveys of populations is the exponential rise in prevalence of OA with increasing age [4]. The prevalence of moderate to severe OA of the hip is 0.2% in those aged 45-54 years and 4% in those aged 65-74 years [107]. The mortality adjusted lifetime risk of THR at age 50 is 12% [108].

1.6.1.2 Gender

In general, OA is more common in males when adults under 45 years of age are considered but conversely more common in females when individuals over the age of 55 years are studied [107]. Factors predisposing women to OA are unclear but oestrogen levels prior to the menopause have been implicated. Oestrogen receptors are present in articular cartilage and oestrogen is known to potentiate cytokines involved in cartilage metabolism [109]. Gender differences for hip OA are less clear than for knee OA. Lawrence and Sebo identified a significant male predominance of moderate to severe

OA of the hip in ten different population surveys involving different races [110] whilst other investigators have reported a slight female predominance [111]. A female to male ratio between 1-2 has been reported in surveys of patients with symptomatic hip OA, including end-stage disease [98, 112, 113]. Some surveys have reported an increased prevalence of males with symptomatic hip OA [114, 115].

1.6.1.3 Race

OA is a world-wide disease. A review by van Saase et al [107] identified similar trends in the prevalence of OA with age in different races. Differences existed between races in the prevalence of OA at any given age [107]. With the exception of knee OA, most surveys indicate that the highest rates of radiographic OA occur in white European populations [107, 110]. Hoaglund et al [103] provide an interesting comparative study of diseases of the hip in Japanese Oriental and American white patients, where secondary osteoarthritis was present in 82% of the Japanese patients but only 10% of Caucasian Americans, and conclude that "primary osteoarthritis of the hip is a disease of European-American whites, of which the origin is not yet known."

1.6.1.4 Activity

The relationship between sport and OA is unclear. Most studies are limited by cross-sectional design with difficulties in summating lifetime sporting activity [96, 116].

Vingård et al [117] studied the recreational background of men who received a THR for idiopathic coxarthrosis with that of controls from the general population. Those with longstanding exposure to sport in general were at greater risk of a THR compared to those with low exposure. In contrast, Puranen et al [118] analysed the pelvic radiographs of elite male Finnish athletes who had run competitively for an average of 21 years with those of age and gender- matched controls without hip pain. The prevalence of coxarthrosis was 4% in athletes and 9% in controls. The authors speculated that athletic fitness protected against the onset of OA.

It has been suggested that prolonged and repetitive use of specific joints in certain occupations can exceed normal tolerances and precipitate joint degeneration [119]. Farming and construction work appear to be associated with hip OA [97, 105, 120–122].

1.6.2 Biomechanical influences

W.H. Harris first presented the hypothesis that all cases of "primary" or "idiopathic" OA of the hip are the result of morphological variance in the acetabulum or the proximal femur, or both [52]. This spectrum of morphological variance ranges from the very mild (subclinical) to the severe but all are associated with an increased risk of OA. Included in this theory are abnormalities such as congenital hip subluxation, SCFE, Legg-Calfé-Perthes disease, and most commonly, DDH. Morphological deformities concentrate

elevated forces over smaller contact areas causing abnormally high focal stress points and subsequent premature joint dysfunction.

Harris' hypothesis on the aetiology of hip OA has more recently been combined with the concept of FAI as an An Integrated Mechanical Concept in the aetiology of OA of the Hip [70]. Several studies have attempted to demonstrate relationships between morphological measurements designed to quantify hip deformities and future OA outcomes [68, 76, 77, 123–128]. These provide some evidence that more subtle subclinical variations in hip morphology are also associated with an increased risk of hip OA in later life. However, each of these previous studies has limitations such as small sample size, selection bias, little or no follow-up period and weak OA outcome measures. In addition, little attention is given to the validation of the morphological measurements used to predict OA.

Longitudinal investigation of how morphological abnormalities of the hip affect long-term risk of OA is needed. If significant associations can be identified using a long follow-up period, morphological measures could be clinically useful in predicting high-risk population cohorts to be targeted for early intervention of potentially modifiable risk factors, future therapeutic trials and ongoing research into the complex disease process and natural history of OA progression.

This thesis aims to consolidate evidence produced in previous studies and address their limitations. A large range of morphological parameters are included in order to scrutinise each one for reproducibility, but also to define the distribution of values in

the general population. Following this validation process, the associations between morpholgical abnormalities with OA (both clinical and radiological), pain and THR are assessed in a unique population-based cohort of women (representative of the UK population). Specific project aims are outlined in the following section.

1.7 Summary of Thesis Aims

This thesis investigates cross-sectional and longitudinal risk factors for OA development, with particular attention to radiological risk factors that may represent potential biomarkers or targets for surgical intervention to prevent disease and/or progression.

The specific objectives are:

1. To develop hip morphology measurement software with attention to identified morphological abnormalities the hip and investigate the intra and inter-observer reproducibility.

2. To describe the demographic characteristics of the cohort investigated and the changes in the cohort during the study which may introduce bias to the subsequent analysis of the role of hip morphology as a risk factor for OA development.

3. To determine hip morphology in a large population cohort and report the prevalence of morphological abnormalities.

4. To determine cross-sectional associations present between hip morphology and

radiographic OA.

5. To determine longitudinal associations between hip morphology and both radiographic OA and THR.

6. To determine longitudinal associations between hip morphology and both pain and symptomatic OA.

7. To determine whether variations in hip morphology occur with age and time in an adult population, thereby considering whether the morphological abnormalities identified truly predate or develop in association with OA.

8. To summarise the important findings and conclusions presented and provide a clinical context for the results in this thesis and recommendations for future work.

Chapter 2

Assessment of radiographic hip morphology

2.1 Introduction

Epidemiologic studies indicate that osteoarthritis (OA) of the hip frequently occurs in the absence of OA in other large joints, suggesting that local factors are important in its pathogenesis [70, 94, 114, 127, 129]. Biomechanical factors have attracted increased attention since Harris [52] suggested that more than 90% of patients with so-called primary or idiopathic osteoarthritis showed demonstrable abnormalities in the hip joint at the cessation of growth. Cross-sectional studies have supported this hypothesis [71] and there is a growing body of supportive evidence from longitudinal studies [86, 130].

The deformities can be broadly divided into acetabular dysplasia, i.e. a shallow hip socket and FAI, characterised by an abnormality of either femoral head-neck junction or acetabulum [60].

Accurate measurement of hip anatomy is required to enable the recognition and quantification of deformities that may predispose to the development of OA and to measure anatomical progression of joint damage. While lateral projections of the hip are most sensitive for detecting FAI [131], anteroposterior (AP) pelvis radiographs are the most commonly used imaging modality for the hip and also the only imaging of the hip available in large cohort studies [132–136].

Measurement of joint space width (JSW) using standard anteroposterior (AP) radiographs remains the recommended method for assessment of structure-modifying drugs for OA [137, 138] and is the only method approved by the FDA[139].

Studies reporting in detail the reproducibility of morphology measurements performed on AP pelvis radiographs are scarce and show varied results [86, 140, 141]. Measurement of JSW manually has generally shown good intra-observer reproducibility but poorer inter-observer reproducibility. Development of software for the measurement of hip and knee JSW has seen significant improvement in inter-observer reproducibility. There remains a need for a standard method for assessment of pelvic/hip morphology and radiographic features of osteoarthritis.

This study describes the development and performance of HipMorf 3.0 in measuring hip morphology on AP pelvis radiographs.

2.2 Rationale for inclusion criteria of morphological measurements

Thorough review of the literature revealed numerous measurements that have been used to describe morphological abnormalities of the hip, some of which have previously been associated with hip OA. A summary of this data is provided in Table 2.1. Figures 2.1 - 2.11 illustrate the morphological measurements listed.

HipMorf 1.0 was originally designed in collaboration with the Oxford Orthopaedic Engineering Centre using Matlab (version R2007a, The Mathworks Inc., Natick, MA, USA). The software provided a platform for making simple geometric calculations on a 2-dimensional radiograph. The software had the ability to measure α-angle and anterior offset ratio on lateral radiographs of the hip as well as lateral centre edge (LCE) angle, acetabular index and acetabular depth:width ratio on AP pelvis radiographs. HipMorf 2.0, developed on this software for a prior nested case-control study which investigated the role of hip morphology in the risk of THR [86].

Alternative commercial and non-commercial imaging software was considered, including in particular Hip^{2}Norm (University of Bern). Strengths and limitations include previous reliability and validation [148], similar to that previously undertaken with HipMorf 2.0. Ultimately development of HipMorf was chosen to allow maximum control and responsiveness to project needs, as well as better check routines for data validation

Table 2.1 – Hip Morphology Variables with normal values where available

AP Pelvis Morphological Measurement	Previous Associations with OA	Associated Deformity	Normal Value	Figure
PELVIS				
Inter-head centre distance (mm)	Nil	Nil	-	Figure 2.1
Inter-teardrop width (mm)	Nil	Nil	-	Figure 2.1
ACETABULUM				
Acetabular Depth to Width ratio	Murphy et al, 1995[124]	DDH	0.48	Figure 2.2
Lateral Centre Edge Angle (°)	Wiberg, 1939[142];	DDH	>25	Figure 2.3
Extrusion Index (ratio)	Heyman & Herdon, 1950[143]; Li & Ganz, 2003[126]	DDH	<25%	Figure 2.4
Horizontal Toit Externe (°)	Tonnis, 1976[144]; Li & Ganz, 2003[126]	DDH	0-10	Figure 2.5
Sharps Angle (degrees)	Sharp, 1961[145]; Cooperman et al, 1983[123]	DDH	33-38	Figure 2.6
PROXIMAL FEMUR				
Triangular Index (dichotomous)	Gosvig et al, 2007[77]	Cam FAI	Absent	Figure 2.7
Triangular index height (mm)	Gosvig et al, 2007[77]	Cam FAI	-	Figure 2.7
Alpha Angle (°)	Notzil et al, 2002[75]; Gosvig et al 2007[77]	Cam FAI	59	Figure 2.8
Femoral neck width to length ratio	Dincel et al, 2008[146]	NOF Fracture	0.4	Figure 2.9
Femoral head to neck ratio	Doherty et al, 2008[76]	PGD	1.4	Figure 2.9
Femoral neck shaft angle (°)	Moore et al, 1994[147]	Varus/valgus	125	Figure 2.10
Medial proximal femoral angle (°)	Bardakos & Villar, 2008[128]	GT overgrowth	84	Figure 2.10
OTHER				
Minimum JSW (mm)	Kellgren & Lawrence, 1957[19]; Conrozier et al, 1998[104]	ROA	>2.5mm	Figure 2.11

suitable for a large population study. HipMorf 3.0 development was in collaboration with the Oxford Orthopaedic Engineering Centre and NDORMS Epidemiology Group. My role in development included design, validation and testing, as well as writing the user manual and training new readers.

HipMorf 3.0 improves on previous iterations of the software. Where appropriate, measurements are now constrained to the shape or plane in which they must occur. Fine contrast and brightness adjustment as well as magnification of the images is now possible, which ensures anatomical features are adequately visualised for measurement. These features were introduced in an attempt to improve reproducibility. In addition, date, time, duration of measurement, identification of study and observer for each radiograph are recorded, automatic detection of scaling from DICOM images is used and/or use of a calibration object. Once the reading is complete the measurements are recorded (including both the output data and vector data of all points marked). Data is recorded in an MySQL (Oracle Corporation, Redwood City, CA, USA) database . It is possible to store this data locally or on a remote server for collaborative studies. Data can then be exported in comma-separated values (CSV) format preventing transcription errors and imported into any statistical package. The vector data can also be used to review marked up images. HipMorf 3.0 is able to measure all morphological parameters listed in Table 2.1.

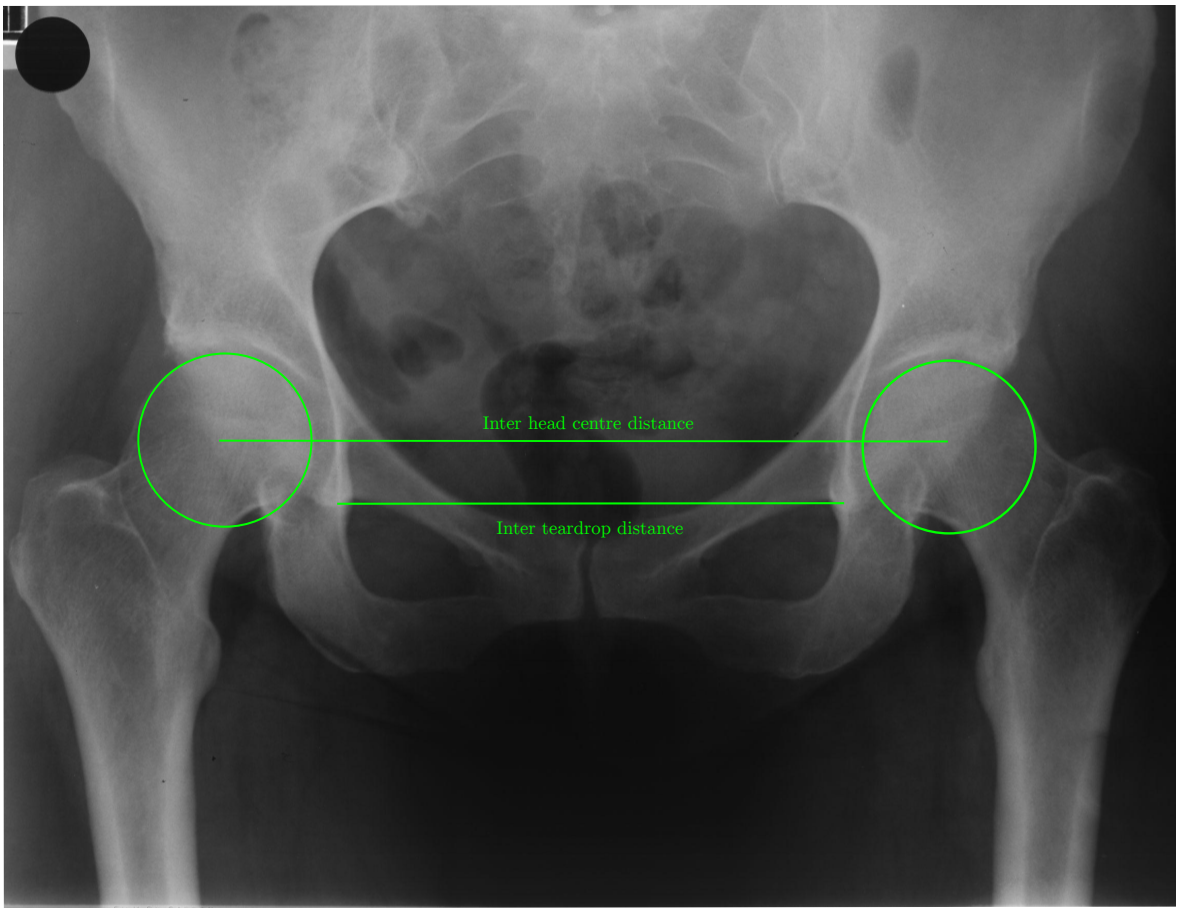


Figure 2.1 – Inter head centre distance and inter-teardrop distance.

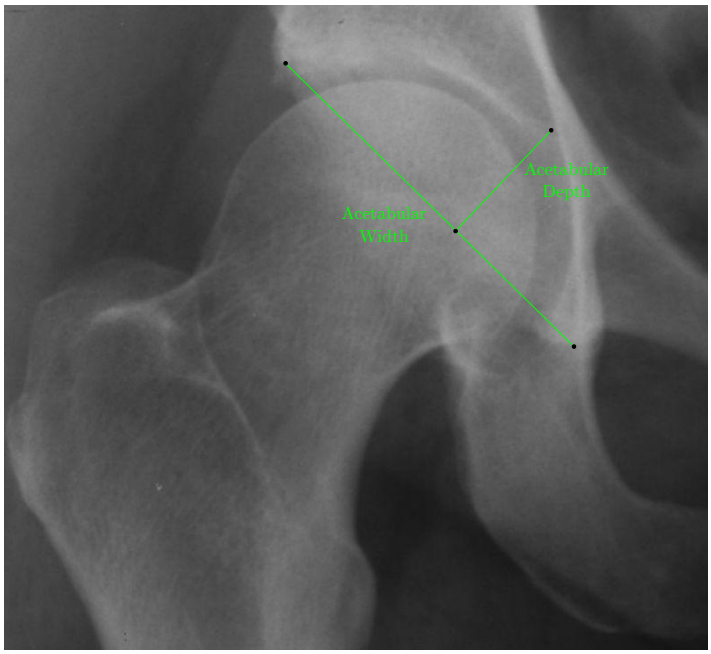


Figure 2.2 – Acetabular Depth and Width. Width measured from teardrop to lateral edge of sourcil. Depth measured perpendicular to width from the line defining with to acetabular floor.

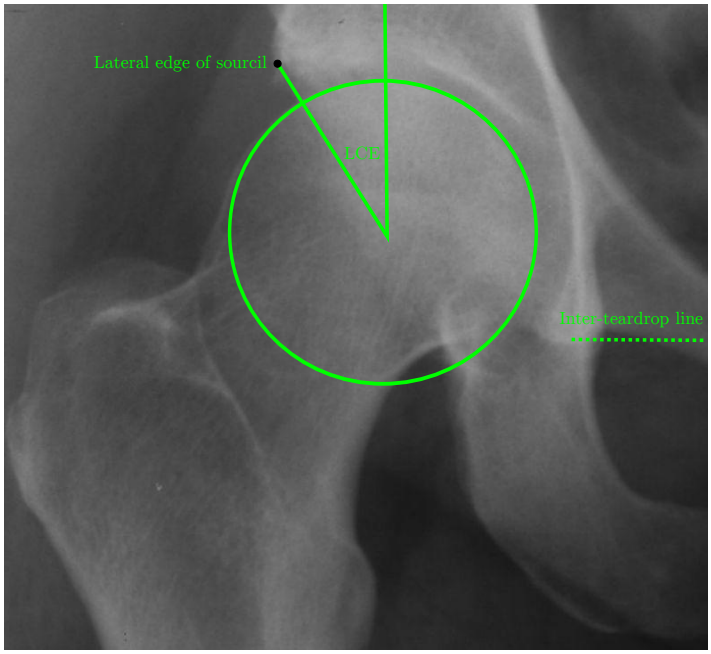


Figure 2.3 – Lateral Centre Edge Angle[142]. Vertical axis defined as perpendicular to the inter-teardop line. The LCE angle is measured between the vertical axis and the line drawn from the centre of the femoral head to the lateral edge of sourcil.

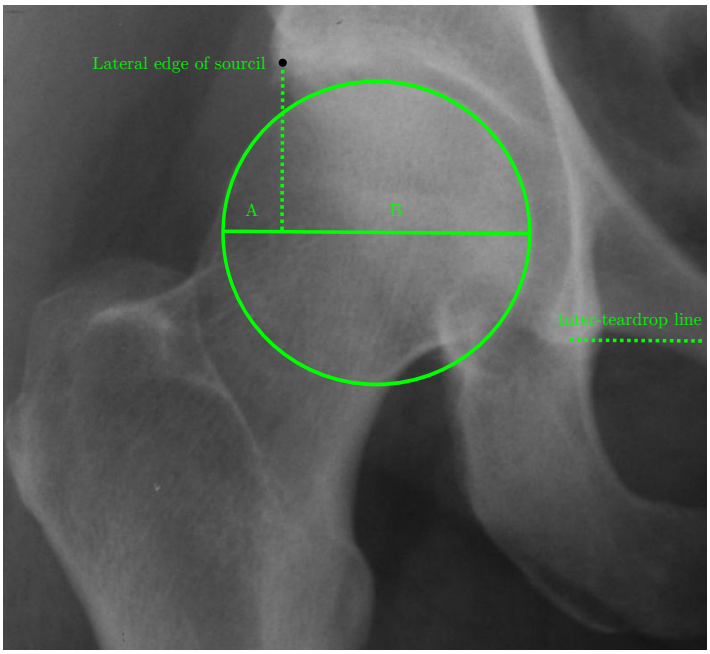


Figure 2.4 – Extrusion Index defined by A/(A+B), where A is the proportion of femoral head uncovered (i.e. beyond lateral edge of sourcil) and A+B is the diameter of the femoral head.

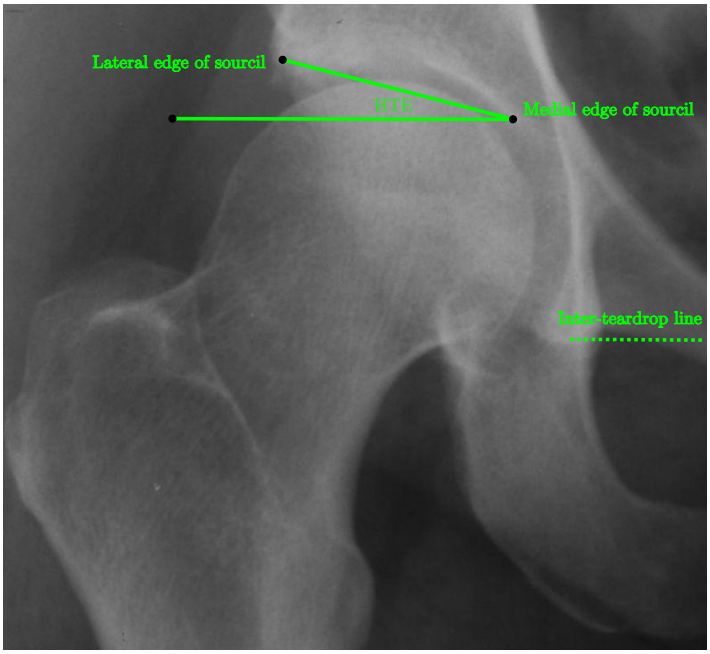


Figure 2.5 – Horizontal Toit Externe[144] (HTE). Measured as the angle between the horizontal and the line between the medial and lateral edge of the sourcil.

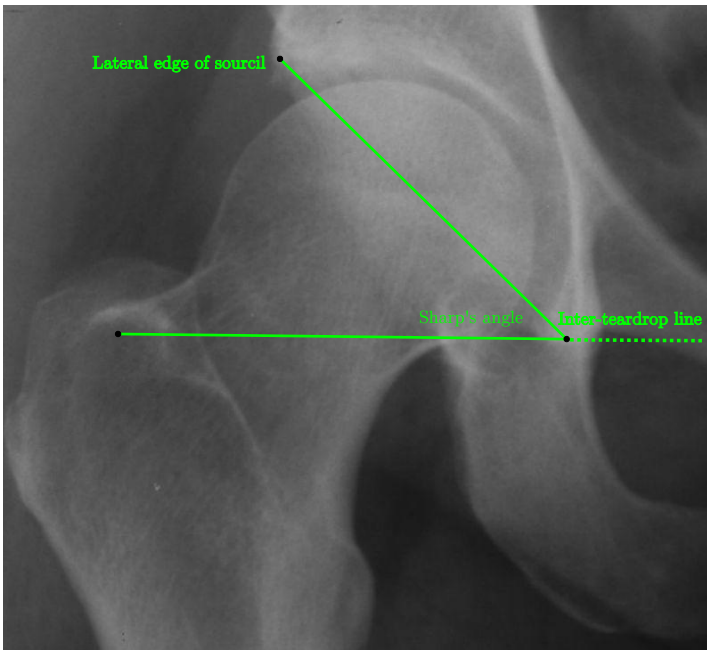


Figure 2.6 – Sharp's angle[145] is formed between the line from the lateral sourcil and inferior aspect of the teardrop with the horizontal (inter-teardrop line).

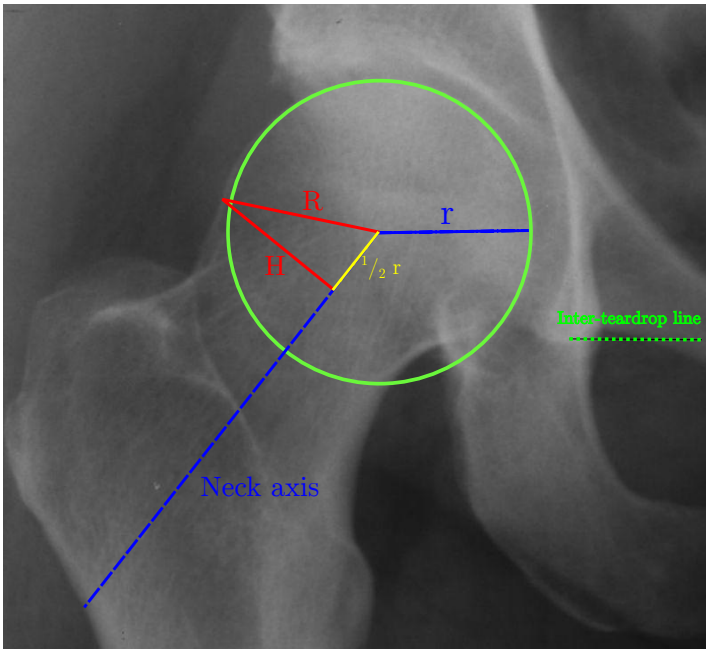


Figure 2.7 – The radius (r) of the femoral head is measured and at $^1/_2$r along the neck axis the corresponding perpendicular height (H) to the cortex is measured. The perpendicular height is termed Triangular Index Height (TIH). Triangular index is defined as positive if R r + 2 mm on a radiograph, with 1.2 magnification. Triangular index has been used previously to identify cam deformity and is highly related to alpha-angle [77].

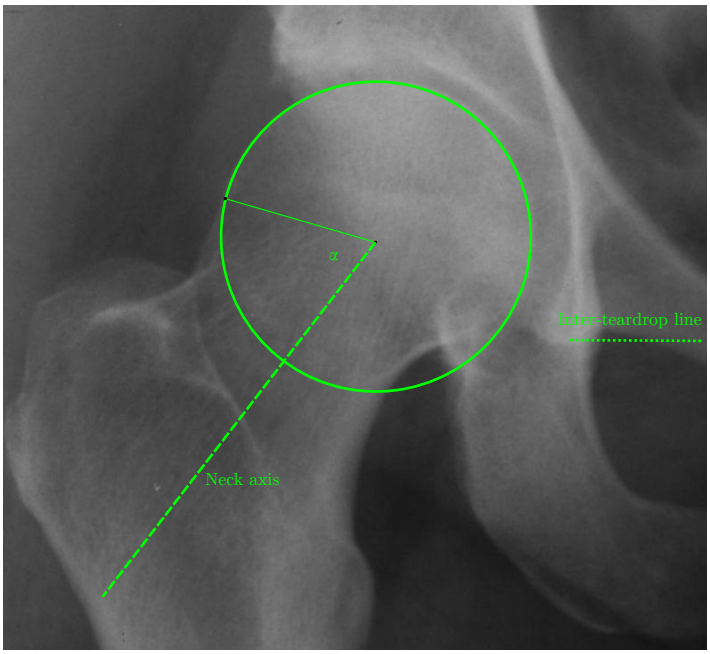


Figure 2.8 – The α–angle defined by Notzli et al.[75] modified to the anteroposterior plane refers to the angle between the neck axis and the line drawn from the centre of the femoral head to the lateral departure of the head-neck junction from the radius of the femoral head.

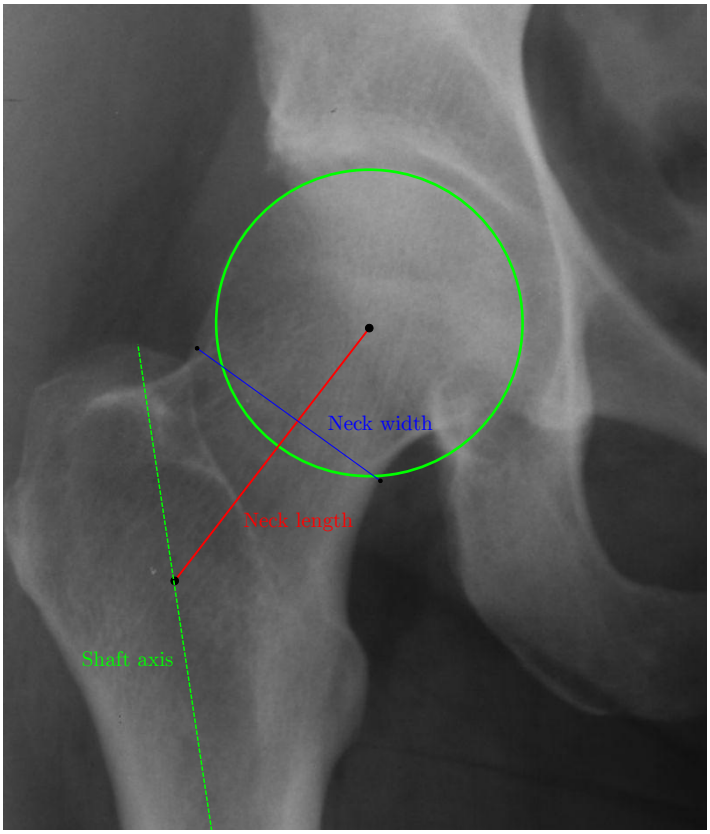


Figure 2.9 – Head:Neck ratio and Neck Width:Length ratio. Diameter of femoral head and minimum neck width measured. Neck length measured as the distance from the centre of femoral head to the intersection of the neck axis with the shaft axis.

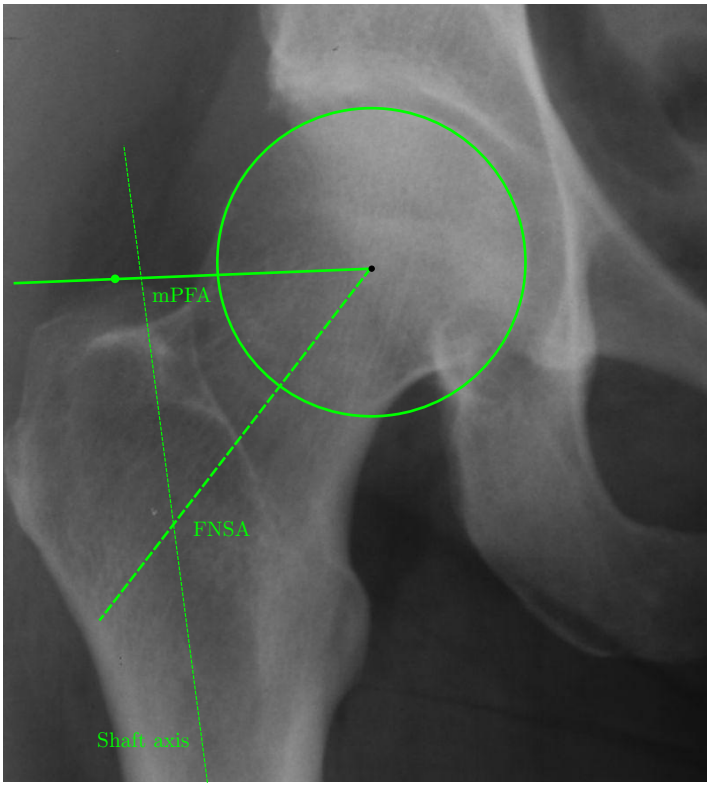


Figure 2.10 – Femoral neck shaft angle (FNSA) and medial Proximal femoral angle (mPFA). FNSA measured as the angle between the shaft axis and the line drawn from the centre of the femoral head through the mid-point of the minimum neck width. mPFA measured as the angle between the shaft axis and the line drawn from the centre of the femoral head to the most superior point of the greater trochanter.

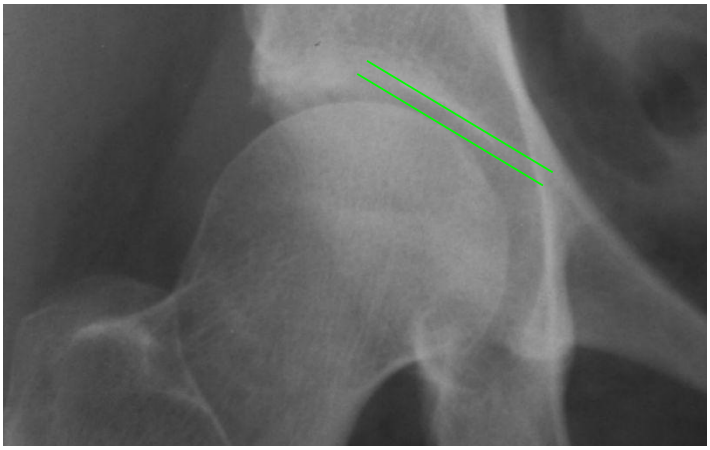


Figure 2.11 – Minimum Joint Space Width (mJSW) measured using calliper system.

2.3 Reliability and reproducibility of Hip-Morf 3.0

2.3.1 Radiographic Protocols

AP pelvis radiographs were acquired using a standardised protocol (see Table 3.3), in the supine position with the knees flexed (small sand bag under knees) and the feet straight in the sagittal plane to control femoral rotation. The X-ray beam was vertical, perpendicular to the film and centered two inches above the symphysis pubis. The imaging system in all cases used a film size of 35/43 cm and a film focus distance of 100 cm. Radiograph quality was assessed at the time of image acquisition. All images were of sufficient quality in terms of exposure and visualisation of anatomical features of interest.

2.3.2 Blinding of radiographs

Radiographs were assigned a numeric identifier. The readers were blinded to patient details and each others results as well as to any prior measurements on the same radiograph. 20 radiographs were randomly selected from the Chingford Study for this reproducibility analysis.

2.3.3 Measurement of hip morphology and JSW

Agreement was reached on the measurement protocol prior to commencement of the study and a manual for measurement was generated. DICOM files with image scaling embedded in the file were automatically read by the imaging software. Measurements were performed by two observers using Hipmorf 3.0 (University of Oxford, UK). The software has been specially developed for measurement of hip joint morphology and JSW. Measurements were performed after consensus agreement of the measurement technique and subsequent generation of the user manual. The manual was distributed to each investigator and aimed to reduce inter-observer variability in exact-point discrimination of the constituent anatomical landmarks used to calculate the morphological measurements. Table 2.2 lists the measurements performed. The interval between repeat measures was at least 30 days. Figure 2.12 shows Hipmorf 3.0 following measurement of one hip from an AP pelvis radiograph.

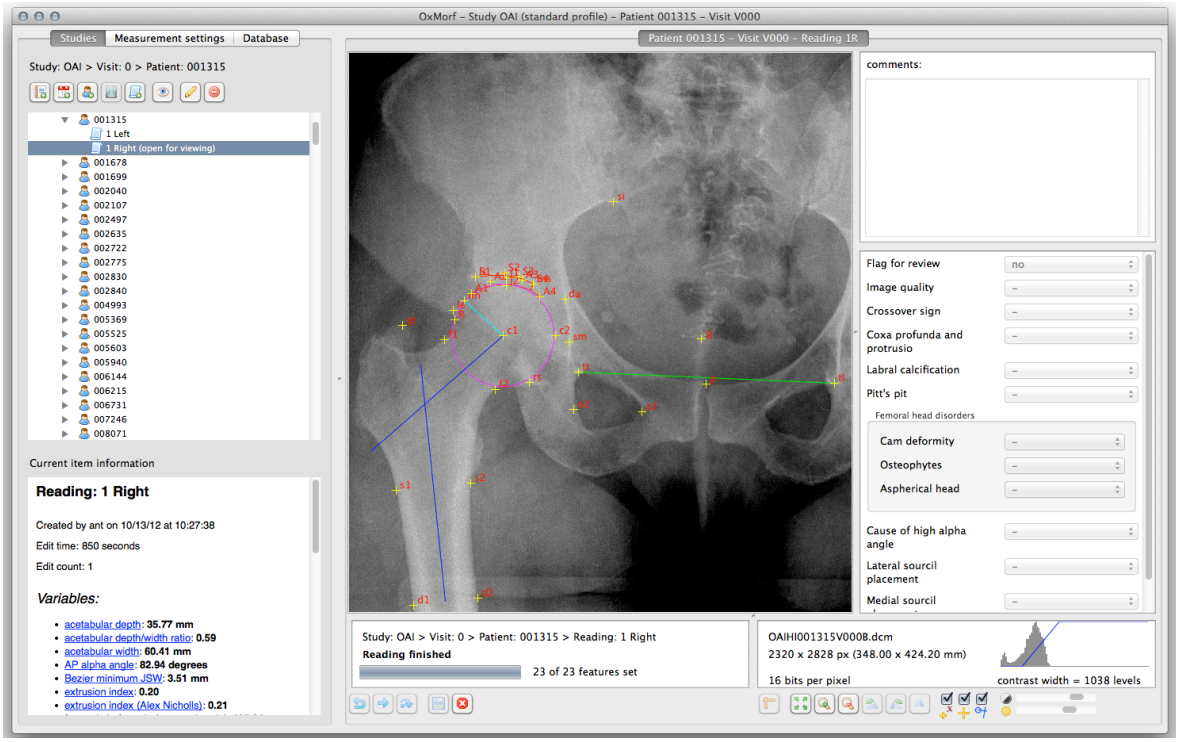


Figure 2.12 – Hipmorf 3.0 - Marked up image of right hip from AP pelvis radiograph.

2.3.4 Statistical Analysis

The results for each measurement and for each observer were examined. Intra-observer and inter-observer reproducibility was assessed using the intraclass coefficient of correlation (ICC), the within-subject standard deviation (SD), the coefficient of variation (CV) and using the Bland-Altman plotting method. Dichotomous output variables were assessed using Kappa statistic.

Statistical analysis was performed using Stata 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Table 2.2 – Hip Morphology Variables

Pelvis	**Proximal Femur**
Inter-teardrop distance (mm)	Femoral head diameter (mm)
Inter-femoral head distance (mm)	AP α-angle (°)
Sacrococcygeal Joint to Pubis Distance (mm)	Femoral neck width (mm)
	Femoral neck length (mm)
Sacroiliac Joint to Pubis Distance (mm)	Femoral Head : Neck ratio
	Femoral neck shaft angle (FNSA) (°)
Foramen Obturator Index	Medial Proximal femoral angle (mPFA) (°)
	Triangular Index Height (mm)
Acetabulum	Triangular Index
Acetabular Width (mm)	Triangular Ratio
Acetabular Depth (mm)	
Acetabular Depth to Width ratio	**Other**
Lateral Centre Edge Angle (°)	Minimum Joint Space Width (JSW) (mm)
Extrusion Index	
Horizontal Toit Externe (HTE) (°)	
Sharps Angle (degrees)	

2.4 Results

The time taken to complete measurement of a radiograph ranged between 5 and 10 minutes. Intra-observer reproducibility of morphological measurements are shown in Table 2.3. The Bland-Altman plots for α-angle, TIH, LCE angle and extrusion index are shown in Figure 2.13. 95% limits of agreement are shown. Kappa statistic for Triangular Index was 1.0.

Table 2.3 – Intra-observer reproducibility

Measurement	Reader 1			Reader 2		
	ICC	95% CI		ICC	95% CI	
Acetabular Depth	0.938	0.854	0.975	0.957	0.896	0.983
Acetabular Depth:Width	0.882	0.730	0.951	0.849	0.664	0.937
Acetabular Width	0.957	0.897	0.983	0.928	0.831	0.971
AP α-angle	0.992	0.981	0.997	0.992	0.979	0.997
Extrusion Index	0.965	0.915	0.986	0.990	0.975	0.996
Femoral Neck Shaft Angle	0.954	0.890	0.982	0.968	0.920	0.987
Femoral Offset	0.986	0.964	0.994	0.974	0.936	0.989
Foramen Obturator Index	0.986	0.966	0.994	0.989	0.972	0.995
Head Diameter	0.987	0.969	0.995	0.989	0.974	0.996
Head: Neck Ratio	0.922	0.816	0.968	0.943	0.863	0.977
Horizontal Toit Externe	0.974	0.938	0.990	0.757	0.488	0.895
Inter Head Centre Distance	0.990	0.975	0.996	0.998	0.995	0.999
Inter Teardrop Distance	0.996	0.990	0.998	0.994	0.985	0.998
Lateral Centre Edge Angle	0.980	0.951	0.992	0.994	0.985	0.998
Mid SI Joint to Pubic Symphysis	0.991	0.977	0.996	0.998	0.994	0.999
Minimum JSW	0.986	0.966	0.995	0.954	0.889	0.981
Medial Proximal Femoral Angle	0.986	0.964	0.994	0.986	0.965	0.994
Neck Length	0.988	0.970	0.995	0.977	0.943	0.991
Neck Width	0.999	0.997	1.000	0.997	0.993	0.999
Sacrococcygeal to Pubis Symphysis	0.969	0.925	0.988	0.992	0.981	0.997
Sharp's Angle	0.960	0.904	0.984	0.867	0.699	0.945
Triangular Index Height	0.995	0.988	0.998	0.979	0.949	0.992
Triangular Ratio	0.991	0.979	0.997	0.951	0.882	0.980

Inter-observer reproducibility of morphological measurements are shown in Table 2.4.

Table 2.4 – Hip morphology inter-observer reproducibility

Measurement	ICC	95% CI	
Acetabular Depth	0.932	0.838	0.972
Acetabular Depth:Width	0.819	0.603	0.924
Acetabular Width	0.940	0.857	0.975
AP α-angle	0.988	0.972	0.995
Extrusion Index	0.960	0.903	0.984
Femoral Neck Shaft Angle	0.959	0.899	0.984
Femoral Offset	0.973	0.948	0.988
Foramen Obturator Index	0.986	0.965	0.994
Head Diameter	0.994	0.986	0.998
Head: Neck Ratio	0.905	0.825	0.956
Horizontal Toit Externe	0.889	0.746	0.954
Inter Head Centre Distance	0.993	0.986	0.997
Inter Teardrop Distance	0.994	0.986	0.998
Lateral Centre Edge Angle	0.980	0.950	0.992
Mid SI Joint to Pubic Symphysis	0.994	0.986	0.998
Minimum JSW	0.962	0.908	0.985
Medial Proximal Femoral Angle	0.981	0.962	0.992
Neck Length	0.986	0.964	0.994
Neck Width	0.999	0.997	1.000
Sacrococcygeal to Pubis Symphysis	0.960	0.923	0.982
Sharp's Angle	0.919	0.850	0.963
Triangular Index Height	0.988	0.971	0.995
Triangular Ratio	0.977	0.944	0.991

ICC ranged from 0.82 for acetabular depth:width ratio to >0.99 for all measures of pelvic width. The Bland-Altman plots for α-angle, TIH, LCE angle and extrusion index are shown in Figure 2.14. 95% limits of are shown. Kappa statistic for Triangular Index was 1.0. Using these findings the minimum detectable change for each of the morphological measures are shown in Table 2.5. Coefficient of variance was less than

10% in most of the morphological measurements. The exceptions were Horizontal Toit Externe (which has a mean of close to zero, causing a spuriously large coefficient of variance) and sacrococcygeal to pubis distance.

Table 2.5 – Coefficient of variance and minimum detectable change for all morphology measurements

Measurement	Mean	Common within-subject SD	CV	Minimum detectable change
Acetabular Depth	36.707	1.071	2.819	4.056
Acetabular Depth:Width	0.589	0.001	5.333	0.123
Acetabular Width	62.702	3.543	3.002	7.379
AP α-angle	65.559	5.264	3.027	-
Extrusion Index	0.194	0.001	6.691	0.051
Femoral Neck Shaft Angle	127.56	1.397	0.927	4.633
Femoral Offset	45.618	1.095	2.400	4.292
Foramen Obturator Index	0.986	0.000	2.211	0.085
Head Diameter	55.718	0.356	1.071	2.339
Head: Neck Ratio	1.454	0.021	1.410	0.08
Horizontal Toit Externe	0.637	10.478	283.638	-
Inter Head Centre Distance	206.138	0.198	0.216	1.745
Inter Teardrop Distance	130.516	1.580	0.963	4.927
Lateral Centre Edge Angle	31.514	1.163	3.422	4.228
Mid SI Joint to Pubic Symphysis	74.234	2.485	2.124	6.180
Minimum JSW	3.535	0.056	6.721	0.931
Medial Proximal Femoral Angle	79.749	0.920	1.202	3.759
Neck Length	57.749	1.318	1.988	4.500
Neck Width	38.452	0.073	0.701	1.057
Sacrococcygeal to Pubis Distance	22.968	27.406	22.793	20.521
Sharp's Angle	37.281	1.658	3.454	5.047
Triangular Index Height	23.519	0.357	2.539	2.341
Triangular Ratio	0.980	0.001	1.863	0.072

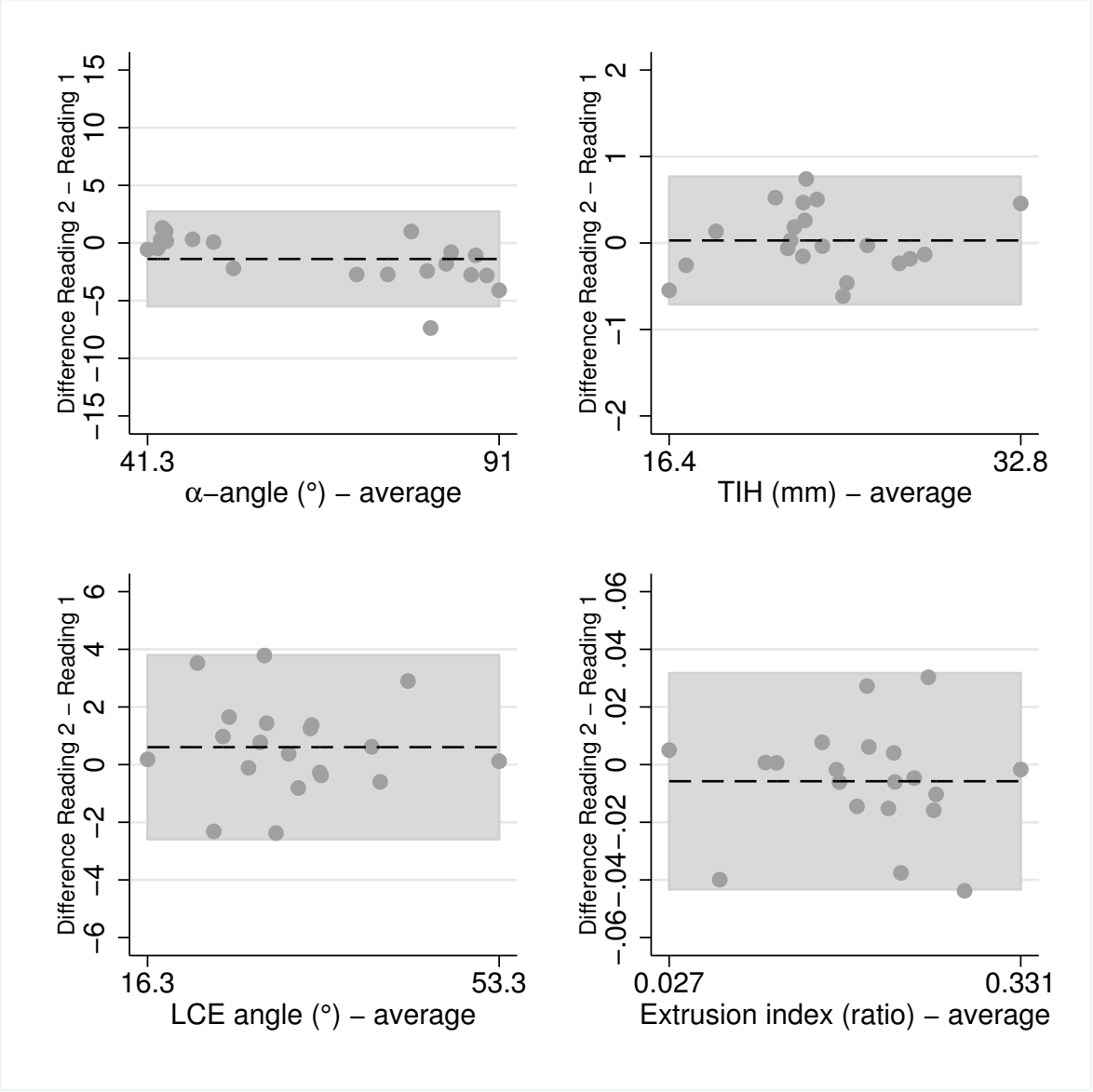


Figure 2.13 – Bland-Altman plots of intra-observer measurements of α-angle, LCE angle and extrusion index.

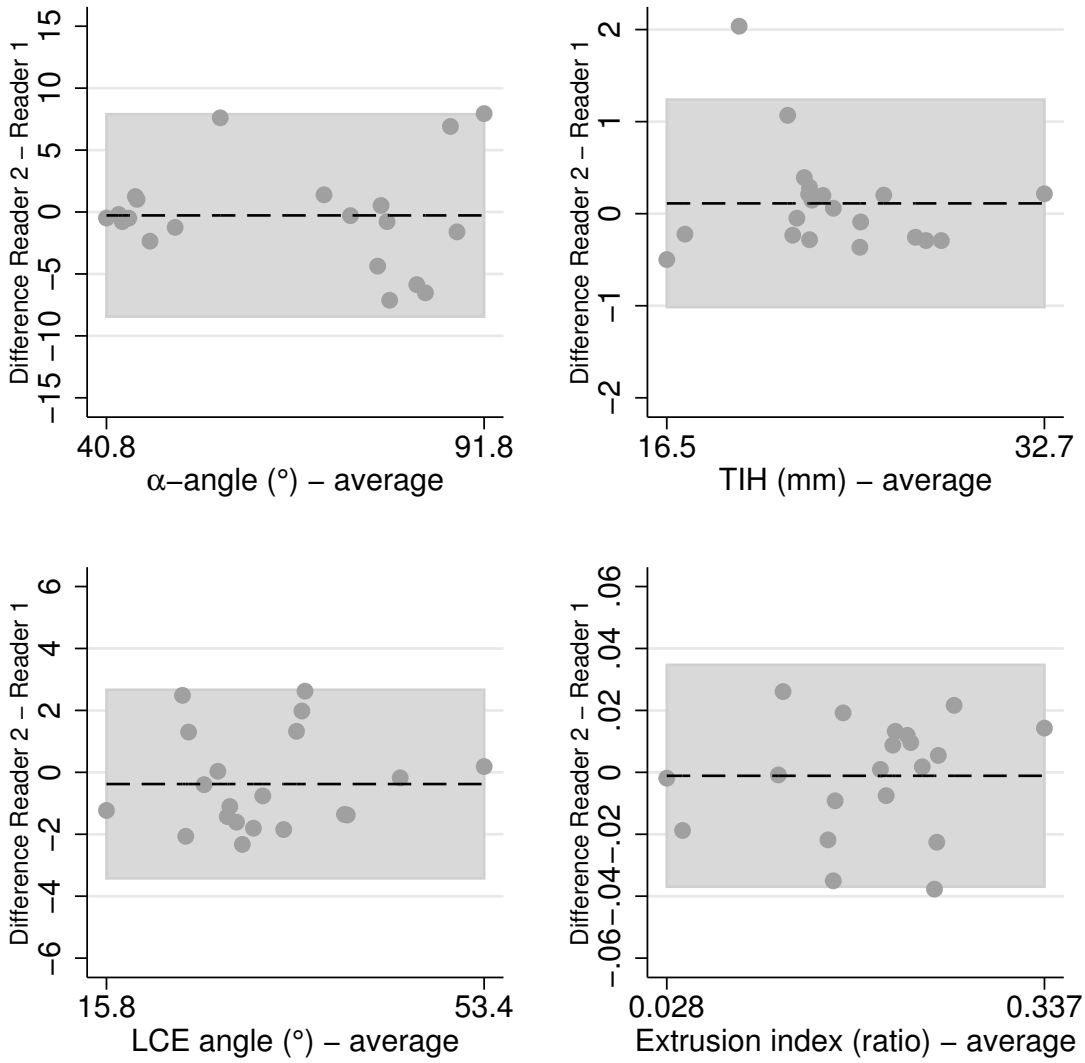


Figure 2.14 – Bland-Altman plots of inter-observer measurements of α-angle, LCE angle and extrusion index.

2.5 Discussion

Measurement of hip morphology with an earlier version of this software program showed acceptable intra- and inter-observer reproducibility [86]. Conversely, Clohisy et al. [140] have reported limited reproducibility among a group of experienced hip surgeons in terms of categorical classifications of hip morphology. Objective measurements of hip morphology using the current software has shown significant improvement in terms of reproducibility and in turn will allow more reproducible classification of pathological features both for clinical and epidemiological research.

HipMorf 3.0 provides good documentation of the reading date, time, duration of measurement, identification of study and observer for each radiograph are recorded. Automatic detection of scaling from DICOM images is used and/or use of a calibration object. Data export in comma-separated values (CSV) format also helps prevent transcription errors. Review of marked up images by an expert reader has also proved useful.

The current software measurement of hip joint morphology and JSW offers good intra-observer reproducibility, better than that of the previous version of the program. For the better of the two observers ICCs were in excess of 0.88 (95% CI 0.73-0.95), the worst being for the composite measure of acetabular depth:width ratio. In addition the inter-observer reproducibility was much better than that obtained previously, with

a minimum ICC of 0.82 (95% CI 0.60-0.92), for the same measurement.

The improvements in relation to fine contrast and brightness adjustment as well as magnification of the images to ensure anatomical features were adequately visualised for measurement. In addition, where appropriate, measurements are now constrained to the shape or plane in which they must occur. These features in combination explain the overall excellent inter-observer reproducibility. The current program is not automated and these results potentially represent a best case scenario when readings are performed by expert observers with significant experience of hip morphology measurement and clinical experience of assessing pelvic radiographs. Individual anatomical characteristics of the hip are not always easily visualised and frequently, due to poor quality radiographs (particularly in obese patients) significant time is spent on contrast/brightness adjustment. It is important to obtain high quality well centred radiographs and care is required in digitisation (if this is needed).

2.6 Summary

In summary, this study demonstrates that this new software program, HipMorf 3.0, for measurement of radiographic hip joint morphology provides much better intra and inter-observer reproducibility than previously reported, the data generated is traceable and can be easily shared with collaborators. The improved reproducibility should allow more reproducible classification of pathological features both for clinical and

epidemiological research.

Chapter 3

The Chingford 1000 Women Study

3.1 Introduction

The Chingford 1000 Women Study is a population-based cohort of 1003 randomly selected volunteers that was initiated in 1989 by researchers at St Thomas Hospital, London. The Chingford Study population was established as a retrospective case-control study to determine prevalence rates of OA and osteoporosis in middle-aged women in the general population, and to assess a number of known risk factors and their associations with these two diseases. It has since become a prospective population-based longitudinal cohort of women seen annually and described in detail (by D.J. Hart & T.D. Spector) [149].

1353 women aged between 44 and 67 years of age who were registered at the Handsworth General Practitioners Surgery (Chingford, Essex) were invited to par-

ticipate. The original response rate of the sample was 78%. 1003 participants were recruited. Annual clinic visits have allowed collection of morphometric, clinical, biologic, and radiographic data. The local ethics committee approved the study and written consent was obtained from each woman (Outer North East London Research Ethics Committee (formerly Barking & Havering and Waltham Forest RECs), LREC (R&WF) 96).

At the beginning of the 15th year of the study 680 women were still attending the clinic, 68% of the original cohort. Unfortunately there has been significant attrition in the last five years with only 462 attending (46% of the original cohort) at the beginning of the 20th year. Two hundred women have died, and a further 341 are lost to follow-up.

Table 3.1 demonstrates the reasons for individuals leaving the study. It should be noted that missing individuals are listed as absentees since this table denotes presence or absence at follow-up clinics held in the respective years. Some individuals who missed these clinics or decided to drop out subsequently attended future clinics.

Between baseline and year 2 there were 46 absentees and a further 156 where AP Pelvis radiographs are unavailable.

Prior to analysis of hip morphology, focus was given to the epidemiological characteristics of the entire Chingford cohort and the sub-group (n=801) that attended at year 2 for AP Pelvis radiographs, as well as the participants actively enrolled at year 20. The purpose of this exercise is to identify any differences in the baseline attributes of each group. Such differences may act as confounders when morphology data

Table 3.1 – Study Participation

Follow-Up Clinic	Attendees (n)	Non-attendees (n)	Reasons for non attendance
Year 1	1003	n/a	n/a
Year 2	957	46	Died 1; Moved 14; DNA 10; Dropped Out 2; N/R 18; Abroad 1; Radiographs unavailable 156
Year 5	861	142	Died 15; Moved 40; DNA 43; Dropped Out 44
Year 10	812	191	Died 41; Moved 60; DNA 10; Dropped Out 80
Year 20	463	541	Died 199; Moved 72; Dropped Out 217; N/R 46; Illness 6

is subsequently considered.

Data used in this chapter was collected by the original investigation team from the Twins Research and Genetic Epidemiology Unit at St Thomas' Hospital, London.

3.2 Descriptive statistics

The baseline descriptive statistics of the Chingford study population are show in Table 3.2.

Table 3.2 – Baseline Descriptive Statistics of the Chingford study population

Characteristic	Whole Cohort (n=1003)
Age, median (IQR) years	54 (49, 60)
Height, mean (SD) m	1.616 (0.059)
Weight, median (IQR) kg	65.0 (58.5, 73.0)
BMI, median (IQR) kg/m^2	24.86 (22.63, 27.61)
Ever smoked, %	46.16
Physical activity score, median (IQR) (scale 0-12)	7 (6, 8)

All variables were examined for missing or improbable data. In all cases, the data available were complete and plausible. Histograms of descriptive statistics are shown in Figure 3.1. No cleaning of this data was therefore required.

This data and response rate of 78% suggests the study population is broadly representative of the UK female population [149]. The study did not consider a wide range of ethnic groups, with a 98% Caucasian and predominantly middle class population.

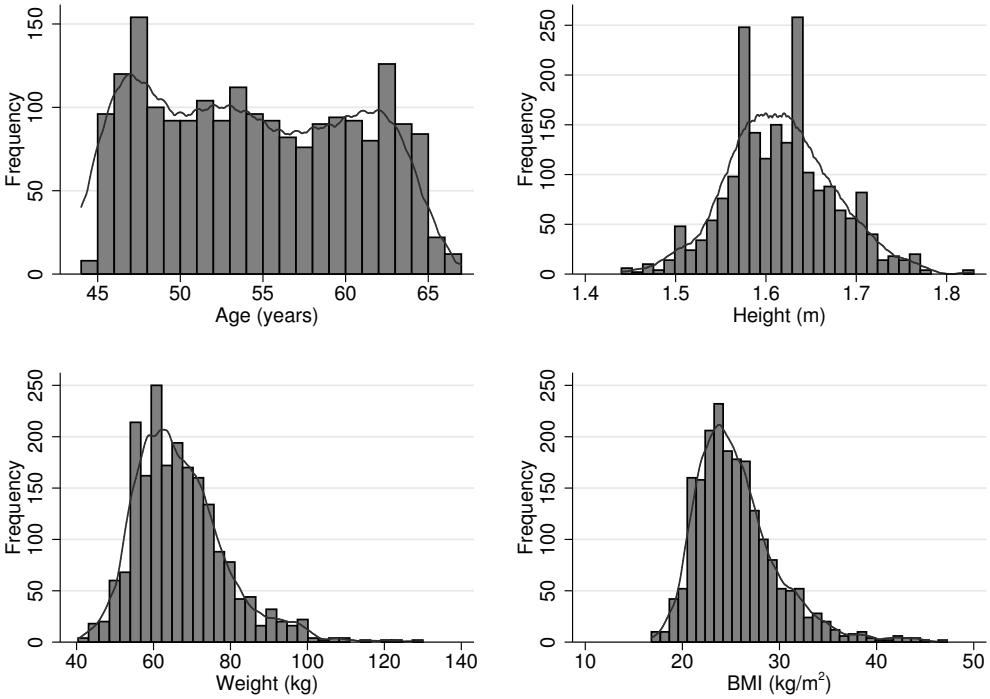


Figure 3.1 – Histograms demonstrating distribution of age, height, weight and BMI.

3.3 Descriptive statistics for participants with pelvis radiographs

As part of an earlier focus to determine prevalence rates of OA in the general population, 801 women of the Chingford 1000 women study underwent AP pelvis radiographs at the beginning of year 2. The radiographers protocol used in taking these radiographs is listed in Table 3.3.

Table 3.3 – Radiographer Protocol: AP Pelvis Radiographs

Patient supine
Knees flexed (small sand bag under knees)
Feet straight (sagital plane)
Centre beam at 2 inches above pubic symphysis at midline
Film size 35/43 cm
Focal distance 100 cm
65 kVp, 40 mAs

The baseline descriptive statistics of the participants who underwent radiographic assessment is shown in Table 3.4 and compared to the whole study population. All data was again assessed for distribution. Height was normally distributed, while weight and BMI were positively skewed. Comparison of the data by group was performed using Student's two-tailed t-tests or Wilcoxon rank-sum tests dependant on the distribution of the data. Smoking status includes current and ex-smokers and is assessed using Fisher's exact test.

Kernel density plots of descriptive statistics of the whole cohort and participants with AP Pelvis radiographs are shown in Figure 3.2. There were no significant differences between the whole study population and participants with pelvis radiographs.

Table 3.4 – Descriptive statistics of participants with AP pelvis radiographs

Characteristic	Whole Cohort (n=1003)	Participants without pelvis radiographs (n=202)	Participants with pelvis radiographs (n=801)	p-value
Age, median (IQR) years	54 (49, 60)	55 (49, 60)	54 (49, 59)	0.066
Height, mean (SD) m	1.616 (0.059)	1.618 (0.060)	1.616 (0.590)	0.607
Weight, median (IQR) kg	65.0 (58.5, 73.0)	66.0 (59.6, 75.4)	65.0 (58.4, 72.7)	0.105
BMI, median (IQR) kg/m^2	24.86 (22.63, 27.61)	25.21 (22.58, 28.22)	24.75 (22.65, 27.50)	0.211
Ever smoked, %	46.16	48.8	45.5	0.404

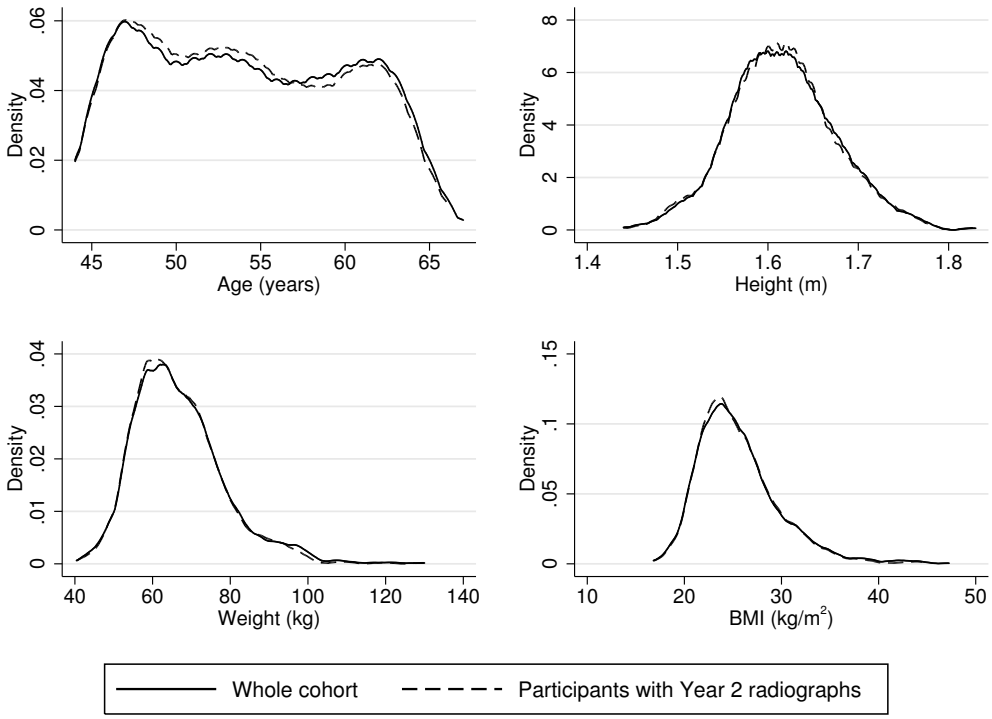


Figure 3.2 – Kernel density plots of age, height, weight and BMI for the whole cohort and participants with AP Pelvis radiographs.

3.4 Descriptive statistics at year 20

The baseline descriptive statistics of the participants who remained enrolled in the study at Year 20 are compared with those of the whole study population.

This data is shown in Table 3.5. The data is demonstrated to identify relative differences between those two groups. Participants who remained actively enrolled in the Chingford 1000 Women study at year 20 were younger, taller and included fewer smokers. Age is a risk factor for OA, therefore it is possible that there was a higher incidence of OA in the drop-out group.

This may introduce conservative bias to the subsequent analysis of the association between hip morphology and OA. No significant difference was present in terms of BMI, which is a risk factor for OA in other large joints, but less reliably associated with hip OA.

Table 3.5 – Descriptive statistics of participants at year 20

Characteristic	Whole Cohort (n=1003)	Participants absent at year 20 (n=540)	Participants at year 20 (n=463)	p-value
Age, median (IQR) years	54 (49, 60)	57 (51, 61)	52 (48, 56)	<0.001
Height, mean (SD) m	1.616 (0.059)	1.613 (0.058)	1.620 (0.060)	0.043
Weight, median (IQR) kg	65.0 (58.5, 73.0)	65.7 (58.5, 74.0)	64.45 (58.5, 71.8)	0.172
BMI, median (IQR) kg/m^2	24.86 (22.63, 27.61)	25.15 (22.67, 28.21)	24.58 (22.60, 27.01)	0.045
Ever smoked, %	46.16	51.2	40.4	<0.001

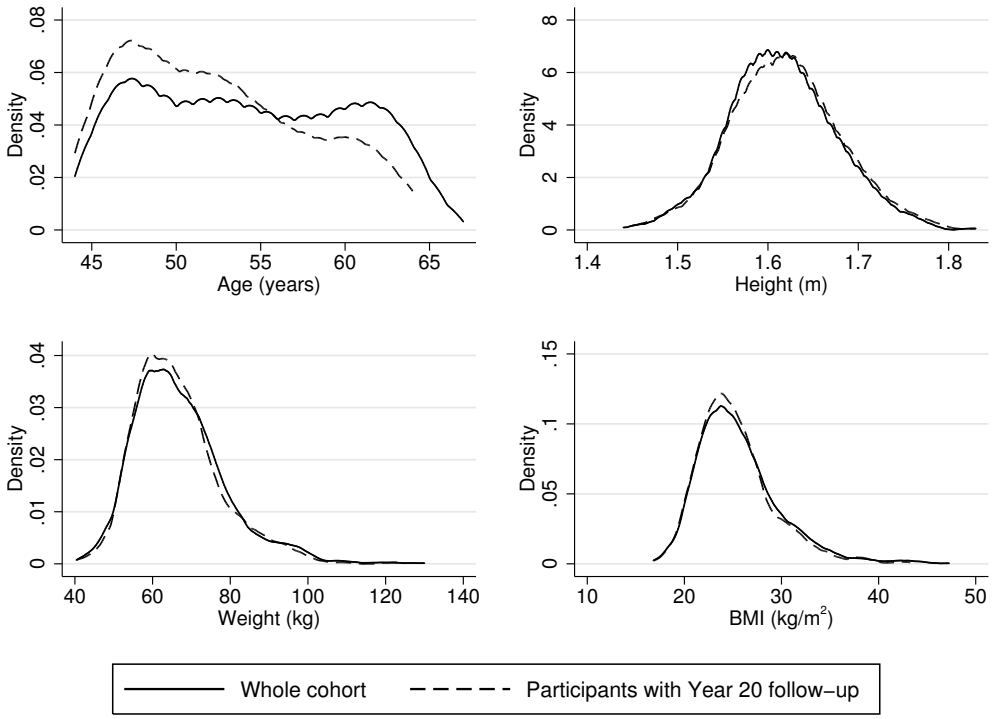


Figure 3.3 – Kernel density plots of baseline age, height, weight and BMI for the whole cohort and participants with year 20 follow-up.

3.5 Summary

In summary the Chingford 1000 Women study is a longitudinal population cohort, with 20 year follow-up of 46% of the study population. The study population was representative of the UK population terms of weight (65 kg in the UK, 67 kg in Chingford), height (1.61 m versus 1.62 m) and BMI (25.4 versus 25.6 kg/m^2 when the study was initiated [150]. Loss to follow-up was initially non-differential but at year 20, participants who remain actively enrolled are younger, taller, have a lower BMI and includes fewer smokers. Conservative bias with respect OA may be introduced because of the loss of those older participants.

Chapter 4

Hip morphology characteristics of the cohort

4.1 Introduction

Epidemiologic studies indicate that osteoarthritis (OA) of the hip frequently occurs in the absence of OA in other large joints, suggesting that local factors are important in its pathogenesis. Hip morphology has been recognised as a significant biomechanical risk factor for the development of hip osteoarthritis (OA). Harris [52] suggested that more than 90% of patients with so-called primary or idiopathic osteoarthritis showed demonstrable abnormalities in the hip joint at the cessation of growth. Cross-sectional studies have supported this theory [71] and longitudinal data is beginning to emerge

[86]. These deformities can be divided into acetabular dysplasia, i.e. a shallow hip socket and FAI, characterised by an abnormality of femoral head-neck junction or acetabulum [60]. In addition FAI has been documented as a cause of hip and groin pain [66], long before the term was coined.

Many overlapping morphological measures to characterise these malformations have been reported, primarily with respect to pathological conditions. A detailed description of morphology in a large population cohort has not previously been undertaken and the distribution of these malformations in the general population is largely unknown. In this study, a detailed description of hip morphology in a large population cohort of women is presented.

The specific aims of this study were to:

1. describe hip morphology in a population cohort using radiological measurements.

2. determine the relationship between morphological measurements.

4.2 Methods

4.2.1 Study Participants

The Chingford 1000 Women Study [151] is a population-based cohort of 1003 randomly selected Caucasian volunteers that was initiated in 1989. Descriptive characteristics at baseline and follow up are discussed in the preceding chapter. The cohort includes

women between 44 and 67 years of age. Standardised AP pelvis radiographs were taken at year 2. The present study includes all participants who had undergone an AP pelvis radiograph. The local ethics committee approved the study and written consent was obtained from each woman (Outer North East London Research Ethics Committee (formerly Barking & Havering and Waltham Forest RECs), LREC (R&WF) 96).

4.2.2 Exclusions

Exclusion criteria were applied to ensure that radiographs were of an acceptable standard. Five hip joints (5 individuals) were excluded because they had a dynamic hip screw in situ, indicating previous femoral neck fracture. Seventy-two hip joints (36 individuals) were excluded because they had excessive rotation or tilt, as assessed by the foramen obturator index or the sacrococcygeal joint to pubic symphysis distance respectively. Twenty individuals were excluded due to poor radiograph quality. Poor radiograph quality was a subjective exclusion criterion applied when a radiograph was either grossly over- or under-exposed to the extent that constituent anatomic landmarks were not visible for the purposes of analysis. A total of 119 hips in 61 individuals were excluded. Baseline characteristics of those excluded from analysis were not significantly different from those included in the analysis.

4.2.3 Radiographic assessment of morphology

Hip morphology was measured using the software program described in Chapter 2, HipMorf 3.0. The reproducibility of which is shown in Table 2.5. The morphological measurements considered are shown in Table 2.2. Triangular Index Height (TIH) is a modification of the Triangular Index, described by Gosvig - the radius (r) of the femoral head is measured - then at 1/2 r along the axis of the femoral neck, the corresponding perpendicular height (H) to the superior border of the head-neck junction is then measured. From the height (H) the corresponding distance (R) to the centre of the femoral head can be calculated. TIH refers to this distance H and we have also expressed the distance R as a ratio with respect to femoral head radius (r) i.e. R:r as Triangular ratio. Each radiograph was anonymised. All morphological measurements were performed by the principal investigator (GERT). Intra- and inter-observer reproducibility was assessed (using 20 random radiographs) with ICCs in excess of 0.81 for all continuous measurements and Kappa statistic of 1.0 for Triangular Index. In addition radiographs were scored according to the method of Kellgren and Lawrence (KL) [19] using the Atlas of Standard Radiographs [152].

4.2.4 Statistical Analysis

The distribution of morphological measurements was examined using histograms and kernel density plots. Continuous data are presented as means, standard deviations, range, median and interquartile range. Prevalence estimates are given as simple percentages. Correlations between measurements were assessed by Pearson product-moment correlation coefficient and shown visually using scatter plots. All statistical calculations were performed using Stata 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and statistical significance was assumed when the p-value was < 0.05.

4.3 Results

The baseline characteristics of the participants included in this study are summarised in Table 4.1. 1455 Hips (733 participants) were included in the analysis.

Table 4.2 shows a summary of the morphology results for the whole cohort. Data was normally distributed for all continuous variables (Figure 4.1) with the exception of α-angle (Figure 4.2).

Table 4.1 – Baseline descriptive characteristics of study population

Characteristics	Full cohort (n=1003)	Subjects not included in this analysis (n=270)	Subjects included in this analysis (n=733)	p-value
Age (years), median (IQR)	54 (49, 60)	54 (50, 58)	54 (48, 59)	0.05
Height (m) mean (SD)	1.62 (0.06)	1.62 (0.06)	1.63 (0.06)	0.05
Weight (kg) median (IQR)	65.0 (58.5, 73.0)	66.2 (58.4, 71.8)	65.4 (60.8, 71.4)	0.19
BMI (kg/m^2) median (IQR)	24.9 (22.6, 27.6)	25.2 (22.5, 27.0)	25.1 (23.5, 26.8)	0.05

Table 4.2 – Summary of morphology measurements

Measurement	Mean	S.D.	Min	Max	25th percentile	Median	75th percentile
Acetabular Depth	25.88	4.26	12	43.91	22.9	25.75	28.66
Acetabular Depth:Width	0.44	0.07	0.2	0.67	0.39	0.43	0.48
Acetabular Width	59.51	3.62	47.51	72.58	57.03	59.42	61.9
AP α-angle	56.28	18.82	34.61	128.41	43.61	47.22	64.48
Extrusion Index	0.19	0.08	-0.05	0.44	0.13	0.19	0.24
Femoral Neck Shaft Angle	129.80	5.89	112.83	146.72	125.88	129.88	133.80
Femoral Offset	42.39	7.38	19.82	68.52	37.32	42.24	47.27
Foramen Obturator Index	1.01	0.1	0.71	1.38	0.95	1	1.06
Head Diameter	54.78	3.21	46.83	66.49	52.55	54.67	56.98
Head: Neck Ratio	1.43	0.07	1.18	1.73	1.38	1.43	1.48
Horizontal Toit Externe	0.51	5.96	-14.62	23.36	-3.31	0.39	4.15
Inter Head Centre Distance	223.88	12.5	190.89	263.75	215.53	223.71	232.89
Inter Teardrop Distance	149.01	8.74	122.18	176.42	143.15	148.42	154.93
Lateral Centre Edge Angle	30.78	6.85	10.22	54.34	26.19	30.72	35.45
Mid SI Joint to Pubic Symphysis	104.01	13.48	68.35	136.06	94.43	103.9	113.87
Minimum JSW (Manual)	4.07	0.71	0.27	6.51	3.62	4.04	4.52
Medial Proximal Femoral Angle	85.81	5.58	63.83	103.78	82.07	85.95	89.54
Neck Length	55.34	7.2	33.99	80.91	50.36	55.44	60.01
Neck Width	38.32	2.87	29.63	48.88	36.31	38.28	40.21
Sacrococcygeal to Pubis Symphysis	52.48	16.28	8.01	100.58	41.4	52.58	64.12
Sharp's Angle	39.27	3.63	26.36	51.36	37.02	39.28	41.62
Triangular Index Height	23.05	2.16	17.42	32.48	21.51	22.9	24.44
Triangular Ratio	0.98	0.05	0.83	1.27	0.94	0.98	1.01

All size measurements are inflated by approximately 20% because of radiograph magnification.

Using a cut-point of 65° (based on distribution of the data), a raised α-angle was present in 24% and gross cam-type FAI (positive triangular index) was present in 4.4%. Pincer-type FAI (LCE angle >40°) was present in 8.3% of hips. Prevalence of severe acetabular dysplasia (LCE angle >20°) was 5.4%.

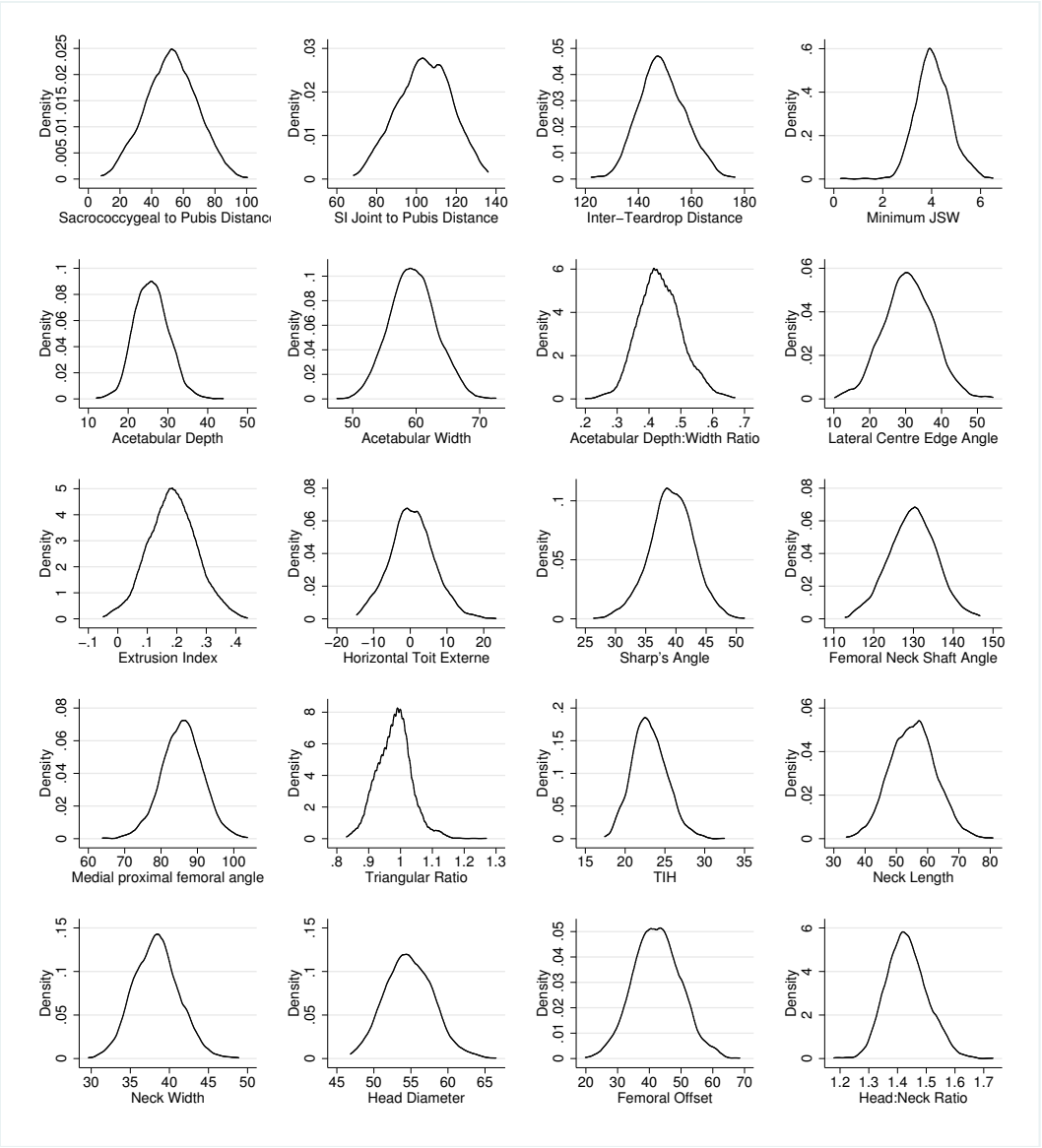


Figure 4.1 – Kernel density plots of morphology measurements.

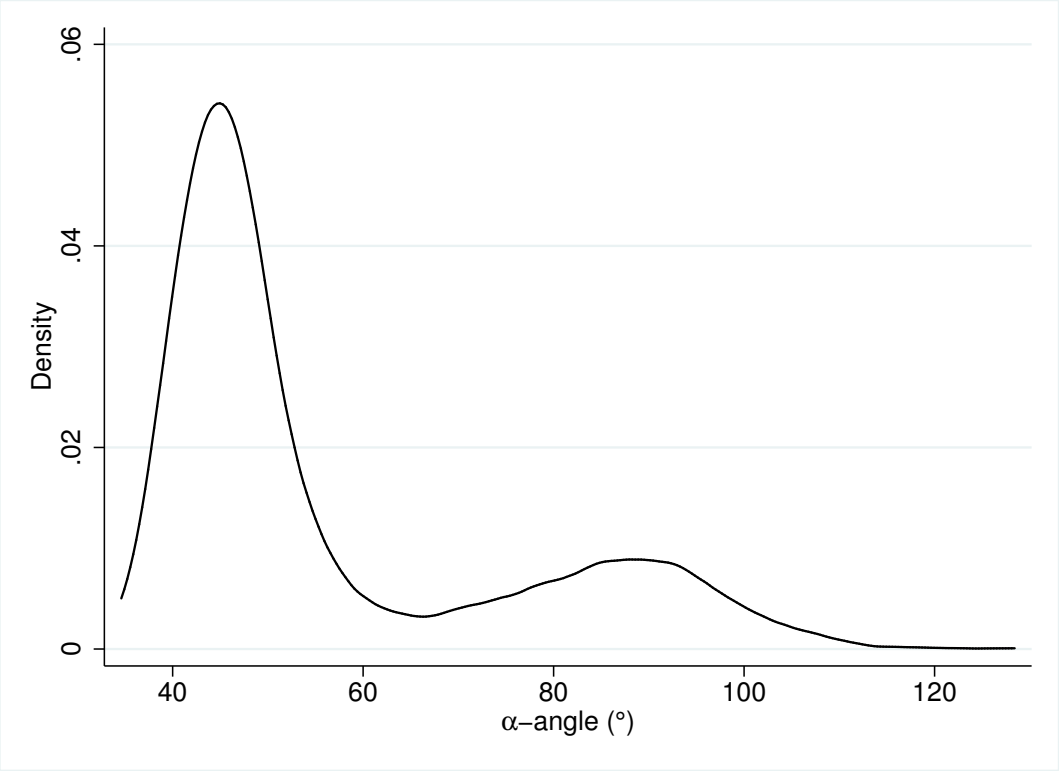


Figure 4.2 – Kernel density plot of α-angle.

All morphological measurements were grossly symmetrical (with a Pearson's correlation coefficient of greater than 0.6, Figure 4.3), α-angle, was the exception demonstrating significant asymmetry (Figure 4.4).

Correlations between morphological measurements were examined. Correlation coefficients greater than 0.6 were limited to sacrococcygeal joint to pubic symphysis distance and sacroiliac joint to pubic symphysis distance (measures of pelvic tilt); lateral centre edge angle and extrusion index (measures of acetabular coverage); acetabular depth and acetabular depth:width ratio; femoral shaft angle - femoral neck length - offset; modified triangular height and triangular ratio. (Table 4.3, Figures 4.5 - 4.7).

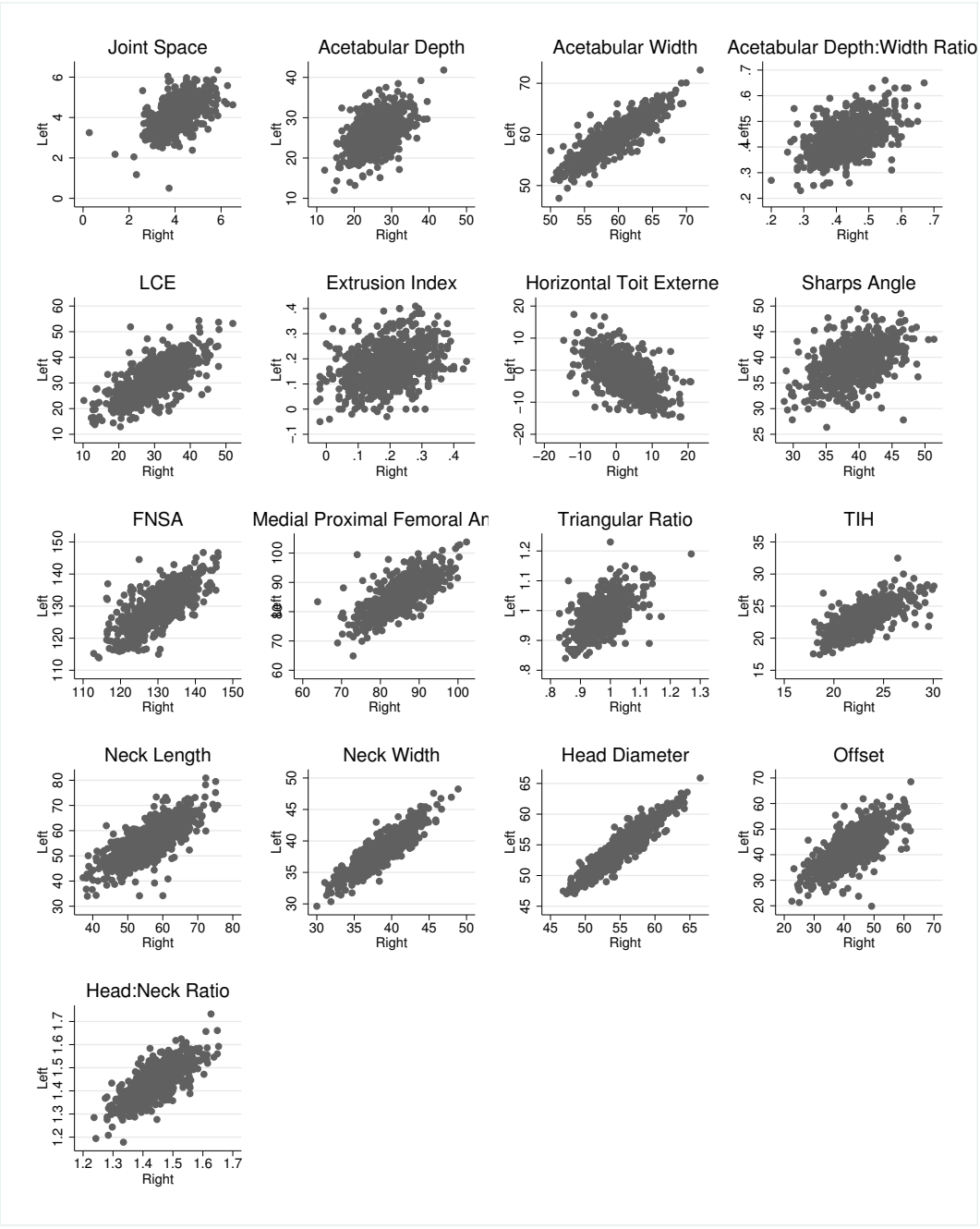


Figure 4.3 – Scatter plot of bilateral morphology measurements by side.

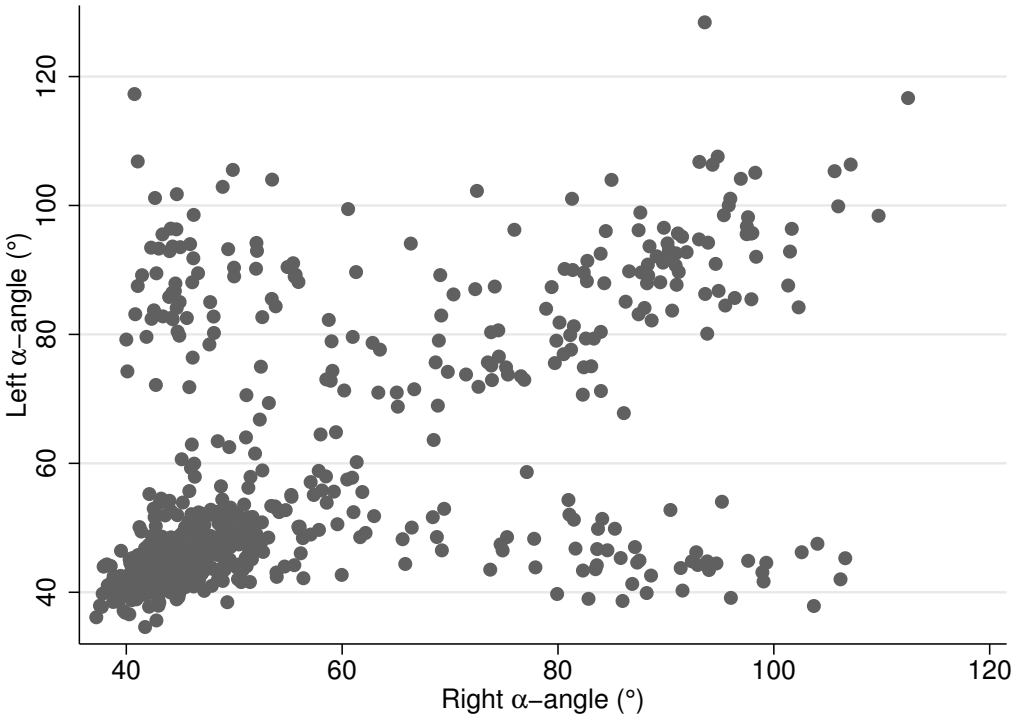


Figure 4.4 – Scatter plot of α-angle by side.

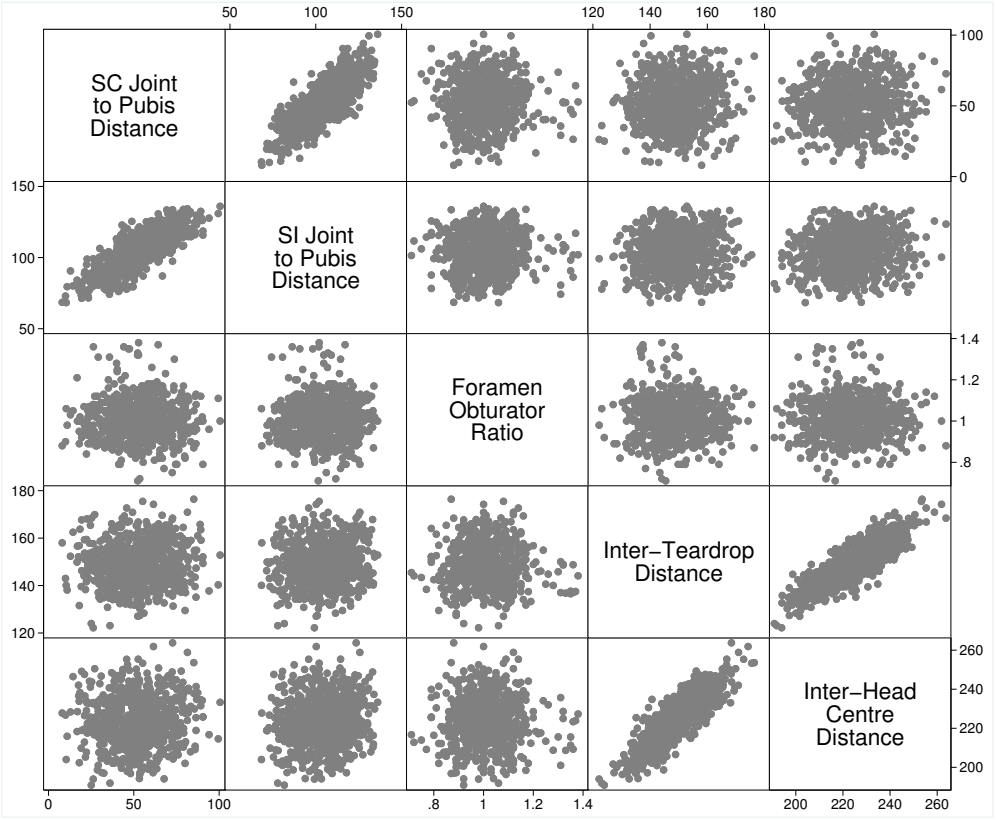


Figure 4.5 – Correlation matrix of pelvic morphology measurements.

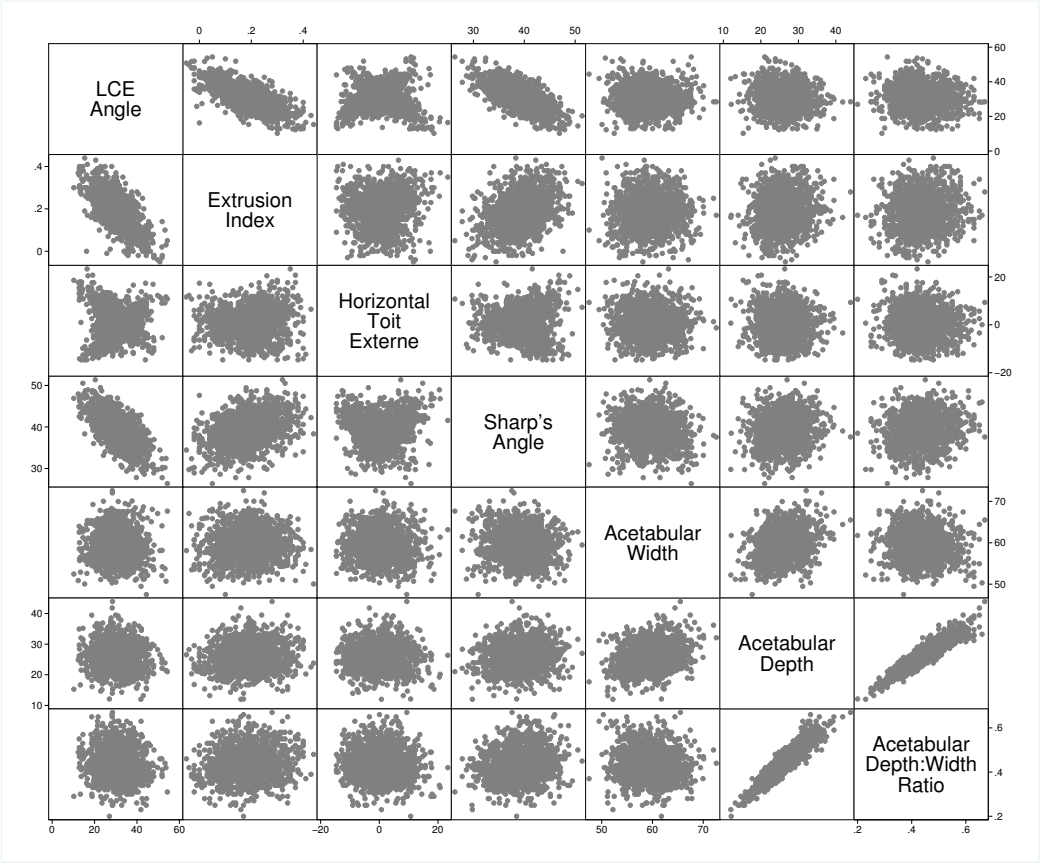


Figure 4.6 – Correlation matrix of acetabular morphology measurements.

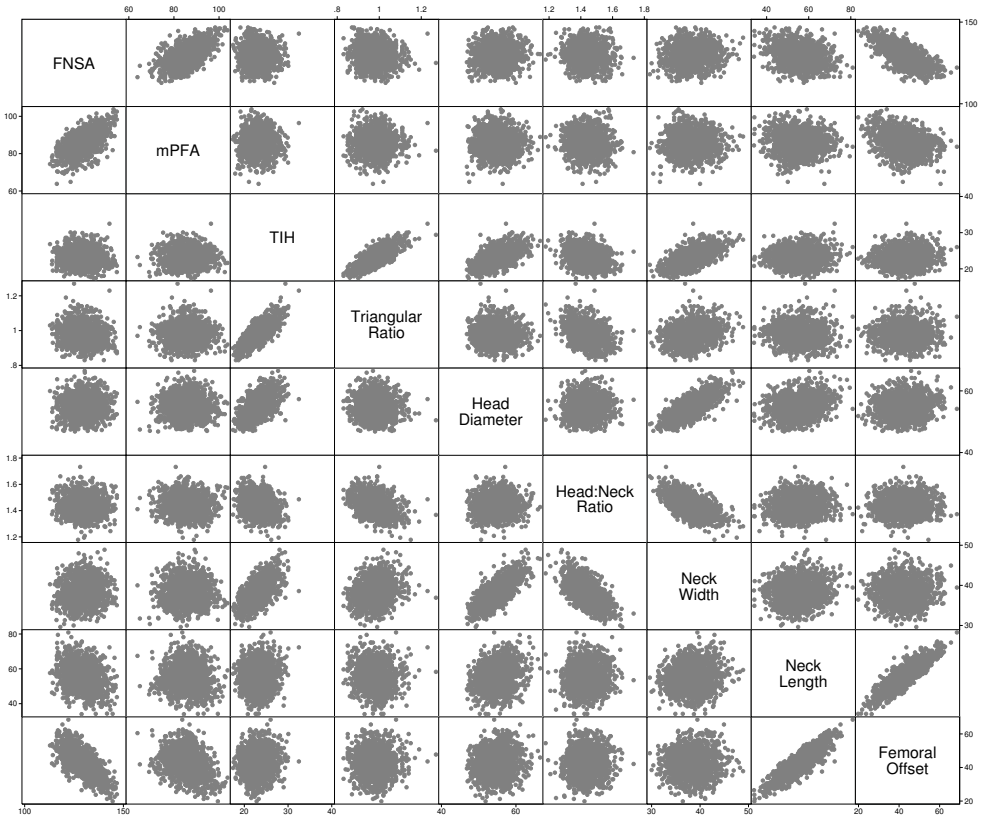


Figure 4.7 – Correlation matrix of femoral morphology measurements.

Table 4.3 – Correlation matrix for hip morphology measurements.

	Foramen Obturator Ratio	SCJ to Pubis Distance	SIJ to Pubis Distance	Inter-Teardrop Distance	Inter-Head Distance	Inter-Acetabular Distance	Minimum JSW	LCE Angle	Extrusion Index	Horizontal Toit Externe	Sharp's Angle	Acetabular Width	Acetabular Depth	Acetabular Depth:Width	∝-angle	FNSA	MPFA	TIH	Triangular Ratio	Head Diameter	Neck Length	Neck Width	Head:Neck Ratio	Femoral Offset
Foramen Obturator Ratio	1																							
SCJ to Pubis Distance	0.01	1																						
SIJ to Pubis Distance	0.02	0.80 ***	1																					
Inter-Teardrop Distance	0	0.06 **	0.10 ***	1																				
Inter-Head Distance	0.01	0.07 ***	0.13 ***	0.85 ***	1																			
Inter-Acetabular Distance	0.01	0.10 ***	0.12 ***	0.80 ***	0.81 ***	1																		
Minimum JSW	0	-0.01	0.02	0.10 ***	0.22 ***	0.08 ***	1																	
LCE Angle	0.01	-0.05 *	-0.05 **	-0.02	-0.22 ***	-0.09 ***	-0.23 ***	1																
Extrusion Index	0.04	0.02	0.02	0.07 **	0.23 ***	0.14 ***	0.14 ***	-0.72 ***	1															
Horizontal Toit Externe	-0.03	0.03	0.02	0.03	0.02	0.01	-0.07 ***	-0.04 *	0.05 **	1														
Sharp's Angle	0.01	0.15 ***	0.20 ***	0.03	-0.03	-0.02	0.08 ***	-0.66 ***	0.36 ***	0.02	1													
Acetabular Width	0.03	-0.04	0.04	0.50 ***	0.68 ***	0.46 ***	0.22 ***	-0.04	0.01	0	-0.08 ***	1												
Acetabular Depth	0.02	-0.07 **	-0.02	0.20 ***	0.15 ***	0.17 ***	0.07 ***	-0.10 ***	0.10 ***	-0.04	0.14 ***	0.30 ***	1											
Acetabular Depth:Width	0.01	-0.05 **	-0.03	0.02	-0.11 ***	0	-0.02	-0.08 ***	0.10 ***	-0.04	0.17 ***	-0.07 ***	0.93 ***	1										
∝-angle	0.05 *	0.03	0.04 *	0.10 ***	0.10 ***	0.12 ***	-0.10 ***	0.04	0.11 ***	0.02	-0.01	0.11 ***	0.07 ***	0.04	1									
FNSA	-0.02	-0.04	-0.03	-0.03	0.07 ***	-0.03	0.16 ***	-0.14 ***	0.11 ***	0	0.05 **	0.02	-0.13 ***	-0.14 ***	-0.11 ***	1								
MPFA	-0.01	-0.07 ***	-0.07 ***	-0.02	0.01	-0.03	0.13 ***	-0.13 ***	0.17 ***	-0.03	0.10 ***	0	0	0	-0.03	0.59 ***	1							
TIH	0.08 ***	-0.07 **	-0.03	0.39 ***	0.51 ***	0.39 ***	0.03	-0.01	0.22 ***	0.02	-0.10 ***	0.59 ***	0.18 ***	-0.04	0.45 ***	-0.05 *	0.02	1						
Triangular Ratio	0.10 ***	-0.09 ***	-0.11 ***	0.06 **	0.05 *	0.09 ***	-0.13 ***	0.07 ***	0.20 ***	0	-0.09 ***	0.06 **	0.03	0.01	0.52 ***	-0.13 ***	0.03	0.78 ***	1					
Head Diameter	0.01	0.01	0.10 ***	0.55 ***	0.75 ***	0.50 ***	0.22 ***	-0.12 ***	0.10 ***	0.04 *	-0.04 *	0.86 ***	0.26 ***	-0.06 **	0.05 **	0.09 ***	-0.01	0.60 ***	-0.03	1				
Neck Length	0	0.14 ***	0.15 ***	0.21 ***	0.24 ***	0.24 ***	0.05 *	-0.08 ***	0.03	0.03	0.08 ***	0.27 ***	0.15 ***	0.05 **	0.08 ***	-0.32 ***	-0.06 **	0.05 *	-0.11 ***	0.22 ***	1			
Neck Width	0.04	-0.02	0.06 **	0.42 ***	0.63 ***	0.41 ***	0.14 ***	-0.15 ***	0.22 ***	0.01	0	0.70 ***	0.20 ***	-0.06 **	0.26 ***	0.10 ***	0.03	0.63 ***	0.20 ***	0.76 ***	0.11 ***	1		
Head:Neck Ratio	-0.05 *	0.04	0.02	0.01	-0.06 **	-0.02	0.05 **	0.09 ***	-0.21 ***	0.03	-0.05 **	-0.04	0	0.02	-0.33 ***	-0.04 *	-0.06 **	-0.24 ***	-0.34 ***	0.04	0.09 ***	-0.62 ***	1	
Femoral Offset	0.01	0.12 ***	0.13 ***	0.16 ***	0.13 ***	0.18 ***	-0.04 *	0.01	-0.02	0.02	0.04	0.18 ***	0.17 ***	0.11 ***	0.12 ***	-0.71 ***	-0.32 ***	0.06 **	-0.01	0.11 ***	0.88 ***	0.03	0.08 ***	1

*** if p-value<0.001, ** if p-value<0.01, * if p-value<0.05

4.4 Discussion

This study provides the most detailed description to date, of hip morphology in a large population based cohort. Wide variation in hip morphology is present with the vast majority of measures showing a normal distribution. The distribution of α-angle was bimodal, with a range of 36° to 118° and antimode of 65°. In addition the asymmetry of α-angle is an interesting finding which may in part explain unilateral hip osteoarthritis. Measurement of α-angle on AP pelvis radiographs has previously been reported [71, 77, 153], but a bimodal distribution was first recognised in this cohort [154] and confirmed in a recent collaboration with the CHECK study [155]. Gosvig et al reported a range in women from the Copenhagen Osteoarthritis Study of 32° to 108° and used the mean and standard deviation (SD) of 45° and 5° to define a pathological threshold of 57° in women (based on mean + 2SD) [77]. Methodologically this is inappropriate and a general threshold of 65° (based on the antimode of the bimodal distribution) for the AP α-angle in women is more appropriate, though attention to the specific outcome (eg. Pain vs THR) may be required when defining a threshold [155]. Fortunately the threshold of 57° is not dissimilar to the antimode of the bimodal distribution seen in this cohort. Further data is required to revisit the threshold (which was previously calculated as 83°) in men.

The morphological measures included in the analysis have been used to describe

pathological malformations [75–77, 123, 124, 126, 128, 142–147, 156]. The LCE angle is one of the most commonly used uniplanar discriminators of acetabular dysplasia and pincer type FAI. Significant interrelationships have been reported among LCE angle, Sharps angle, acetabular depth:width ratio and extrusion index in the assessment of acetabular malformations [157]. These findings were confirmed in this study. The mean LCE angle in the cohort was 30.7° with a SD of 6.9°. Acetabular dysplasia has traditionally been defined as an LCE of <20° and pincer-type FAI as an LCE >40°[80, 158], these threshold are used in our description of prevalence. Acetabular dysplasia was present in 5.4% of the cohort, similar to the 3-5% which has been previously reported [71, 157, 159]. A deep acetabular socket (pincer-type FAI) has a prevalence of 8.3%, less common than previously reported in women [71]. Pistol grip malformation (i.e. severe cam-type FAI) has been reported in 8% of 2655 human skeletons [54] and Gosvig et al. reported a prevalence for pistol grip deformity of 5.2% in women, similar to the 4.4% in our study who were found to have a positive triangular index. The prevalence of some degree of head asphericity suggestive of a more subtle cam-type deformity was significantly greater at 24%.

The main strengths of this study are the size of the cohort, standardisation of the radiographs according to a protocol and the use of objective measures of morphology, which have shown significantly better reproducibility than categorical descriptive measures [140]. This study also provides a clearer framework in which to consider radiographic morphology measurements in the future. The major weakness is that

morphology was only measured on anteroposterior radiographs, while lateral projections of the hip are more sensitive for detecting FAI [131]. AP pelvis radiographs are the most commonly used imaging modality for the hip and the only available in the majority of large cohort studies [132–136]. Gosvig et al concluded that only 3.6% of pistol grip malformations in men and 11% of pistol grip malformations in women detected on lateral hip radiographs went undetected on AP pelvis radiographs when the triangular index was used [153]. Only women are included in the study, though baseline characteristics of women included in the study were similar to the UK general population in terms of weight (65 kg in the UK, 67 kg in Chingford), height (1.61 m v 1.62 m) and BMI (25.4 v 25.6 kg/m2) [150]. 98% of the women included in the study are Caucasian, which limits the generalisability of these results.

The patho-aetiology of the cam-type malformation has been discussed extensively over the last five decades [55, 76, 160], with some postulating that it is secondary to remodelling of the femoral head [160]. Murray proposed that it results from a prior asymptomatic slipped capital femoral epiphysis [50]. The bimodal distribution of α-angle as well as asymmetry, suggests a discrete pathological entity and acquired pathology.

4.5 Summary

In conclusion, wide variation in hip morphology is present in the normal population, with the majority of morphological measurements showing a normal distribution. α-angle showed a bimodal distribution as well as asymmetry, suggesting a discrete pathological entity and acquired pathology. Morphological abnormalities of the hip are common, in this cohort some form of abnormality was found in 35.4% of hips.

Chapter 5

Hip morphology and cross-sectional associations with radiographic osteoarthritis

5.1 Introduction

Multiple risk factors have been associated with the development of hip OA and are discussed in detail in Chapter 1. Age, sex, weight, activity/occupation, anatomical abnormalities and paediatric hip disease have all been implicated. Despite these association the majority of end-stage OA continues to be described as idiopathic in most arthroplasty registers.

There is increasing evidence for the association between hip osteoarthritis and morphological abnormalities of the hip such as acetabular dysplasia [46, 47], protrusio acetabuli[161] and FAI [71]. These studies have focussed on acetabular dysplasia [46, 47, 157] and more recently on categorical descriptions of FAI such as coxa profunda and/or protrusio acetabuli as well as pistol grip deformity[71]. Unfortunately these categorical measures have shown poor reproducibility[140].

The aim of this study was to report the baseline prevalence of hip OA in the Chingford Cohort and to characterise the cross-sectional associations been morphological abnormalities hip joint and radiographic OA at their baseline visit.

5.2 Methods

The study population and radiographic assessment of morphology are described in Chapters 2 and 3 respectively.

5.2.1 Radiographic assessment of OA

Radiographs were scored blind to clinical details according to the method of Kellgren and Lawrence[19] using the Atlas of Standard Radiographs. OA was subsequently defined by a KL Grade of 2 or greater.

5.2.2 Statistical Analysis

The distribution of morphological measurements by OA group was examined using histograms and kernel density plots. All data are presented as means, standard deviations, range, median and interquartile range. Normally distributed variables were compared using the independent 2-tailed t-test; non-normally distributed variables were compared using the Wilcoxon rank sum test.

Logistic regression analysis was performed to describe the crude univariate association of the morphological measurements with radiographic OA as a binary outcome. Secondary analyses were performed by further adjusting for age and BMI. Interactions between the acetabular and femoral morphological measurements were explored. Logistic regression analyses were with robust standard errors and clustering by subject identifier to account for the dependency of two hips from one subject.

Area Under Receiver Operating Characteristic (AUROC) as well as McFaddens's pseudo R^2 statistic [162] were used to evaluate the discriminatory ability of the morphological measurements. AUROC measures accuracy. An area of 1 represents a perfect test in this case a model that perfectly predicts OA or THR. McFaddens pseudo R2 statistic is a measure of predictive value of the model. Values of R2 between 0.2-0.4 are considered to be indicative of extremely good model fits. Simulations by Domenich and McFadden (1975) suggest equivalence of this range to 0.7 to 0.9 for a linear function.

All the statistical calculations were performed using Stata 12.1 (StataCorp. 2011.

Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and statistical significance was assumed when the p-value was <0.05.

5.3 Results

KL Grading is shown in Table 5.1. Prevalence of radiographic OA was 13.8%.

Table 5.1 – Baseline Kellgren & Lawrence Grading

KL Grade	Hips (n)	Percentage
0	1,284	80.25
1	94	5.88
2	214	13.38
3	6	0.38
4	2	0.12

Table 5.2 shows the baseline demographic characteristics of the cohorts by OA status. Participants with radiographic OA were on average 2 years older. Height, weight, BMI and smoking status were not significantly associated with radiographic OA.

Table 5.2 – Baseline Demographic Characeteristics by OA status (Kellgren and Lawrence ≤ 1 versus ≥ 2)

	No OA							OA							
	Mean	SD	Min	Max	25th percentile	Median	75th percentile	Mean	SD	Min	Max	25th percentile	Median	75th percentile	p-value
Age (years)	53.81	5.91	44	66	48	53	59	55.43	5.80	45	66	50	56	61	<0.001
Height (m)	1.62	0.06	1.44	1.83	1.58	1.61	1.65	1.61	0.05	1.47	1.75	1.58	1.62	1.65	0.47
Weight (kg)	66.56	11.22	40.4	130	58.4	65	72.9	65.96	11.10	44.2	97.8	58	63.95	70.9	0.25
B.M.I. (kg/m^2)	25.46	4.00	16.81	44.46	22.67	24.81	27.49	25.35	4.10	17.58	38.78	22.6	24.37	27.52	0.35
Smoker (%)	44.7							50.5							0.11

Table 5.3 shows morphology measurements by OA status. Participants with osteoarthritis at baseline had a higher α-angle, triangular index height and triangular ratio, as well as increased neck width and lower head:neck ratio. Figure 5.1 shows the variation in distribution of α-angle by OA status and Figure 5.2 the small but statistically significant differences in triangular index height, triangular ratio, neck width and head:neck ratio. Minimum JSW was significantly different between Kellgren and Lawrence ≤ 1 versus ≥ 2, though the absolute difference was small, this is not an unusual finding in a population study. Note these results do not take account of clustering with two hips from one participant in the majority of cases and size measurements inflated by approximately 20%. Subsequent logistic regression does account for clustering.

Table 5.3 – Morphology measurements by OA status (Kellgren and Lawrence ≤ 1 versus ≥ 2

Morphology measurement	No OA							OA							
	Mean	S.D.	Min	Max	25th percentile	Median	75th percentile	Mean	S.D.	Min	Max	25th percentile	Median	75th percentile	p-value
Acetabular Depth	25.99	4.21	13.19	43.91	22.98	25.88	28.79	25.3	4.53	12	36.9	22.77	25.23	27.85	0.058
Acetabular Depth:Width	0.44	0.07	0.25	0.67	0.39	0.43	0.48	0.43	0.07	0.2	0.62	0.37	0.43	0.47	0.062
Acetabular Width	59.47	3.54	49.48	70.09	57.07	59.35	61.75	59.38	3.72	47.51	66.88	57.02	59.38	62.07	0.781
AP α-angle	55.12	17.96	35.63	117.29	43.52	46.73	58.74	61.73	21.04	39.28	107.12	44.19	50.01	84.43	0.009
Extrusion Index	0.19	0.08	-0.05	0.43	0.13	0.19	0.24	0.2	0.08	0	0.44	0.14	0.2	0.26	0.079
FNSA	129.71	5.71	113.84	146.72	125.87	129.8	133.62	129.79	5.95	114.15	144.79	126.12	130.07	134.09	0.864
Femoral Offset	42.42	7.37	21.27	68.52	37.31	42.15	47.27	43.04	6.93	27.81	62.14	38.47	42.67	47.93	0.318
Foramen Obturator Index	1.01	0.09	0.71	1.38	0.95	1	1.06	1.02	0.11	0.71	1.38	0.97	1	1.09	0.083
Head Diameter	54.74	3.17	47.02	64.62	52.6	54.65	56.87	54.73	3.15	46.83	63.19	52.31	54.45	56.89	0.960
Head: Neck Ratio	1.44	0.07	1.18	1.73	1.39	1.43	1.48	1.42	0.08	1.19	1.58	1.36	1.42	1.47	0.004
Horizontal Toit Externe	0.39	5.93	-14.62	23.36	-3.32	0.06	4.1	1.13	6.46	-14.62	20.48	-3.91	1.4	5.09	0.148
Head Centre Distance	223.69	12.54	191.9	263.75	215.18	223.15	232.61	224.31	12.21	194.25	252.47	216.21	224.11	232.01	0.561
Inter Teardrop Distance	149.1	8.84	123.09	176.42	143.05	148.46	155.07	148.29	8.39	127.4	169.64	142.21	147.8	153.5	0.279
LCE	30.74	6.79	12.29	54.34	26.15	30.81	35.43	30.02	7.11	12.88	47.59	25.47	30.14	34.53	0.221
SIJ to Pubic Symphysis	104.19	13.37	68.35	134.28	95.11	104.17	114.07	102.04	13.18	75.6	132.09	91.3	101.92	111.69	0.061
Minimum JSW	4.09	0.69	0.5	6.51	3.63	4.06	4.53	3.88	0.84	0.27	6.05	3.45	3.9	4.39	<0.001
MPFA	85.81	5.52	63.83	103.78	82.1	85.95	89.43	85.38	5.7	64.88	102.2	81.89	84.84	89.03	0.359
Neck Length	55.3	7.32	33.99	80.91	50.2	55.25	60.1	56.13	6.51	40.08	75.11	51.48	56.54	60.07	0.178
Neck Width	38.23	2.8	30.36	48.88	36.24	38.26	40.08	38.72	3.1	31.73	47.98	36.58	38.36	40.35	0.042
SCJ to Pubis Symphysis	52.61	16.36	8.01	99.5	41.82	52.53	63.9	50.98	14.69	10.95	87.46	40.58	51.57	60.91	0.235
Sharp's Angle	39.43	3.57	26.36	50.53	37.15	39.56	41.85	38.92	3.77	29.79	49.46	36.75	38.59	40.84	0.097
Triangular Index Height	22.95	2.07	17.42	30.01	21.51	22.85	24.27	23.55	2.43	18.9	30.07	21.65	23.29	24.99	0.001
Triangular Ratio	0.98	0.05	0.83	1.19	0.94	0.98	1.01	1	0.07	0.86	1.27	0.94	0.99	1.04	<0.001

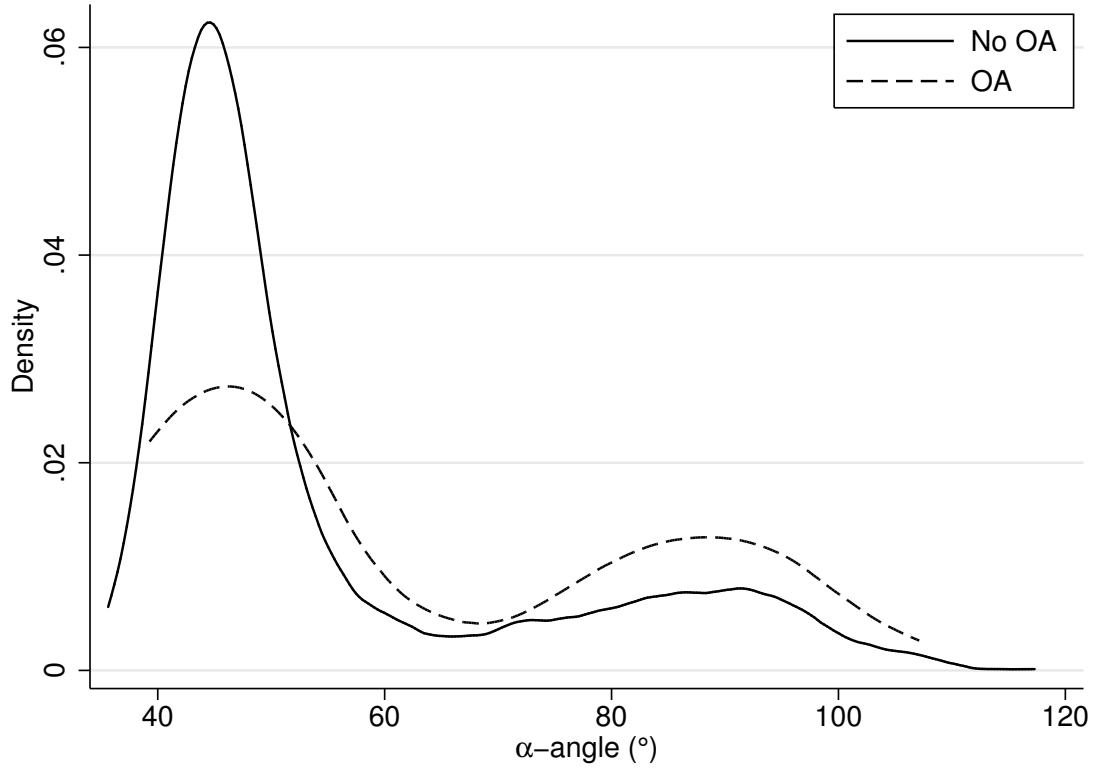


Figure 5.1 – Kernel density plot of α-angle by OA status.

Logistic regression analyses both univariate and adjusting for age and BMI are shown in Table 5.4. Univariate analysis revealed that only measures of proximal femoral morpholgy were associated with OA. Each degree increase in α-angle was associated with a 1.7% increased risk of OA and each millimetre increase in TIH associated with a 13.8% increased risk. OA risk increased by 42.9% per SD increase in triangular ratio

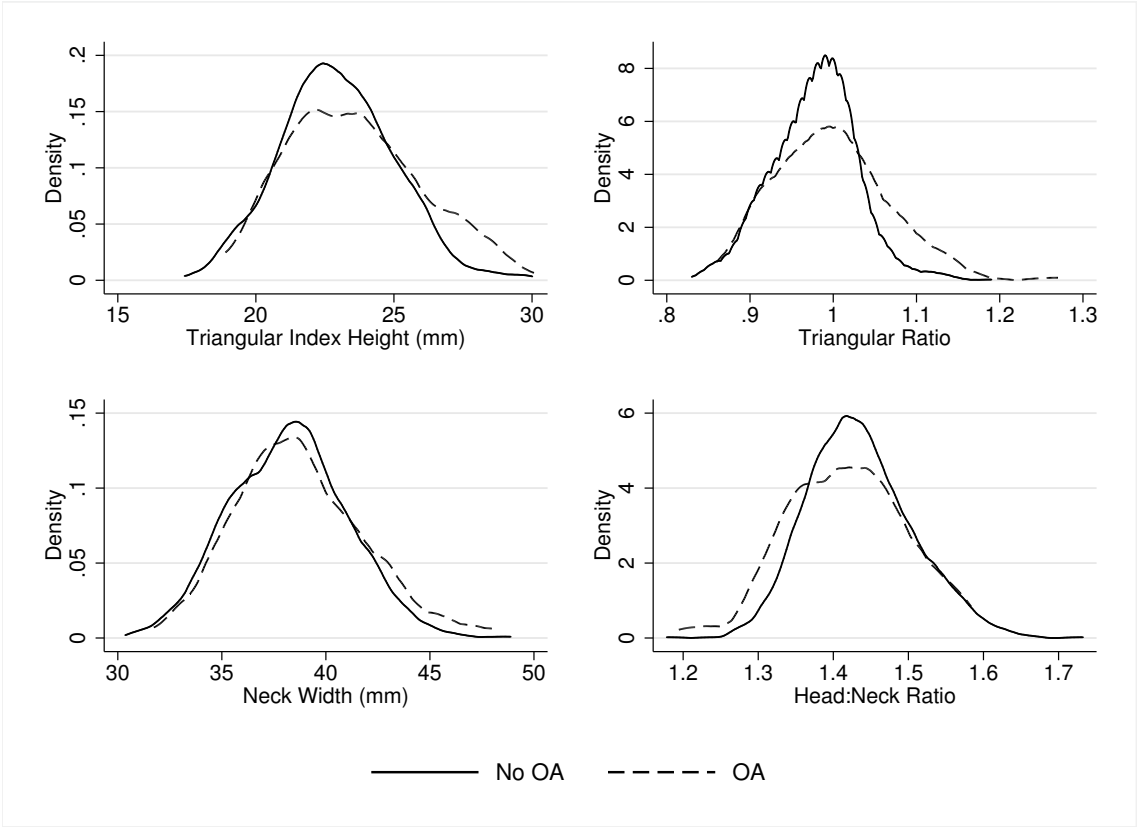


Figure 5.2 – Kernel density plots of morphology measures by OA status.

and increasing Head:Neck ratio decreased risk 22.3% per SD. All remained significantly associated when adjusting for age and BMI. Extrusion index only became significantly associated after adjusting for age and BMI with a 16% increase in risk of OA per SD increase.

Table 5.4 – Logistic regression: Morphology measurements and association with radiographic OA

Morphology measurement	Univariate		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
α-angle (per °)	1.017 (1.008-1.026)	<0.001	1.018 (1.009-1.026)	<0.001
TIH (per mm)	1.138 (1.035-1.251)	0.007	1.130 (1.027-1.243)	0.012
Triangular Ratio (per SD)	1.429 (1.171-1.744)	<0.001	1.433 (1.172-1.751)	<0.001
Neck Width (per mm)	1.062 (0.987-1.143)	0.107	1.056 (0.980-1.137)	0.155
Head:Neck Ratio (per SD)	0.777 (0.632-0.955)	0.016	0.773 (0.632-0.947)	0.013
Extrusion Index (per SD)	1.160 (0.981-1.373)	0.083	1.197 (1.008-1.422)	0.041

Multivariate logistic regression revealed that only α-angle and age were significantly associated with OA when combined in the same model. No significant interactions were identified between femoral and acetabular measures.

Area Under Receiver Operating Characteristic (AUROC) statistic for the non-morphological covariates as predictors of OA was 57.9% and increased marginally to 62.2% with inclusion of α-angle, triangular ratio, head:neck ratio and extrusion index. McFadden's pseudo R^2 statistic increased from 1.14% to 3.87% (Table 5.6).

Table 5.5 – Multivariate logistic regression: Morphology measurements and demographic characteristics and association with radiographic OA

	Multivariate	
	OR (95% CI)	p-value
α-angle (per °)	1.010 (1.000-1.020)	0.048
Triangular Ratio (per SD)	1.223 (0.963-1.552)	0.098
Head:Neck Ratio (per SD)	0.906 (0.730-1.124)	0.368
Extrusion Index (per SD)	1.090 (0.911-1.304)	0.346
Age (per year)	1.056 (1.020-1.092)	0.002
BMI (per kg/m^2)	0.989 (0.945-1.036)	0.653

Table 5.6 – McFadden's pseudo R^2 and AUROC statistic

Model with age and BMI		Model + morphology measurements	
R^2	AUROC	R^2	AUROC
1.14%	0.5794	3.87%	0.6217

5.4 Discussion

This study provides a detailed description of variations in hip morphology associated with radiographic OA in a large population based cohort of women, whilst considering demographic covariates, that have previously been identified as risk factors for OA.

The only demographic characteristic associated with OA was age, with the OA group being on average 2 years older than the non OA group. Age as a risk factor for OA is consistently identified in radiographic surveys[4, 107]. The prevalence of radiographic OA found in the Chingford Cohort at 14% is lower than that identified in the Johnston County Osteoarthritis Project[163], whose cohort includes no radiological data for women under the age of 50. They report a prevalence (using the same radiological definition of OA) of 18.5% in women aged 50-54. Prevalence of radiographic hip OA among those 45-54 and 55-64 years in NHANES-I were 0.7% and 2.7% respectively[164], though the NHANES-I radiographs may have been under-read by non-radiologist readers, resulting in an underestimate of the true prevalence. The radiographic OA prevalence here lies between these two estimates.

Neither BMI nor weight were significantly associated with OA, in fact the OA group were slightly lighter and had a lower BMI. Obesity is considered to be one of the most important risk factors for knee OA. Numerous longitudinal studies including the Chingford Study[165], the Framingham Study[90], the Baltimore Longitudinal Study

of Aging[166] and other studies from the UK[167], confirm this association. However, the relationship between obesity and hip OA has been less clear[136, 168]. Some cross-sectional studies[99, 164, 169] as well as longitudinal studies[170–172] have identified an association between obesity and hip, whilst some longitudinal studies[136, 166] have failed to identify any significant association. This study further supports this position.

The variation in hip morphology with OA was first assessed by simple comparison of means and rank sum tests for parametric and non-parametric data receptively. Despite the comprehensive assessment of morphology presented, few were found to be significantly different with radiographic OA. α-angle, triangular index height and triangular ratio were increased and head:neck ratio decreased in the OA group. These are all indicators of cam-type FAI. The distribution of α-angle in particular was different in the OA group (Figure 5.1). Several studies have reported α-angle measurement on AP pelvis radiographs [71, 77, 153] and associated increased α-angle with OA. The first of these studies is also responsible for the introduction of triangular index as a measure of cam-type FAI, and association with OA. Some measurements used in this study are modifications, allowing a continuous variable to be assessed, rather than a dichotomous variable. Triangular index height was on average 0.6 mm greater in the OA group and triangular ratio 1.0 in the OA group versus 0.98 in the no OA group. The variation here is smaller than the 2 mm cut-off used in triangular index[77]. Head:neck ratio was decreased by 0.02 on average in the OA group. This is consistent with a case-control study[76], which used head:neck ratio as its primary measure of nonspherical femoral

head shape.

Comparison of means did not reveal any significant differences between the no OA and OA groups in terms of acetabular morphology. This is consistent with previously published evidence from the UK and Japan [45–47], but inconsistent with some evidence that mild acetabular dysplasia [173] as well as DDH [43, 44] are associated with OA.

Logistic regression analysis provides further evidence of an association between morphology and radiographic OA, accounting for clustering and covariates. Following adjustment for the covariates of age and BMI, α-angle, triangular index height, triangular ratio and head:neck ratio were all significantly associated with OA. Neck width was no longer significantly associated. Extrusion index only became significantly associated with OA following adjustment for the covariates. α-angle had a relatively small effect with each degree increase leading to an increase in risk of only 1.8%. Triangular ratio, head:neck ratio and extrusion index are all considered per SD increase in the value (their total range being less than a whole unit). Each SD increase in triangular ratio and extrusion index increased risk of OA by 43% and 20% respectively. Increased head:neck ratio decreased OA risk by 23% per SD increase in its value.

Multivariate logistic regression had a significant impact on these results with only α-angle and age having any significant association in the final model. The effect of α-angle was again small at 1% increased risk per degree increase (above 65°and age increasing risk by 6% per year across the 20 year age range considered.

Using McFadden's pseudo R^2 and AUROC, to assess the discriminatory ability of

the model reveals broadly that the model including age and BMI fails, with a small improvement in the model with inclusion of hip morphology. Only the Copenhagen Osteoarthritis Substudy [71] has previously studied the risk of hip osteoarthritis with attention to both femoral and acetabular morphological abnormalities in a population cohort. Age and pistol grip deformity were also significantly associated with OA in their cross-sectional study, as well as an association between OA and a deep acetabular socket (LCE angle >45°). A deep acetabular socket was not associated with OA in this study and a recent 5-year longitudinal study in an enriched cohort found no significant association between pincer-type FAI and OA [174].

The strengths of this study include the size of the cohort, radiograph standardisation and the use of objective measures of morphology, which have shown significantly better reproducibility than categorical descriptive measures (Chapter 2, Table 2.4).

Limitations of this study are the cross-sectional study design where exposure and outcome are simultaneously assessed. That is, there is no evidence of a temporal relationship between exposure and outcome. The evidence is unclear as to whether morphology is an inherent trait or one that may change with the development of OA. Causality is therefore unclear. The female only cohort, of largely caucasians limits generalisability, but here there is no reason to believe that the mechanism by which morphological abnormalities may lead to OA is sex dependant. There is evidence that morphology is different in men [71], with cam-type deformity in particular being more common. In addition only anteroposterior pelvic radiographs are used to assess mor-

phology, while lateral projections of the hip are more sensitive for detecting FAI [131]. Only 3.6% of pistol grip malformations in men and 11% of pistol grip malformations in women detected on lateral hip radiographs went undetected on anteroposterior radiographs when the triangular index was used. Thus, the underestimate of cam-type FAI prevalence is approximately 0.5% [77].

5.5 Summary

In summary, age and cam-type FAI (α-angle measurement in particular) were significantly associated with hip OA in this cross-sectional study. Although an increased α-angle was more common in participants with OA, it was not uncommon in participants who showed no radiological evidence of OA.

Chapter 6

Longitudinal Risk of Osteoarthritis and Total Hip Replacement

6.1 Introduction

Osteoarthritis (OA) of the hip is a common disease, with a cumulative prevalence of up to 27%[4, 175–177]. The mortality adjusted lifetime risk of Total Hip Replacement (THR) at age 50 is 12%[108]. Losses of earnings due to disability and direct treatment costs have made OA and other rheumatic diseases among the most expensive of all items in any healthcare budget and a major burden to society. Health expenditure towards arthritis related care represents 2.5% of the United States entire Gross Domestic Product[99]. Hip Replacement accounts for almost half of the hospitalization costs as-

sociated with OA, with over four hundred thousand total hip replacements performed in the United States in 2007[178], which is projected to increase to five hundred and seventy four thousand by 2030[179].

Historically, 10% of hip OA has been termed secondary and attributed to major deformities of the hip, such as developmental acetabular dysplasia, Legg-Calvé-Perthes disease or SCFE [71]. The remaining 90% of hip OA was termed 'primary' or 'idiopathic' and presumed some underlying abnormality of articular cartilage. For nearly 50 years authors have suggested some relationship between more subtle deformities of the proximal femur and/or acetabulum and subsequent development of OA of the hip[50–52]. More recently cross-sectional studies have supported this theory; although cannot prove causality [71]. These deformities can be broadly divided into milder forms of acetabular dysplasia, which results in a shallow hip socket, and FAI, which describes morphological abnormalities of the femoral head-neck junction, acetabulum, or both[60]. Both can be quantified using measurements taken on plain radiographs. These deformities are thought to result in a focal mechanical overload of articular cartilage, leading to subsequent osteoarthritis and joint replacement[60].

FAI and acetabular dysplasia are prevalent and are common in patients with established osteoarthritis of the hip, with concomitant hip malformations seen in 36.6% of women and 71.0% of men with hip osteoarthritis[71]. However, it is not known whether these malformations pre-date or are a result of the OA pathogenic process and therefore whether they are truly causal. If the radiographic measurements of mild

acetabular dysplasia and FAI are predictive of developing hip OA, they may represent targets for preventative strategies and treatment. Surgical interventions, such as osteotomy and osteochondroplasty have already been developed for these conditions, though their treatment efficacy is unproven. Pharmaceutical and physical treatments may also become available in the future[180]. Such interventions may ultimately reduce the burden of end-stage hip osteoarthritis and THR.

The aim of this study was to determine whether subtle deformities of the hip are associated with the development of radiographic osteoarthritis and end-stage OA (defined by THR) in a population based prospective cohort. To date, no studies have been able to assess the role of hip morphology in the development of structural change and THR in a population cohort, making this a unique project. The hypothesis was that a causal relationship exists between subtle deformities of the hip and subsequent osteoarthritis.

6.2 Methods

6.2.1 Study Participants

The Chingford 1000 Women Study is a population-based cohort of 1003 women and is discussed in detail in Chapter 3. Standardised AP pelvis radiographs were taken at years 2, 8 and 20. The local ethics committee approved the study and written consent

was obtained from each woman (Outer North East London Research Ethics Committee (formerly Barking & Havering and Waltham Forest RECs), LREC (R&WF) 96).

Figure 6.1 summarises recruitment, loss to follow-up, exclusions and the cohort included in final analyses.

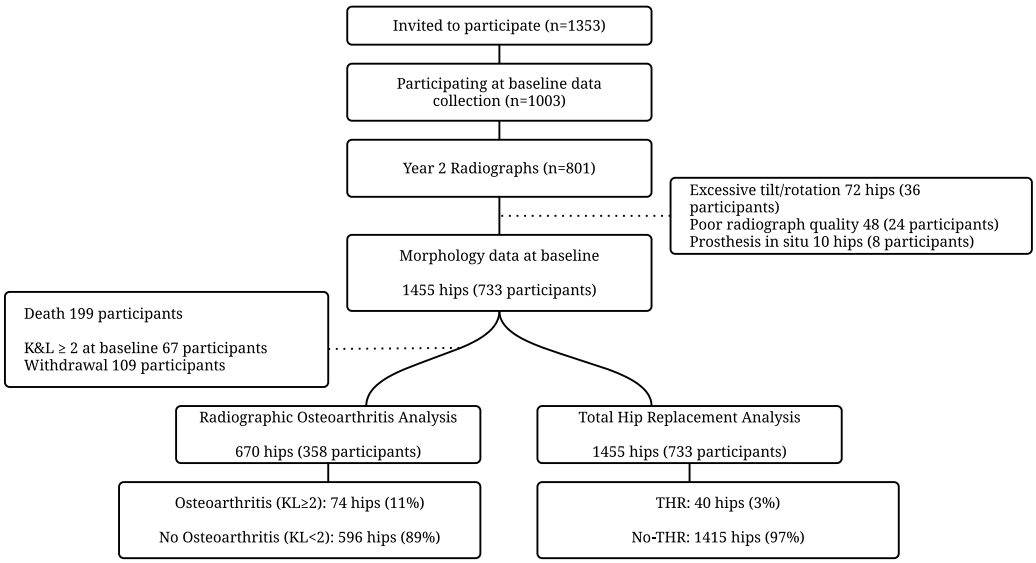


Figure 6.1 – Flow diagram summarising recruitment, loss to follow-up, exclusions and cohort included in final analyses.

6.2.2 Exclusions

Exclusion criteria were applied to ensure that year 2 radiographs were of a minimum acceptable standard. Twenty six individuals were excluded due to poor radiograph quality. Poor radiograph quality was a subjective exclusion criterion applied by the principal investigator (GERT) when a radiograph was either grossly over- or under-exposed to the extent that constituent anatomic landmarks were not visible for the

purposes of analysis. Five hip joints (three individuals) were excluded because they already had a THR in situ. Five hip joints (five individuals) were excluded because it had a dynamic hip screw in situ, indicating previous femoral neck fracture. Seventy-two hip joints (36 individuals) were excluded because they had excessive rotation (measured using Obturator Foramen Index, reference range 0.7-1.4 [181]) or tilt (measured according to the distance between the sacrococcygeal joint and the pubic symphysis) [182]. In total 68 individuals were excluded. Baseline characteristics of those excluded from analysis were not significantly different from those included in the analysis.

6.2.3 Radiographic assessment of morphology

Hip morphology was analysed using the HipMorf 3.0 software described in Chapter 2. An *a priori* selection of radiological measurements were used **.** For acetabular dysplasia and pincer-type FAI, the measurements were the LCE angle [142] and extrusion index [143]. LCE measures acetabular coverage of the femoral head and extrusion index measures the proportion of femoral head located within the acetabulum. A low LCE indicates acetabular dysplasia, while a high LCE is indicative of pincer-type FAI. The converse is true with respect to Extrusion Index. Two measurements for cam-type FAI were also used; the alpha angle [75] and Gosvig's TIH [77] (the perpendicular height of the femoral head/neck at ½r along the femoral neck axis, where r is the radius of the femoral head). These measurements are in routine clinical use and can be made

on standard anteroposterior pelvis radiographs. Each radiograph was anonymised. All morphological measurements were performed by the principal investigator, blinded to outcome. Reproducibility of hip morphology measurement was assessed with intra-observer Intraclass Correlation Coefficient (ICC) in excess of 0.75 for all measures and inter-observer ICC in excess of 0.81.

6.2.4 Radiographic assessment of OA

At baseline Year 2 (n = 801) and at Year 20 (n = 463) radiographs were scored blind to clinical details according to the method of Kellgren and Lawrence (KL) [19] using the Atlas of Standard Radiographs by the principal investigator [152]. OA was defined as KL $\geq$ 2.

6.2.5 Total Hip Replacement (End-stage Hip Osteoarthritis)

Details of any operations undergone in the previous year are recorded at each Chingford visit. Confirming that a patient had undergone THR for end-stage OA was done by contacting the patient's general practitioner and checking the medical records at the hospital at which the surgery was performed.

6.2.6 Statistical Analysis

The distribution of morphological measurements (α-angle, TIH, LCE angle and extrusion index) was examined using histograms and kernel density plots. Normally distributed variables were compared using the Student's t test; non-normally distributed variables were compared using the Wilcoxon rank sum test. Participants were only included in an analysis if they had not had the outcome at the start of the study; that is no radiographic OA (KL <2) or no THR at baseline. Outcomes were assessed at year 20 according to whether or not the patients had (1) Radiographic OA; (2) THR. A sensitivity analysis was also performed for development of Radiographic OA which included only hips with baseline KL = 0.

The morphological measurements detailed above were the predictors of interest. We visually assessed evidence of linearity of continuous variables with the outcomes using fractional polynomial plots. Where evidence of non-linearity was observed, variables were fitted with linear splines. LCE angle was fitted as a linear spline using tertiles (27.96° and 33.67°). This is consistent with clinical observations, as acetabular over and under-coverage are both implicated in the development of OA. α-angle was fitted as a linear spline at 65°, the antimode of its bimodal distribution. Logistic regression analysis was performed to describe the crude (univariate) association of the predictors listed above with radiographic OA and THR as binary outcomes. Secondary analysis was performed by further adjusting for confounders of baseline age, Body Mass Index

(BMI) and joint space width. Interactions between the acetabular and femoral morphological measurements were explored. Logistic regression analyses were with robust standard errors and clustering by subject identifier to account for the dependency of two hips from one subject. Area Under Receiver Operating Characteristic (AUROC) as well as McFaddens's pseudo R^2 statistic were used to evaluate the discriminatory ability of the morphological measurements. The cut point for non-linearity was examined for alpha angle, as a function of radiographic OA and THR. The alternative statistical cut points were determined using fractional polynomial regression modelling which provides a visual assessment of the relationship of alpha angle with outcome (Figure 6.2), and cut points specific to each outcome chosen on this basis. Logistic regression with these thresholds was performed.

Predictive value of normal versus abnormal morphology with respect to THR was considered with attention to α-angle (>65°) and LCE angle (>25°and <45°).

All statistical analyses were performed using STATA 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and statistical significance was assumed when the p-value was <0.05.

6.3 Results

The baseline characteristics of the participants included in this study are summarised in Table 6.1. 358 participants (670 hips) were included in the analysis of radiographic

OA and 733 (1455 hips) in the THR analysis. Participants included in the analysis of radiographic OA were younger and taller.

6.3.1 Radiographic OA

Incident radiographic OA was seen in 11% of hips at Year 20 (37% of OA was bilateral).

6.3.1.1 Femoral measures

α-angle and TIH were significantly greater in the radiographic OA vs no OA group ($P < 0.001$ in both cases) (Table 6.2), with marked differences in kernel density plots by group.

Table 6.1 – Baseline descriptive characteristics of participants used in analysis

Characteristics	Full cohort (n=1003)	Radiographic Osteoarthritis			Total Hip Replacement		
		Subjects not used in this analysis (n=645)	Subjects used in this analysis (n=358)	p-value	Subjects not used in this analysis (n=270)	Subjects used in this analysis (n=733)	p-value
Age (years), median (IQR)	54 (49, 60)	57 (50, 61)	52 (48, 56)	<0.001	54 (50, 58)	54 (48, 59)	0.05
Height (m) mean (SD)	1.62 (0.06)	1.61 (0.06)	1.62 (0.06)	0.04	1.62 (0.06)	1.63 (0.06)	0.05
Weight (kg) median (IQR)	65 (58.5, 73.0)	65.7 (58.45, 73.8)	64.6 (58.5, 71.8)	0.194	66.2 (58.4, 71.8)	69.4 (60.8, 71.4)	0.194
BMI (kg/m^2) median (IQR)	24.86 (22.63, 27.61)	25.15 (22.67, 28.19)	24.59 (22.60, 27.01)	0.05	25.2 (22.5, 27.0)	26.1 (23.5, 26.8)	0.05

Table 6.2 – Baseline morphology measurements by radiographic OA and THR outcome group

Morphology measurement	Radiographic Osteoarthritis			Total Hip Replacement		
	No OA	OA	p-value	No THR	THR	p-value
α-angle (°), median (IQR)	46.48 (43.53, 55.23)	55.81 (44.09, 87.60)	<0.001	46.75 (43.53, 58.83)	73.10 (47.47, 94.57)	<0.001
TIH (mm), mean (SD)	22.90 (2.09)	23.69 (2.52)	<0.001	22.97 (2.12)	24.15 (3.13)	0.005
LCE angle (°), mean (SD)	30.56 (6.44)	30.03 (8.11)	0.456	30.94 (6.78)	25.94 (7.53)	<0.001
Extrusion Index (ratio), mean (SD)	0.25 (0.11)	0.27 (0.15)	0.4563	0.18 (0.08)	0.25 (0.09)	<0.001

Increasing α-angle above 65° and TIH were significantly associated with the development of radiographic OA, and remained significantly associated after adjusting for confounders (Table 6.3).

6.3.1.2 Acetabular measures

The acetabular measures, LCE and Extrusion Index were found to be similar in those with and without radiographic OA (Table 6.2). Kernel density plots revealed an increased incidence of acetabular under and over coverage (i.e. acetabular dysplasia and pincer-type FAI) in those who went on to develop radiographic OA.

Decreasing LCE angle below 28° was significantly associated with the development of radiographic OA, and remained significantly associated after adjusting for confounders.

6.3.1.3 Interactions

When femoral and acetabular measures were included in the same model, with use of the same covariates, an α-angle of greater than 65° was associated with a 5% increased risk of radiographic OA per degree increase in alpha angle (OR 1.05 [95% confidence interval [95% CI] 1.01-1.09], p = 0.009), the increase in risk of radiographic OA per 1° reduction in LCE angle was 14% (OR 0.86 [95% CI 0.77-0.96], p = 0.007). Over

Table 6.3 – Logistic regression: Morphology measurements and longitudinal association with radiographic OA

Morphology measurement		Univariate		Adjusted*	
		OR (95% CI)	p-value	OR (95% CI)	p-value
α-angle (per degree)	<65	1.00 (0.95, 1.05)	0.942	1.00 (0.95, 1.05)	0.951
	>65	1.05 (1.01, 1.09)	0.023	1.05 (1.01, 1.09)	0.02
LCE angle (per degree)	<28	0.86 (0.77, 0.96)	0.007	0.85 (0.76, 0.95)	0.004
	28-33.7	1.15 (0.98, 1.35)	0.079	1.15 (0.98, 1.36)	0.084
	>33.7	1.02 (0.90, 1.15)	0.747	1.01 (0.89, 1.15)	0.845
Extrusion Index (per SD)		1.07 (0.69, 1.66)	0.77	1.12 (0.72, 1.76)	0.616
TIH (per mm)		1.12 (1.00, 1.26)	0.043	1.12 (0.99, 1.26)	0.072

Adjusted for age, BMI and JSW.

coverage, consistent with Pincer FAI, was not significantly associated with radiographic OA.

6.3.1.4 Model fit

AUROC statistic for non-morphological covariates (age, BMI, joint space width) alone as predictors of incident radiographic OA was 57.5% and increased significantly to 66.7% with the inclusion of both LCE and alpha angle ($p < 0.001$). McFadden's pseudo R^2 statistic increased from 1.21% to 7.48% (Table 6.4).

Table 6.4 – McFadden's pseudo R^2 and AUROC statistic used to evaluate discriminatory ability of model - radiographic OA

Model with age and BMI		Model + morphology measurements	
R^2	AUROC	R^2	AUROC
1.07%	0.5640	7.98%	0.6741

6.3.2 Total Hip Replacement

Total Hip Replacement had been performed on 40 of the studied hips in 31 participants.

6.3.2.1 Femoral measures

α-angle and TIH were both significantly greater in hips that went on to undergo THR. (Table 6.2) TIH was significantly associated with THR and remained significantly associated when adjusting for the covariates (OR 1.14 [95% CI 1.00-1.30], p=0.046). α-angle was significant in only the univariate analysis (OR 1.04 [95% CI 1.00-1.08], p=0.038), (Table 6.5).

6.3.2.2 Acetabular measures

Acetabular dysplasia at baseline was significantly more common in hips that went on to undergo THR (mean LCE 25.94°SD 7.53°, mean Extrusion Index 0.25 SD 0.09) than non-THR (LCE 30.94°SD 6.78°, Extrusion Index 0.18, SD 0.08), p <0.001 in both cases (Table 6.2). Univariate logistic regression showed that low LCE was significantly

associated with THR and remained significantly associated when adjusting for the same covariates (OR 0.77 [95% CI 0.63-0.93], p=0.008) (Table 6.5).

Table 6.5 – Logistic regression: Morphology measurements and longitudinal association with THR

Morphology measurement		Univariate		Adjusted*	
		OR (95% CI)	p-value	OR (95% CI)	p-value
α-angle (per degree)	<65	1.02 (0.97, 1.08)	0.384	1.03 (0.97, 1.09)	0.326
	>65	1.04 (1.00, 1.08)	0.038	1.03 (1.00, 1.07)	0.082
LCE angle (per degree)	<28	0.84 (0.77, 0.91)	0.000	0.82 (0.75, 0.89)	0.000
	28-33.7	0.91 (0.74, 1.11)	0.346	0.88 (0.72, 1.09)	0.243
	>33.7	1.00 (0.87, 1.15)	0.984	0.97 (0.84, 1.12)	0.666
Extrusion Index (per SD)		2.23 (1.63, 3.06)	0.000	2.50 (1.78, 3.49)	0.000
TIH (per mm)		1.27 (1.13, 1.43)	0.000	1.25 (1.10, 1.43)	0.001

Adjusted for age, BMI and JSW.

6.3.2.3 Interactions

When femoral and acetabular measures were included in the same model, with use of the same covariates, modified triangular index height was associated with THR with a 9% increase per unit (OR 1.19 [95% CI 1.01 -1.40], p=0.039. The increase in risk of radiographic OA per 1° reduction in LCE angle was 21% (OR 0.79 [95% CI 0.72-0.87], p <0.001).

6.3.2.4 Model fit

AUROC statistic for non-morphological covariates as predictors of THR was 63.73% and increased significantly to 83.36% with the inclusion of LCE, α-angle and TIH ($p<0.001$). McFadden's pseudo R^2 statistic increased from 4.75% to 22.84% (Table 6.6).

Table 6.6 – McFadden's pseudo R^2 and AUROC statisticused to evaluate discriminatory ability of model - THR

Model with age and BMI		Model + morphology measurements	
R^2	AUROC	R^2	AUROC
4.75%	0.6373	22.84%	0.8436

6.3.3 Alpha Angle Thresholds by Outcome

The cut point for non-linearity varies according to outcome, statistically the threshold for non-linearity for Alpha Angle with Radiographic OA is 41° and with THR is 82° (Figure 6.2). Logistic regression with these thresholds showed that each degree increase in alpha angle increased the risk of developing radiographic OA by 3% (OR 1.03 [95% CI 1.02-1.05], $p <0.001$) and THR by 6% (OR 1.06 [95% CI 1.01-1.11], $p = 0.011$). (Table 6.7)

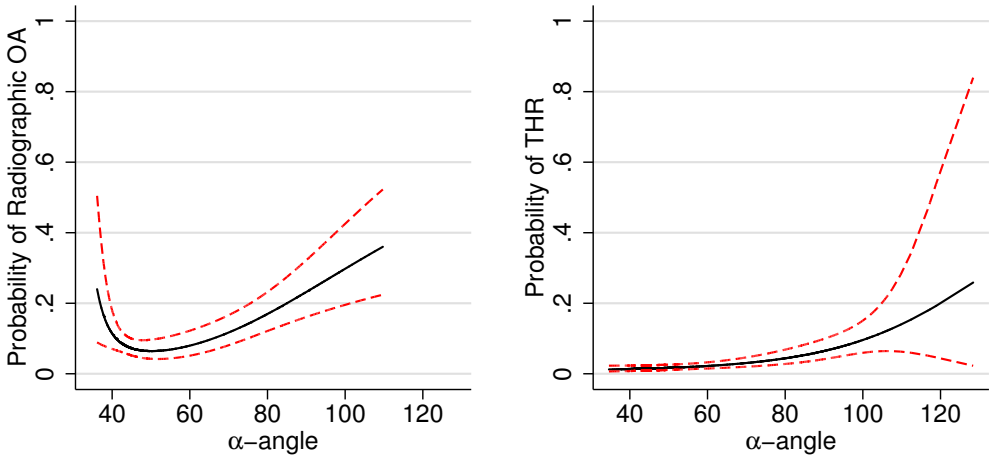


Figure 6.2 – Fractional polynomial plots to assess evidence of linearity of α-angle with radiographic OA and THR.

Table 6.7 – Comparison of logistic regression analysis for association of α-angle with 20 year outcomes using distribution based and statistical thresholds of non-linearity

Outcome	Distribution Threshold		OR (95% CI)	p-value	Outcome Threshold		OR (95% CI)	p-value
Radiographic Osteoarthritis	α-angle	<65 (per unit)	1.00 (0.95, 1.05)	0.942	α-angle	<41 (per unit)	0.53 (0.38, 0.75)	0
		>65 (per unit)	1.05 (1.01, 1.09)	0.023		>41 (per unit)	1.03 (1.02, 1.05)	0
Total Hip Replacement	α-angle	<65 (per unit)	1.02 (0.97, 1.08)	0.384	α-angle	<82 (per unit)	1.02 (1.00, 1.05)	0.045
		>65 (per unit)	1.04 (1.00, 1.08)	0.038		>82 (per unit)	1.06 (1.01, 1.11)	0.011

6.3.4 Sensitivity Analysis

Inclusion of only hips with no signs of radiographic OA (KL Grade 0 Radiographic Osteoarthritis Analysis 556 hips), resulted in no significant change to the results discussed above.

Table 6.8 – Logistic regression: Morphology measurements and longitudinal association with radiographic OA (Baseline KL Grade=0)

Morphology measurement		Univariate		Adjusted*	
		OR (95% CI)	p-val	OR (95% CI)	p-val
α-angle (per degree)	<65	1.00 (0.95, 1.06)	0.862	1.00 (0.95, 1.06)	0.869
	>65	1.04 (1.00, 1.09)	0.05	1.04 (1.00, 1.09)	0.046
LCE angle (per degree)	<28	0.85 (0.76, 0.95)	0.004	0.84 (0.75, 0.94)	0.002
	28-33.7	1.18 (1.00, 1.38)	0.044	1.18 (1.00, 1.38)	0.050
	>33.7	0.99 (0.88, 1.10)	0.801	0.98 (0.88, 1.10)	0.746
Extrusion Index (per SD)		1.10 (0.71, 1.71)	0.672	1.15 (0.73, 1.80)	0.553
TIH (per mm)		1.10 (0.97, 1.23)	0.124	1.09 (0.96, 1.24)	0.180

Adjusted for age, BMI and JSW.

Table 6.9 – McFadden's pseudo R^2 and AUROC statistic used to evaluate discriminatory ability of model - Radiographic Osteoarthritis (baseline KL Grade=0)

Model with age and BMI		Model + morphology measurements	
R^2	AUROC	R^2	AUROC
0.69%	0.5491	7.41%	0.6747

6.3.5 Predictive value

THR was performed in 40 hips only 5 of which had normal hip morphology at baseline. (Table 6.10 & Figure 6.3).

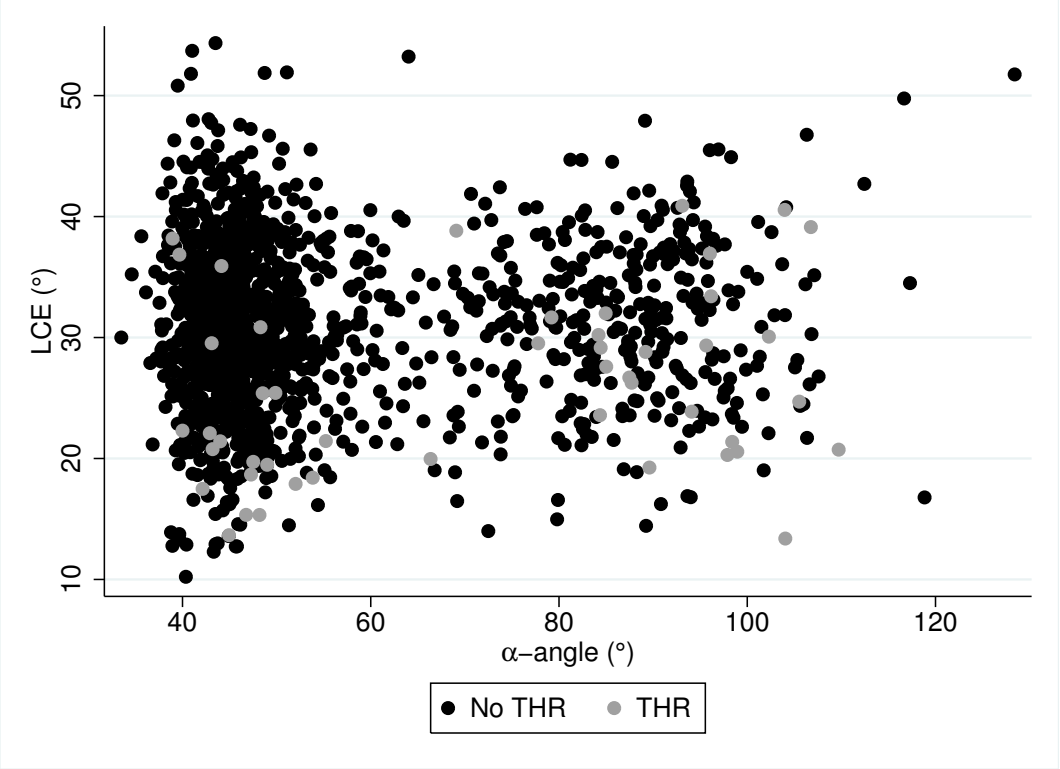


Figure 6.3 – Scatter plot of α-angle versus LCE angle THR cases identified.

Table 6.10 – THR versus morphology

	THR at year 20	
	Present	Absent
Abnormal Morphology	35	576
Normal Morphology	5	829

THR risk was 5.7% in the abnormal morphology group but only 0.6% in the normal

morphology group. Sensitivity and specificity of abnormal morphology is therefore 87.5% and 59.00% respectively. Positive predictive value is calculated as 5.73% and negative predictive value as 99.40%.

6.4 Discussion

This study of a population-based cohort confirms our hypothesis and demonstrates that radiographic measurements of subtle hip deformities are associated with the longitudinal development of hip osteoarthritis and THR. Deformities associated with cam-type FAI and mild acetabular dysplasia of the hip were independently predictive of radiographic osteoarthritis and THR 18 years after baseline imaging. These measurements were independently predictive of outcome even when controlling for baseline age, BMI and joint space width and significantly increased the predictive value of the model. This is the first study to demonstrate these findings in a longitudinal population cohort.

Cross-sectional associations between abnormal morphology and OA are relatively well established [71, 153], with further evidence provided by the preceding chapter, but prospective longitudinal data, which may provide more convincing evidence of a causal relationship, is lacking. Previous studies examining the development of OA have focused on acetabular dysplasia [123, 124]. Two recent studies have associated cam deformity with OA, but are limited by their cross-sectional nature and used outcome measures which may not be as relevant as using the hard endpoint of THR for example

[71, 76]. Longitudinal data is limited to a nested case control using the Chingford cohort [86] and an enriched cohort of symptomatic osteoarthritis patients [130].

This work demonstrates that women with cam-type deformities identified by an α-angle of greater than 65° have an increased risk of radiographic OA and THR with each degree increase in α-angle conferring a 5% and 3% increase in risk respectively. More severe cam-type deformities identified by increased TIH are predictive of THR with each millimetre increase conferring a 19% increased risk.

Mild acetabular dysplasia significantly increased the risk of radiographic OA development and THR with each degree reduction in LCE angle associated with a 14% and 21% increase in risk respectively. No significant associations were seen with pincer-type FAI alone. Evaluation of the models showed statistically significant improvements in our ability to predict radiological OA and THR ($p < 0.001$ in both cases) with the inclusion of morphological measurements as compared to established risk factors of age, BMI and joint space width.

Although cut-points for non-linearity based on the distribution of the data were used initially, this statistically might not be the case. On further exploration it was found that the cut point for non-linearity of α-angle varies according to outcome. The threshold for non-linearity of α-angle with radiographic OA is 41° and with THR is 82°. When using these outcome thresholds we see a more pronounced association, with a risk increase for THR of 6% per degree when the α-angle is greater than 82°. These two methods for calculating the thresholds for non-linearity may have different clinical

applications. The use of a threshold based on the distribution has a lower cut off with a lower specificity and a higher sensitivity for OA and THR. These lower thresholds may be used for low-risk treatments for OA. For example, a physical therapy or weight loss treatment might use the lower threshold. Conversely, a higher threshold might be more appropriate for surgical interventions for example.

It has been proposed that FAI leads to shear forces being applied to acetabular cartilage with displacement of the labrum [68]. This may lead to delamination of the acetabular cartilage, and detachment of the labrum at the chondrolabral junction. Developmental dysplasia leads to increased contact stress and cartilage degeneration [183]. The mechanism by which morphological abnormalities lead to OA are likely to be similar in both men and women.

This study has several strengths and potential limitations. This is the only cohort study at present which includes long term follow up in a normal population with validated records of THR. Loss to follow-up appears to be non-differential in terms of morphology data. Baseline age of those participants with radiographic follow-up at year 20 was lower, which is to be expected with the median age of the cohort reaching 74. Only women are included in the study, with baseline characteristics similar to the UK general population at the initiation of the study - weight (65 kg in the UK, 67 kg in Chingford), height (1.61 m vs 1.62 m) and BMI (25.4 vs 25.6 kg/m^2). The use of AP pelvis radiographs only for the assessment of morphology has been discussed previously, but must be acknowledged as a limitation, while lateral projections of the

hip and cross-sectional imaging are more sensitive for detecting FAI no large population cohort exists which includes these forms of imaging. In addition radiographic OA was not considered as an exclusion criteria in the THR analysis.

Cam-type FAI appears to be twice as frequent in men as in women [153, 184], and acetabular dysplasia approximately 20% more frequent in women as in men [71]. The role of cam-type FAI in OA may therefore be underestimated in this population cohort and a long-term epidemiological study involving male subjects is needed to confirm the natural history of these anatomical abnormalities in men.

6.5 Summary

In summary this study provides the first longitudinal evidence in a large population cohort that radiological measurements of hip morphology characteristic of cam-type FAI and undiagnosed acetabular dysplasia are predictive of OA development (both radiographic OA and THR), independent of age, BMI and JSW. These measurements can be made on a simple AP pelvis radiograph, and significantly improve our ability to identify individuals at risk of hip OA development. Pincer-type FAI was not identified as a significant predictor of radiographic OA or THR.

Chapter 7

Longitudinal Risk of Pain and Symptomatic Osteoarthritis

7.1 Introduction

OA is characterised by pain and functional disability, with diagnosis of OA usually based on symptoms and confirmed by radiography [185]. ACR criteria for classification of hip OA [29] require the combination of pain and the presence of radiographic evidence of OA (osteophytes and/or joint space narrowing). Disease expression varies significantly between patients with OA and the association identified between radiographic and clinical OA has been inconsistent [186, 187], particularly in hip OA [188]. Standardisation of radiographic protocols might be important in our ability to demon-

strate an association between radiographic and clinical OA [189]. In addition it should be noted that radiographs allow direct evaluation of bone but both cartilage and synovium (tissues involved in the OA process) are evaluated either indirectly or not at all. Despite these limitations radiographs remain the gold standard for demonstrating structural change [19, 190, 191].

Hip pain is common with 14.3% of participants over the age 60 in the third National Health and Nutrition Examination Survey (NHANES III) reporting significant hip pain on most days[192]. In addition one in four people may develop symptomatic hip OA in his or her lifetime[177]. Hip pain and symptomatic OA may be highly disabling and is the most common indication for THR. Chapter 7 uses THR as the clinical endpoint for hip OA. There may be situations, even with a National Health Service that is free at the point of use, where women with severe symptomatic OA may not go on to have surgery, medical co-morbidities being the most obvious example. In addition, despite a higher prevalence of hip OA, under use of THR for personal reasons is three times more common in women than men[193], which is particularly relevant in this study.
The aims of this study were to:

1. investigate the prevalence and incidence of hip pain and symptomatic OA

2. investigate the association between hip morphology and both hip pain and symptomatic OA.

7.2 Methods

7.2.1 Study Participants

The Chingford 1000 Women Study cohort as well as loss to follow-up is described in Chapter 3. In addition to the AP pelvis radiographs taken at years 2, 8 and 20, pain data was collected from year 3 onwards (year 3, 5, 10, 20). The present study included participants who had both AP pelvis radiographs for assessment of hip morphology and pain data at both year 3 and year 20.

7.2.2 Radiographic assessment

Hip morphology was analysed using the software described in Chapter 2. The *a priori* selection of radiological measurements are as described in the preceding chapter, namely α-angle, TIH, LCE angle and extrusion index. Radiographic OA was assessed by a single observer according to the method of Kellgren and Lawrence (KL) [19] using the Atlas of Standard Radiographs. OA was defined as KL≥2.

7.2.3 Hip pain

Data on self-reported hip pain was collected using the question - "Have you had any hip pain in either hip in the last month?". Participants who responded "yes" were asked to

specify side/both. Participants who underwent THR were classified as having a positive pain status thereafter. Only participants who were pain free on initial questioning were included in the analysis for hip pain.

7.2.4 Symptomatic OA

Symptomatic OA was defined by the ACR Criteria for classification of hip osteoarthritis [31], that is hip pain and radiographic evidence of osteoarthritis.

7.2.5 Exclusions

Exclusion criteria were applied to ensure that year 2 radiographs were of an acceptable standard to be included in the study. These were radiograph quality (inclusion of necessary morphological landmarks, exposure/penetration), tilt and rotation. Tilt and rotation was not imposed as an inclusion/exclusion criterion for year 20 radiographs.

Only participants who were pain free on initial questioning were included in the analysis for hip pain and only participants who were both pain free and OA free in the analysis for symptomatic OA.

7.2.6 Statistical Analysis

The distribution of morphological measurements (α-angle, TIH, LCE angle and extrusion index) was examined using histograms and kernel density plots. Normally dis-

tributed variables were compared using the independent 2-tailed t-test; non-normally distributed variables were compared using the Wilcoxon rank sum test. Outcomes were assessed at year 20 according to whether or not the participants had hip pain or symptomatic OA. The morphological measurements detailed above were the predictors of interest. LCE angle was fitted as a linear spline at these points (27.96° and 33.67°). Dividing LCE angle into tertiles is consistent with the biologically plausible theory that acetabular over and under-coverage may both be implicated in the patho-aetiology of OA. α-angle was fitted as a linear spline at a cut-point of 65°, that is the antimode of its bimodal distribution. Logistic regression analysis was performed to describe the univariate association of the predictors listed above with pain and symptomatic OA as binary outcomes. Secondary analysis were performed by further adjusting for confounders of baseline age, BMI and JSW. Area Under Receiver Operating Characteristic (AUROC) as well as McFadden's pseudo R^2 statistic were used to evaluate the discriminatory ability of the morphological measurements. The cut point for non-linearity was examined for α-angle, for both outcome. Logistic regression with these thresholds was performed.

All statistical analyses were performed using STATA 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and statistical significance was assumed when the p-value was <0.05.

7.3 Results

The baseline characteristics of the participants included in this study are summarised in Table 7.1. 375 participants (680 hips) were included in the analysis of pain and 266 participants (459 hips) in the analysis of symptomatic OA. Participants included in hip pain analysis were younger, and in the symptomatic OA analysis, both younger and lighter.

7.3.1 Pain

Incident hip pain was reported in 26.3% of hips at year 20.

7.3.1.1 Femoral measures

No significant differences in α-angle or TIH were present in relation to pain outcome status.

Table 7.1 – Baseline descriptive characteristics of participants used in analysis

Characteristics	Full cohort (n=1003)	Pain			Symptomatic OA		
		Subjects not used in this analysis (n=628)	Subjects used in this analysis (n=375)	p-value	Subjects not used in this analysis (n=737)	Subjects used in this analysis (n=266)	p-value
Age (years), median (IQR)	54 (49, 60)	54 (50, 61)	54 (48, 59)	0.046	55 (50, 61)	51 (48, 56.5)	<0.001
Height (m) mean (SD)	1.62 (0.06)	1.62 (0.06)	1.61 (0.06)	0.20	1.62 (0.06)	1.62 (0.06)	0.59
Weight (kg) median (IQR)	65 (58.5, 73.0)	65.2 (58.0, 73.8)	65.0 (58.7, 73.0)	0.90	65.8 (58.4, 73.9)	64.0 (58.5, 71.0)	0.05
BMI (kg/m^2) median (IQR)	24.86 (22.63, 27.61)	24.84 (22.33, 27.35)	24.87 (22.68, 27.7)	0.64	25.1 (22.7, 28.0)	24.3 (22.6, 27.0)	0.001

Table 7.2 – Baseline morphology measurements by pain and symptomatic OA outcome group

Morphology measurement	Pain			Symptomatic OA		
	No pain	Pain	p-value	No symptomatic OA	Symptomatic OA	p-value
∝-angle (°), median (IQR)	47.22 (43.715, 60.99)	47.60 (43.52, 76.11)	0.29	46.69 (43.56, 57.90)	68.40 (46.07, 88.48)	0.003
TIH (mm), mean (SD)	19.52 (2.11)	19.83 (2.65)	0.07	19.43 (2.21)	20.79 (3.70)	<0.001
LCE angle (°), mean (SD)	31.04 (6.78)	29.61 (7.05)	0.006	30.61 (6.58)	30.65 (7.59)	0.97
Extrusion Index (ratio), mean (SD)	0.18 (0.08)	0.20 (0.08)	0.005	0.19 (0.08)	0.20 (0.08)	0.56

Logistic regression analyses revealed that only α-angle was significantly associated with hip pain and remained significantly associated when adjusting for confounders (OR 1.04 per degree [95% CI 1.01-1.07], p=0.007) (Table 7.3).

7.3.1.2 Acetabular measures

A higher prevalence of dysplasia at baseline was seen in those with pain versus those without pain at year 20, demonstrated by a significantly decreased LCE (p=0.006) and increased extrusion index (p=0.005). LCE angle and extrusion index were significantly associated with pain in the univariate analysis, and remained significantly associated in the adjusted model (OR 0.90 [95% CI 0.84-0.97], p=0.006 and OR 1.30 [95% CI 1.02-1.64], p=0.033 respectively) (Table 7.3).

Table 7.3 – Logistic regression: Morphology measurements and longitudinal association with pain

Morphology measurement		Univariate		Adjusted*	
		OR (95% CI)	p-value	OR (95% CI)	p-value
α-angle (per degree)	<65 (per unit)	0.98 (0.95, 1.01)	0.19	0.98 (0.95, 1.01)	0.150
	>65 (per unit)	1.04 (1.01, 1.07)	0.009	1.04 (1.01, 1.07)	0.007
TIH (per mm)		1.06 (0.97, 1.15)	0.197	1.07 (0.98, 1.16)	0.114
LCE angle (per degree)	<28 (per unit)	0.91 (0.85, 0.98)	0.01	0.90 (0.84, 0.97)	0.006
	28-33.7 (per unit)	1.04 (0.94, 1.16)	0.436	1.05 (0.94, 1.17)	0.435
	>33.7 (per unit)	0.96 (0.87, 1.06)	0.386	0.95 (0.86, 1.05)	0.284
Extrusion Index (per SD)		1.27 (1.01, 1.60)	0.042	1.30 (1.02, 1.64)	0.033

Adjusted for age, BMI and JSW.

7.3.1.3 Model Fit

AUROC statistic for non-morphological covariates as predictors of incident pain was 55.7% and increased to 61.5% with the inclusion of α-angle, TIH and LCE (p=0.067). McFadden's pseudo R^2 statistic increased from 0.92% to 4.18%.

Table 7.4 – McFadden's pseudo R^2 and AUROC statistic used to evaluate discriminatory ability of model - Pain

Model with age and BMI		Model + morphology measurements	
R^2	AUROC	R^2	AUROC
0.92%	0.5566	4.18%	0.6152

7.3.2 Symptomatic OA

7.3.2.1 Femoral measures

Both α-angle and TIH were significantly higher in those with pain and symptomatic OA (p=0.003 and p<0.001 respectively).

Logistic regression analyses revealed that both α-angle was significantly associated with symptomatic OA and remained significantly associated when adjusting for confounders (OR 1.08 per degree above 65°(95% CI 1.02-1.14), p=0.012) (Table 7.5).

7.3.2.2 Acetabular measures

No significant differences in LCE angle or extrusion index were present in relation to incident symptomatic OA.

LCE angle was significantly associated with symptomatic OA in the univariate analysis, and remained significantly associated in the adjusted model (OR 0.79 per degree below 28°(95% CI 0.66-0.93), p=0.012).

Table 7.5 – Logistic regression: Morphology measurements and longitudinal association with symptomatic OA

Morphology measurement		Univariate		Adjusted*	
		OR (95% CI)	p-value	OR (95% CI)	p-value
α-angle (per degree)	<65 (per unit)	0.96 (0.88, 1.03)	0.261	0.95 (0.88, 1.03)	0.202
	>65 (per unit)	1.07 (1.01, 1.14)	0.018	1.08 (1.02, 1.14)	0.012
LCE angle (per degree)	<28 (per unit)	0.81 (0.69, 0.95)	0.009	0.79 (0.66, 0.93)	0.005
	28-33.7 (per unit)	1.20 (0.93, 1.56)	0.167	1.23 (0.96, 1.59)	0.108
	>33.7 (per unit)	0.96 (0.83, 1.12)	0.622	0.96 (0.82, 1.12)	0.583
Extrusion Index (per SD)		1.21 (0.62, 2.38)	0.578	1.18 (0.61, 2.29)	0.614
TIH (per mm)		1.12 (0.94, 1.34)	0.202	1.12 (0.94, 1.32)	0.199

Adjusted for age, BMI and JSW.

7.3.2.3 Model Fit

AUROC statistic for non-morphological covariates (age, BMI, JSW) alone as predictors of symptomatic OA was 61.8% and increased to 73.6% with the inclusion of α-angle,

TIH and LCE (p=0.067). McFadden's pseudo R^2 statistic increased from 3.59% to 13.72%.

Table 7.6 – McFadden's pseudo R^2 and AUROC statistic used to evaluate discriminatory ability of model - Symptomatic OA

Model with age and BMI		Model + morphology measurements	
R^2	AUROC	R^2	AUROC
3.59%	0.6182	13.72%	0.7357

7.3.3 Alpha Angle Threshold by Outcome

There is a non-linear association between α-angle and outcome and variation in the strength and threshold for this association dependant on the outcome considered. The cut-point identified for pain was 73 and with symptomatic OA 41° (Figure 7.1).

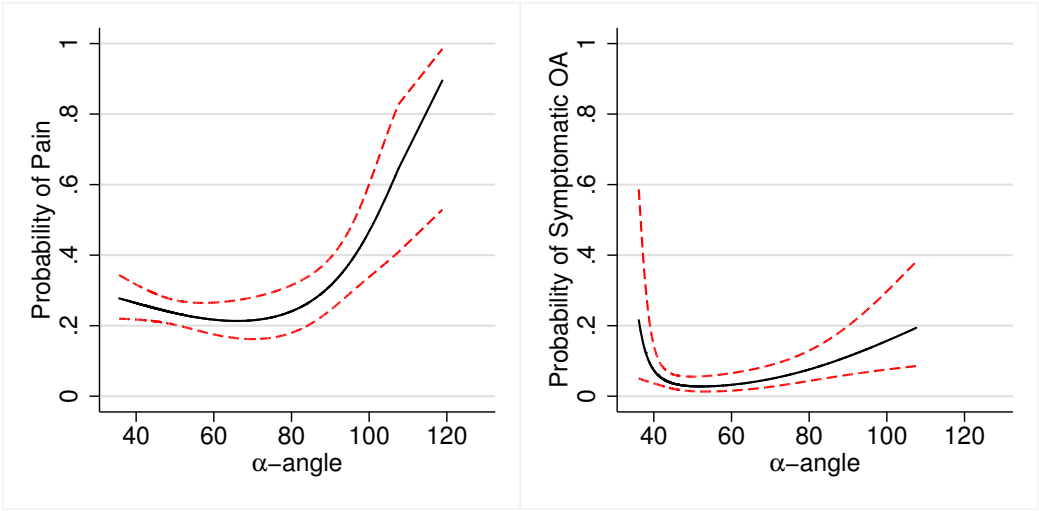


Figure 7.1 – Fractional polynomial plots to assess evidence of linearity of α-angle with pain and symptomatic OA.

Logistic regression with these thresholds showed that each degree increase in alpha angle above 72° increased the risk of developing pain by 5% (OR 1.05 [95% CI 1.01-1.08], p<0.008), while each degree increase in α-angle above 41° increased the risk of developing symptomatic OA by 3% (OR 1.03 [95% CI 1.01-1.05), p=0.009) (Table 7.7).

7.4 Discussion

This study of a population-based cohort confirms our hypothesis that subtle hip deformities as measured radiologically are associated with the longitudinal development of pain and symptomatic OA. Measurements of morphological features associated with cam-type FAI and and acetabular dysplasia of the hip were independently predictive of pain and symptomatic OA at 18 years follow-up. These measurements were independently predictive of outcome when controlling for baseline age, BMI and JSW and significantly increased the predictive value of the model. This is the first study to demonstrate these relationships in a longitudinal cohort. This information is important in defining the natural history of these deformities and OA.

Cross-sectional associations of abnormal morphology and OA are established [71, 153], prospective longitudinal data, which may provide more convincing evidence of a causal relationship, is lacking. Previous studies examining the development of OA have focused on acetabular dysplasia [123, 124], whilst pain as an outcome measure has rarely been studied. One study investigated the prevalence of associated deformities

Table 7.7 – Comparison of logistic regression analysis for association of α-angle with 20 year outcomes using distribution based and statistical thresholds of non-linearity

Outcome	Distribution Threshold		OR (95% CI)	p-value	Outcome Threshold		OR (95% CI)	p-value
Pain	α-angle	<65 (per unit)	1.00 (0.95, 1.05)	0.942	α-angle	<41 (per unit)	0.53 (0.38, 0.75)	0
		>65 (per unit)	1.05 (1.01, 1.09)	0.023		>41 (per unit)	1.03 (1.02, 1.05)	0
Symptomatic OA	α-angle	<65 (per unit)	1.02 (0.97, 1.08)	0.384	α-angle	<82 (per unit)	1.02 (1.00, 1.05)	0.045
		>65 (per unit)	1.04 (1.00, 1.08)	0.038		>82 (per unit)	1.06 (1.01, 1.11)	0.011

and hip pain in symptomatic patients with cam-type FAI [194]. Painful hips had a significantly higher α-angle than asymptomatic hips and an α-angle of more than 60° was associated with a more than two-fold increased risk of hip pain. Gosvig et al. found no such association in their cross-sectional study of a population cohort [71].

In this study, cam-type FAI identified by an α-angle of greater than 65° is associated with an increased risk of developing hip pain and symptomatic OA, with each degree increase in α-angle conferring a 4% and 8% increase in risk respectively. Interestingly TIH was not significantly associated with either outcome.

Acetabular dysplasia identified by LCE angle and extrusion index were also significantly associated with the development of hip pain and symptomatic OA, while pincer-type FAI was not significantly associated with either outcome. Each degree reduction in LCE angle below 28° was associated with 10% and 21% increase in risk of developing pain and symptomatic OA respectively.

Evaluation of the models using AUROC and McFadden's pseudo R^2 showed improvement in our ability to predict both hip pain and symptomatic OA with the inclusion of morphological measurements as compared to age, BMI and JSW alone. These improvements were relatively modest and highlight the poor correlation between radiologically determined OA and pain [195, 196].

Thresholds for non-linearity based on the distribution of α-angle in the population were used in the logistic regression analysis. Fractional polynomial regression analysis was used to investigate the thresholds for non-linearity of α-angle by outcome mea-

sure. In the pain analysis a higher threshold of 72° was found, whilst symptomatic OA as the outcome measure reduced the threshold for non-linearity to 41°. This is the only study at present which includes long term follow up in a normal population with hip morphology data, symptom reporting and radiographic follow-up. The main limitations are the inclusion of only women and the use of only AP pelvis radiographs. However, baseline characteristics of women in the study were similar to the UK general population in terms of weight (65 kg in the UK, 67 kg in Chingford), height (1.61 m v 1.62 m) and BMI (25.4 v 25.6 kg/m^2) [150].

7.5 Summary

In summary this study provides the first longitudinal evidence in a large population cohort that measurements of hip morphology characteristic of FAI and acetabular dysplasia are predictive of pain and symptomatic OA, independent of age, BMI and JSW. These measurements can be made on a simple anteroposterior pelvis radiograph, and significantly improve our understanding of the natural history of these morphological abnormalities.

Chapter 8

Hip Morphology and Change Over Time

8.1 Introduction

Hip morphology has been identified as a significant predictor of OA development in the preceding chapters, the question remains as to whether these morphological abnormalities truly precede OA and are causal, or develop in association with OA, and are simply early signs of OA.

The etiology of cam-type FAI in particular remains unclear. There are potentially a number of causes including sequellae of SCFE, Legg-Calvé-Perthes disease, postinfectious and traumatic. Resnick in 1983 suggested that cam-type FAI deformity was

"osteophytosis of the femoral head and neck"[160], having previously described "tilt deformity" as a poor indicator of previous SCFE [55]. Numerous other authors take an opposing view, suggesting that the "tilt deformity" or cam-type FAI is the result of SCFE [50, 52, 60, 70], or more recently a distinct pathological entity [197]. The majority of cam-type deformity arise without apparent pre-existing hip disease. Cam morphology has also been reported to develop as early as ten years of age, with prevalence in the adolescent patient population similar to that reported in the adult literature [198].

Acetabular dysplasia and DDH have previously been associated with OA [43, 44, 157, 173], and the risk factors for these morphological abnormalities more well established [41]. Despite some of these deformities remaining silent until OA develops there is little debate with regards to the temporal sequence of events. When considering pincer-type FAI (which was not identified as a significant predictor of OA in the preceding chapters), a wide variety of causes are cited [67].

The aim of this study was to investigate variation in hip morphology with age, as well as changes in morphology during the course of the study.

8.2 Methods

The study population and measurement techniques for radiographic assessment of morphology are described in chapters 2 and 3. Hip morphology characteristics of the

population at baseline are shown in chapter 4.

Further AP pelvis radiographs were taken at year 8, using the same radiographic protocol shown in Table 3.3. Radiographic assessment of morphology was as previously described. Focus is given here to the *a priori* selection of α-angle, TIH, LCE angle and extrusion index.

8.2.1 Statistical analysis

Correlation between age and morphological measurements was assessed using Pearson product-moment correlation coefficient for parametric data and Spearmans rank correlation coefficients for non-parametric data. The distribution of the morphological measurements by age group were also assessed using histograms and kernel density plots.

Year 8 morphology data was compared with paired Year 2 data. Normally distributed variables were compared using paired t-tests; non-normally distributed variables were compared using the Wilcoxon rank sum test and displayed visually using Bland-Altman plots.

All statistical analyses were performed using STATA 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) and statistical significance was assumed when the p-value was <0.05.

8.3 Results

Baseline descriptive statistics are shown in Table 3.2.

No correlation exists between age and the morphological measurements of interest (α-angle, TIH, LCE angle, extrusion index). Table 8.1 shows Pearson product-moment correlation coefficient for parametric data (TIH, LCE angle and extrusion index) and Spearmans rank correlation coefficients for non-parametric data (α-angle). Scatter plots of the correlations are shown in Figure 8.1. Histograms with kernel density plots of α-angle, TIH, LCE angle, extrusion index by age group are shown in Figures 8.2-8.5.

Table 8.1 – Correlation between age and morphological measurements

Morphology measurement	Correlation coefficient	p-value
α-angle	-0.0380	0.146
TIH	0.0923	0.0003
LCE angle	0.0858	0.0001
Extrusion	-0.0774	0.0012

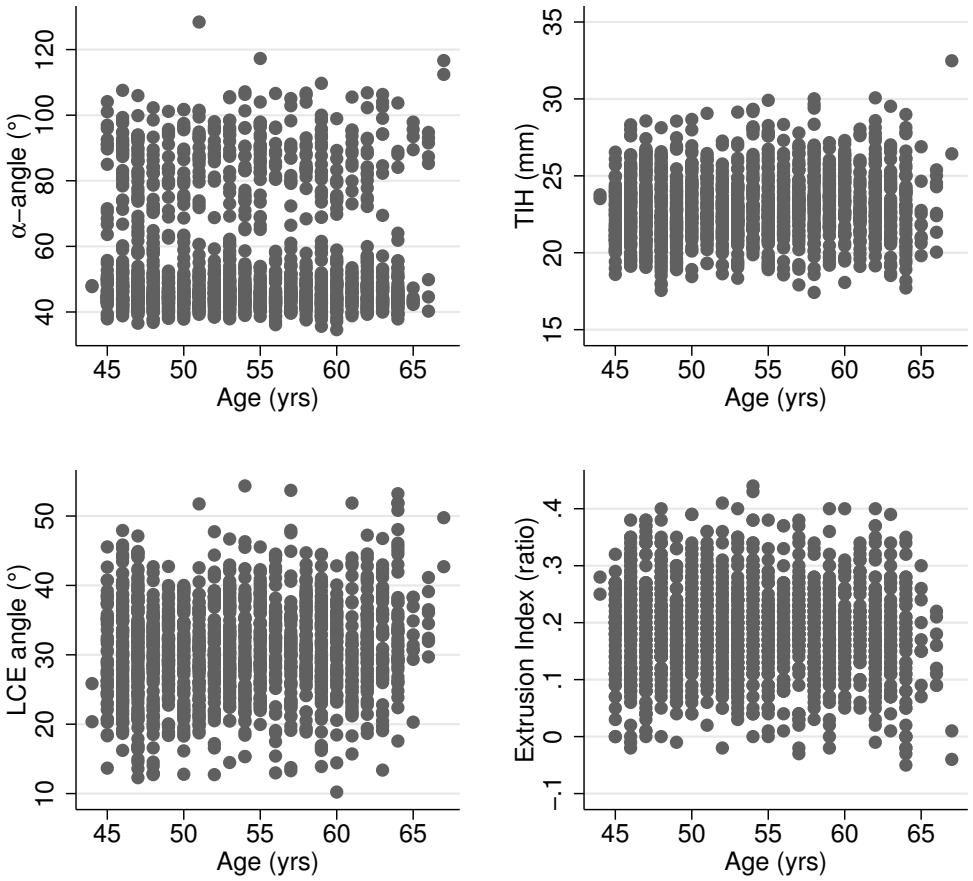


Figure 8.1 – Scatter plots of age versus α-angle, TIH, LCE angle and extrusion index.

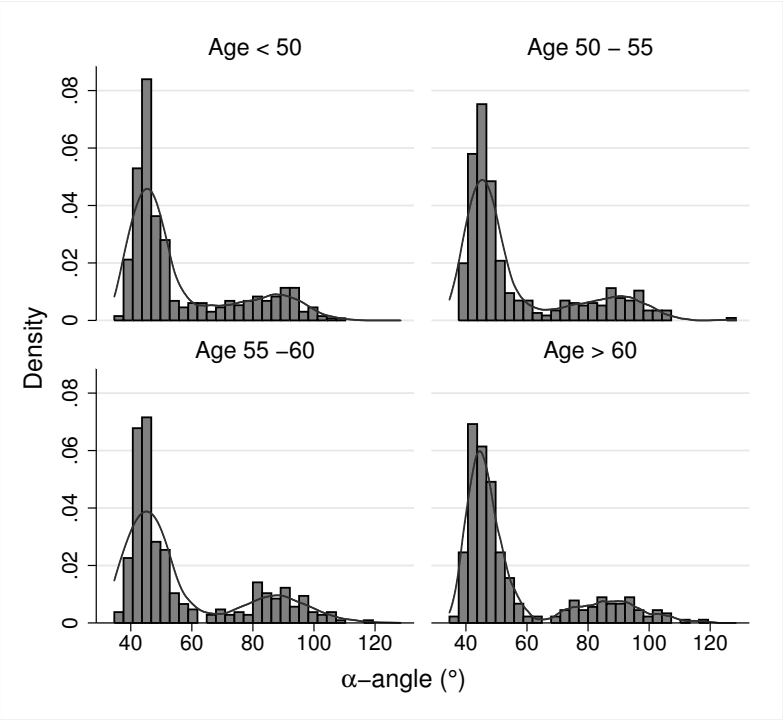


Figure 8.2 – Histograms and kernel density plots of α-angle by age group.

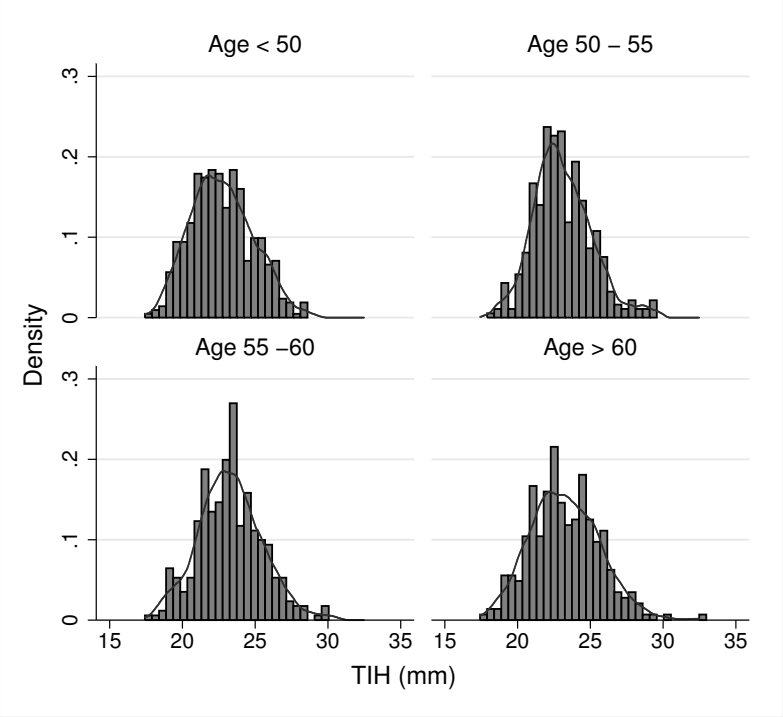


Figure 8.3 – Histograms and kernel density plots of TIH by age group.

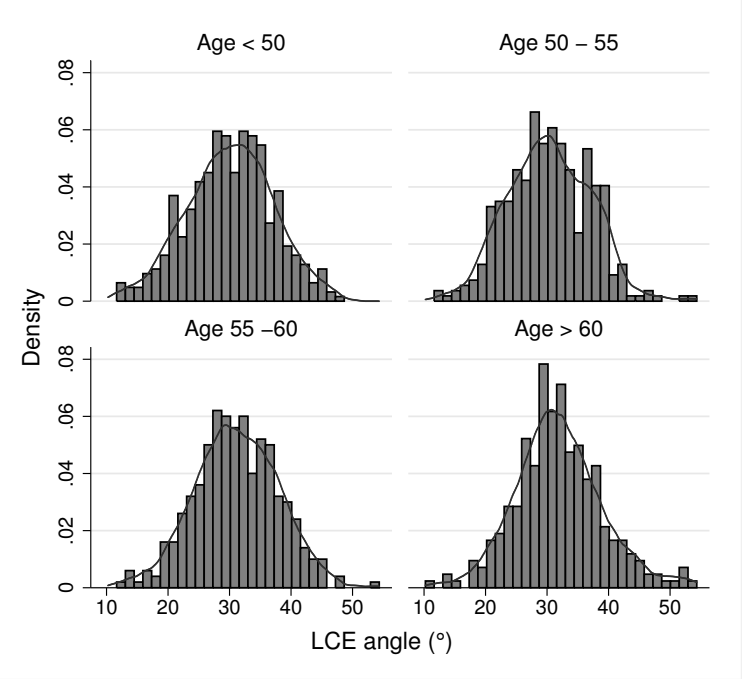


Figure 8.4 – Histograms and kernel density plots of LCE angle by age group.

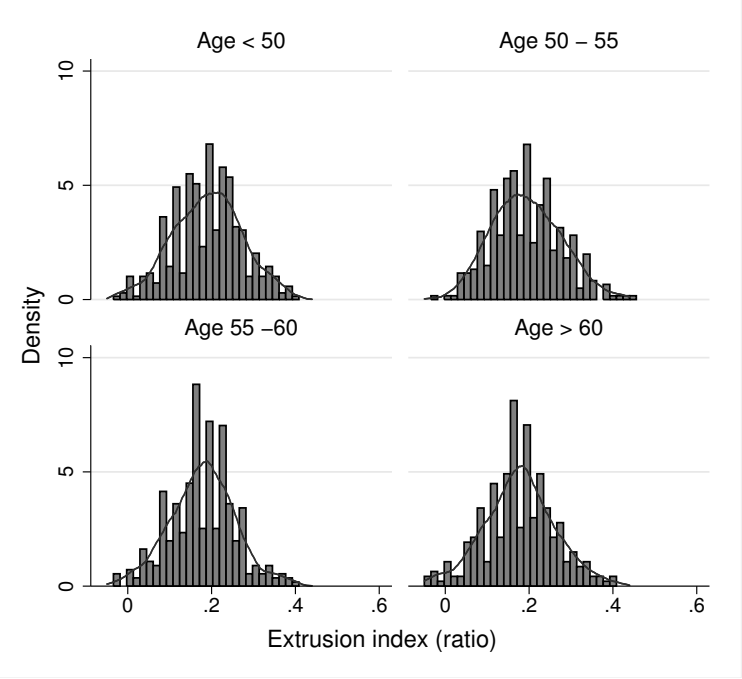


Figure 8.5 – Histograms and kernel density plots of extrusion index by age group.

No significant differences between year 2 and year 8 morphology measurements were found (Table 8.2). Bland-Altman plots are shown in Figure 8.6.

Table 8.2 – Comparison of morphology measurements at year 2 and year 8

Morphology measurement	Year 2 (n=733)	Year 8 (n=592)	p-value
α-angle (°), median (IQR)	47.22 (43.61, 64.48)	47.13 (43.57, 62.82)	0.722
TIH (mm), mean (SD)	23.05 (2.16)	23.02 (2.12)	0.788
LCE angle (°), mean (SD)	30.78 (6.85)	30.65 (6.83)	0.691
Extrusion Index (ratio), mean (SD)	0.186 (0.08)	0.188 (0.08)	0.708

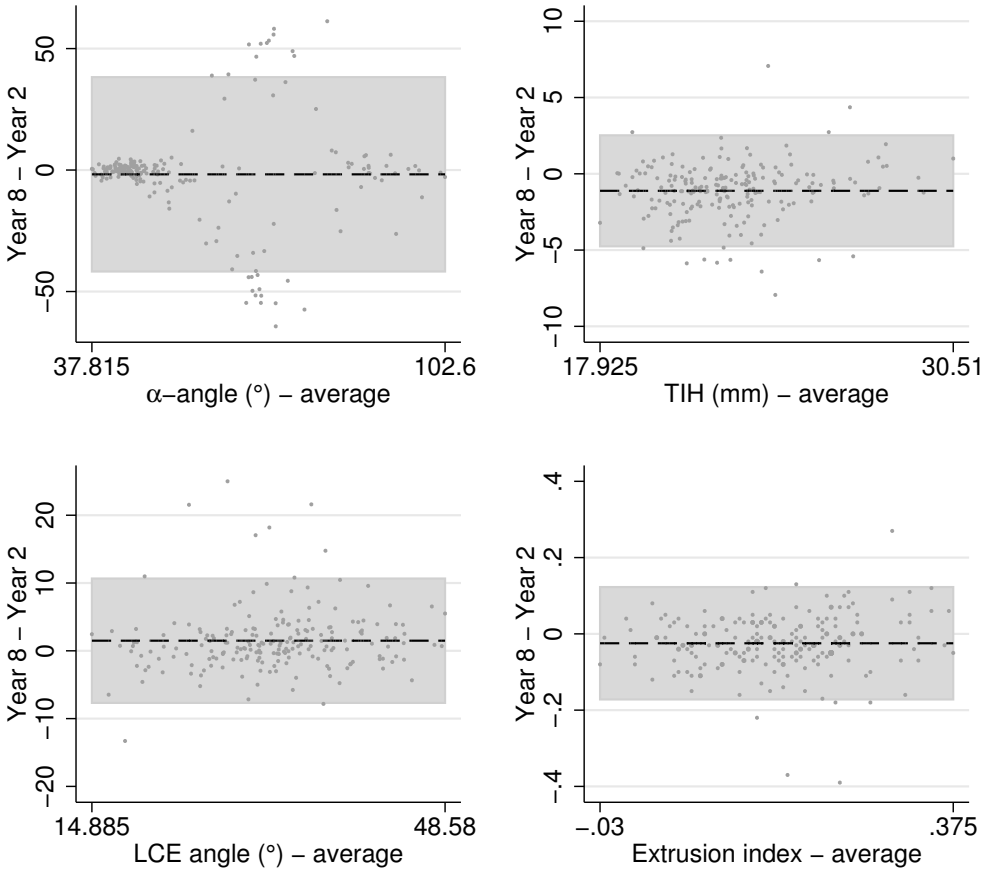


Figure 8.6 – Bland-Altman plots of α-angle, TIH, LCE angle and extrusion index (Year 2 and 8 measurements).

8.4 Discussion

The patho-aetiology of cam-type malformation has been discussed extensively over the last five decades [55, 76, 160], with some postulating that it is secondary to remodelling of the femoral head[55, 160], while Murray proposed that it results from a prior asymptomatic slipped capital femoral epiphysis[50].

This study of a population based cohort finds that no correlation exists between age and measurements of hip morphology characteristic of cam-type FAI and acetabular dysplasia, which are predictive of OA development. Changes in hip morphology between time points were not significant, and all were within the measurement error determined by the reproducibility assessment seen in Chapter 2. In particular the distribution of α-angle remained constant during the course of the study, though α-angle increased in some participants, it was equally likely to fall, suggestive of measurement error (and/or variation associated with femoral rotation) rather than cam-type FAI development.

The fact that morphology is static in this adult cohort of women provides further support to the theory that that cam-type FAI is causally related to OA development rather than a consequence of hip OA and secondary remodelling of the femoral head-neck junction [54, 71, 199]. Morphologically cam-type FAI is similar to SCFE as has been suggested by a number of authors [50, 52, 60, 70], this study supports this

observation.

8.5 Summary

In summary this study provides evidence that no correlation exists between age and hip morphology and in this longitudinal population cohort no significant change in morphological features characteristic of cam-type FAI or acetabular dysplasia occurs as an adult.

Chapter 9

Discussion

9.1 Introduction

Understanding the natural history of disease is important to clinicians and public health professionals in establishing appropriate treatment and accurate prognosis, as well as when considering disease prevention and control strategies. Although the natural history of a particular disease will vary somewhat from individual to individual, and different diseases will each have their own distinct natural histories.

Risk factors for progression of hip OA and the natural history of the disease remain controversial [94]. Most of the studies published on the natural history of hip OA have been based on cohorts with clinical symptoms of OA at study entry [93]. Few studies exist on the natural history of hip OA in a community setting [86, 99, 200]. Many studies performed so far also have a relatively short followup [201, 202] and vary in

the end point considered, some using THR [104, 203, 204], and others using features of radiographic OA such as joint space narrowing [202, 205]. A review of the literature published in 2009, identified only 18 studies on hip OA progression that were deemed to be of acceptable quality, 15 of which came from the same three cohorts, and only four had more than 1,000 subjects [94]. This represents a relative paucity of data when the cumulative prevalence of hip OA at up to 27% [4] is considered, and the mortality adjusted lifetime risk of THR at age 50 is 12% [108]. The Chingford cohort provides a unique opportunity to investigate the associations between morpholgical abnormalities of the hip with OA (both clinical and radiological), pain and THR in a large population cohort representative of the UK female population.

The pathogenesis of OA in the hip is multifaceted and involves articular cartilage failure induced by an interplay of genetic, metabolic, biochemical, and biomechanical factors [89]. Despite well established risk factors, OA continues to be a very difficult disease to predict [90–93]. Few variables have been found to be strongly associated with the progression of hip OA, and a variety of variables only weakly predictive [94]. Whilst there is ongoing investigation into all areas of the complex and broad pathogenesis, the focus of this thesis is on the biomechanical factors and specifically morphological variants within the hip joint.

Nearly 50 years ago, Murray [50], Solomon et al. [51, 206], and Harris et al. [52, 207] made the observation that so called primary or idiopathic hip OA could frequently be attributed to minor morphologic abnormalities. The pathophysiology of this concept

remains under debate, but has sparked interest and research, not to mention an exponential increase in surgery aimed at hip preservation [208, 209]. The number of surgical procedures performed each year to treat FAI in particular has risen 442% over the past 10 years [209], despite limited evidence to support its long term efficacy.

Young adult hip disease remains a significant clinical problem that is relatively poorly understood and widely treated with interventions of unproven long term efficacy. Understanding the natural history of hip OA in a large population cohort and in particular the role of hip morphology in the development of OA will significantly inform future research, as well as aid in the identification of at risk individuals and prognostication. The work included in this thesis has developed methods for better evaluation of hip morphology, characterised in detail hip morphology in a large population cohort and identified morphological abnormalities associated with the development of pain and hip OA.

9.2 Main Findings

Over the last decade increasing evidence has emerged from epidemiologic studies indicate that osteoarthritis (OA) of the hip frequently occurs in the absence of OA in other large joints, suggesting that local factors are important in its pathogenesis [70, 94, 114, 127, 129]. The rational for inclusion in this study of the various morphology measurements is summarised in Table 2.1. An earlier study from our insti-

tution indicated that measurement of hip joint morphology with an earlier version of our software program showed acceptable intra- and inter-observer reproducibility [86]. Conversely, Clohisy et al. [140] have reported limited reproducibility among a group of experienced hip surgeons in terms of categorical classifications of hip morphology. Objective measurements of hip morphology using the current software has shown significant improvement in terms of reproducibility and in turn would allow more reproducible classification of pathological features for epidemiological research.

Excellent intra-observer reproducibility, better than that of the previous version of the program is reported. For the better of the two observers (GERT) ICCs were in excess of 0.88 (95% CI 0.73-0.95), the worst being for the composite measure of acetabular depth:width ratio. In addition the inter-observer reproducibility was significantly better than that obtained previously, with a minimum ICC of 0.82 (95% CI 0.60-0.92), for the same measurement [86]. The reasons for these improvements include the introduction of fine contrast and brightness adjustment as well as magnification tools similar to Picture archiving and communication system (PACS) software used clinically. In addition, where appropriate, measurements are now constrained to the shape or plane in which they must occur. The software is not automated and the results potentially represent a best case when readings are performed by expert observers. Individual anatomical characteristics of the hip are not always easily visualised and more frequently, due to poor quality radiographs (particularly in obese patients) significant time is spent on contrast/brightness adjustment. It is important to obtain high qual-

ity well centered radiographs and care is required in digitisation. Fortunately this is largely the case in the Chingford cohort.

The Chingford 1000 Women Study population is discussed in chapter 3. The study population was representative of the female U.K. population at the time the study was initiated, with a 78% response rate from eligible subjects at a North London General Practioners' Practice. Loss to follow-up at year 2, when 801 participants underwent radiographic assessment with AP pelvis radiographs was non-differential. This was no longer the case at year 20, when participants lost to follow-up were found to be older, included more smokers and less active individuals than those who remained actively enrolled.

Age in particular is a risk factor for OA, therefore it is possible that there was a higher incidence of OA in the participants lost to follow-up. This may introduce conservative bias to the longitudinal analysis of the association between hip morphology and OA.

An understanding of morphology in a population cohort is essential when considering morphological abnormalities. The vast majority of the measurements listed in Table 2.1 and discussed further in Chapter 2, have only been measured in cohorts with disease, consequently the normal range of these measurements is largely unknown[75–77, 123, 124, 126, 128, 142–147, 156].

This study provides the most detailed description to date, of hip morphology in a large population based cohort of women. Wide variation is present with the vast

majority of measures normally distributed. Interestingly the distribution of α-angle when measured on AP pelvis radiographs was bimodal, with a range of 36° to 118° and antimode of 65°. α-angle measurement on AP pelvis radiographs has previously been reported in a number of studies [71, 77, 153], but a bimodal distribution was first recognised in this cohort [154] and confirmed in a recent collaboration with the CHECK study [130]. The bimodal distribution of α-angle as well as the asymmetry seen, suggests a discrete pathological entity and acquired pathology.

The relationships between LCE angle, extrusion index, Sharps angle and acetabular depth:width ratio in the assessment of acetabular malformations was confirmed. The mean LCE angle in the cohort was 30.7° with a SD of 6.9°. Using the traditionally definitions of dysplasia as a LCE angle <20° and pincer-type FAI as an LCE angle >40° [80, 158], dysplasia was present in 5.4% of the cohort, similar to the 3-5% which has been previously reported[71, 157, 159]. Pincer-type FAI showed a prevalence of 8.3%, less common than previously reported in women[71]. Triangular index was positive in 4.4%, similar to the 5.2% previously reported [77]. The prevalence of some degree of head asphericity suggestive of a more subtle cam-type FAI was significantly greater at 24%.

Cross-sectional associations between hip morphology and radiographic OA are subsequently considered in chapter 6. The only demographic characteristic associated with OA was age, with the OA group being on average two years older than the non OA group, this is consistent with numerous previous studies[4, 107]. The prevalence

of radiographic OA was at 14%, which lies between the estimates from the Johnston County Osteoarthritis Project [163] and NHANES-I [164]. BMI was not significantly associated with OA. The relationship between obesity and hip OA has been less clear[136, 168]. Some cross-sectional studies[99, 164, 169] as well as longitudinal studies[170–172] have identified an association between obesity and hip, whilst some longitudinal studies[136, 166] have failed to identify any significant association. This study further supports this position.

Few morphological measurements were significantly different in the presence of radiographic OA, α-angle, TIH and triangular ratio were increased and head:neck ratio decreased in the OA group. These are all indicators of cam-type FAI. The distribution of α-angle in particular was different in the OA group. No significant difference was seen in terms of acetabular morphology. This is consistent with previously published evidence from the UK and Japan [45–47], but inconsistent with some evidence that mild acetabular dysplasia [173] as well as DDH[43, 44] are associated with OA.

Interestingly only α-angle and age were significantly associated with radiographic OA in the final multivariate logistic regression model. Each degree increase in α-angle was associated with a 1% increased risk of OA and age increased risk by 6% per year. Only the Copenhagen Osteoarthritis Substudy [71, 157] has previously studied the risk of hip osteoarthritis with attention to both femoral and acetabular morphological abnormalities in a population cohort. Age and pistol grip deformity were also significantly associated with OA in their cross-sectional study, as well as an association between OA

and a deep acetabular socket (LCE angle >45°). A deep acetabular socket was not associated with OA in this study and a recent 5-year longitudinal study in an enriched cohort found no significant association between pincer-type FAI and OA [174].

Longitudinal associations between hip morphology and incident radiographic OA and THR are considered. An a priori selection of morphological measurements are used in the analysis. The hypothesis that subtle hip deformities are associated with the longitudinal development of hip OA and THR is confirmed. Deformities associated with cam-type FAI and mild acetabular dysplasia of the hip were independently predictive of radiographic OA and THR. These measurements were independently predictive of outcome even when controlling for baseline age, BMI and joint space width and significantly increased the predictive value of the model assessed by McFadden's pseudo R^2 and AUROC. This is the first study to demonstrate these findings in a longitudinal population cohort.

Evidence that morphological abnormalities are cross-sectionally associated with OA are relatively well established [71, 153], whilst prospective longitudinal data, which may provide more convincing evidence of a causal relationship, is lacking. Previous studies examining the development of OA have focused on severe acetabular dysplasia [123, 124]. Two studies have identified an association between cam-type FAI and radiographic OA, but are limited by their cross-sectional nature, as is the data from chapter 5 [71, 76]. This work demonstrates that women with a cam-type FAI identified by an α-angle of greater than 65° have an increased risk of radiographic OA and THR with

each degree increase in α-angle above 65° conferring a 5% and 3% increased risk respectively. More severe cam-type deformities identified by increased TIH are predictive of THR at 18 year follow-up with each millimetre increase conferring a 19% increased risk. Mild acetabular dysplasia significantly increased the risk of radiographic OA and THR with each degree reduction in LCE angle associated with a 14% and 21% increase in risk respectively. No significant associations were seen with pincer-type FAI.

Evaluation of the models showed statistically significant improvements in our ability to predict radiological OA and THR ($p<0.001$ in both cases) with the inclusion of morphological measurements as compared to established risk factors of age, BMI, joint space width.

Thresholds for non-linearity based on the α-angle distribution data were used initially, with further analyses of non-linearity using fractional polynomial regression. The outcome data suggests a lower threshold of 41° for radiographic OA and a higher threshold of 82° for THR. AUROC statistic for non-morphological covariates (age, BMI, joint space width) alone as predictors of incident radiographic OA was 57.5% and increased significantly to 66.7% with the inclusion of both LCE and α-angle ($p<0.001$). McFadden's pseudo R^2 statistic increased from 1.21% to 7.48%. AUROC statistic for non-morphological covariates as predictors of THR was 63.73% and increased significantly to 83.36% with the inclusion of LCE, α-angle and TIH ($p<0.001$). McFadden's pseudo R^2 statistic increased from 4.75% to 22.84%. This represents excellent predictive value for the final model.

The longitudinal association between hip morphology with pain and symptomatic OA were considered in a similar manner. Incident hip pain was significantly more common than radiographic OA at 26% and symptomatic OA less common at 5%.

FAI has been extensively documented as a cause of groin pain as long ago as 1936 [66], though evidence from population studies is limited [71].

Each degree increase in α-angle above 65° was associated with an increase in risk of pain and symptomatic OA of 4% and 8% respectively. Whilst each degree reduction in LCE angle below 28° was associated with an increased risk of pain and symptomatic OA of 10% and 21%.

AUROC statistic for non-morphological covariates (age, BMI, joint space width) alone as predictors of incident hip pain was 55.7% and increased to 61.5% with the inclusion of both LCE and α-angle ($p<0.001$). McFadden's pseudo R^2 statistic increased from 0.92% to 4.18%. AUROC statistic for non-morphological covariates as predictors of symptomatic OA was 61.82% and increased significantly to 73.6% with the inclusion of LCE and α-angle. McFadden's pseudo R^2 statistic increased from 3.59% to 13.7%. Our relative inability to predict pain highlights the poor correlation between radiologically determined OA and pain [195, 196].

The final results chapter considers changes in hip morphology during the course of the study, with particular attention to α-angle and other measures of cam-type FAI. The patho-aetiology of the cam-type malformation has been discussed extensively over the last five decades [55, 76, 160], with some postulating that it is secondary to

remodelling of the femoral head[55, 160], while Murray proposed that it results from a prior asymptomatic slipped capital femoral epiphysis[50].

No association between age and hip morphology was found. Changes in hip morphology between time points were relatively small, in all instances within the measurement error determined by the reproducibility assessment seen in Chapter 2. In particular the distribution of α-angle remained constant during the course of the study, though α-angle increased in some participants, it was equally likely to fall, suggestive of measurement error rather than cam development. Providing further evidence that that cam-type FAI is likely a consequence of a silent SCFE rather than a consequence of hip osteoarthritis and secondary remodelling of the femoral head-neck junction [54, 71, 199].

9.3 Strengths and Limitations

The focus of this thesis is the biomechanical factors and specifically morphological variants within the hip joint that predict hip OA. Consequently development of rigorous and consistent methodology for the measurement of hip morphology was required. The objective measurements of hip morphology using the current software shows significant improvement in terms of reproducibility as compared to previous iterations and categorical classifications of hip morphology. This improved reproducibility is a strength both in terms of the data presented in this thesis and its contribution to future epidemiological research.

This is the only study at present which includes long term follow up in a normal population with regular reporting of pain as well as validated records of THR. Loss to follow-up appears to be non-differential in terms of hip morphology if not descriptive characteristics of the study population, which is not unexpected with the median age of the cohort reaching 74.

Unfortunately, only women are included in the study, although the baseline characteristics of these women were similar to the UK general population in terms of weight (65 kg in the UK, 67 kg in Chingford), height (1.61 m versus 1.62 m) and BMI (25.4 versus 25.6 kg/m^2) [150]. Cam-type FAI appears to be twice as frequent in men as in women [153, 184], and acetabular dysplasia approximately 20% more frequent in women as in men [71]. The role of cam-type FAI in OA may therefore be underestimated in this population cohort and the role of acetabular dysplasia overestimated. In addition 98% of the women were Caucasian again limiting the generalisability of the data.

Further limitations include the use of AP pelvis radiographs only, while lateral projections of the hip are more sensitive for detecting FAI [131], AP pelvis radiographs are the most commonly used imaging modality for the hip and the only available in the majority of large cohort studies [132–136]. A prior study showed that only 3.6% of pistol grip malformations in men and 11% of pistol grip malformations in women detected on lateral hip radiographs went undetected on AP radiographs when the triangular index was used with an underestimate of the prevalence pistol grip deformity

of approximately 0.5% [153]. Three-dimensional assessment of morphology with MRI and/or CT certainly represents the gold standard in terms of radiological assessment of structural abnormalities of the hip but it is likely to be many years before any such population cohort is available.

9.4 Contribution to existing knowledge

The cross-sectional morphology data is the most comprehensive assessment of hip shape presented to date in any cohort and strengthened by its population nature and size. Wide variation in hip morphology is present with the vast majority of measures showing a normal distribution, α-angle is the notable exception here. In addition the asymmetry of α-angle is an interesting finding which may in part explain unilateral hip osteoarthritis. The α-angle data has been used in collaboration with the CHECK cohort to determine threshold values for the definition of a cam deformity on AP pelvic radiographs [155]. A definite bimodal distribution of the α-angle was found in both cohorts with a normal distribution up to 60°, when the cohorts were combined, indicating a clear distinction between normal and abnoα-angleangles. A pathological threshold of 78° for end-stage OA resulted in maximal AUROC statistic.

Cross-sectional association of morphology and demographic characteristics with radiographic OA were relatively limited, with only age and α-angle remaining significantly associated in the final model. This is interesting given that numerous previous stud-

ies have identified cross-sectional associations between acetabular dysplasia and OA [43, 44, 157, 173]. This is likely to be a result of the age of cohort at radiographic assessment. The Copenhagen Osteoarthritis Substudy for example includes participants from age 22 to 93 years [157]. Longitudinal associations of hip morphology with incident radiographic OA, THR, pain and symptomatic OA in a population cohort are all significant contributions to our understanding of the patho-aetiology of hip osteoarthritis. This is the first study of a longitudinal population cohort to identify these association. Longitudinal evidence to date had been limited to severe acetabular dysplasia [123, 124]. Cam-type FAI and mild acetabular dysplasia were significantly associated with all of the above outcome measures. No significant association was seen between pincer-type FAI and any of outcome measures. This is consistent with recent longitudinal evidence from a symptomatic cohort [174].

The discriminatory ability of the morphological measurements were evaluated using AUROC statistic as well as McFadden's pseudo R^2. Logistic regression models which included age, BMI and joint space (established risk factors for OA) were compared with models which also included morphological measurements. All models were improved with the inclusion of morphological measurements. The THR model in particular increasing McFadden's pseudo R^2 to 22.8%, which represents excellent fit.

Normal hip morphology reduces THR risk significantly to 0.6% at 18 years follow-up compared with a 6% in the abnormal morphology group. This equates to a negative predictive value of 99.4% with the threshold for abnormality on an AP Pelvis radio-

graph set at 65° for α-angle and LCE angle >25° and <45°.

9.5 Implications for Clinical Practice and Further Research

Cam lesions have been observed in >50% of patients undergoing hip replacement [210], and significant cartilage damage has also been seen intra-operatively at the specific sites where impingement occurs [211]. The evidence that subtle morphological abnormalities of the hip are significantly associated with OA development further supports the role of biomechanics in the pathogenesis of hip OA. Hip arthroscopy aimed at treating cam-type FAI in particular has risen 442% over the past 10 years[208]. Despite promising medium term results of hip arthroscopy [87], evidence is limited largely to case series. It is likely that the evidence of an association between cam-type FAI and OA development will be used to support the use of hip arthroscopy and osteochondroplasty, despite no evidence that is possible to alter the natural history. There is now urgent need for higher quality evidence, in the form of randomised controlled trials to assess efficacy and longer term outcomes. This an obvious area of further research.

The software developed as part of this thesis is being used to expand the morphology data available beyond the Chingford 1000 Women Study. The Osteoarthritis Initiative (OAI) is well known as a public access research database from the largest

prospective study of biomarkers (MRI, biochemical, genetic) of knee OA incidence and progression. It is less well known that the OAI is also a prospective study of hip OA with 4976 participants. Using the software described in this thesis for radiograph reading assessment of the association between hip morphology and the development of OA in this cohort has now begun. In addition to validation of the results seen in the Chingford cohort, work on correction for tilt and rotation of pelvis as well as femoral rotation is in progress for use in the OAI cohort. Collaboration with the CHECK cohort (an enriched population cohort of symptomatic individuals) is also already in place, where data from this thesis is being used to validate alternative measurement techniques including statistical shape modelling.

Future directions for research include three dimensional assessment of morphology, with the hypothesis that it may be possible to further improve our ability to predict disease progression with better characterisation of morphology. In addition to the static assessment there is also a role for hip movement, as the name suggests FAI is a dynamic problem characterised by abutment of femoral head-neck junction and acetabulum. This may be with modelling of hip movements or true dynamic assessment of impingement positions.

The pathogenesis of OA is multifaceted and involves articular cartilage failure induced by an interplay of biomechanical, biochemical, genetic and metabolic factors. The evidence that biomechanical factors are significantly associated but do not fully predict OA draws attention to the need for further research into those biochemical,

genetic and metabolic factors.

9.6 Conclusions

The natural history of disease is the uninterrupted progression (of the disease) in an individual from the moment of exposure to causal agents until recovery or death. Knowledge of the natural history of disease ranks alongside causal understanding in importance for disease prevention and control, and is one of the major elements of descriptive epidemiology.

The practice of orthopaedic surgery and the treatment of arthritis has progressed in a largely empirical manner, based on treatment of pain and reduced function, often with little attention to understanding of the disease process. Treatment of FAI is a prime example, where treatments pre-date conclusive evidence of its role in the patho-aetiology of OA.

The pathogenesis of OA in the hip is multifaceted and involves joint failure induced by an interplay of genetic, metabolic, biochemical, and biomechanical factors [89]. Few studies exist on the natural history of hip OA in a community setting [86, 99, 200].

New software was developed and validated, which allows measurement of 25 morphological features in the pelvis, acetabulum and proximal femur. This software was used to characterise hip morphology in the population along with investigation of variations in disease. The relationship between hip morphology and OA development was

subsequently considered.

Increased α-angle is identified as a discrete pathological entity in the population, along with the normal distribution of all other morphological features. Radiographic measurements of subtle hip deformities are associated with the longitudinal development of hip osteoarthritis as measured by symptoms, radiographic features and/or replacement, independent of age, BMI and joint space narrowing. The models identified significantly improve our ability to predict hip OA development, in particular our ability to predict need for THR. Further research is required to expand these observations to men.

Evidence that hip morphology is significantly associated with the development of OA lays the foundation for future investigation and the rationale for further research into treatment of morphological abnormalities of the hip. Surgical interventions aimed at treating FAI and acetabular dysplasia are already becoming increasingly common, whilst this research provides further theoretical support for their use, high quality evidence, in the form of randomised controlled trials to assess their efficacy and long term outcomes are urgently required.

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